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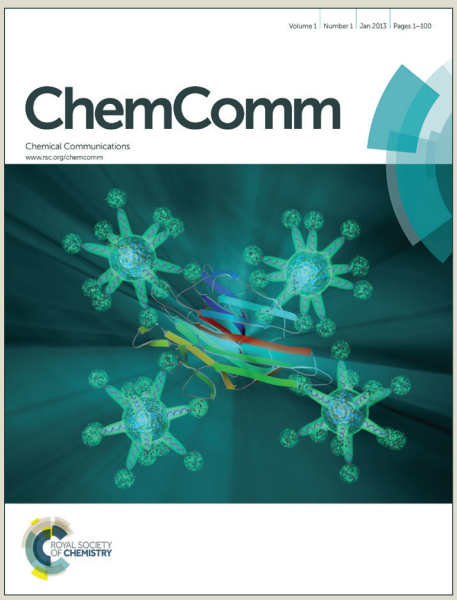

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Copper-catalyzed intermolecular and regioselective aminofluorination of styrenes: Facile access to β-fluoro-*N*-protected phenethylamines

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Jorge Saavedra-Olavarría,[a] Gean C. Arteaga,[a] Jhon J. López[a] and Edwin G. Pérez[a*]

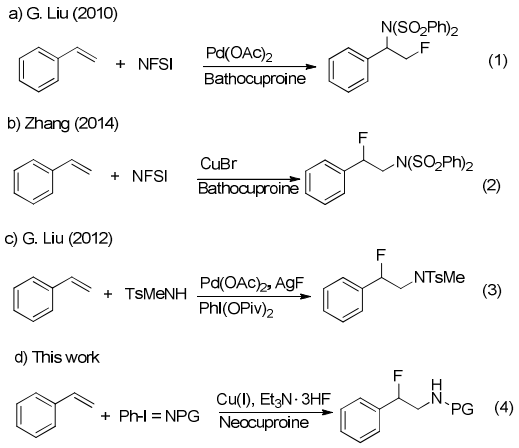
A copper-catalyzed regio- and intermolecular aminofluorination of styrenes has been developed. In this reaction Ph-I=N-Ts and Et_3N•3HF act as nitrogen and fluorine sources, respectively. The obtained β-fluoro-*N*-Ts-phenethylamines can be *N*-alkylated with subsequent deprotection affording the corresponding β-fluoro-*N*-alkylated phenethylamines which are interesting building blocks for compounds acting on neuronal targets.

Compounds containing the 1,2-aminofluoro moiety are valuable as building blocks because they are used in the synthesis of anticholinergic, anticancer and anti-inflammatory drugs, as well as therapeutic β-peptides.[1] Molecules bearing fluorine atoms present improved solubility, hydrophobicity and metabolic stability, explaining why 30 % of all agrochemicals and 20% of all pharmaceuticals contain at least one fluorine atom.[2] In addition, the C-F bond dramatically affects the acid-base properties of fluorine-containing molecules.

1,2-Fluoroamines are not usually obtained in a direct fashion, but rather using multistep procedures.[3] However, in recent years some methodologies for the direct aminofluorination of alkenes have been reported, including intramolecular amination-intermolecular fluorination and intermolecular aminofluorination, by different mechanisms.[4] Recently, Liu[5] and Zhang[6] reported palladium- and copper-catalyzed aminofluorination of styrenes using *N*-fluorobenzenesulfonimide (NFSI) as both an amino and a fluorine source, obtaining products with opposite regiochemistry (equations 1 and 2, Scheme 1). Conversely, the removal of one or both benzenesulfonyl groups from the nitrogen atom has been shown to be difficult and harsh conditions are necessary.[7] In addition, Liu[8] reported another palladium-catalyzed oxidative aminofluorination of styrenes using *N*-methyl-*p*-toluenesulfonamide (TsMeNH) and AgF as nitrogen and fluorine sources respectively (equation 3, Scheme 1).

Copper-catalyzed vicinal difunctionalization of alkenes is a very active field because of its low cost and toxicity as well as the variety of reactions that can be carried out.[9]

Here we describe the successful development of a regioselective aminofluorination of styrenes which affords *N*-protected β-fluorophenethylamines, potential building blocks in the synthesis of many bioactive compounds.



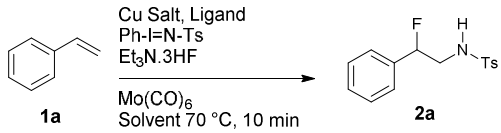
Scheme 1. Metal-catalyzed vicinal aminofluorinations of styrenes.

In our initial attempt we investigated the copper-catalyzed aminofluorination of styrene using *N*-*p*-toluenesulfonylimino-phenyliodinane (Ph-I=N-Ts)[10] and Et_3N•3HF[11] as *N*-Ts group and fluorine atom sources, respectively. No reaction was observed using 10 mol % $Cu(MeCN)_4BF_4$-neocuproine as catalyst and 1,2-dichloroethane as solvent, either at room temperature or at 70 °C (Table 1, entries 1 and 2). Nevertheless, the addition of $Mo(CO)_6$ and

heating at 70 °C led to the desired fluorosulfonamide product **2a** in 71% yield (Table 1, entry 3).

Different copper salts were tried but only $Cu(MeCN)_4PF_6$ and $Cu(BF_4)_2•H_2O$ showed similar results to $Cu(MeCN)_4BF_4$ and no reaction occurred in the absence of Cu salt (Table 1, entries 4–10). Among the different solvents tested, only $MeNO_2$ showed comparable results to DCE (Table 1, entries 10-12). Ligands other than neocuproine (Table 1, entries 13-15) were found to be less effective. Decreasing the quantity of copper salt or $Et_3N•3HF$ resulted in a significant decrease in the chemical yield (Table 1, entries 16-17). Finally, when 1.3 or 1.0 equivalents of Ph-I=N-Ts were used, the isolated yields were reduced to 55 and 44%, respectively (Table 1, entries 18-19).

Table 1. Optimization of the reaction conditions.[a]



Entry	Copper salt 10%	Ligand 10%	Solvent	Yield [%][b,c]
1[d]	$Cu(MeCN)_4BF_4$	neocuproine	DCE	0
2[e]	$Cu(MeCN)_4BF_4$	neocuproine	DCE	0
3	$Cu(MeCN)_4BF_4$	neocuproine	DCE	71 (78)
4	$Cu(MeCN)_4PF_6$	neocuproine	DCE	67 (72)
5	$Cu(BF_4)_2•H_2O$	neocuproine	DCE	70 (75)
6	CuOAc	neocuproine	DCE	(45)
7	$CuBr_2$	neocuproine	DCE	(33)
8	CuCl	neocuproine	DCE	(39)
9	$Cu(OSO_2CF_3)_2$	neocuproine	DCE	(30)
10	---	neocuproine	DCE	0
11	$Cu(MeCN)_4BF_4$	neocuproine	$MeNO_2$	66 (69)
12	$Cu(MeCN)_4BF_4$	neocuproine	EtOAc	(15)
13	$Cu(MeCN)_4BF_4$	neocuproine	1,4-dioxane	(24)
14	$Cu(MeCN)_4BF_4$	bipyridyl	DCE	(33)
15	$Cu(MeCN)_4BF_4$	phenanthroline	DCE	(42)
16	$Cu(MeCN)_4BF_4$	bathocuproine	DCE	(33)
17[f]	$Cu(MeCN)_4BF_4$	neocuproine	DCE	(15)
18[g]	$Cu(MeCN)_4BF_4$	neocuproine	DCE	(24)
19[h]	$Cu(MeCN)_4BF_4$	neocuproine	DCE	55(63)
20[i]	$Cu(MeCN)_4BF_4$	neocuproine	DCE	44(51)

[a]Reactions were carried out with **1a** (1.0 mmol) in 3.0 mL of solvent, Ph-I=N-Ts (1.5 equiv), $Et_3N•3HF$ (6 equiv), $Mo(CO)_6$ (0.25 equiv) in an open tube, unless otherwise noted. [b]Isolated yields. [c]NMR-determined yields using **1a** (0.2 mmol) in 0.6 mL of solvent and $PhCF_3$ as internal standard are shown in parentheses. [d]Reaction at rt without $Mo(CO)_6$. [e]Reaction at 70 °C without $Mo(CO)_6$. [f]Catalyst (5%). [g]$Et_3N•3HF$ (3 equiv). [h]Ph-I=N-Ts (1.3 equiv). [i]Ph-I=N-Ts (1.3 equiv).

Using the optimized conditions, a number of substituted styrenes were transformed into the corresponding fluorosulfonamides **2a**–**n** in yields ranging from 39 to 81%. (Table 2). These reactions all proceeded with complete regioselectivity. Thus, *para*- and *meta*-methylstyrenes produced the corresponding **2b** (58%) and **2c** (70%).

Different halo-substituted styrenes were compatible with the reaction conditions and afforded the corresponding products **2d**, **2e**, **2f**, **2g** and **2h** in moderate to good yields. While *para*-methoxy styrene failed to give the aminofluorination product, *ortho*-methoxy styrene afforded **2i** in 55%. Other styrenes with electron donating groups at the *para* position such as *tert*-butyl and OAc, led to the corresponding fluoroamine products **2j** and **2k** in 49 and 61% yields, respectively. 2-Vinylnaphthalene afforded **2l** in 52% yield. Interestingly, internal alkenes such as *trans*-β-methylstyrene and indene also afforded **2m** and **2n** in 73 and 39% yields, respectively.

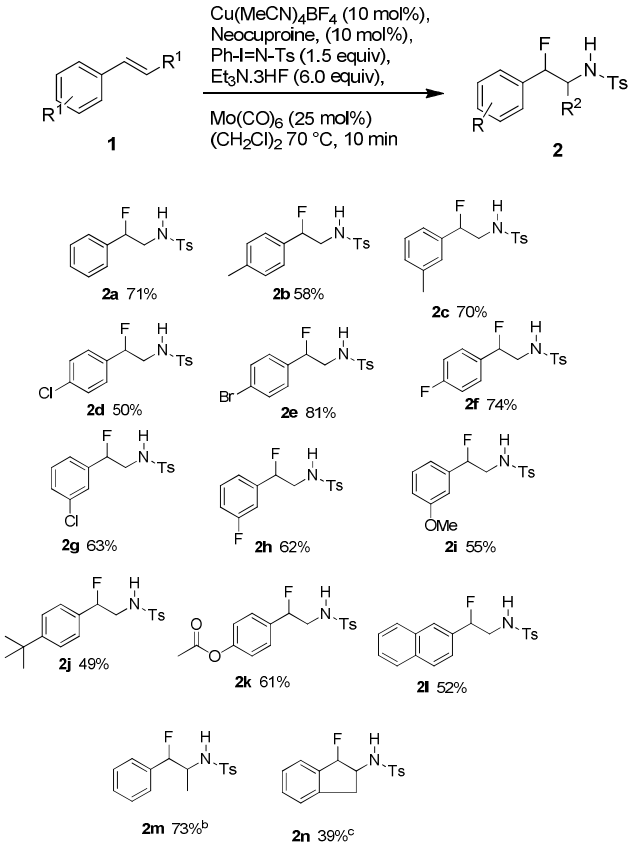
The structure of **2e** was unequivocally assigned by X-ray diffraction analysis.[12]

Unfortunately, with unactivated olefins, including 1-octene and cyclohexene, the desired β-fluorosulfonamides were not obtained and the corresponding aziridines were the principal products.[13]

The successful combination of fluorination with other sulfonamides as nitrogen sources was demonstrated with some styrenes (Table 3). Thus, *para*-nitrobenzenesulfonamide (H_2N-SO_2-*p*-NO_2-Ph) and *ortho*-nitrobenzenesulfonamides, (H_2N-SO_2-o-NO_2-Ph), as well as *ortho*-methylbenzenesulfonamide (H_2N-SO_2-*o*-Me-Ph), *para*-chlorobenzenesulfonamide (H_2N-SO_2-*p*-Cl-Ph) and methanesulfonamide (H_2N-SO_2Me) were used as nitrogen sources. These reactions produced the desired fluorosulfonamides **3a-k** in yields ranging from 63 to 91%.

To show the applicability of the new compounds as building blocks in organic synthesis and taking advantage of the acidity of the Ts-N-H bond, we decided to use **2a, 2c, 3a, 3d, 3e** and **3g** to synthesize *N*-alkyl derivatives **4a-j** using basic alkylation or Mitsunobu conditions. **4a-j** were obtained in yields in the 17-92% range. (Table 4).

Table 2. Scope of the aminofluorination.[a]



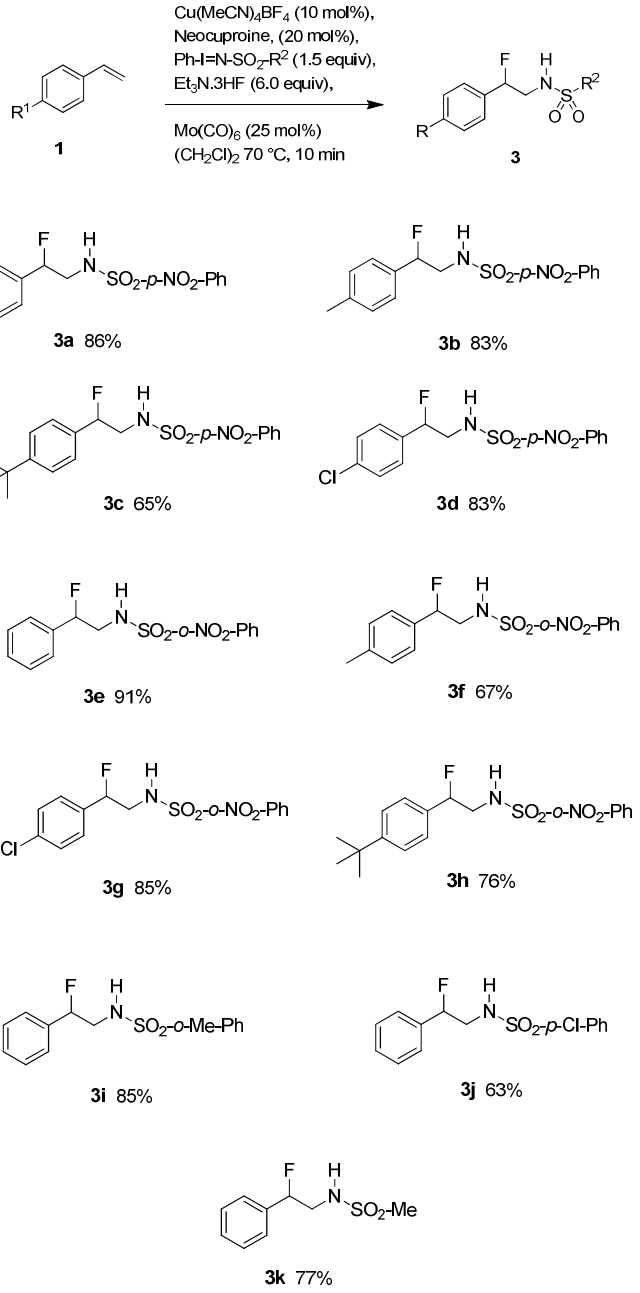
[a]Yields of isolated products after column chromatography of reactions on a 1 mmol scale. [b]5:1 *threo:erythro* ratio of diastereomers determined by ^{19}F NMR of the crude product. [c]Isolated yield of the predominant *anti*-diastereomer.

Finally, compounds **4a** and **4j** were subsequently deprotected. Thus, the Ts group was removed using Mg in methanol with ultrasound[14] activation, and *o*-Ns was removed using 2-mercaptoethanol and DBU in DMF[15] affording the secondary phenethylamines **5a-5b** (Scheme 2).

Conclusions

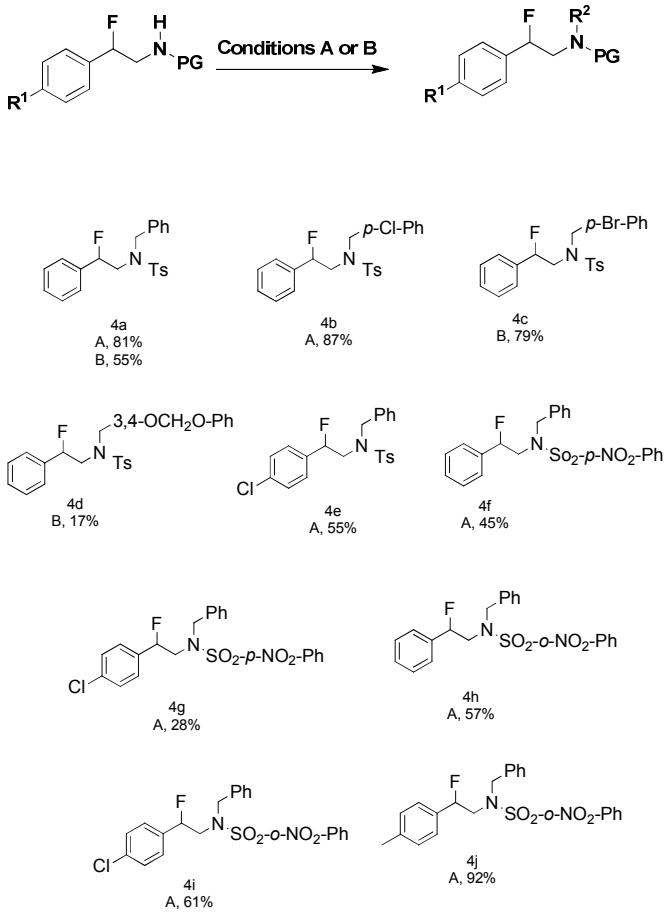
In summary, we have developed a new copper-catalyzed regioselective aminofluorination of styrenes. The reaction proceeds under mild conditions using $Cu(MeCN)_4BF_4$-neocuproine and $Mo(CO)_6$ as the catalytic system and Ph-I=N-Ts and $Et_3N{\bullet}3HF$ as nitrogen and fluorine sources respectively. The reaction employs commercially available reagents and is completed in 10 minutes. The reported reactivity should be of interest for the development of β-fluorophenethylamines. Currently, detailed mechanistic studies and the extension of this reaction to other classes of alkenes are under way.

Table 3. Regioselective aminofluorination of styrenes with different sulfonimides as the nitrogen source.[a]

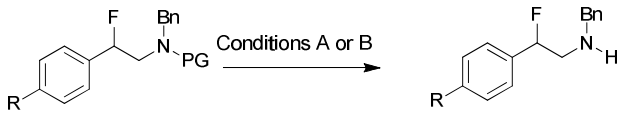


[a]Yields of isolated products after column chromatography of reactions on a 1 mmol scale.

Table 4. *N*-alkylation of fluorosulfonamides.[a]



[a]Yields of isolated products after column chromatography of reactions on a 0.5 mmol scale. Conditions: (A): Fluorosulfonamide (1.0 equiv), NaH (1.1 equiv), DMF, benzyl halide (1.1 equiv), 0 °C to rt,12 h. (B): Fluorosulfonamide (1.0 equiv), triphenylphosphine (1.4 equiv), benzyl alcohol (1.4 equiv), DEAD (2 .0 equiv), THF, 0 °C, 12 h.



4a: R = H, PG = Ts, Conditions A
4j: R = Cl, PG = SO_2-*o*-NO_2-Ph, Conditions B
5a: R = H, 80%
5b: R = Cl, 65%

Scheme 2. Deprotection of β-fluoro-*N*-benzyl-*N*-protected phenethylamines. Conditions: (A): Mg, MeOH, ultrasound, rt, 1 h. (B): 2-mercaptoethanol, DBU, DMF, rt, 12 h. Bn: Benzyl.

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Notes and references

[a] Department of Organic Chemistry, Faculty of Chemistry, Pontificia Universidad Católica de Chile, Av. Vicuña Mackenna 4860, Casilla 306, Correo 22, Santiago (Chile).

E-Mail: eperezh@uc.cl

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1 K. Müller, C. Faeh, F. Diederich, *Science*, 2007, **317**, 1881; D. O'Hagan, *J. Fluor. Chem*., 2010, **131**, 1071; T. Liang, C. N. Neumann, T. Ritter, *Angew. Chem., Int Ed*., 2013, **52**, 8214; T. Furuya, A. S. Kamlet, T. Ritter, *Nature,* 2011, **473**, 470.

2 S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev*., 2008, **37**, 320; Jeschke, P, *ChemBioChem,* 2004**, 5**, 570; J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok, H. Liu, *Chem. Rev*., 2014, **114**, 2432.

3 G. Verniest, E. Van Hende, R. Surmont, N. De Kimpe, *Org. Lett.,* 2006, **21**, 4767; G. Verniest, F. Colpaert, E. Van Hende, De Kimpe, N, *J. Org. Chem.,* 2007, **72**, 8569; O. O. Fadeyi, C. W. Lindsley, *Org. Lett.,* 2009, **11**, 943; A. J. Cresswell, S. G. Davies, J. A. Lee, P. M. Roberts, A. J. Russell, J. E. Thomson, M. J. Tyte, *Org. Lett.,* 2010, **12**, 2936; B. Duthion, D. G. Pardo, J. Cossy, *Org. Lett.,* 2010, **12**, 4620; M. L.Schulte, C. W. Lindsley, *Org. Lett*., 2011, **13**, 5684; R. J. Phipps, K. Hiramatsu, F. D. Toste, *J. Am. Chem. Soc.,* 2012, **134**, 8376; J. A. Kalow, D. E.Schmitt, A. G. Doyle, *J. Org. Chem*., 2012, **77**, 4177; R. Cheerlavancha, A. Lawer, M. Cagnes, M. Bhadbhade, L. Hunter, *Org. Lett.,* 2013, **15**, 5562; D-F. Lu, G-S. Liu, C-L. Zhu, B. Yuan, H. Xu, *Org. Lett.,* 2014, **16**, 2912-2915.

4 T. Wu, G. Yin, G. Liu, J. *Am. Chem. Soc*., 2009, **131**, 16354; T. Xu, X. Mu, H. Peng, G. Liu, *Angew. Chem., Int Ed*., 2011, **50**, 8176; J. Qian, Y. Liu, J. Zhu, B. Jiang, Z. Xu, *Org. Lett*., 2011, **13**, 4220; T. Xu, S. Qiu, G. Liu, *Chin. J. Chem*., 2011, **29**, 2785; G. Liu, *Org. Biomol. Chem*., 2012, **10**, 6243; T. Xu, G. Liu, *Org. Lett*., 2012, **14**, 5416; T. Wu, J. Cheng, P. Chen, G. Liu, *Chem. Commun*., 2013, **49**, 8707; A. Arcadi, E. Pietropaolo, A. Alvino, V. Michelet, *Org. Lett*., 2013, **15**, 2766; W. Kong, E. Merino, C. Nevado, *Chimia,* 2014, **68**, 430; H. Peng, Z. Yuan, H-y. W, Y-I. G, G. Liu, *Chem. Sci*., 2013, **4**, 3172.

5 S. Qiu, T. Xu, J. Zhou, Y. Guo, G. Liu, *J. Am. Chem. Soc*., 2010, **132**, 2856.

6 H. Zhang, Y. Song, J. Zhao, J. Zhang, and Q. Zhang, *Angew. Chem., Int. Ed*., 2014, **53**, 11079.

7 Á. Iglesias, E. G. Pérez, K. Muñiz, *Angew. Chem., Int. Ed*., 2010, **49**, 8109; Á. Iglesias, Á. Rosana, A. R. de Lera, K. Muñiz, *Angew. Chem., Int. Ed.,* 2012, **51**, 2225; P. A. Sibbald, F. E. Michael, *Org. Lett*., 2009, **11**, 1147; B. Zhang. A. Studer, *Org. Lett*., 2014, **16**, 1790.

8 Z. Haitao, G. Liu, *Acta Chim. Sinica*, 2012, **70**, 2404.

9 S. E. Allen, R. R. Walvoord, R. Padilla-Salinas, M. C. Kozlowski, *Chem. Rev.,* 2013, **113**, 6234; Y. Shimizu, M. Kanai, *Tetrahedron Lett.,* 2014, **55**, 3727.

10 V. V. Zhdankin, P. J. Stang, *Chem. Rev*., 2008, **108**, 5299; G. Dequirez, V. Pons, P. Dauban, *Angew. Chem., Int. Ed*., 2012, **51**, 7384.

11 Z. Zhang, F. Wang, X. Mu, P. Chen, G. Liu, *Angew. Chem., Int. Ed.,* 2013, **52**, 7549.

12 CCDC 1037958 *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.

13 D. A. Evans, M. M. Faul, M. T. Bilodeau, *J. Am. Chem. Soc*., 1994, **116**, 2742.

14 B. Nyasse, L. Grehn, U. Ragnarsson, *Chem. Commun.,* 1997, 1017; D. A. Alonso, P. G. Andersson, *J. Org. Chem*., 1998, **63**, 9455.

15 T. Kan, T. Fukuyama, *Chem. Commun.,* 2004, 353; R. De Marco, M. L. Di Gioia, A. Leggio, A. Liguori, M. C. Viscomi, *Eur. J. Org. Chem.* 2009, 3795.

