REPORT DOCUMENTATION PAGE

Form Approved OMB NO. 0704-0188

The public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggesstions for reducing this burden, to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington VA, 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to any oenalty for failing to comply with a collection of information if it does not display a currently valid OMB control number.
PLEASE DO NOT RETURN YOUR FORM TO THE ABOVE ADDRESS.

1. REPORT DATE (DD-MM-YYYY)	2. REPORT TYPE	3. DATES COVERED (From - To)
	New Reprint	-

4. TITLE AND SUBTITLE
Intermolecular Addition of Glycosyl Halides to Alkenes Mediated by Visible Light

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W911NF-04-D-0004

5c. PROGRAM ELEMENT NUMBER
611102

6. AUTHORS
R. Stephen Andrews, Jennifer J. Becker, Michel R. Gagné

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAMES AND ADDRESSES
University of North Carolina - Chapel Hill
Office of Sponsored Research
The University of North Carolina at Chapel Hill
Chapel Hill, NC 27599 -1350

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Research Office
P.O. Box 12211
Research Triangle Park, NC 27709-2211

10. SPONSOR/MONITOR'S ACRONYM(S)
ARO

11. SPONSOR/MONITOR'S REPORT NUMBER(S)
55041-CH-SR.9

12. DISTRIBUTION AVAILIBILITY STATEMENT
Approved for public release; distribution is unlimited.

13. SUPPLEMENTARY NOTES
The views, opinions and/or findings contained in this report are those of the author(s) and should not contrued as an official Department of the Army position, policy or decision, unless so designated by other documentation.

14. ABSTRACT
Catching Photons: Visible light, an amine reductant, and a Ru(bpy)32+ photocatalyst can be used to mediate the addition of glycosyl halides into alkenes to synthesize important C-glycosides. This method highlights the growing potential of photocatalysis to effectively drive useful and difficult chemical transformations.

15. SUBJECT TERMS
catalysis, c-glycosides

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	15. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			Jennifer Becker
UU	UU	UU	UU		19b. TELEPHONE NUMBER: 919-549-4224

Report Title

Intermolecular Addition of Glycosyl Halides to Alkenes Mediated by Visible Light

ABSTRACT

Catching Photons: Visible light, an amine reductant, and a Ru(bpy)32+ photocatalyst can be used to mediate the addition of glycosyl halides into alkenes to synthesize important C-glycosides. This method highlights the growing potential of photocatalysis to effectively drive useful and difficult chemical transformations.

REPORT DOCUMENTATION PAGE (SF298)
(Continuation Sheet)

Continuation for Block 13

ARO Report Number 55041.9-CH-SR
Intermolecular Addition of Glycosyl Halides to Al ...

Block 13: Supplementary Note
© 2010 . Published in Angewandte Chemie International Edition, Vol. Ed. 0 49, (40) (2010), ((40). DoD Components reserve a royalty-free, nonexclusive and irrevocable right to reproduce, publish, or otherwise use the work for Federal purposes, and to authroize others to do so (DODGARS §32.36). The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision, unless so designated by other documentation.

Approved for public release; distribution is unlimited.

C-Glycosides

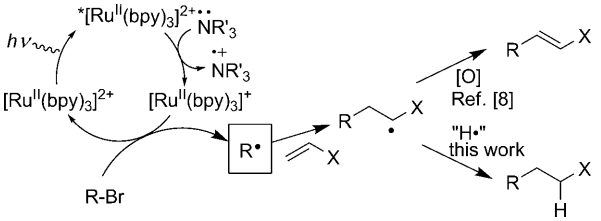
DOI: 10.1002/anie.201004311

Intermolecular Addition of Glycosyl Halides to Alkenes Mediated by Visible Light**

*R. Stephen Andrews, Jennifer J. Becker, and Michel R. Gagné**

C-glycosides are an important class of bioactive compounds most notable for their resistance to metabolic processing and their prevalence in natural products.[1–3] Perhaps the most identifiable methodology for their synthesis is the Bu_3SnH-mediated radical addition of glycosyl bromides to activated alkenes.[4] Since its discovery, several variations of this reaction have been reported, including the utilization of transition metals[5] or UV light[6] to initiate the reaction. Our group recently developed a nickel-catalyzed reductive coupling of glycosyl bromides and alkenes, mechanistic studies on which suggested that the nickel catalyst was playing an electron-transfer (ET) role,[7] which implied that other compounds that are known to facilitate ET processes might behave even better (for example, $[Ru(bpy)_3]^{2+}$; bpy = 2,2′-bipyridyl).

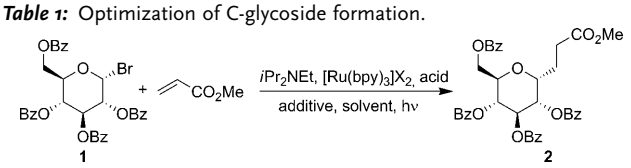
The photoredox properties of $[Ru(bpy)_3]^{2+}$ and visible light has generated recent excitement as an environmentally benign method of promoting odd-electron organic reactions to drive complex bond constructions.[8] The initiating event in these reactions is the reduction of the photogenerated MLCT state, $*[Ru^{III}(bpy)_2(bpy^{\bullet-})]^{2+}$, by amine to generate a potent ligand centered reducing equivalent (herein referred to as $[Ru^{II}(bpy)_3]^{+}$; Scheme 1). Stephenson recently demonstrated that electrophilic radicals could be generated in this fashion and intramolecularly trapped in a cascade process.[8] We report herein that the combination of visible light and $[Ru(bpy)_3]^{2+}$ yields nucleophilic C1 sugar radicals[9] that react intermolecularly with electron-deficient alkenes to provide C-glycosides in yields approaching or exceeding previous bests and with outstanding C1 diastereoselectivites.



Scheme 1. Formation of alkyl radicals mediated by visible light. R = alkyl, bpy = 2,2′-bipyridyl.

Guided by our previous nickel-based methodology,[7] we initiated our investigation on the reaction of α-glucosyl bromide **1** and methyl acrylate with $[Ru(bpy)_3]X_2$ (5 mol%), a stoichiometric reductant, and an acid source to protonate a presumed enolate.[10] The best reductant proved to be *N*,*N*-diisopropylethylamine (**3**), as it provided promising yields of the α-C-glycoside (**2**) and did not require highly polar solvents (Table 1, entries 2 and 7).[3–5]

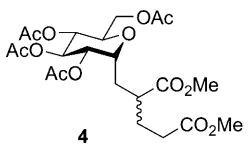
Table 1: Optimization of C-glycoside formation.

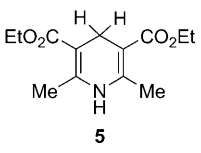


Entry[a]	Acid	Additive	Solvent	X	Yield[a]
1	**3**·HBr	–	DMA	Cl	0
2	**3**·HBr	–	MeCN	Cl	26[b]
3	**3**·HBF_4	–	MeCN	Cl	44[b]
4	**3**·HBF_4	–	MeCN[c]	Cl	50[b]
5	**3**·HBF_4	–	MeCN[c]	BF_4	61[b]
6	**3**·HBF_4	**5**	MeCN[c]	BF_4	72[b]
7	**3**·HBF_4	**5**	CH_2Cl_2[c]	BF_4	80[d]
8	–	**5**	CH_2Cl_2	BF_4	**92**[d]

[a] DMA = *N*,*N*-dimethyl acetamide. Conditions: glucosyl bromide (0.12 mmol, 0.12 M in solvent), methyl acrylate (0.24 mmol), reductant (0.36 mmol), $[Ru(bpy)_3]X_2$ (0.06 mmol), **5** (0.24 mmol) at room temperature with overnight irradiation with a 14 W fluorescent bulb. [b] Yield of isolated product. [c] 0.06 M. [d] Yield determined by supercritical fluid chromatography.

In these trials, the mass balance was dominated by over-conjugate addition (**4**), indicating that α-radical reduction and its subsequent conjugate addition to additional acrylate were competitive. Stimulated by Stephenson's success with H• trapping of benzylic radicals, we found that Hantzsch ester (**5**)





[*] R. S. Andrews, Prof. Dr. M. R. Gagné
Department of Chemistry
University of North Carolina at Chapel Hill
Chapel Hill, NC 27599-3290 (USA)
E-mail: mgagne@email.unc.edu
Dr. J. J. Becker
US Army Research Office
P.O. Box 12211, Research Triangle Park, NC 27709 (USA)

[**] We thank Aaron J. Francis for his contribution to optimization and Prof. Malcolm Forbes for his help with EPR experiments. The Army Research Office Staff Research Funding and Department of Energy (DE-FG02-05ER15630) are gratefully acknowledged for their support.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201004311.

View this journal online at wileyonlinelibrary.com

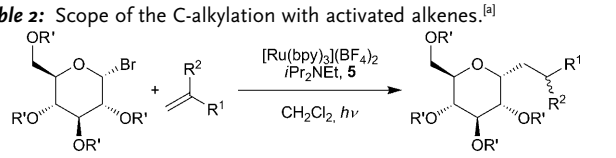
© 2010 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

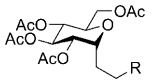
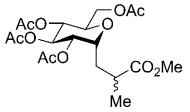
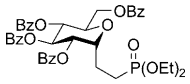
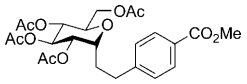
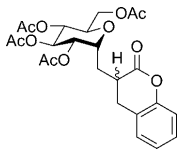
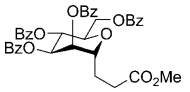
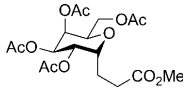
successfully suppressed the oligomerization and led to improved yields, as did a switch to dichloromethane as solvent (suppressed hydrolysis). Final optimization showed the acid to be unnecessary and high reaction concentrations to be beneficial (Table 1, entry 8).[11]

The conditions arrived at in entry 8 were adopted to examine the scope of the coupling (Table 2). In general, alkenes known to rapidly react with alkyl radicals worked well,[12] though when they became too electron deficient, over-conjugate addition became problematic. Typical reaction times were about 15 h, though less electrophilic or bulkier substrates were slower. Higher alkene concentrations were helpful when over-conjugate addition was not rapid (Table 2, entry 6).[13] Mannosyl and galactosyl bromides were also well-behaved (entries 9 and 10), as were acetate and benzoate protecting groups (not pivaloate), and reactions could be successfully scaled to 1.2 mmol of substrate without complications (entry 1 and 6).[14] Although 1,1-disubstituted alkenes were tolerated, β-substituted enoates were not (e.g. methyl crotonate, methyl maleate).

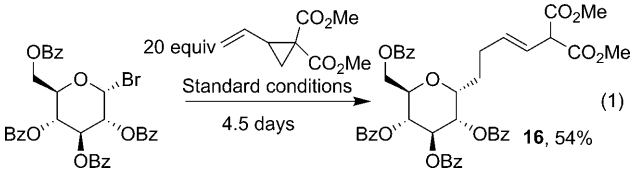
Several control experiments helped to elucidate the role of the reaction components: 1) No products were formed in the absence of $[Ru(bpy)_3]^{2+}$ or visible light, and when **3** was omitted, **5** was quickly converted into the pyridine (< 2 h) accompanied by only a 25% consumption of **1** to **2**; 2) In the presence of an electrophilic hydrogen atom source (*t*BuSH), C1 reductive debromination was the major product accompanied by small amounts of the C-glycoside; 3) Consistent with a C1 radical intermediate was the cyclopropane ring-opening observed in **16** [Eq. (1)] and the detection of carbon-based radicals in time-resolved EPR measurements after pulsed irradiation of the reaction mixture.[9,15]

Table 2: Scope of the C-alkylation with activated alkenes.[a]

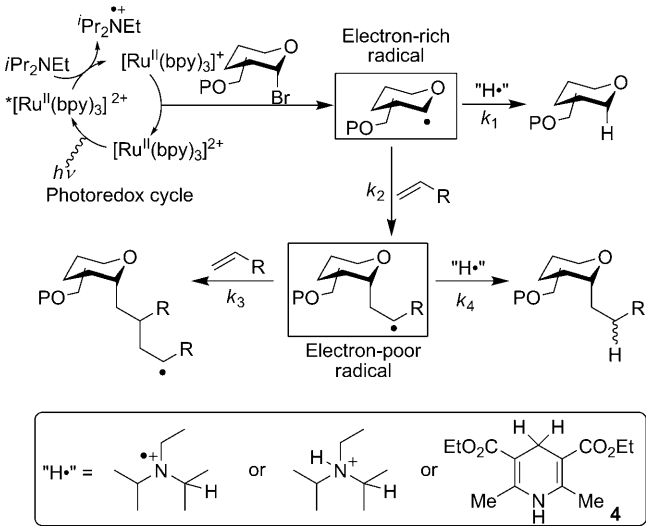


Entry	Product	Entry	Yield[b]
1			**6**, R = CO_2Me: 94%[c] (75%[d])
2			**7**, R = COMe: 86%
3			**8**, R = CHO: 85%
4			**9**, R = CN: 85%
5		6	
	10, 98%, d.r. = 1.5:1		**11**, 42% (63%[e])
7		8	
	12, 51%		**13**, 98% (90%[d]), d.r. = 1.8:1
9		10	
	14, 81%[c]		**15**, 80%

[a] R′ = Ac or Bz. [b] Yield of isolated product; conditions: glycosyl bromide (0.12 mmol, 0.12 M in CH_2Cl_2), alkene (0.24 mmol), **3** (0.36 mmol), $[Ru(bpy)_3](BF_4)_2$ (0.06 mmol), **5** (0.24 mmol), irradiation overnight at room temperature with a 14 W fluorescent bulb. [c] 0.134 mmol **5**. [d] 1.2 mmol glucosyl bromide. [e] 1.2 mmol alkene.



Based on these observations, we propose Scheme 2 as a plausible mechanism. ET from photogenerated $[Ru^{II}(bpy)_3]^+$ to glycosyl bromide generates the C1 radical, which can be reduced (k_1) or added to the alkene (k_2); for electron deficient alkenes $k_2 > k_1$. When $k_1 \approx k_2$, reductive debromination is competitive, though this can be partially compensated with an increase in the alkene concentration. Termination of the electron-deficient α radical is subject to the relative rates of over-conjugate addition (k_3) and reduction (k_4), the latter being accelerated by Hantzsch ester.[16,17]



Scheme 2. A plausible mechanism for the reactions described herein.

In summary, we have developed a reductive room-temperature visible-light-mediated conjugate addition of glycosyl halides into activated alkenes, which leads to fully saturated C-glycosides with exclusive α selectivity. The procedure improves upon the classic Bu_3Sn-H mediated methodologies pioneered by Giese and achieves near best results for each substrate class. Moreover, this procedure advances the growing role of photoredox catalysis in important C–C bond formations and generates an experimentally optimal proce-

 © 2010 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

dure that reduces the amount of toxic byproducts (that is, tin-free). Efforts to observe and characterize the photogenerated radical intermediates by trapping or EPR measurements are underway.

Experimental Section

General procedure: A flame-dried Schlenk tube equipped with a stir bar under argon was charged with $[Ru(bpy)_3](BF_4)_2$ (0.006 mmol, 5 mol%), Hantzsch ester **5** (0.268 mmol, 2.2 equiv), and glycosyl bromide (0.122 mmol, 1 equiv). The flask was evacuated and then backfilled with argon. Solvent (to a sugar concentration of 0.12 M) was added, forming a bright orange heterogeneous solution, followed by iPr$_2$NEt (0.366 mmol, 3 equiv) and alkene (0.244 mmol, 2 equiv). The reaction tube was placed 6–10 cm from a 14 W fluorescent light bulb and stirred at room temperature until thin-layer chromatography showed consumption of starting material (12–72 h). The reaction was quenched by passing it through a plug of silica in Et_2O (100 mL). Flash column chromatography provided the product as a white solid or a colorless oil after removal of solvents.

Received: July 14, 2010
Published online: August 25, 2010

Keywords: alkenes · C-glycosides · homogeneous catalysis · photooxidation · ruthenium

[1] For recent reviews in C-glycoside biology, see: a) C. H. Lin, H. C. Lin, W. B. Yang, *Curr. Top. Med. Chem.* **2005**, *5*, 1431 – 1457; b) P. G. Hultin, *Curr. Top. Med. Chem.* **2005**, *5*, 1299 – 1331; c) W. Zou, *Curr. Top. Med. Chem.* **2005**, *5*, 1363 – 1391; d) P. Compain, O. R. Martin, *Bioorg. Med. Chem.* **2001**, *9*, 3077 – 3092; e) F. Nicotra, *Top. Curr. Chem.* **1997**, *187*, 55 – 83.

[2] a) P. Meo, H. M. I. Osborn, *Best Synthetic Methods: Carbohydrates*, Academic Press, London, **2003**; b) L. Somsák, *Chem. Rev.* **2001**, *101*, 81 – 136; c) Y. Du, R. J. Linhardt, I. R. Vlahov, *Tetrahedron* **1998**, *54*, 9913 – 9959; d) R. J. K. Taylor, G. D. McAllister, R. W. Franck, *Carbohydr. Res.* **2006**, *341*, 1298 – 1311.

[3] a) D. E. Levy, C. Tang, *The Chemistry of C-Glycosides*, Pergamon, Tarrytown, **1995**; b) M. H. D. Postema, *C-Glycoside Synthesis*, CRC, Boca Raton, FL, **1995**.

[4] a) B. Giese, J. Dupuis, *Angew. Chem.* **1983**, *95*, 633 – 634; *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 622 – 623; b) B. Giese, J. A. González-Gómez, T. Witzel, *Angew. Chem.* **1984**, *96*, 51 – 52; *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 69 – 70; c) B. Giese, T. Witzel, *Angew. Chem.* **1986**, *98*, 459 – 460; *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 450 – 451; d) B. Giese, *Angew. Chem.* **1989**, *101*, 993 – 1004; *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 969 – 980.

[5] a) R. P. Spencer, J. Schwartz, *J. Org. Chem.* **1997**, *62*, 4204 – 4205; b) Z. Juhász, K. Micskei, E. Gal, L. Somsak, *Tetrahedron Lett.* **2007**, *48*, 7351 – 7353; c) S. K. Readman, S. P. Marsden, A. Hodgson, *Synlett* **2000**, 1628 – 1630; d) H. Gong, R. Sinisi, M. R. Gagné, *J. Am. Chem. Soc.* **2007**, *129*, 1908 – 1909; e) H. Gong, M. R. Gagné, *J. Am. Chem. Soc.* **2008**, *130*, 12177 – 12183.

[6] S. Yamago, H. Miyazoe, J. Yoshida, *Tetrahedron Lett.* **1999**, *40*, 2339 – 2342.

[7] H. Gong, R. S. Andrews, J. L. Zuccarello, S. J. Lee, M. R. Gagné, *Org. Lett.* **2009**, *11*, 879 – 882.

[8] For recent reviews on $[Ru(bpy)_3]^{2+}$ catalysis with visible light, see: K. Zeitler, *Angew. Chem.* **2009**, *121*, 9969 – 9974; *Angew. Chem. Int. Ed.* **2009**, *48*, 9785 – 9789; J. M. R. Narayanam, C. R. J. Stephenson, *Chem. Soc. Rev.* DOI: 10.1039/b913880n; T. P. Yoon, M. A. Ischay, J. Du, *Nat. Chem.* **2010**, *2*, 527 – 532. This methodology has been used for enantioselective α alkylation of aldehydes; see: D. A. Nicewicz, D. W. C. MacMillan, *Science* **2008**, *322*, 77 – 80; D. A. Nagib, M. E. Scott, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2009**, *131*, 10875 – 10877. For [2+2] cycloadditions, see: M. A. Ischay, M. E. Anzovino, J. Du, T. P. Yoon, *J. Am. Chem. Soc.* **2008**, *130*, 12886 – 12887; J. Du, T. P. Yoon, *J. Am. Chem. Soc.* **2009**, *131*, 14604 – 14605; M. A. Ischay, X. Lu, T. P. Yoon, *J. Am. Chem. Soc.* **2010**, *132*, 8572 – 8574. For reductive dehalogenation, see: J. M. R. Narayanam, J. W. Tucker, C. R. J. Stephenson, *J. Am. Chem. Soc.* **2009**, *131*, 8756 – 8757. For intramolecular addition into alkenes, see: J. W. Tucker, J. M. R. Narayanam, S. W. Krabbe, C. R. J. Stephenson, *Org. Lett.* **2010**, *12*, 368 – 371; J. W. Tucker, J. D. Nguyen, J. M. R. Narayanam, S. W. Krabbe, C. R. J. Stephenson, *Chem. Commun.* **2010**, *46*, 4985 – 4987. For intermolecular addition into arenes, see: L. Furst, B. S. Matsuura, J. M. R. Narayanam, J. W. Tucker, C. R. J. Stephenson, *Org. Lett.* **2010**, *12*, 3104 – 3107.

[9] a) J. Dupuis, B. Giese, D. Rüegge, H. Fishcer, H. G. Korth, R. Sustmann, *Angew. Chem.* **1984**, *96*, 887 – 888; *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 896 – 898; b) H. G. Korth, R. Sustmann, J. Dupuis, B. Giese, *J. Chem. Soc. Perkin Trans. 2* **1986**, 1453 – 1459; c) Y. Araki, T. Endo, M. Tanji, J. Nagasawa, *Tetrahedron Lett.* **1987**, *28*, 5853 – 5856.

[10] The reduction potential of glucosyl bromide tetraacetate has been measured to be −1.27 V (versus SCE). See: S. B. Rondinini, P. R. Mussini, F. Crippa, G. Sello, *Electrochem. Commun.* **2000**, *2*, 491 – 496.

[11] Salt electrolytes were also added, but they were less effective than acid additive.

[12] a) B. Giese, *Rev. Chem. Intermed.* **1986**, *7*, 3; b) B. Giese, *Angew. Chem.* **1983**, *95*, 771 – 782; *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 753 – 764.

[13] The major competing byproduct was reductive debromination of the starting material. Hydrolysis of the glucosyl bromide was also observed in small amounts (< 20%).

[14] Alkenes that are more electron-rich than methyl acrylate were unreactive (acrylamide, ethyl vinyl ether) and led to slow reductive debromination of the starting material.

[15] With M. Forbes (UNC-CH); full details will be provided in a future publication. See the Supporting Information for a typical scan.

[16] a) J.-P. Cheng, Y. Lu, X.-Q. Zhu, Y. Sun, F. Bi, J. He, *J. Org. Chem.* **2000**, *65*, 3853 – 3857; b) X.-Q. Zhu, H.-R. Li, Q. Li, T. Ai, J.-Y. Lu, Y. Yang, J.-P. Cheng, *Chem. Eur. J.* **2003**, *9*, 871 – 880; c) X.-Q. Zhu, L. Cao, Y. Liu, Y. Yang, J.-Y. Lu, J.-S. Wang, J.-P. Cheng, *Chem. Eur. J.* **2003**, *9*, 3937 – 3945.

[17] [4,4-D_2]**5** was shown to provide **3** only partially deuterated in the α position (20–25%), suggesting that multiple pathways for α reduction were operating (Scheme 2, box).

 © 2010 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim