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Anionic O → α- and β-Vinyl Carbamoyl Translocation of 2-(*O*-Carbamoyl) Stilbenes†

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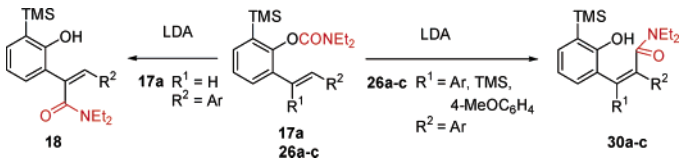
ABSTRACT



New anionic oxygen to α- and β-vinyl carbamoyl migration reactions, 17a and 26a–c → 18 and 30a–c, proceed under LDA-mediated conditions leading stereoselectively to highly substituted stilbenes bearing electron-donating and -withdrawing substituents. Compounds 17a and 26a–c are prepared by combination of efficient, directed ortho metalation, Sonogashira, and Suzuki–Miyaura cross-coupling procedures.

In continuation of efforts (Figure 1, **1**−**6**) to devise useful carbanion-based methodology for the synthesis of aromatics

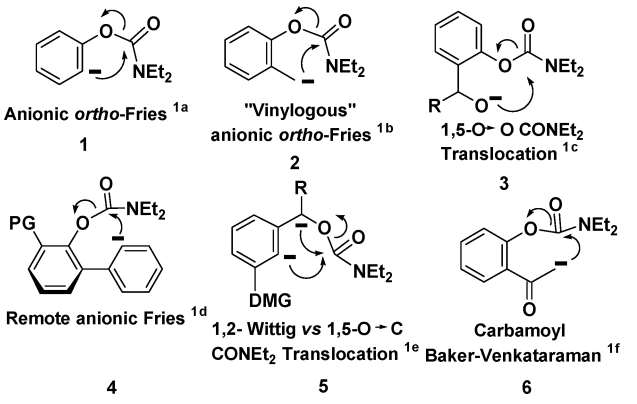
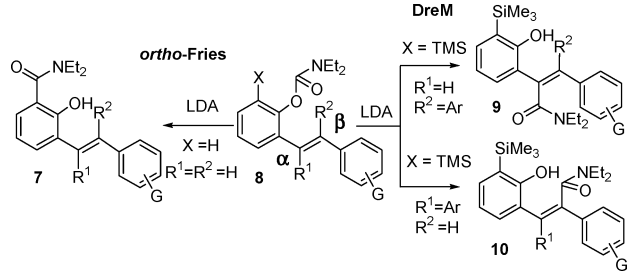


Figure 1.

and heteroaromatics,[1] we have uncovered a stereoselective LDA-mediated O → *ortho*-vinyl carbamoyl rearrangement

Scheme 1



of 2-*O*-carbamoyl stilbenes (Scheme 1). With the obligatory prevention of the anionic Fries rearrangement[1a] (**8** → **7**) by silicon protection (**8**, X = TMS), migration to both α- (**8** → **9**) and β-vinyl (**8** → **10**) positions may be induced, depending

† This paper is dedicated with respect and appreciation to Al Meyers who pointed the way to ortho metalation and provides a rich lore of synthetic organolithium chemistry.

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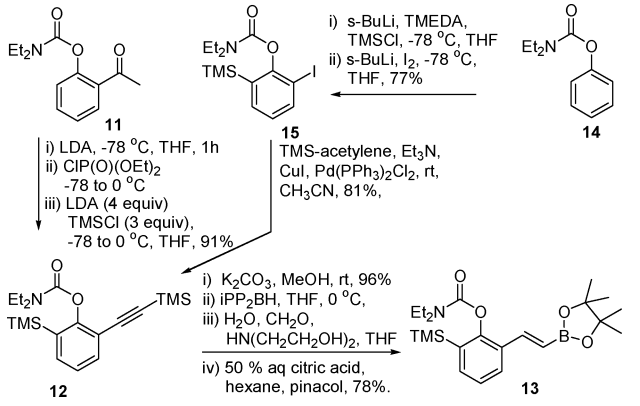
(1) (a) *Anionic ortho-Fries*: Sibi, M. P.; Snieckus, V. *J. Org. Chem.* **1983**, *48*, 1935−1937. (b) *Vinylogous anionic ortho-Fries*: Kalinin, A. V.; Miah, M. A. J.; Chattopadhyay, S.; Tsukazaki, M.; Wicki, M.; Nguen, T.; Coelho, A. L.; Kerr, M.; Snieckus, V. *Synlett* **1997**, *7*, 839−841. (c) *1,5-O→ O CONEt2 translocation*: Chauder, B. A.; Kalinin, A. V.; Taylor, N. J.; Snieckus, V. *Angew. Chem., Int. Ed.* **1999**, *38*, 1435−1438. (d) *Remote anionic Fries*: Wang, W.; Snieckus, V. *J. Org. Chem.* **1992**, *57*, 424−426. (e) *1,2 Wittig versus 1,5-O→ O CONEt2 translocation*: Zhang, P.; Gawley, R. E. *J. Org. Chem.* **1993**, *12*, 3222−3223. (f) *Carbamoyl Baker−Venkatarman reaction*: Kalinin, A. V.; da Silva, A. J. M.; Lopes, C. C.; Lopes, R. S. C.; Snieckus, V. *Tetrahedron Lett.* **1998**, *39*, 4995−4998.

on the open site, and thereby provides new heterocycles. In particular, our method allows the synthesis of 3-arylcoumarin and 3,4-diaryl coumarin approaches to diversely substituted stilbenes and, from these, benzofurananone[2] **19** and coumarin[3] **31**, which, in the context of current studies, may be of future biological interest.[4,5] Although mechanistically somewhat ambiguous (vide infra), the carbamoyl migrations are, to the best of our knowledge, unprecedented in aromatic carbanionic chemistry[6] and may be conceptualized to be driven by the complex-induced proximity effect (CIPE).[7]

The requisite test substrate **8**, X = TMS for the *O*-carbamoyl → α-vinyl migration was prepared by first constructing the intermediate styryl borolane **13** using a two-pronged approach (Scheme 2). Thus, in a five-step synthetic

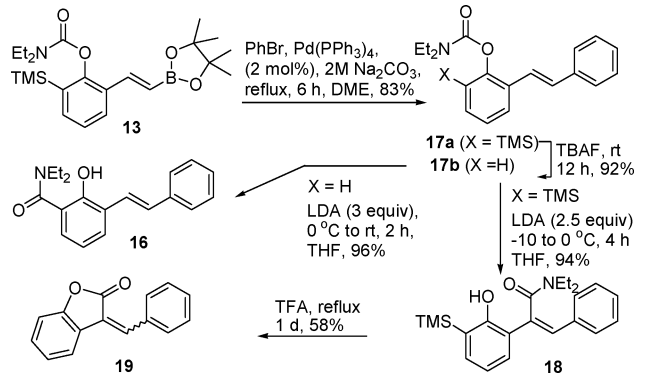
Scheme 2



operation in one pot and following, in part, the interesting Negishi protocol,[8] treatment of the enolate of the readily available 2-*O*-carbamoyl acetophenone **11**[9] with diethyl chlorophosphonate at −78 °C followed by LDA (4 equiv) and TMSCl (3 equiv) gave the bis-silylated aryl acetylene **12** in high yield. Selective desilylation followed by hydroboration with *i*(isopropylprenyl)borane (*i*PP_2BH)[10] gave the vinyl borolane **13**.[11]

In the alternative route, subjection of the *O*-phenyl carbamate **14** to a sequential, one-pot double-directed ortho metalation (DoM)−TMSCl and iodine quench procedure afforded the contiguously substituted iodide **15** (77% yield) which, upon Sonogashira coupling with TMS acetylene furnished the bis-silylated derivative **12** in 81% yield. In view of the high cost of TMS acetylene and the difficulties of scaling-up this route, the procedure starting from **11** was preferred. Suzuki−Miyaura cross coupling of **13** with bromobenzene under standard conditions delivered the requisite 2-*O*-carbamoyl stilbene **17a** in 83% yield (Scheme 3).[12] As expected from general observation,[1a] treatment of

Scheme 3



17b (Scheme 3), derived by selective desilylation (TBAF/rt) of **17a**, with LDA (3 equiv) resulted in quantitative conversion to the anionic *ortho*-Fries rearrangement product **16**. On the other hand, the TMS-protected derivative **17a**, upon treatment with LDA (2.5 equiv) between −10 and 0 °C led smoothly to the formation of the carbamoyl-migrated product **18** in 94% yield. To ensure the position of amide translocation, **18** was cyclized to the known benzofuranone **19** (1:1 *E*:*Z* mixture).[13] A single-crystal X-ray structure analysis of **18**[14] established stereochemical conservation of (*E*)-stilbene in the transformation. Generalization of the

(2) For naturally occurring benzofuranones (isoaurones) with topomerase inhibitory effects, see: (a) Suzuki, K.; Yahara, S.; Maehata, K.; Uyeda, M. *J. Nat. Prod.* **2001**, *64*, 204−207. For recent synthetic work, see: (b) Burke, A. J.; O'Sullivan, W. I. *Tetrahedron* **1997**, *35*, 2539−2543.

(3) For naturally occurring coumarins, some of which exhibit diverse (proapoptotic, antitumor, transcriptional suppression of HIV promoter) bioactivity, see: Bailly, C.; Bal, C.; Barbier, P.; Combes, S.; Finet, J.-P.; Hildebrand, M.-P.; Peyrot, V.; Wattez, N. *J. Med. Chem.* **2003**, *46*, 5437−5444 and references therein.

(4) (a) Guilet, D.; Hélesbeux, J−J.; Séraphin, D.; Sévenet, T.; Richomme, P.; Bruneton, J. *J. Nat. Prod.* **2001**, *64*, 563−568. (b) Murray, R. D. H.; Méndez, J.; Brown, S. A. *The Natural Coumarins: Occurrence, Chemistry and Biochemistry*; J. Wiley: New York, 1982.

(5) ,4-Diarylcoumarins may be considered as restricted tamoxifen derivatives, the latter being an FDA approved drug widely used for treatment of estrogen-dependent breast cancer. For key references and recent synthetic work, see: Yu, D. D.; Forman, B. M. *J. Org. Chem.* **2003**, *68*, 9489−9491. Yus, M.; Ramón, D. J.; Gómez, I. *Tetrahedron* **2003**, *59*, 3219−3225.

(6) Stilbene undergoes reductive dilithiation in the presenece of Li metal as discovered by Schlenk in his prognostic contributions to organolithium chemistry: (a) Schlenk, W.; Bergmann, E. *Annalen* **1928**, *483*, 106; *Houben-Weyl 13/1*, 162 ff. Monolithio and 1,1- or 1,2-dilithio stilbene species have been generated mainly by metal−halogen exchange or Li addition to diphenylacetylene: (b) Maercker, A.; Kemmer, M.; Wang, H. C.; Dong, D.-H.; Szwarc, M. *Angew Chem., Int. Ed.* **1998**, *37*, 2136−2138. (c) Boche, G. *Top. Curr. Chem.* **1988**, *146*, 3−56. Their configurational stability and proton-transfer reactions are highly dependent on solvent and temperature, see: (d) *Houben-Weyl*, **1952**, *13/1*, p 133 and **1989E**, *19d*, pp 176, 483, 498. (e) Maercker, A. *In* Sapse, A. M., Schleyer, P. von R. *Lithium Chemistry. A Theoretical and Experimental Overview*, Wiley: New York, 1995; p 477.

(7) Whisler, M. C.; MacNeil, S.; Snieckus, V.; Beak, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 2206.

(8) Negishi, E.-i.; King, A. O.; Klima, W. L. *J. Org. Chem.* **1980**, *2*, 193−196.

(9) Prepared in 93% yield from 2-hydroxyacetophenone using NaH, $ClCONEt_2$/DMF.

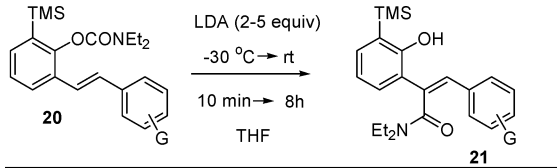
(10) For the general utility of this new hydroboration reagent, see: Kalinin, A.; Scherer, S.; Snieckus, V. *Angew. Chem., Int. Ed.* **2003**, *42*, 3399−3404.

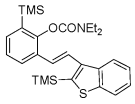
(11) For purification purposes, the intermediate boronic acid was first converted into its crystalline diethanolamine adduct, which was subjected to treatment with pinacol in 50% citric acid/hexane mixture to give analytically pure **13**.

(12) Kalinin, A. V.; Reed, M. A.; Norman, B. H.; Snieckus, V. *J. Org. Chem.* **2003**, *68*, 5992−5999.

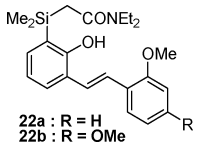
(13) Msaddek, M.; Rammah, M.; Ciamala, K.; Vebrel, J.; Laude, B. *Synthesis* **1997**, 1495−1498.

Table 1. Synthetic 2(*O*-Carbamoyl)stilbene Translocation Reactions **20** into **21**



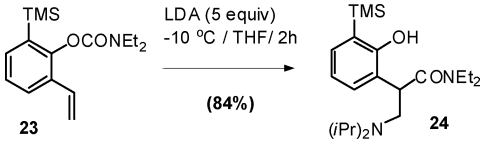
entry	product	G	yld %
1	**21a**[a]	H (*Z*-stilbene)	81
2	**21b**[b]	2-OMe	68
3	**21c**	3-OMe	54
4	**21d**	4-OMe	73
5	**21e**[b]	2,4-OMe	69(88)[c]
6	**21f**[d]	3-NHBoc	56
7	**21g**[e]	4-CHO	59
8	**21h**	4-SO_2NEt_2	81
9	**21i**	4-CO_2t-Bu	75
10	**21j**	4-CN	0
11	**21k**	3-Cl	0
12	**21l**[f]		48

[a] (Z)-Stilbene derivative. [b] In addition, 12 and 15% yields of α-methylsilyl amides **22a** and **22b,** respectively, were obtained. [c] Corresponding TES derivative of **21e** was used. [d] Substrate **20f** was first treated with TMSCl (1.1 equiv)/LDA (1.1 equiv) at −78 °C, warmed to 0 °C, and recooled to −78 °C. [e] Treated with $LiNEt_2$ at −78 °C and stirred for 30 min, and then the conditions shown were followed. [f] Substrate was sequentially treated with TMSCl (1.5 equiv) and LDA (5 equiv).



carbamoyl translocation reaction (**20** → **21**, Table 1) deserves comment. Starting substrates were prepared according to the method described (Schemes 2 and 3) using aryl bromides and aryl iodides as coupling partners (See Supporting Information). Interestingly, the (*Z*)-stilbene derivative corresponding to the (*E*)-isomer **17a**, underwent comparatively faster rearrangement to give isomeric carbamoyl-migrated product **21a** in high yield (entry 1). Stilbenes bearing electron-donating OMe groups, **20b**−**e**, provided the expected products **21b**−**e** (entries 2−5) but also, in two cases (entries 2 and 5), minor amounts of α-methylsilyl amides **22a** and **22b**, presumably due, in balance, to an α-vinyl C−H deacidifying effect of the OMe groups. Following our established circumvention of such byproducts in *O*-biaryl carbamate remote anionic Fries rearrangement,[1d] the *ortho*-triethylsilyl (TES) derivative corresponding to **20e** was prepared and subjected to the LDA conditions to afford cleanly the α-vinyl carbamoyl-migrated product **21e** in 88% yield (entry 5). The *N*-Boc stilbenoid **20f**, upon treatment under the standard excess LDA conditions, led to recovered starting material. Suspecting the possible deactivation effect of the incipient N-anion, we subjected compound **20f** to LDA/TMSCl (1.1:1.1 equiv) followed by LDA (3 equiv) and workup to give the desired product **21f** in modest yield (entry 6). The aldehydic stilbenoid **20g** required initial in situ protection with $LiNEt_2$ (1 equiv)[15] followed by application of the standard LDA conditions to afford **21g** (entry 7). Turning attention to substrates bearing electron-withdrawing groups, both tertiary sulfonamide and *tert*-butyl ester systems, **20h** and **20i**, showed good behavior to furnish products **21h** and **21i**, respectively (entries 8 and 9), while cyano- and chloro-substituted derivatives **20j** and **20k** showed instability in the presence of LDA even at low temperatures and did not lead to the rearranged products **21j** and **21k**, respectively (entries 10 and 11). For these two cases, attack at the CN function[16] and benzyne formation[17] may be the complicating factors. In accord with previous experience on similar systems,[18] and consistent with pK_a considerations, benzothiophene **20l** required prior in situ 2-TMS protection in order to achieve reasonably effective formation of the α-carbamoyl migration product **21l**. Reaction of CF_3-substituted aryl, 2-furanyl, 2-thienyl, and 3- and 4-pyridinyl substituted systems led only to overall decomposition. Treatment of **23** (Scheme 4) under the LDA conditions yielded **24**, perhaps not a surprising result of carbamoyl migration followed by Michael addition or vice versa, which may be viewed as a product of a first step of an intramolecular Baylis−Hillman reaction.[19] To test the *O*-carbamoyl−*β*-vinyl translocation (Scheme 1, **8** → **10**), the α-phenyl stilbenes **26a**−**c** were prepared (Scheme 5). Thus, Suzuki−Miyaura cross coupling of the (*Z*)-stilbene borolane, **25a**,[10] with the previously prepared iodide **15** afforded compound **26a**, while analogous couplings of **27**[20] with **28** gave **29** and then, with 4-Me-$OC_6H_4B(OH)_2$, the corresponding **26c**. Disilylated stilbene **26b** was obtained by the corresponding coupling of **25b** with **15**. All coupling reactions proceeded with complete stereoselectivity.[21] Treatment with LDA at room temperature led to the *β*-vinyl migration products **30a**−**c**, respectively, in

Scheme 4



(14) CCDC 235465 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via the Internet at www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK, fax: +44 1223 336033.

(15) Roschangar, F.; Brown, J. C.; Cooley, B. E.; Sharp, M. J.; Matsuoka, R. T. *Tetrahedron* **2002**, *58*, 1657−1666.

(16) Krizan, T. D.; Martin, J. C. *J. Am. Chem. Soc*. **1983**, *105*, 6155−6157.

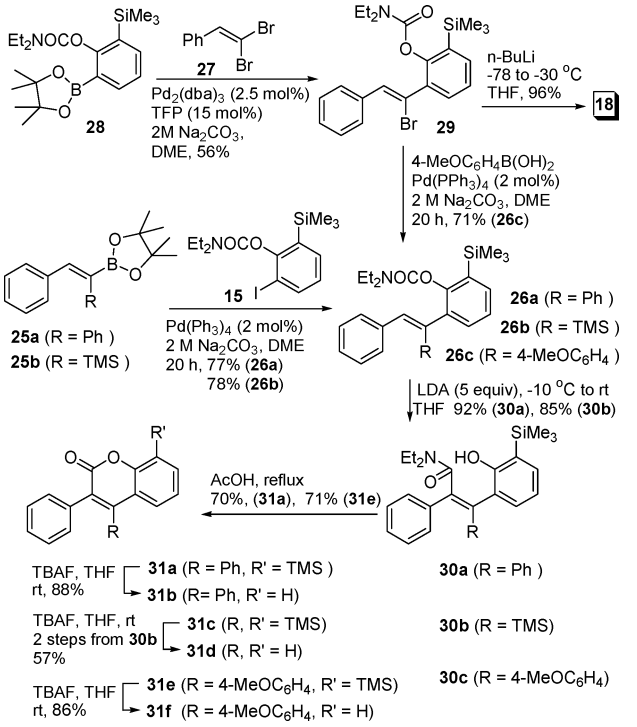
(17) Gohier, F.; Castanet, A.-S.; Mortier, J. *Org. Lett*. **2003**, *5*, 1919−1922.

(18) James, C. Ph.D. Thesis, University of Waterloo, Waterloo, Canada, 1998.

(19) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev*. **2003**, *103*, 811−892.

(20) Prepared by the method in: Shen, W. *Synlett* **2000**, 737−739.

Scheme 5



high yields. The disappearance of the vinyl C−H signal in the ^{1}H NMR discounted the alternative path of remote anionic Fries rearrangement[1a] into the α-phenyl ring. Structural integrity and synthetic utility was shown by conversion, under glacial acetic acid conditions, into compounds **31a**, **31c**, and **31e,** which underwent smooth desilylation to afford the 3-aryl and 3,4-diaryl coumarins **31b**, **31d**, and **31f**, respectively.[22] To obtain evidence for the intermediacy of the α-vinyllithium species in the *O*-carbamoyl migration, compound **29**, prepared from **28**, was subjected to typical metal−halogen exchange conditions (*n*-BuLi/−78 → −30 °C/THF), which led to the formation of product **18**, shown to be identical with that obtained from the LDA-mediated reaction of **17a**. Although not unequivocal, this result coupled with the observation of *β*-vinyl migration (**26a**−**c** → **30a**−**c**) supports the α- and *β*-vinyl anionic pathways as reasonable mechanistic interpretations of the results.[23] Furthermore, the conservation of stereochemistry of the incipient lithio species derived from both **17a** and **26** suggests *O*-carbamate coordinative stabilization, which is unavailable for ortho-unfunctionalized lithiostilbene species and hence may contribute to their configurational instability.[6d,f] Although the conversion of **17b** → **16** implies higher aromaticity over vinyl C−H acidity, comparative pK_a data are not available.[24] A contribution of the CIPE[7] via the *O*-carbamate may also be suggested for the observed anionic rearrangements.

In summary, stereoselective and moderately general oxygen to α- and *β*-vinyl carbamoyl migration reactions **20** → **21** (Table 1) and **26** → **30** have been demonstrated, which may be of mechanistic interest and which provide new routes to benzofuranones **19** and 3-aryl **31d** and 3,4-diaryl **31b** and **31f** coumarins of current biological interest.[4] Of potential added synthetic value may be the methodologies devised for the efficient construction of precursor aromatics **12** and stilbenes **17**[25] whose contiguous substitution patterns are the trademarks of directed ortho metalation-mediated synthetic strategies. Several aspects of these observations are under further study.

Acknowledgment. We are grateful to NSERC Canada for support of our synthetic programs. Dr. Ruiyao Wang provided expert X-ray crystallographic analysis. M.T.C. thanks Pfizer Global Research and Development for a 2004 Pfizer Summer Undergraduate Research Award. Sheldon Lyn, 2003 NSERC Undergraduate Summer Research Awardee, reproduced a number of experiments in this research with great enthusiasm. Frontier Scientific graciously provided a number of boronic acids.

Supporting Information Available: Full spectral data and experimental procedures for the synthesis of compounds **12**, **13**, **15**, **16**, **17a**, **17b**, **18**, **20e**, **21e**, **20i**, **21i**, **23**, **24**, **26a**, and **30a** and X-ray crystallographic data for compound **18**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) Stereoselective trans coupling of 1,2-dibromostilbenes is precedented; see ref 20 and: Gaukroger, K.; Hadfield, J. A.; Hepworth, L. A.; Lawrence, N. J.; McGown, A. T. *J. Org. Chem.* **2001**, *66*, 8135−8138.

(22) **27d**: Yoneda, E.; Sugioka, T.; Hirao, K.; Zhang, S.-W.; Takahashi, S. *J. Chem. Soc, Perkin Trans. 1* **1998**, *3*, 477−483. **27b**: see ref 3d. **27f**: see Supporting Information.

(23) Michael addition of LDA followed by carbamoyl transfer and LDA elimination, envisaged only for the α-vinyl rearrangement result; a type of an intramolecular Baylis−Hillman reaction (ref 19) is an alternate, less likely, explanation.

(24) For *O*-aryl carbamate, pK_a = 37.2, see: Fraser, R. R.; Bresse, M.; Mansour, T. S. *J. Am. Chem. Soc.* **1983**, *105*, 7790−7791.

(25) Stereoselective construction of stilbene is of interest in context of natural product, bioactive molecule, and material science substance synthesis; see *inter alia*: Rathore, R.; Deselinicu, M. I.; Burns, C. L. *J. Am. Chem. Soc.* **2002**, *124*, 14832−14833. Jeffery, T.; Ferber, B. *Tetrahedron Lett.* **2003**, *44*, 193−197. Kabalka, G. W.; Wu, Z.; Ju, Y. *Tetrahedron Lett.* **2001**, *42*, 4759−4760.