ORGANIC LETTERS

2013
Vol. 15, No. 4
832–835

Gold-Catalyzed Intramolecular Hydroamination of *o*-Alkynylbenzyl Carbamates: A Route to Chiral Fluorinated Isoindoline and Isoquinoline Derivatives

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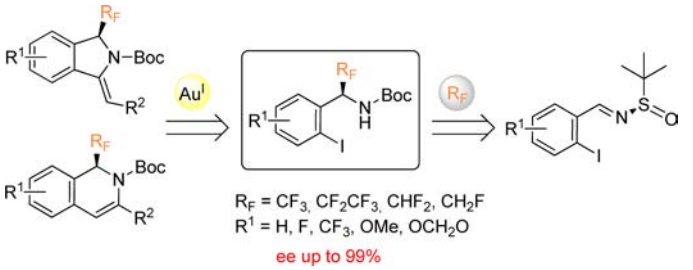
Received December 22, 2012

ABSTRACT



Enantiomerically pure fluorinated isoindoline and dihydroisoquinoline scaffolds have been prepared through a diastereoselective addition of fluorinated nucleophiles to Ellman's *N*-(*tert*-butanesulfinyl)imines followed by a sequence of Sonogashira cross-coupling/gold(I)-catalyzed cycloisomerization of the corresponding carbamate. A more favored 5-*exo*-*dig* mechanism was observed mainly due to an electronic effect of the fluorinated group.

Isoindoline and isoquinoline ring systems are widespread in the alkaloid family and other natural products displaying a wide range of interesting biological properties.[1] They are considered "privileged structures" owing to their general use as building blocks in the total synthesis of natural products but also a common motif in the design of new drugs.[2] On the other hand, selective introduction of fluorine atoms into organic molecules has become one of the most efficient methods for modulation of their biological properties.[3] Thus, preparation of both fluorinated isoindoline and isoquinoline derivatives has received much attention in industry, especially with regard to efforts directed at asymmetric synthesis.

Among the different methods to access these nitrogen-containing heterocycles, transition-metal-catalyzed intramolecular hydroamination reactions are of particular

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(1) For a comprehensive review of isoindolines, see: (a) Portevin, B.; Tordjman, C.; Pastoureau, P.; Bonnet, J.; De Nanteuil, G. *J. Med. Chem.* **2000**, *43*, 4582. (b) Stuk, C. L.; Assink, B. K.; Bates, R. C.; Erdman, B. T.; Fedij, V.; Jennings, S. M.; Lassig, J. A.; Smith, R. J.; Smith, T. L. *Org. Process Res. Dev.* **2003**, *7*, 851. For isoquinolines: (c) Bentley, K. W. *Nat. Prod. Rep.* **2006**, *23*, 444. (d) Vincent, G.; Williams, R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1517. (r) Bhadra, K.; Kumar, S. *Med. Res. Rev.* **2011**, *31*, 821.

(2) The concept of "privileged structures"was first introduced by Evans and was recently updated by Patchett and Nargund. (a) Evans, B. E.; Rittle, K. E.; Bock, M. G.; Dipardo, R. M.; Freidinger, R. M.; Whitter, W. L.; Lundell, G. F.; Veber, D. F.; Anderson, P. S.; Chang, R. S. L.; Lotti, V. J.; Cerino, D. J.; Chen, T. B.; Kling, P. J.; Kunkel, K. A.; Springer, J. P.; Hirschfield, J. J. *J. Med. Chem.* **1988**, *31*, 2235. (b) Patchett, A. A.; Nargund, R. P. *Annu. Rep. Med. Chem.* **2000**, *35*, 289.

(3) (a) Bègué, J.-P.; Bonnet-Delpon, D. *Bioorganic and Medicinal Chemistry of Fluorine*; Wiley: Hoboken, NJ, 2008. (b) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881. (c) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320. (d) O'Hagan, D. *J. Fluorine Chem.* **2010**, *131*, 1071.

10.1021/ol3035142
Published on Web 01/29/2013

value.[4] This process relies on the catalytic activation of the C−C triple bond followed by an attack of an internal nucleophile. In the past few years, gold complexes have emerged as powerful catalysts for this purpose.[5]

To the best of our knowledge, most cycloisomerizations catalyzed by gold lead to the formation of the isoquinoline skeleton as a result of a favored 6-*endo*-*dig* cyclization.[6] In these cases, the corresponding 5-*exo*-*dig* product was not isolated due to either its instability or its nonformation.[6b,c] However, we have found that the gold-catalyzed cycloisomerization of fluorinated *o*-alkynylaryl carbamates evolves preferably toward the isoindoline formation, as opposed to our expectations.

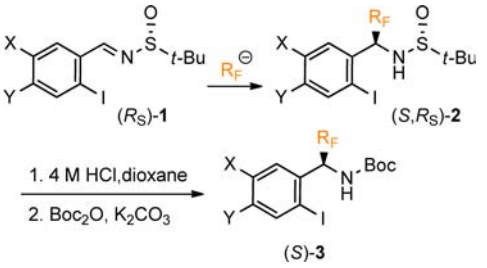
Given our group's interest in organofluorine chemistry, we have recently reported a stereoselective synthesis of fluorinated 1,3-disubstituted isoindolines based on a nucleophilic addition/intramolecular aza-Michael reaction tandem process.[7] The choice of Ellman's (*R*)-*N*-(*tert*-butanesulfinyl)-imines as chiral auxiliaries was crucial in the achievement of excellent diastereoselectivities.[8] Building on these results, we envisioned an alternative and more direct route toward enantioenriched fluorinated isoindoline **5** and isoquinoline **6** scaffolds through a gold(I)-catalyzed intramolecular hydroamination reaction as the key step.

Our strategy implies the use of an appropriate building block to introduce chirality and the fluorinated group into the molecule at the beginning. Hence, 2-iodobenzyl carbamate **3** was regarded as the fluorinated building block of choice in a first approach.

Starting from Ellman's (*R*)-*N*-(*tert*-butanesulfinyl)imines **1**, selective addition of different fluorinated nucleophiles (CF_3TMS, CF_3CF_2TMS, $PhSO_2CF_2H$, $PhSO_2CH_2F$) led to the expected sulfinyl amines **2** in good yields as single diastereoisomers (Table 1).[9,10]

In view of the fact that the stereochemistry of the chiral auxiliary is known (R_S), the absolute configuration of the newly created stereocenter was determined to be *S*

Table 1. Obtention of Enantiomerically Pure Fluorinated 2-Iodobenzyl Carbamates **3**



entry	**2**	% yield[a]	R_F	X	Y	**3**	% yield[a] (er)[b]
1	**2a**	80	CF_3	H	H	**3a**	80 (<99:1)
2	**2b**	70	CF_3	F	H	**3b**	74 (97:3)
3	**2c**	71	CF_3	CF_3	H	**3c**	82[c]
4	**2d**	77	CF_3	OMe	H	**3d**	75 (97:3)
5	**2e**	71	CF_3	$O-CH_2-O$		**3e**	80 (98:2)
6	**2f**	83	C_2F_5	H	H	**3f**	60 (99:1)
7	**2g**	92	CF_2R	H	H	**3g**	75[c]
8	**2h**	88[d]	CFHR	H	H	**3h**	88[d]

[a] Isolated yield. [b] Determined by chiral HPLC analysis. [c] Incompletely separated enantiomeric mixture. [d] Obtained as a diastereomeric mixture (1:2), determined by ^{19}F NMR analysis of crude reaction mixture. R = SO_2Ph.

according to previous reports[7,11] and definitely confirmed by X-ray analysis.[12] Since we proved that the cycloisomerization did not take place in the presence of the *tert*-butanesulfinyl group (*t*-BuSO), the conversion of *t*-BuSO into another nitrogen-protecting group compatible with the intramolecular hydroamination was required. With this purpose, chiral intermediates **2** were treated with 4 M HCl in dioxane yielding the corresponding free amines after basification. Unisolated amines were then protected as carbamates under standard conditions, giving the fluorinated building blocks **3** in good to excellent yields and enantioselectivities (Table 1).

Next, the functionalization of synthon **3** with selected terminal acetylenes by means of a typical Sonogashira cross-coupling reaction afforded alkynyl carbamates **4** in excellent yields (Table 2). To our delight, the enantioselectivity was well preserved during the process.

According to our synthetic plan, the next step would be the intramolecular hydroamination reaction catalyzed by a transition metal complex. In order to find optimum conditions, alkynyl carbamate (±)-**4a** was subjected to the intramolecular protocol in the presence of different Lewis acid catalysts.

When the model substrate **4a** was treated with CuI, $Pd(OAc)_2$, or $AuCl_3$, cyclization products were not detected even after prolonged reaction times (2−3 days).[13] Although

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(5) (a) Zigang, L.; Brouwer, Ch.; He, Ch. *Chem. Rev.* **2008**, *108*, 3239. (b) Jiménez-Nuñez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326. (c) Müller, T. E.; Hultzsch, K. C.; Yus, M.; Foubelo, F.; Tada, M. *Chem. Rev.* **2008**, *108*, 3795. (d) Corma, A.; Leyva-Pérez, A.; Sabater, M. J. *Chem. Rev.* **2011**, *111*, 1657.

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(8) For a recent and exhaustive review on *tert*-butanesulfinamide and its use in synthesis, see: Robak, M. T.; Herbage, M. A.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 3600.

(9) For the asymmetric synthesis of fluoroalkyl amines, see also: Soloshonok, V. A.; Ono, T. *J. Org. Chem.* **1997**, *62*, 3030 and references cited therein.

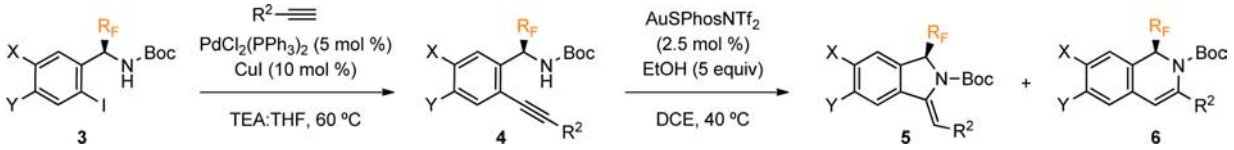
(10) Racemic mixtures were prepared in a similar manner starting from (±)-*N*-(*tert*-butanesulfinyl)imines **1**. For experimental details, see the Supporting Information.

(11) Krishnamurti, R.; Bellew, B. R.; Prakash, G. K. S. *J. Org. Chem.* **1991**, *56*, 984.

(12) Suitable crystals of products **7** (CCDC 916244) and **10** (CCDC 916245) were obtained for X-ray diffraction analysis. For details, see the Supporting Information.

(13) An in-depth investigation on the reaction conditions was carried out. See the Supporting Information for a detailed study.

Table 2. Sonogashira Cross-Coupling Reaction/Gold(I)-Catalyzed Intramolecular Hydroamination Sequence



entry	4	% yield[a] (er)[b]	R_F	X	Y	R^2	[5:6]	5	% yield[a] (er)[b]	6	% yield[a] (er)[b]
1	**4a**	94 (99:1)	CF_3	H	H	Ph	4:1	**5a**	80 (97:3)	**6a**	20 (97:3)
2	**4b**	93 (98:2)	CF_3	H	H	4-$MeOC_6H_4$	1:3	**5b**	26 (99:1)	**6b**	74 (98:2)
3	**4c**	97 (98:2)	CF_3	H	H	4-MeC_6H_4	1:1	**5c**	54 (93:7)	**6c**	43 (95:5)
4	**4d**	99 (>99:1)	CF_3	H	H	4-FC_6H_4	3:1	**5d**	60 (96:4)	**6d**	20 (97:3)
5	**4e**	91 (96:4)	CF_3	H	H	3-$MeOC_6H_4$	5:1	**5e**	70 (96:4)	**6e**	18[e] (98:2)
6	**4f**	90 (95:5)	CF_3	H	H	3-$CF_3C_6H_4$	>30:1[c]	**5f**	80 (93:7)	**6f**	n.d.
7	**4g**	60 (97:3)	CF_3	H	H	3,5-di$MeOC_6H_3$	12:1	**5g**	80 (97:3)	**6g**	n.d.
8	**4h**	88 (96:4)	CF_3	H	H	3,5-diFC_6H_3	>30:1[c]	**5h**	85 (95:5)	**6h**	n.d.
9	**4i**	45[d] (99:1)	CF_3	H	H	3,5-di$CF_3C_6H_3$	>30:1[c]	**5i**	>99 (98:2)	**6i**	n.d.
10	**4j**	94 (97:3)	CF_3	H	H	*n*-Hex	3:1	**5j**	50 (94:6)	**6j**	37[e,g]
11	**4k**	68[f]	CF_3	H	H	*t*-Bu		**5k**	n.r.	**6k**	n.r.
12	**4l**	88 (97:3)	CF_3	F	H	Ph	2:1	**5l**	62 (97:3)	**6l**	36 (97:3)
13	**4m**	86[g]	CF_3	CF_3	H	Ph	1:1	**5m**	47 (92:8)	**6m**	41 (92:8)
14	**4n**	83 (96:4)	CF_3	OMe	H	Ph	3:1	**5n**	70 (91:9)	**6n**	24[e] (96:4)
15	**4o**	86 (98:2)	CF_3	O–CH_2–O		Ph	17:1	**5o**	75 (95:5)	**6o**	n.d.
16	**4p**	80 (>99:1)	C_2F_5	H	H	Ph	4:1	**5p**	81 (>99:1)	**6p**	19 (>99:1)
17	**4q**	58[h,g]	CF_2H	H	H	Ph	7:1	**5q**	51 (n.d.)[i]	**6q**	<5
18	**4r**	49[h,g]	CH_2F	H	H	Ph	1:1.5	**5r**	36 (n.d.)[i]	**6r**	54 (98:2)

[a] Isolated yield. [b] Determined by chiral HPLC analysis. [c] The other isomer was not observed on ^1H and ^{19}F NMR spectra. [d] 50% conversion. [e] The yield refers to an inseparable mixture of (*E*)-**5** isomer and **6**. [f] Only the racemic mixture was prepared. [g] Incompletely separated enantiomeric mixture. [h] Overall yield after two steps: Sonogashira cross-coupling/desulfonation reaction. [i] Not stable enough to be determined. n.r. = no reaction; n.d. = not determined.

the cationic gold(I) complex generated in situ from Ph_3PAuCl and $AgNTf_2$ was not very effective by itself either, the addition of protic additives (5 equiv EtOH) promoted the cyclization at room temperature,[6b,c,14] furnishing the 5-*exo*-*dig* product (±)-**5a** and 6-*endo*-*dig* product (±)-**6a** in 60:40 ratio and moderate conversion (62% after 48 h).[13] To our delight, a slight increase in temperature (40 °C) accelerated the process significantly, reaching completion in 3 h and improving the yield up to 90% (50:50 ratio).[13]

We also evaluated the influence of the nitrogen-protecting group on the process (Boc, Cbz, *t*-BuSO, *t*-$BuSO_2$, H), and the *tert*-butyloxycarbonyl (Boc) group was eventually chosen to be the best protecting group.

Additionally, various silver salts were screened to test the influence of the counterion, the softer, less-coordinating bis(trifluoromethanesulfonyl)imidate (NTf_2) being the anion of choice. DCE was the best solvent, while the use of other solvents such as THF, MeCN, or toluene led to unfavorable results.

We further optimized the reaction conditions for alkyne **4a** using gold(I) catalysts bearing bulkier biarylphosphine ligands (SPhos, XPhos, JhonPhos) in order to evaluate their effect on the regioselectivity. Preformed air-stable $AuSPhosNTf_2$ was confirmed as the most promising catalyst, providing excellent yield and regioselectivity (Table 2, entry 1).[15]

Encouraged by these results, we further explored the scope of this reaction. Thus, chiral intermediates **4** underwent a gold(I)-catalyzed cycloisomerization reaction under the established conditions (Table 2). In most cases, the cooperative catalysis between $AuSPhosNTf_2$ and EtOH generated mixtures of regioisomers (**5**:**6**).[16]

Electron-donating alkyne substitution led preferably to 6-*endo*-*dig* cyclization (entries 2 and 3), while an electron-withdrawing effect favored isoindoline formation (entry 4).[14b,17] It should be noted that when *p*-$MeOC_6H_4$ (**4b**) was changed to *m*-$MeOC_6H_4$ (**4e**), isoindoline **5e** was formed as the main product versus **6e** (entry 5). Interestingly, exclusive 5-*exo*-*dig* cyclization was observed with alkynyl **4f**–**i**, furnishing isoindolines **5f**–**i** as the only product (entries 7–9). However, the reaction of **4k** (R^2 = *t*-Bu, entry 11) did not take place at all, and the starting material was

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(15) Interestingly, the absence of AgCl in the medium improved the catalytic activity: Leyva, A.; Corma, A. *J. Org. Chem.* **2009**, *74*, 2067.

(16) A parcial racemization of compounds **5** and **6** was observed probably due to an *enantiomer self-disproportionation* effect on achiral silica gel: (a) Soloshonook, V. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 766. (b) Sorochinsky, A. E.; Aceña, J. L.; Soloshonok, V. D. *Synthesis* **2013**, *45*, 141.

(17) (a) Park, J. H.; Bhilare, S. V.; Youn, S. W. *Org. Lett.* **2011**, *13*, 2228. (b) Patil, N. T.; Nijamudheen, A.; Datta, A. *J. Org. Chem.* **2012**, *77*, 6179.

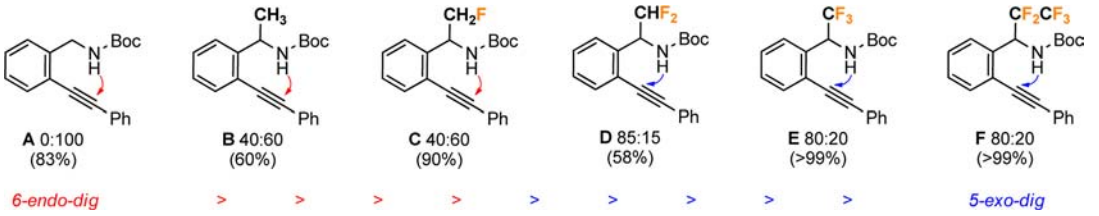
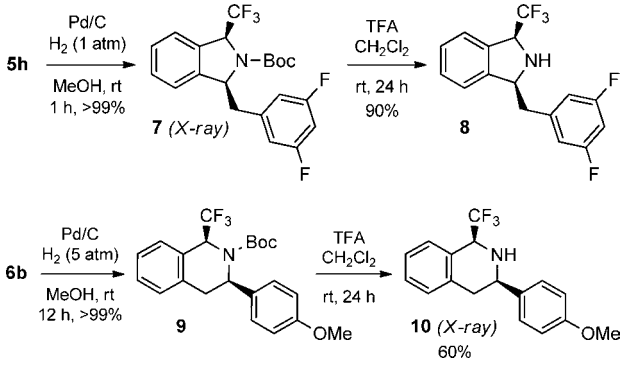


Figure 1. α-Substituent effect on the gold(I)-catalyzed cycloisomerization reaction.

Scheme 1. Reduction and Deprotection of **5h** and **6b**



recovered, probably owing to the steric hindrance of the bulkier *t*-Bu group. In all cases but **5j**,[18] (*Z*)-isomers of isoindolines were formed stereoselectively. Likewise, we also explored differently substituted arene rings (Table 2, entries 12−15). In this case, an electron-rich aromatic ring strongly favors a nucleophilic attack to afford the 5-*exo-dig* product (entry 15) owing to its effect on the polarization of the triple bond.[14b]

On the other hand, the replacement of one or more hydrogen atoms by fluorine in the vicinity of an amine function results in a lower basicity. Presumably, this fact has a significant influence on the regioselectivity of the process. In contrast to published results (Figure 1, **A**),[6b,c] we observed that the gradual introduction of fluorine atoms at the α-position (CH_3 < CH_2F < CHF_2,CF_3,C_2F_5) promotes the 5-*exo-dig* mechanism, leading to isoindoline **5** as a major product under the optimized conditions (Figure 1).[19] Hence, we can conclude that the regioselectivity between 5-*exo-dig* **5** and 6-*endo-dig* **6** did not only depend on the nature and position of the substituents in R^2 but also on the α-substitution of the nitrogen.

In order to expand our methodology and make it synthetically more useful, we carried out the diastereoselective hydrogenation of the generated double bond giving rise to *N*-Boc-protected derivatives **7** and **9** (Scheme 1). Next, the Boc protecting group was removed affording the free NH isoindoline **8** and tetrahydroisoquinoline **10** in 90% and 60% yield, respectively. The absolute configuration was confirmed by X-ray diffraction analysis (see the Supporting Information). These chiral fluorinated derivatives would potentially be good candidates as ligands in the design and development of new catalytic species, which could find applications, for instance, in organocatalysis.[20]

In summary, we have developed an asymmetric synthesis of fluorinated isoindolines **1** and 1,2-dihydroisoquinolines **2** by means of a gold(I)-catalyzed cycloisomerization as the key step. By tuning the electronic property of the alkyne moiety, the regioselectivity can be controlled and directed toward one major product. Also, a significant effect by the fluorinated group was observed, leading the cyclization process through a more favored 5-*exo-dig* mechanism. Applying the principles of diversity-oriented synthesis,[21] access to new libraries of chiral fluorinated molecules would be feasible from our small fluorinated building blocks. Further applications of the new substrates are underway in our laboratory.

Acknowledgment. We would like to thank the Spanish Ministerio de Ciencia e Innovación (CTQ2010-19774) and Generalitat Valenciana (PROMETEO/2010/061) for its financial support. S.C. and P.B. express their thanks for a Juan de la Cierva contract.

Supporting Information Available. Experimental procedures and NMR spectra for all new compounds, as well as crystallographical data for compounds **7** and **10**, including their CIF files. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(18) Isoindoline **5j** was obtained as a mixture of (*E*)- and (*Z*)-isomers in a 50:50 ratio, determined by ^{19}F NMR of the crude reaction mixture. Compounds **5e** and **5n** in 2:98 and 10:90 *E*/*Z* ratio, respectively.

(19) Certain instability was noticed in chloride solvents for isoindoline analogues particularly, which was successfully circumvented by increasing the fluorine loading.

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