JOC The Journal of Organic Chemistry

Note

pubs.acs.org/joc

Microwave-Assisted Pd/Cu-Catalyzed C-8 Direct Alkenylation of Purines and Related Azoles: An Alternative Access to 6,8,9-Trisubstituted Purines

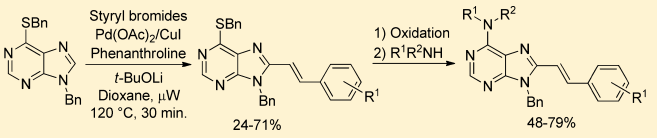
Roxane Vabre,[†,‡] Franciane Chevot,[†,‡] Michel Legraverend,[‡] and Sandrine Piguel*[,†,‡]

[†]Univ Paris-Sud, Orsay, F-91405, France

[‡]Institut Curie/CNRS, UMR 176, Bât. 110-112, Centre Universitaire, 91405 Orsay France

Supporting Information

ABSTRACT: An efficient microwave-assisted palladium/copper comediated C-8 direct alkenylation of purines with styryl bromides has been developed. The method is regioselective, functional group tolerant, rapid, and compatible with other related azoles. Combined with subsequent nucleophilic substitution, it provides an easy access to new 6,8,9-trisubstituted purines.



The purine scaffold is an ubiquitous feature in both biological systems and synthetic compounds finding applications as biologically active compounds and fluorescent probes.[1−3] The broad spectrum of properties displayed by purines is conferred by the number and diversity of substituents that can be introduced on the seven peripheral atoms. As a consequence, a plethora of methodologies for the construction and functionalization of purines has been intensively explored.[4−6] In the context of a medicinal chemistry program, we were interested in generating a variety of C-8 vinyl-substituted purines based on the direct alkenylation of a suitably substituted purine, which could subsequently be used for further functionalization on the other positions. Increasing interest in C-8 substituted purines has driven the development of more or less efficient methods for their elaboration, including the heterocyclization of aminopyrimidine derivatives with aldehydes,[7] carboxylic acids[8,9] or amides,[10] metal-catalyzed cross-coupling reactions of appropriate C-8-halogenated purines,[11−17] and direct metalation.[18,19] A Pd-catalyzed allylic substitution for the preparation of various C-8-alkenylated purines has also been reported.[20] In addition, transition-metal-catalyzed C−H bond functionalization of purines has gained significant attention in recent years. In particular, the direct arylation[21−26] and to a lesser extent direct alkenylation[27] and benzylation[28] have been developed. A preliminary and single example of microwave-assisted direct alkenylation of 9-benzyladenine has been reported, requiring elevated temperature (160 °C) and an excess of copper (2 equiv).[29] Following this work, the same group has examplified the direct alkenylation process on caffeine and 9-benzyladenine with various alkenyl halides; however, substantially modified conditions and classical heating were used.[27] Furthermore, no *E*-styryl bromides bearing electron-withdrawing or electron-donating groups were studied.

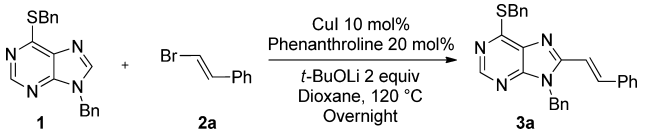
Herein, we report our efforts to expand the type of reactions that can be used to functionalize the purine ring and especially the C8-position through a rapid and functional group tolerant direct alkenylation with various styryl bromides under microwave conditions using a Pd/Cu cocatalyst system. Furthermore, our process is feasible on a purine bearing a labile group in position 6 that can be further functionalized on that position, giving access to new 6,8,9-trisubstituted purines.

As the direct C-8 alkenylation of 6-chloropurine was unsuccessful,[30] we envisaged the use of the 6-benzylsulfanyl-9-benzylpurine **1**. Indeed, the thio-ether substituent is known to be inert toward various conditions, including SNAr and cross-coupling reactions, and as the results show, this motif is also unreactive in the direct alkenylation conditions described here.[31] Furthermore, the sulfur atom could serve as a leaving group after oxidation to the corresponding sulfone for subsequent substitution with suitable nucleophiles, thus providing new 6,8,9-trisubstituted purines. Compound **1** was readily prepared in a two-step literature procedure starting from 6-chloropurine in an overall yield of 47%.[31,32]

In the pursuit of our program directed toward the development of copper-catalyzed C−H bond functionalization of azoles, we initially investigated the reaction between purine **1** and (*E*)-*β*-bromostyrene **2a** by screening a series of copper/ligand sources with LiO*t*Bu as a base in dioxane at 120 °C (Table 1).[33−35] Unfortunately, despite extensive optimization, we were unable to find an efficient copper-catalyzed protocol. The yield of the alkenylated purine **3a** did not exceed 20% with CuI or CuBr·SMe_2 in combination with phenantroline as ligand, even after prolonged heating (Table 1, entries 1−2). Other copper/ligand sources resulted in no conversion. Even the system CuI/phenanthroline/K_3PO_4 used by You et al. for the related direct arylation of caffeine failed.[36] Adding a small amount of palladium cocatalyst $Pd(OAc)_2$ to the reaction mixture, which previously had been effective,[33] did not significantly improve the yield (Table 1, entry 3, 22% yield).

Received: September 13, 2011
Published: October 17, 2011

Table 1. Optimization of the Thermal Direct Alkenylation Conditions[a]



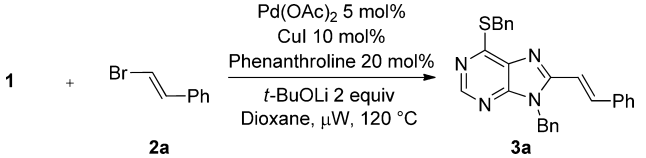
entry	Pd source (5 mol %)	solvent	yield (%)[b]
1		dioxane	16[c]
2		dioxane	18
3	$Pd(OAc)_2$	dioxane	22
4	$Pd(OAc)_2$	dioxane	65[d]
5	$PdCl_2(CH_3CN)_2$	dioxane	62[d]
6	$Pd(acac)_2$	dioxane	42[d]
7	$Pd(OAc)_2$	dioxane	51[d,e]
8	$Pd(OAc)_2$	DMF	38[d]
9	$Pd(OAc)_2$	toluene	43[d]
10	$Pd(acac)_2$	THF	37[f]

[a]All reactions were performed in a sealed tube at 0.2 M of purine (1 equiv), styryl bromide (2 equiv), *t*-BuOLi (2 equiv) in dioxane at 120 °C overnight; *β*-bromostyrene **2a** was used as a mixture of *E*/*Z*: 8/2 isomers. [b]Isolated yields. [c]CuBr·SMe_2 was used. [d]Premixing CuI and phenanthroline for 30 min. [e]10 and 5 mol % copper and ligand were used, respectively. [f]$P(o\text{-tolyl})_3$ was used as ligand: Alami conditions.

Surprisingly, the problem was overcome by premixing the copper source with phenanthroline for 30 min before adding the rest of the reactants. In this way, the alkenylated product **3a** was isolated in 65% yield as the single *E*-stereoisomer (Table 1, entry 4). A comparable result was obtained by using $PdCl_2(CH_3CN)_2$, whereas $Pd(acac)_2$ gave the expected product in a moderate 42% yield (Table 1, entries 5−6). Dioxane proved to be the better solvent, as reactions in DMF or toluene resulted in lower yields (Table 1, entries 8−9). In control reactions, where the copper catalyst, the ligand, the palladium, or the base was left out, only trace amounts of **3a** were formed (not shown). In addition, the reaction conditions reported by Alami et al. for direct alkenylation between caffeine and alkenyl halides were not suitable for our substrate, as the yield of our target compound was low (Table 1, entry 10).[27] These findings are consistent with the majority of direct C−H bond functionalization of purines, where a Pd/Cu cocatalyst is generally required, although this is not always the case.[34,36,37]

Next, we turned our attention to the use of microwave irradiation to shorten reaction times (Table 2). With microwave heating, the targeted 8-styrylpurine **3a** was cleanly obtained in a slightly better yield, 74%, in only 30 min compared to 16 h for conventional heating (Table 2, entry 1). But more importantly, preactivation of the copper/ligand duet was no longer needed. The yield of **3a** remained unchanged upon increasing the reaction time to 60 min (Table 2, entry 2), whereas lower yields were obtained with a reaction time of 15 min or a temperature of 100 °C (Table 2, entries 3−4). Replacing LiO*t*Bu with Cs_2CO_3 was detrimental to the direct alkenylation process, returning the starting material essentially unchanged (Table 2, entry 5). Changing the ratio of CuI to phenanthroline from 1:2 to 1:1 gave a negative effect, giving **3a** in 52% yield (Table 2, entry 6). For comparison, the same reaction carried out for 30 min using traditional oil bath heating afforded the alkenylated purine **3a** in only 35% yield after 30 min premixing of the copper/ligand pair (Table 2, entry 7). Thus, the optimum conditions were shown to be CuI (10 mol %), phenanthroline (20 mol %), $Pd(OAc)_2$ (5 mol %) in dioxane at 120 °C under microwave irradiation for 30 min.

Table 2. Optimization of the Microwave-Assisted Direct Alkenylation Conditions[a]



entry	reaction time (min)	yield (%)[b]
1	30	74 (73)[c]
2	60	70
3	15	61
4	30	44[d]
5	30	<5[e]
6	30	52[f]
7	30	35[g]

[a]All reactions were performed at 0.2 M of purine (1 equiv) and styryl bromide (2 equiv) in dioxane heated at 120 °C in a microwave reactor. [b]Isolated yields. [c]Yield in parentheses was obtained for a reaction run on a gram-scale. [d]Reaction run at 100 °C. [e]Cs_2CO_3 was used as base. [f]Only 10 mol % ligand were used. [g]Thermal heating with premixing CuI and phenanthroline for 30 min.

This optimized protocol was subsequently applied to the direct C-8 alkenylation of purine **1** with various readily accessible *E*-*β*-bromostyrenes (Scheme 1). These building blocks were prepared in a two-step sequence starting from the commercially available aldehydes via the Ramirez procedure followed by the Hirao reduction.[38,39] Both electron-rich and electron-deficient *β*-bromostyrenes reacted at the C-8 position of the purine in moderate to good yields. These conditions are compatible with a range of functional groups including nitro, cyano, and halides, which may be used for further transformations. However, the dimethoxy substituent gave a disappointing 24% yield. Noteworthy was the acetal group, which survived the reaction conditions and underwent coupling to afford the alkenylated purine **3j** in a satisfactory 44% yield.

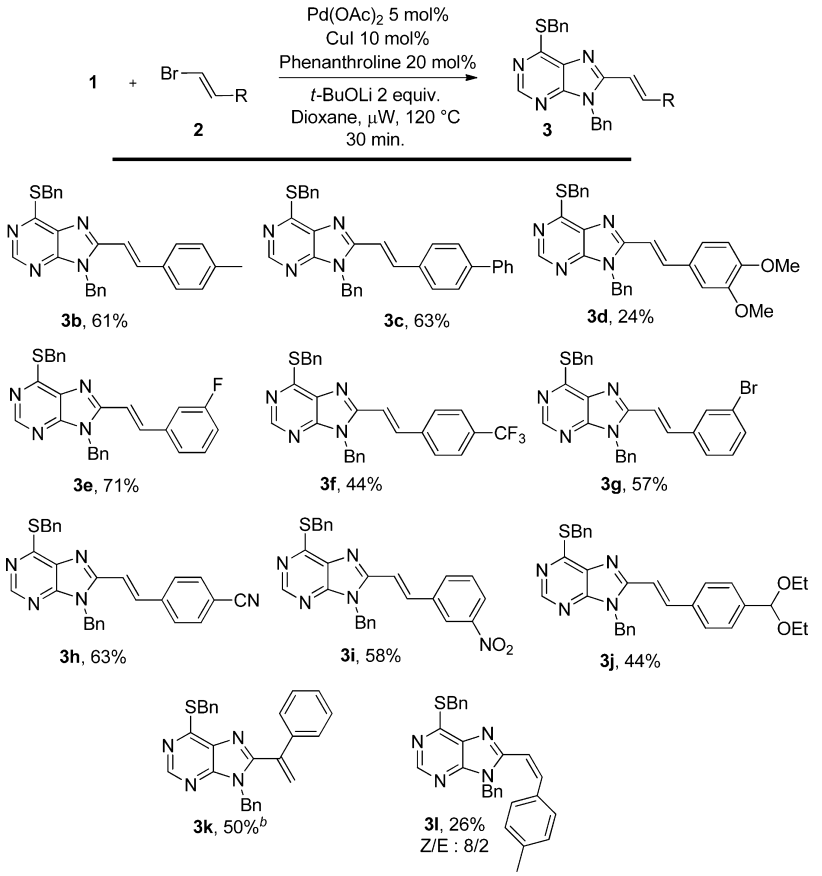
Unfortunately, related *β*-bromoalkenes bearing a simple alkyl substituent were not reactive. *Z*-*β*-bromostyrenes, as illustrated by the use of *Z*-*β*-bromo-4-methylstyrene, gave the expected compound **3l** in a 26% yield as an 8:2 mixture of *Z*/*E* isomers. These results are still unclear at this stage.

An array of additional related azoles was also compatible with the microwave-assisted catalyzed direct alkenylation conditions, although varied reactivities were observed. Surprisingly, caffeine coupled in a low 32% yield as well as 1,3,4-oxadiazole. Other heterocycles such as 5-phenyloxazole, *N*-methylbenzimidazole, benzothiazole, and 1,2,4-triazole gave moderate to good yields. Oxazole itself was regioselectively alkenylated at the C-2 position (Scheme 2).

After having successfully alkenylated position 8 of the functionalized purine, we were keen to investigate the subsequent reaction at position 6 in order to check whether the double bond would be compatible with the oxidation conditions required for the activation of the 6-benzylsulfanyl group. Pleasingly, selective activation of the sulfur atom was then achieved by oxidation of compound **3a** with *m*-CPBA in CH_2Cl_2 to afford the corresponding sulfone in a quantitative yield and that was sufficiently pure to be used in the next step without further purification. This result is particularly noteworthy, as it leaves the C=C double bond untouched and

dx.doi.org/10.1021/jo201893h | J. Org. Chem. 2011, 76, 9542−9547

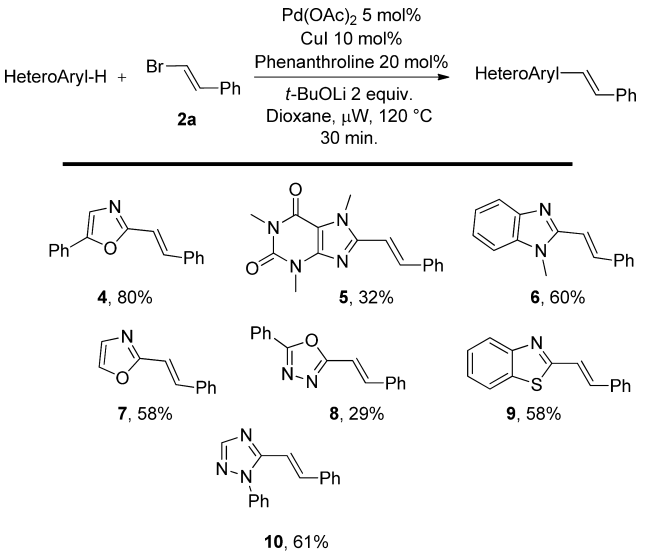
Scheme 1. Scope of Microwave-Assisted Direct Alkenylation of Purines with Alkenyl Bromides[a]



[a]Yields are calculated on isolated products (average of two runs).

[b]Commercially available α-bromostyrene was used as coupling partner **2**.

Scheme 2. Scope with Respect to the Heterocycles[a]



[a]Yields are calculated on isolated products (average of two runs).

allows subsequent functionalization on the 6 position to access new 6,8,9-trisubstituted purines of biological interest. Indeed, the sulfone **11** underwent facile conversion to the compounds **12a**–**g** upon reaction with the requisite amine in EtOH at 110 °C via SNAr. Thus, the 6-amino-8-styrylpurines **12a**–**g** were obtained in a two-step sequence from **3a** with an overall yield ranging from 48 to 79% (Scheme 3).

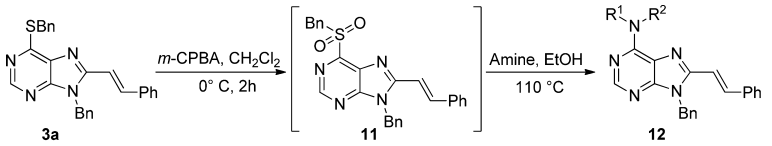
In summary, a microwave-enhanced C-8 direct alkenylation of purines and related azoles with various styryl bromides has been developed, expanding the scope of previously described methods. The high functional group tolerance and the speed of the reaction render this method suitable for the combinatorial synthesis of polyfunctionalized purines that is complementary to existing methodologies. Subsequently, by combining with nucleophilic substitution, the purine ring can now be functionalized at positions 8 and 6, respectively, providing access to new 6,8,9-trisubstituted purines that are actively being investigated as valuable compounds for their biological and physical properties. The presence of the benzylsulfanyl group and its stability in the direct alkenylation conditions opens the way to solid-phase synthesis of polyfunctionalized purines using a sulfur-linked resin as a traceless linker.[31]

EXPERIMENTAL SECTION

General Experimental Methods. Commercially available reagents and solvents were used without further purification unless otherwise stated. Yields refer to isolated and purified products. Reactions were monitored by thin-layer chromatography carried out on silica gel plates (60F-254) visualized under UV light. Column chromatography was performed on silica gel 60, 40–63 μm. Chemical shifts of ^{1}H NMR and ^{13}C NMR were reported in ppm (δ units), and residual nondeuterated solvent was used as internal reference. The following abbreviations were used to designate the multiplicities: s =

dx.doi.org/10.1021/jo201893h | J. Org. Chem. 2011, 76, 9542–9547

Scheme 3. Functionalization at Position 6 of the Purine via SNAr Displacement



12a R^1 = benzyl ; R^2 = H 74%
12b R^1 = propyl ; R^2 = H 79%
12c R^1 = 2-methoxyethyl ; R^2 = H 75%
12d R^1, R^2 = pyrrolidinyl 76%
12e R^1 = benzyl ; R^2 = CH_3 48%
12f R^1 = 4-OMe-benzyl ; R^2 = H 78%
12g R^1 = 2-dimethylaminoethyl ; R^2 = H 66 %

singlet, d = doublet, t = triplet, q = quadruplet, bs = broad singlet, bd = broad doublet, m = multiplet. Microwave irradiation was performed on CEM Explorer (CEM Corporation). Temperature measurement of the reaction mixture within the Discovery series was achieved by an IR sensor. The method was set with a maximum power of 150 W with a maximum pressure of 17 bar and used without powermax. Reaction times refer to the hold time at the desired set temperature. Reaction cooling was performed by compressed air after the heating period was over.

General Procedure As Illustrated for the Preparation of (*E*)-4-(2-Bromovinyl)-1,1′-biphenyl (2c). To a solution of 4-(2,2-dibromovinyl)-1,1′-biphenyl[35] (507.2 mg, 1.838 mmol, 1 equiv) in diethyl phosphonate (761.5 mg, 5.514 mmol, 3 equiv) was added triethylamine (557.9 mg, 5.514 mL, 3 equiv). The reaction mixture was stirred at room temperature for 1.5 h. Diethyl ether was added, and the salts were removed by filtration. After evaporation of the filtrate, the residue was purified by flash chromatography on silica gel, eluting with cyclohexane to afford the title compound as a white solid (271 mg, 75%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (t, J = 7.7 Hz, 4H), 7.47−7.36 (m, 5H), 7.14 (d, J = 14.0 Hz, 1H), 6.81 (d, J = 14.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.0, 140.4, 136.7, 134.9, 132.5, 131.9, 129.4, 128.8, 127.5, 127.4, 127.0, 126.9, 126.5, 106.5. MS (ES+) m/z (%) 280.90 (100): $[M + Na]^+$. HRMS (ESI) calcd for $C_{14}H_{11}BrNa$ $[(M + Na)^+]$ 280.9942, found 280.9947.

Compounds **2b**,[40] **2d**,[41] **2e**,[42] **2f**,[43] **2g**,[44] **2h**,[45] **2i**,[40] and **2l**[46] showed satisfactory spectroscopic data in agreement with those reported in the literature.

(*E*)-1-(2-Bromovinyl)-4-(diethoxymethyl)benzene (2j). A light yellow oil (857.7 mg, 73%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (d, J = 8.2 Hz, 2H), 7.29 (d, J = 8.3 Hz, 2H), 7.11 (d, J = 14.0 Hz, 1H), 6.78 (d, J = 14.0 Hz, 1H), 5.48 (s, 1H), 3.64−3.50 (m, 4H), 1.24 (t, J = 7.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.2, 136.9, 135.9, 127.1, 125.9, 106.8, 101.1, 61.0, 15.2. MS (ES+) m/z (%): 307.2 (90) $[M + Na]^+$. HRMS (ESI) calcd for $C_{13}H_{17}BrNaO_2$ $[(M + Na)^+]$ 307.0310, found 307.0315.

1-Phenyl-1*H*-[1,2,4]triazole[47] and 9-benzyl-6-chloro-9*H*-purine[32] were prepared according to procedures described in the literature.

9-Benzyl-6-(benzylthio)-9*H*-purine (1). Benzylmercaptan (2.67 g, 21.46 mmol, 2.1 equiv) and triethylamine (2.17 g, 21.46 mmol, 2.1 equiv) were added to a solution of 9-benzyl-6-chloro-9*H*-purine (2.5 g, 10.22 mmol, 1 equiv) in EtOH (40 mL). The reaction mixture was heated at 60 °C overnight. After evaporation, the residue was extracted with DCM and washed with NH_4Cl, and the organic layer was dried ($MgSO_4$) and concentrated. After purification by flash chromatography on silica gel (DCM), the title compound was obtained as a white solid (3.12 g, 92%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.78 (s, 1H), 7.92 (s, 1H), 7.47 (d, J = 6.8 Hz, 2H), 7.36−7.24 (m, 8H), 5.41 (s, 2H), 4.67 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.7, 152.1, 148.7, 142.5, 137.4, 135.1, 131.0, 129.2, 129.1, 128.6, 128.5, 127.8, 127.3, 47.3, 32.8. MS (ES+) m/z (%): 333.2 (100) $[M + H]^+$. HRMS (ESI) calcd for $C_{19}H_{17}N_4S$ $[(M + H)^+]$ 333.1174, found 333.1188.

General Procedure for the Direct Alkenylation As Illustrated for the Preparation of (*E*)-9-Benzyl-6-(benzylthio)-8-styryl-9*H*-purine (3a). A flame-dried tube filled with argon was charged with **1** (120 mg, 0.361 mmol, 1 equiv), CuI (6.9 mg, 0.036 mmol, 10 mol %), phenanthroline (13 mg, 0.072 mmol, 20 mol %), $Pd(OAc)_2$ (4.1 mg, 0.018 mmol, 5 mol %), *t*BuOLi (57.8 mg, 0.722 mmol, 2 equiv), distilled *β*-bromostyrene (132.2 mg, 0.722 mmol, 2 equiv), and dioxane (2 mL). The tube was sealed with a rubber cap and heated to 120 °C for 30 min under microwave irradiation. The reaction mixture was taken into EtOAc and washed with water, and the organic layer was dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography on silica gel, eluting with cyclohexane/EtOAc (100/0 → 85/15). The title compound was obtained as a yellow solid (116.2 mg, 74%): mp = 148−150 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.72 (s, 1H), 8.02 (d, J = 15.8 Hz, 1H), 7.51−7.47 (m, 4H), 7.34−7.21 (m, 11H), 6.96 (d, J = 15.8 Hz, 1H), 5.54 (s, 2H), 4.70 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.7, 151.4, 151.3, 150.0, 139.5, 137.5, 135.7, 135.4, 131.2, 129.6, 129.2, 129.1, 128.9, 128.5, 128.2, 127.5, 127.2, 126.8, 112.3, 45.7, 32.9. MS (ES+) m/z (%): 435.3 (30) $[M + H]^+$, 457.3 (100) $[M + Na]^+$. HRMS (ESI) calcd for $C_{27}H_{23}N_4S$ $[(M + H)^+]$ 435.1643, found 435.1626.

(*E*)-9-Benzyl-6-(benzylthio)-8-(4-methylstyryl)-9*H*-purine (3b). A yellow solid (91.2 mg, 61%): mp = 162−164 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.71 (s, 1H), 8.01 (d, J = 15.6 Hz, 1H), 7.51−7.16 (m, 14H), 6.92 (d, J = 16.2 Hz, 1H), 5.54 (s, 2H), 4.70 (s, 2H), 2.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.5, 151.6, 151.3, 150.0, 140.0, 139.6, 137.5, 135.7, 132.6, 131.3, 129.6, 129.2, 129.1, 128.5, 128.2, 127.5, 127.2, 126.8, 111.2, 45.7, 32.9, 21.5. MS (ES+) m/z (%): 449.2 (100) $[M + H]^+$, 471.2 (40) $[M + Na]^+$. HRMS (ESI) calcd for $C_{28}H_{25}N_4S$ $[(M + H)^+]$ 449.1800, found 449.1816.

(*E*)-8-(2-([1,1′-Biphenyl]-4-yl)vinyl)-9-benzyl-6-(benzylthio)-9*H*-purine (3c). A yellow solid (116 mg, 63%): mp = 172−174 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.73 (s, 1H), 8.07 (d, J = 15.8 Hz, 1H), 7.60−7.21 (m, 19H), 7.00 (d, J = 15.8 Hz, 1H), 5.57 (s, 2H), 4.71 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.7, 151.4, 151.3, 150.0, 142.3, 140.2, 139.0, 137.5, 135.7, 134.3, 131.3, 129.2, 129.1, 128.9, 128.5, 128.2, 128.0, 127.7, 127.5, 127.2, 127.0, 126.8, 112.1, 45.7, 32.9. MS (ES+) m/z (%): 511.3 (85) $[M + H]^+$, 533.3 (55) $[M + Na]^+$. HRMS (ESI) calcd for $C_{33}H_{27}N_4S$ $[(M + H)^+]$ 511.1956, found 511.1960.

(*E*)-9-Benzyl-6-(benzylthio)-8-(3,4-dimethoxystyryl)-9*H*-purine (3d). After crystallization from cyclohexane/Et_2O, the title compound was obtained as a yellow solid (42 mg, 24%): mp = 132−134 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.71 (s, 1H), 7.96 (d, J = 15.8 Hz, 1H), 7.50 (d, J = 6.9 Hz, 2H), 7.34−7.20 (m, 8H), 7.09 (d, J = 8.3 Hz, 1H), 6.96 (s, 1H), 6.86 (d, J = 8.4 Hz, 1H), 6.80 (d, J = 15.8 Hz, 1H), 5.55 (s, 2H), 4.70 (s, 2H), 3.91 (s, 3H), 3.90 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.3, 151.7, 151.3, 150.6, 150.1, 149.1, 139.3, 137.5, 135.8, 131.3, 129.2, 129.1, 128.5, 128.2, 127.2, 126.8, 121.5, 111.1, 110.3, 109.6, 56.0, 55.9, 45.7, 32.9. MS (ES+) m/z (%): 495.3 (100) $[M + H]^+$, 517.3 (20) $[M + Na]^+$. HRMS (ESI) calcd for $C_{29}H_{27}N_4O_2S$ $[(M + H)^+]$ 495.1855, found 495.1842.

(*E*)-9-Benzyl-6-(benzylthio)-8-(3-fluorostyryl)-9*H*-purine (3e). A yellow solid (116 mg, 71%): mp = 168−170 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.73 (s, 1H), 7.98 (d, J = 15.8 Hz, 1H), 7.50 (d, J = 6.8 Hz, 2H), 7.36−7.14 (m, 11H), 7.03 (td, J = 8.4, 2.9 Hz, 1H), 6.95 (d, J = 15.8 Hz, 1H), 5.55 (s, 2H), 4.70 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.7, 161.4, 159.0, 151.6, 150.7, 150.0, 138.1, 138.0, 137.7, 137.6, 137.4, 135.6, 131.2, 130.4, 129.22, 129.16, 128.5, 128.3, 127.3, 126.8, 123.7, 123.6, 116.6, 116.3, 113.7, 113.6, 113.4, 45.7, 32.9. MS (ES+) m/z (%) 453.3 (45) $[M + H]^+$, 475.3 (100) $[M + Na]^+$.

dx.doi.org/10.1021/jo201893h | *J. Org. Chem.* 2011, 76, 9542−9547

HRMS (ESI) calcd for $C_{27}H_{22}FN_4S$ [(M + H)$^+$] 453.1549, found 453.1558.

(*E*)-9-Benzyl-6-(benzylthio)-8-(4-(trifluoromethyl)styryl)-9*H*-purine (3f). A yellow solid (57 mg, 44%): mp = 174−176 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.74 (s, 1H), 8.03 (d, J = 15.9 Hz, 1H), 7.63−7.55 (m, 4H), 7.50 (d, J = 6.9 Hz, 2H), 7.35−7.19 (m, 8H), 7.02 (d, J = 15.8 Hz, 1H), 5.57 (s, 2H), 4.70 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.3, 151.8, 150.5, 150.0, 138.7, 137.5, 137.4, 135.6, 131.2, 130.8, 129.22, 129.19, 128.5, 128.4, 127.6, 127.3, 126.8, 125.9, 125.8, 122.1, 114.8, 45.8, 32.9. MS (ES+) m/z (%) 503.3 (35) [M + H]$^+$, 525.3 (100) [M + Na]$^+$. HRMS (ESI) $C_{28}H_{22}F_3N_4S$ calcd for [(M + H)$^+$] 503.1517, found 503.1497.

(*E*)-9-Benzyl-6-(benzylthio)-8-(3-bromostyryl)-9*H*-purine (3g). A yellow solid (107 mg, 57%): mp = 182−184 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.73 (s, 1H), 7.93 (d, J = 15.8 Hz, 1H), 7.60 (s, 1H), 7.51−7.44 (m, 3H), 7.39−7.19 (m, 10H), 6.94 (d, J = 15.8 Hz, 1H), 5.56 (s, 2H), 4.70 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 151.6, 150.7, 150.0, 137.7, 137.5, 137.4, 135.5, 132.3, 131.2, 130.4, 129.9, 129.21, 129.16, 128.5, 128.3, 127.3, 126.8, 126.3, 123.0, 113.7, 45.7, 32.9. MS (ES+) m/z (%) 513.2 (65) [M + H]$^+$, 537.2 (50) [M + Na]$^+$. HRMS (ESI) calcd for $C_{27}H_{22}BrN_4S$ [(M + H)$^+$] 513.0749, found 513.0757.

(*E*)-4-(2-(9-Benzyl-6-(benzylthio)-9*H*-purin-8-yl)vinyl)-benzonitrile (3h). A yellow solid (105 mg, 63%): mp = 206−208 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.75 (s, 1H), 8.00 (d, J = 15.8 Hz, 1H), 7.65 (d, J = 8.3 Hz, 2H), 7.56−7.48 (m, 4H), 7.35−7.28 (m, 6H), 7.21−7.18 (m, 2H), 7.03 (d, J = 15.8 Hz, 1H), 5.57 (s, 2H), 4.70 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.5, 151.9, 150.1, 149.9, 139.6, 137.4, 136.9, 135.5, 132.6, 131.2, 129.2, 128.5, 128.4, 127.8, 127.3, 126.7, 118.5, 115.8, 112.5, 45.8, 32.9. MS (ES+) m/z (%) 460.3 (100) [M + H]$^+$. HRMS (ESI) calcd for $C_{28}H_{22}N_5S$ [(M + H)$^+$] 460.1596, found 460.1589.

(*E*)-9-Benzyl-6-(benzylthio)-8-(3-nitrostyryl)-9*H*-purine (3i). A yellow solid (101.5 mg, 58%): mp = 186−188 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.75 (s, 1H), 8.31 (s, 1H), 8.17 (d, J = 8.1 Hz, 1H), 8.04 (d, J = 15.8 Hz, 1H), 7.74 (d, J = 7.7 Hz, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.50 (d, J = 7.0 Hz, 2H), 7.34−7.23 (m, 8H), 7.07 (d, J = 15.8 Hz, 1H), 5.59 (s, 2H), 4.70 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.5, 151.8, 150.1, 150.0, 148.7, 137.4, 137.1, 136.4, 135.5, 133.5, 131.2, 130.0, 129.2, 128.5, 128.4, 127.3, 126.8, 123.8, 121.3, 115.4, 45.8, 32.9. MS (ES+) m/z (%) 480.2 (100) [M + H]$^+$, 502.3 (60) [M + Na]$^+$. HRMS (ESI) calcd for $C_{27}H_{22}N_5O_2S$ [(M + H)$^+$] 480.1494, found 480.1487.

(*E*)-9-Benzyl-6-(benzylthio)-8-(4-(diethoxymethyl)styryl)-9*H*-purine (3j). A yellow oil (86 mg, 44%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.72 (s, 1H), 8.03 (d, J = 15.8 Hz, 1H), 7.48 (s, 6H), 7.34−7.20 (m, 8H), 6.97 (d, J = 15.8 Hz, 1H), 5.55 (s, 2H), 5.50 (s, 1H), 4.70 (s, 2H), 3.64−3.51 (m, 4H), 1.28−1.18 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.7, 151.5, 151.3, 150.0, 140.7, 139.1, 137.5, 135.7, 135.4, 131.3, 129.2, 129.1, 128.5, 128.3, 127.4, 127.2, 126.8, 112.5, 101.1, 61.1, 45.7, 32.9, 15.2. MS (ES+) m/z (%) 537.4 (100) [M + H]$^+$, 559.4 (80) [M + Na]$^+$. HRMS (ESI) calcd for $C_{32}H_{33}N_4O_2S$ [(M + H)$^+$] 537.2324, found 537.2305.

9-Benzyl-6-(benzylthio)-8-(1-phenylvinyl)-9*H*-purine (3k). α-Bromostyrene was distilled before use. A yellow solid (79 mg, 50%): mp = 128−130 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.78 (s, 1H), 7.50 (d, J = 7.0 Hz, 2H), 7.33−7.18 (m, 11H), 6.95−6.92 (m, 2H), 5.93 (s, 1H), 5.75 (s, 1H), 5.08 (s, 2H), 4.70 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.9, 153.4, 151.9, 150.2, 138.7, 137.6, 137.0, 135.7, 130.7, 129.2, 128.9, 128.8, 128.53, 128.49, 127.8, 127.2, 126.8, 123.2, 46.7, 32.8. MS (ES+) m/z (%) 435.2 (100) [M + H]$^+$, 457.1 (70) [M + Na]$^+$. HRMS (ESI) calcd for $C_{27}H_{23}N_4S$ [(M + H)$^+$] 435.1643, found 435.1627.

(*Z*)-9-Benzyl-6-(benzylthio)-8-(4-methylstyryl)-9*H*-purine (3l). A yellow oil obtained as an inseparable mixture of *E*/*Z* (2:8) isomers (42.1 mg, 26%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.72 (s, 1H), 7.49 (d, J = 7.0 Hz, 2H), 7.40−7.23 (m, 9H), 7.08−7.05 (m, 4H), 6.93 (d, J = 12.6 Hz, 1H), 6.35 (d, J = 12.6 Hz, 1H), 5.16 (s, 2H), 4.69 (s, 2H), 2.30 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.6, 151.8, 150.4, 149.6, 139.6, 139.5, 137.6, 135.8, 132.4, 131.0, 129.33, 129.26, 128.8, 128.5, 128.0, 127.3, 127.1, 114.6, 46.1, 33.0, 21.4. MS (ES+) m/z (%): 449.5 (100) [M + H]$^+$. HRMS (ESI) calcd for $C_{28}H_{25}N_4S$ [(M + H)$^+$] 449.1800, found 449.1801.

Compounds **4**,[33] **5**,[27] **6**,[48] **7**,[33] **9**,[33] and **10**[49] showed satisfactory spectroscopic data in agreement with those reported in the literature.

(*E*)-2-Phenyl-5-styryl-1,3,4-oxadiazole (8). A brown solid (98 mg, 29%): mp = 134−136 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14−8.11 (m, 2H), 7.66−7.53 (m, 6H), 7.44−7.39 (m, 3H), 7.11 (d, J = 16.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.3, 164.0, 138.9, 134.8, 131.8, 130.0, 129.09, 129.05, 127.5, 127.0, 123.8, 110.0. MS (ES+) m/z (%) 271.1 (100) [M + Na]$^+$. HRMS (ESI) calcd for $C_{16}H_{13}N_2O$ [(M + H)$^+$] 249.1028, found 249.1027.

General Procedure for the Amination As Illustrated for the Preparation of (*E*)-*N*,9-Dibenzyl-8-styryl-9*H*-purin-6-amine (12a). A solution of *m*-CPBA (162.9 mg, 0.944 mmol, 2.2 equiv) in DCM (1.5 mL) was dried on $MgSO_4$ and added dropwise to a solution of **3a** (186 mg, 0.429 mmol, 1 equiv) in DCM (15 mL) at 0 °C. The reaction mixture was stirred for 2 h in an ice bath and then quenched by the addition of a saturated solution of $Ca(OH)_2$. This mixture was extracted with DCM and washed with water, and the organic layer was dried ($MgSO_4$) and evaporated under reduced pressure. A solution of the resulting sulfone, sufficiently pure to be used directly in the next step, and benzylamine (115 mg, 1.073 mmol, 2.5 equiv) in EtOH (2 mL) was introduced in a sealed tube and heated at 110 °C until the reaction mixture became clear (2 h). After evaporation, the residue was purified by flash column chromatography on silica gel (cyclohexane/EtOAc 100/0 → 80/20) to afford the title compound as a yellow solid (133.7 mg, 74%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.44 (s, 1H), 7.76 (d, J = 15.9 Hz, 1H), 7.47−7.22 (m, 15H), 6.96 (d, J = 15.9 Hz, 1H), 6.14 (bs, 1H), 5.51 (s, 2H), 4.91 (bs, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.0, 153.0, 150.5, 148.4, 138.5, 136.8, 136.1, 135.6, 129.2, 129.0, 128.9, 128.7, 128.1, 127.9, 127.5, 127.2, 126.8, 119.8, 113.1, 45.6, 44.8. MS (ES+) m/z (%): 418.3 (100) [M + H]$^+$. HRMS (ESI) calcd for $C_{27}H_{24}N_5$ [(M + H)$^+$] 418.2032, found 418.2041.

(*E*)-9-Benzyl-*N*-propyl-8-styryl-9*H*-purin-6-amine (12b). Propylamine was distilled before use. Reaction time: 1 h. A yellow oil (125.2 mg, 79%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.40 (s, 1H), 7.77 (d, J = 15.9 Hz, 1H), 7.46 (d, J = 7.6 Hz, 2H), 7.37−7.23 (m, 8H), 6.96 (d, J = 15.9 Hz, 1H), 5.99 (bs, 1H), 5.50 (s, 2H), 3.66 (bs, 2H), 1.79−1.72 (m, 2H), 1.05 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.3, 153.0, 148.1, 136.7, 136.1, 135.7, 129.2, 129.0, 128.9, 128.1, 127.2, 126.8, 119.6, 113.2, 45.6, 42.7, 23.0, 11.5. MS (ES+) m/z (%): 370.5 (100) [M + H]$^+$, 392.5 (25) [M + Na]$^+$. HRMS (ESI) calcd for $C_{23}H_{24}N_5$ [(M + H)$^+$] 370.2032, found 370.2031.

(*E*)-9-Benzyl-*N*-(2-methoxyethyl)-8-styryl-9*H*-purin-6-amine (12c). 2-Methoxyethylamine was distilled before use. Reaction time: 2 h. A yellow oil (124 mg, 75%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.40 (s, 1H), 7.79 (d, J = 15.9 Hz, 1H), 7.47 (d, J = 6.4 Hz, 2H), 7.36−7.20 (m, 8H), 6.95 (d, J = 15.9 Hz, 1H), 6.29 (bs, 1H), 5.50 (s, 2H), 3.90 (bs, 2H), 3.66 (t, J = 5.2 Hz, 2H), 3.41 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.2, 152.8, 148.3, 136.8, 136.1, 135.7, 129.2, 129.0, 128.9, 128.0, 127.2, 126.8, 119.8, 113.2, 71.3, 58.9, 45.6. MS (ES+) m/z (%): 386.8 (100) [M + H]$^+$, 408.8 (50) [M + Na]$^+$. HRMS (ESI) calcd for $C_{23}H_{24}N_5O$ [(M + H)$^+$] 386.1981, found 386.1992.

(*E*)-9-Benzyl-6-(pyrrolidin-1-yl)-8-styryl-9*H*-purine (12d). Reaction time: 30 min. A yellow solid (124.3 mg, 76%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.37 (s, 1H), 7.76 (d, J = 15.9 Hz, 1H), 7.47 (d, J = 7.3 Hz, 2H), 7.38−7.19 (m, 8H), 6.96 (d, J = 15.9 Hz, 1H), 5.51 (s, 2H), 4.29 (bs, 2H), 3.81 (bs, 2H), 2.06 (bs, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.7, 152.6, 151.5, 147.0, 136.4, 136.0, 135.7, 128.95, 128.88, 128.8, 127.9, 127.1, 126.7, 120.5, 113.6, 45.4, 29.7. MS (ES+) m/z (%): 382.6 (100) [M + H]$^+$. HRMS (ESI) calcd for $C_{24}H_{24}N_5$ [(M + H)$^+$] 382.2032, found 382.2045.

(*E*)-*N*,9-Dibenzyl-*N*-methyl-8-styryl-9*H*-purin-6-amine (12e). *N*-Methyl-1-phenylmethan-amine was distilled before use. Reaction time: 16 h. A yellow oil (89.6 mg, 48%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.41 (s, 1H), 7.76 (d, J = 15.9 Hz, 1H), 7.47 (d, J = 7.1 Hz, 2H), 7.38−7.24 (m, 13H), 6.97 (d, J = 15.8 Hz, 1H), 5.55 (s, 2H), 3.53 (bs, 2H), 1.62 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ

154.3, 152.3, 152.1, 146.7, 138.1, 136.4, 136.2, 135.9, 129.0, 128.8, 128.6, 128.0, 127.9, 127.3, 127.2, 126.8, 120.2, 113.4, 53.5, 45.5, 43.5. MS (ES+) *m*/*z* (%): 432.5 (100) $[M + H]^+$, 454.5 (40) $[M + Na]^+$. HRMS (ESI) calcd for $C_{28}H_{26}N_5$ $[(M + H)^+]$ 432.2188, found 432.2201.

(*E*)-9-Benzyl-*N*-(4-methoxybenzyl)-8-styryl-9*H*-purin-6-amine (12f). Reaction time: 1 h. A yellow oil (150.1 mg, 78%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.44 (s, 1H), 7.76 (d, J = 15.9 Hz, 1H), 7.45 (d, J = 6.8 Hz, 2H), 7.37−7.21 (m, 10H), 6.95 (d, J = 15.9 Hz, 1H), 6.89 (d, J = 8.5 Hz, 2H), 6.04 (bs, 1H), 5.51 (s, 2H), 4.84 (bs, 2H), 3.81 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.0, 153.9, 153.0, 150.6, 148.3, 136.8, 136.1, 135.6, 130.5, 129.3, 129.2, 129.0, 128.9, 128.1, 127.2, 126.8, 119.8, 114.0, 113.1, 55.3, 45.6, 44.3. MS (ES+) *m*/*z* (%): 448.5 (100) $[M + H]^+$, 470.6 (80) $[M + Na]^+$. HRMS (ESI) calcd for $C_{28}H_{26}N_5O$ $[(M + H)^+]$ 448.2137, found 448.2131.

(*E*)-N^1-(9-Benzyl-8-styryl-9*H*-purin-6-yl)-N^2,N^2-diethylethane-1,2-diamine (12g). *N*,*N*-Diethylethylenediamine was distilled before use. Reaction time: 30 min. The residue was purified by flash column chromatography on silica gel (DCM/EtOH 100/0 → 80/20) to afford the title compound as a yellow oil (127.7 mg, 66%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.39 (s, 1H), 7.80 (d, J = 15.9 Hz, 1H), 7.48 (d, J = 6.4 Hz, 2H), 7.37−7.22 (m, 8H), 6.96 (d, J = 15.9 Hz, 1H), 6.35 (bs, 1H), 5.51 (s, 2H), 3.76 (bs, 2H), 2.78 (t, J = 6.2 Hz, 2H), 2.65 (q, J = 7.1 Hz, 4H), 1.08 (t, J = 7.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.3, 153.0, 148.1, 136.7, 136.2, 135.8, 129.2, 129.0, 128.9, 128.0, 127.2, 126.8, 119.9, 113.3, 51.7, 46.7, 45.6, 29.7, 11.5. MS (ES+) *m*/*z* (%): 427.6 (100) $[M + H]^+$. HRMS (ESI) calcd for $C_{26}H_{31}N_6$ $[(M + H)^+]$ 427.2610, found 427.2609.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H and ^{13}C for all compounds **1**, **2c**, **2j**, **3a**−**l**, **4**−**10**, and **12a**−**g**. This material is available free of charge via the Internet at http://pubs.acs.org..

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: sandrine.piguel@curie.u-psud.fr.

■ ACKNOWLEDGMENTS

R.V. and F.C. thank the Ministère de l'Enseignement Supérieur et de la Recherche for doctoral fellowships. Marianne Bombled is acknowledged for obtaining MS data.

■ REFERENCES

(1) Legraverend, M.; Grierson, D. S. *Bioorg. Med. Chem.* **2006**, *14*, 3987.
(2) Rosemeyer, H. *Chem. Biodiversity* **2004**, *1*, 361.
(3) Sinkeldam, R. W.; Greco, N. J.; Tor, Y. *Chem. Rev.* **2010**, *110*, 2579.
(4) Legraverend, M. *Tetrahedron* **2008**, *64*, 8585.
(5) Agrofoglio, L. A.; Gillaizeau, I.; Saito, Y. *Chem. Rev.* **2003**, *103*, 1875.
(6) Hocek, M. *Eur. J. Org. Chem.* **2003**, 245.
(7) Dang, Q.; Brown, B. S.; Erion, M. D. *Tetrahedron Lett.* **2000**, *41*, 6559.
(8) Ibrahim, N.; Legraverend, M. *J. Comb. Chem.* **2009**, *11*, 658 and references cited therein.
(9) Hockemeyer, J.; Burbiel, J. C.; Müller, C. E. *J. Org. Chem.* **2004**, *69*, 3308.
(10) Ibrahim, N.; Legraverend, M. *J. Org. Chem.* **2009**, *74*, 463 and references cited therein.
(11) Nolsøe, J. M. J.; Gundersen, L.-L.; Rise, F. *Acta Chem. Scand.* **1999**, *53*, 366 and references cited therein.
(12) Hocek, M.; Pohl, R. *Synthesis* **2004**, 2869 and references cited therein.
(13) Collier, A.; Wagner, G. *Org. Biomol. Chem.* **2006**, *4*, 4526.
(14) Vrábel, M.; Pohl, R.; Klepetářová, B.; Votruba, I.; Hocek, M. *Org. Biomol. Chem.* **2007**, *5*, 2849.
(15) Lagisetty, P.; Zhang, Li; Lakshman, M. K. *Adv. Synth. Catal.* **2008**, *350*, 602.
(16) Saito, Y.; Koda, M.; Shinohara, Y.; Saito, I. *Tetrahedron Lett.* **2011**, *52*, 491 and references cited therein.
(17) Sedláček, O.; Břehová, P.; Pohl, R.; Holý, A.; Janeba, Z. *Can. J. Chem.* **2011**, *89*, 488 and references cited therein.
(18) Mosrin, M.; Knochel, P. *Org. Lett.* **2009**, *11*, 1837.
(19) Zimdars, S.; Mollat du Jourdin, X.; Crestey, F.; Carell, T.; Knochel, P. *Org. Lett.* **2011**, *13*, 792.
(20) Tobrmanová, M.; Tobrman, T.; Dvořák, D. *Collect. Czech. Chem. Commun.* **2011**, *76*, 311.
(21) Ackermann, L.; Althammer, A.; Fenner, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 201. Chiong, H.-A.; Daugulis, O. *Org. Lett.* **2007**, *9*, 1449.
(22) Sahnoun, S.; Messaoudi, S.; Brion, J.-D.; Alami, M. *Org. Biomol. Chem.* **2009**, *7*, 4271 and references cited therein.
(23) Storr, T. E.; Strohmeier, J. A.; Baumann, C. G.; Fairlamb, I. J. S. *Chem. Commun.* **2010**, *46*, 6470 and references cited therein.
(24) Čerňa, I.; Pohl, R.; Klepetářová, B.; Hocek, M. *J. Org. Chem.* **2010**, *75*, 2302 and references cited therein.
(25) Liu, B.; Qin, X.; Li, K.; Li, X.; Guo, Q.; Lan, J.; You, J. *Chem.—Eur. J.* **2010**, *16*, 11836.
(26) Vaňková, B.; Krchňák, V.; Soural, M.; Hlaváč, J. *ACS Comb. Sci.* **2011**, *13*, 496.
(27) Sahnoun, S.; Messaoudi, S.; Brion, J.-D.; Alami, M. *Eur. J. Org. Chem.* **2010**, *31*, 6097.
(28) Sahnoun, S.; Messaoudi, S.; Brion, J.-D.; Alami, M. *ChemCatChem* **2011**, *3*, 893.
(29) Sahnoun, S.; Messaoudi, S.; Peyrat, J.-F.; Brion, J.-D.; Alami, M. *Tetrahedron Lett.* **2008**, *49*, 7279.
(30) Indeed, the substitution of the chloro atom by the *t*-BuOLi was predominant, meaning that this reaction is much faster than the direct alkenylation.
(31) Brun, V.; Legraverend, M.; Grierson, D. S. *Tetrahedron* **2002**, *58*, 7911.
(32) Lu, W; Sengupta, S.; Petersen, J. L.; Akhmedov, N. G.; Shi, X. *J. Org. Chem.* **2007**, *72*, 5012.
(33) Besselièvre, F.; Piguel, S.; Mahuteau-Betzer, F.; Grierson, D. *Org. Lett.* **2008**, *10*, 4029.
(34) Besselièvre, F.; Piguel, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 9553.
(35) Pacheco Berciano, B.; Lebrequier, S.; Besselièvre, F.; Piguel, S. *Org. Lett.* **2010**, *12*, 4038.
(36) Zhao, D.; Wang, W.; Yang, F.; Lan, J.; Yang, L.; Gao, G.; You, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 3296.
(37) Zhao, D.; Wang, W.; Lian, S.; Yang, F.; Lan, J.; You, J. *Chem.—Eur. J.* **2009**, *15*, 1337.
(38) Ramirez, F.; Desai, N. B.; Mc Kelvie, N. *J. Am. Chem. Soc.* **1962**, *84*, 1745.
(39) Hirao, T.; Masunaga, T.; Ohshiro, Y.; Agawa, T. *J. Org. Chem.* **1981**, *46*, 3745.
(40) Kuang, C.; Senboku, H.; Tokuda, M. *Tetrahedron* **2002**, *58*, 1491.
(41) O'Byrne, A.; Evans, P. *Tetrahedron* **2008**, *64*, 8067.
(42) Kuang, C.; Senboku, H.; Tokuda, M. *Tetrahedron* **2005**, *61*, 637.
(43) Haack, R. A.; Penning, T. D.; Djurić, S. W.; Dziuba, J. A *Tetrahedron Lett.* **1988**, *29*, 2783.
(44) Horibe, H.; Fukuda, Y.; Kondo, K.; Okuno, H.; Mutarami, Y.; Aoyama, T. *Tetrahedron* **2004**, *60*, 10701.
(45) Qian, M.; Huang, Z.; Negishi, E. *Org. Lett.* **2004**, *6*, 1531.
(46) Paquette, L. A.; Fristad, W. E.; Dime, D. S.; Bailey, T. R. *J. Org. Chem.* **1980**, *45*, 3017.
(47) Romagnoli, R.; Baraldi, P. G.; Cruz-Lopez, P.; Lopez Cara, C.; Carrion, M. D.; Brancale, A.; Hamel, E.; Chen, L.; Bortolozzi, R.; Basso, G.; Viola, G. *J. Med. Chem.* **2010**, *53*, 4248.
(48) Abbotto, A.; Bradamante, S.; Pagani, G. A. *J. Org. Chem.* **1996**, *61*, 1761.
(49) Abbotto, A.; Bradamante, S.; Facchetti, A.; Pagani, G. A. *J. Org. Chem.* **1999**, *64*, 6756.