Tetrahedron Letters 51 (2010) 3815–3819

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Pd-catalyzed one-pot chemoselective hydrogenation protocol for the preparation of carboxamides directly from azides

Sudhir N. Bavikar [a,†], Deepak B. Salunke [a,b,†], Braja G. Hazra [a,*], Vandana S. Pore [a], Josiane Thierry [b], Robert H. Dodd [b,*]

[a] Division of Organic Chemistry, National Chemical Laboratory, Pune, India
[b] Centre de Recherche de Gif-sur-Yvette, Institut de Chimie des Substances Naturelles, UPR 2301 CNRS, Avenue de la Terrasse, 91198 Gif-sur-Yvette, France

ARTICLE INFO

Article history:
Received 15 February 2010
Revised 8 May 2010
Accepted 17 May 2010
Available online 21 May 2010

Keywords:
Azide
Carboxamide
Succinimide ester
Chemoselective
Palladium
Catalytic hydrogenation

ABSTRACT

Carboxamides were obtained efficiently in high yields from azides on reaction with the corresponding pre-formed activated carboxylic acids in a single-step reductive transformation using hydrogen atmosphere (balloon) under $Pd/BaSO_4$ or $Pd/CaCO_3$ catalysis. The method is highly chemoselective and compatible with extremely labile functional groups such as benzyl carbamates, benzyl ethers, benzyl esters, and olefins.

The conversion of azides to amines is an important transformation in organic synthesis.[1] Amines are further utilized for the synthesis of the corresponding carboxamides which is one of the most common functionalities in many biologically interesting molecules. Several methods have been developed for amide bond formation using carboxylic acids and amines.[2] To overcome the situation where free amines cannot be used because of structural wavering, azides have been used to directly form an amide bond (Fig. 1). The classical method of conversion of azide to amide includes Staudinger-type ligation involving the acylation of an iminophosphorane.[3] A one-pot self-regulated approach for the synthesis of amides based on two redox reactions has been described earlier by Ghosh et al.[4] By treatment with Woollins' reagent in toluene, carboxylic acids were converted to selenocarboxylic acids and further reacted with azides to form amides by Knapp and Darout.[5] A one-pot procedure for the similar selenocarboxylate/azide amidation was documented by Hu and Wu.[6] In their protocol, selenocarboxylates are prepared by the reaction of carboxylic acids with LiAlHSeH and exposed in situ to azides to form amides. Other attractive methods include the Williams thio acid/azide amidation,[7] which was also documented as an improved method for the synthesis of *N*-acyl sulfonamides.[8] A chemical ligation method was also reported by Raines and co-workers, in which phosphinobenzenethiol was used to link a thioester and an azide to form an amide bond.[9]

As part of our ongoing program on the synthesis of biologically interesting bile acid-amino acid conjugates,[10] we required an efficient method for the chemoselective transformation of azides to carboxamides. There are several reports on the reduction of azides by hydrogenation followed by acylation with activated carboxylic acids.[11] However, this two-step classical protocol suffers from the potential problem of inadequate chemoselectivity and instability of the intermediate amine formed. The major drawback of the Staudinger-type ligation involves the difficult purification of products whereas the Williams thioacid/azide amidation and selenocarboxylate/azide amidation require the conversion of acids to thio acids and selenocarboxylates, respectively. This scenario demands an exceptionally chemoselective and operationally simple protocol for the synthesis of carboxamides directly from azides.

For our purposes, we were particularly attracted to the reductive transformation of azides to *N*-(*tert*-butoxycarbonyl)amines via catalytic hydrogenation described by Saito et al.[12] and Baskaran and co-workers.[13] Various methods have been developed for such a type of transformation using triethylsilane[14] or polymethyl-hydrosiloxane[15,16] as hydrogen source. Based on these observations we describe herein a new and efficient 'one-pot' chemoselective

* Corresponding authors. Tel.: +91 20 25898164; fax: +91 20 25902629 (B.G.H.); tel.: +33 1 69824594; fax: +33 1 69077247 (R.H.D.).
E-mail addresses: bg.hazra@ncl.res.in (B.G. Hazra), robert.dodd@icsn.cnrs-gif.fr (R.H. Dodd).
† These authors contributed equally in this work.

0040-4039/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2010.05.066

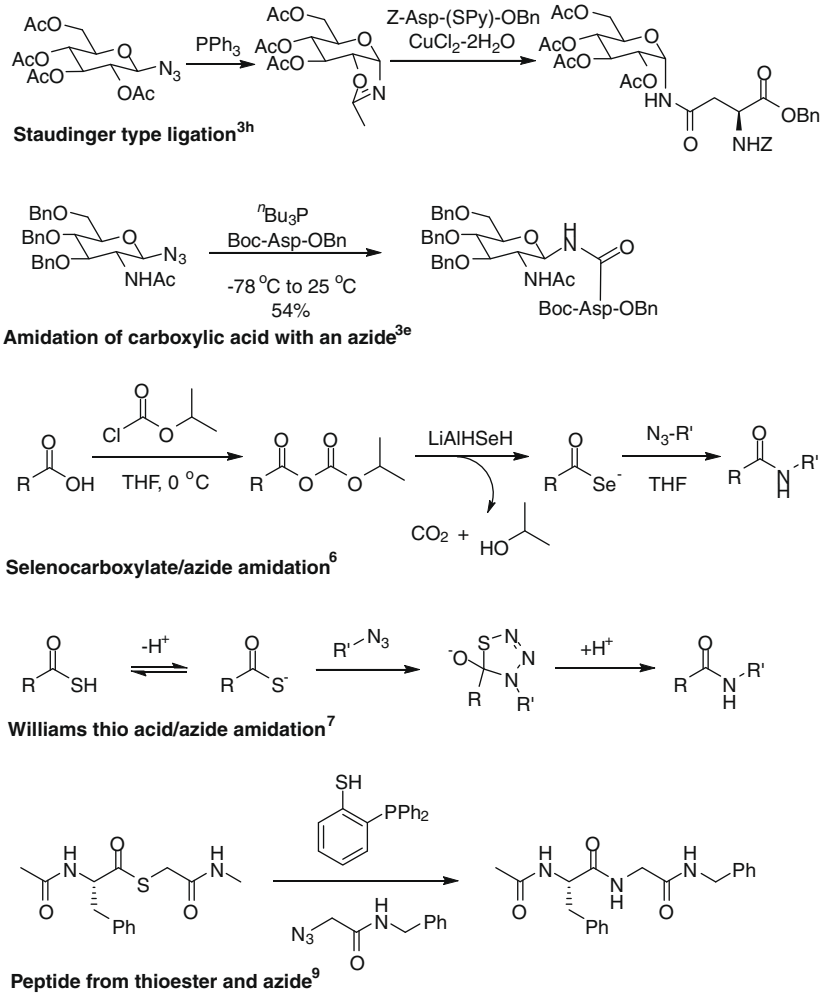
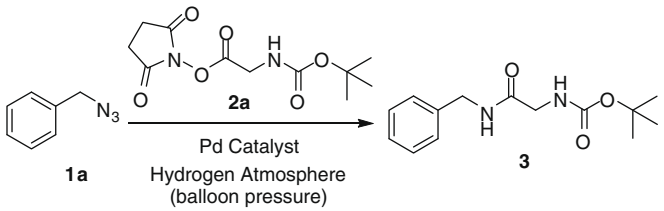


Figure 1. Literature reports on the conversion of azides to carboxamides.

protocol for the preparation of carboxamides directly from azides. With this procedure, carboxamides were obtained efficiently in high yields from azides on reaction with the corresponding pre-formed activated carboxylic acids in a single-step reductive transformation using hydrogen atmosphere (balloon) under $Pd/BaSO_4$ or $Pd/CaCO_3$ catalysis (Scheme 1).

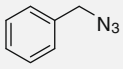
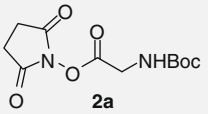
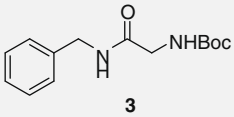
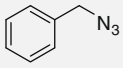
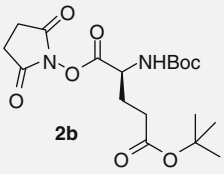
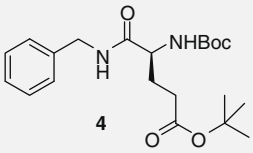
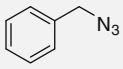
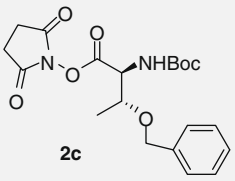
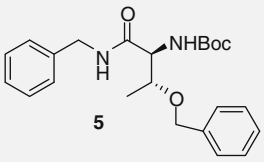
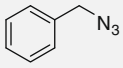
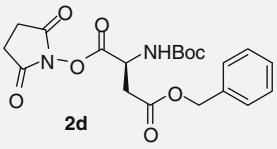
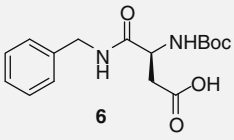
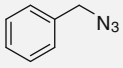
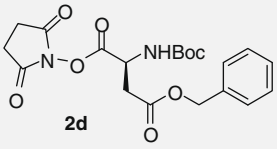
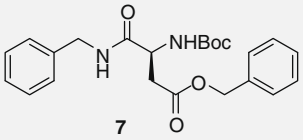
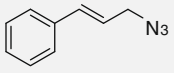
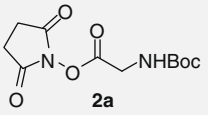
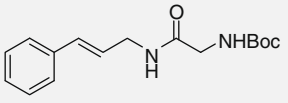
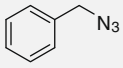
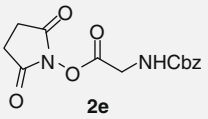
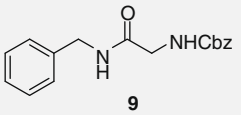
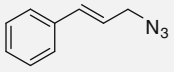
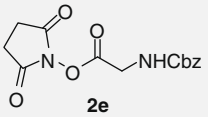
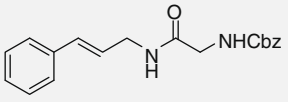
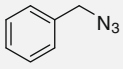
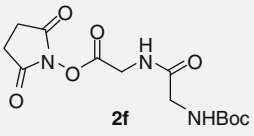
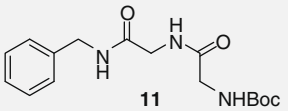
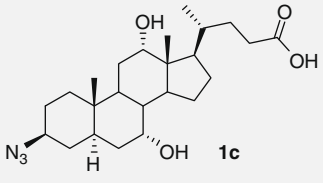
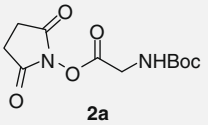
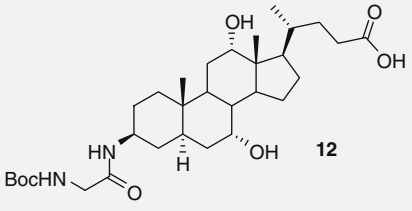
The first successful result for the amidation of benzyl azide **1a** with Boc-Gly-OSu **2a** was obtained using $Pd/BaSO_4$ in THF to furnish Boc-protected 2-amino-benzylacetamide **3** in 86% yield. Continuous 18 h of H_2 (balloon) atmosphere was required for the complete consumption of the starting materials at 25 °C (Table 1, entry 1), whereas at 0 °C no reaction was observed even after 20 h. Under these reaction conditions, compound **4** was obtained in good yield when benzyl azide **1a** was treated with Boc-Glu(O*t*-Bu)-OSu **2b** (entry 2). Similarly, compound **5** was obtained in 82% yield when benzyl azide **1a** was treated with Boc-Thr(Bzl)-OSu **2c** (entry 3). This was our first evidence for chemoselective reductive transformation of azides to carboxamides in the presence of a benzyl ether functionality. Unfortunately, we could not achieve the required chemoselectivity for the reduction of azides in the presence of benzyl esters (entry 4), as the benzyl ester functionality in compound Boc-Asp(OBzl)-OSu **2d** was hydrogenolyzed under the present reaction conditions to give **6** in 79% yield and the desired product **7** was not realized. The longer reaction time may be one of the reasons for the observed hydrogenolysis of the benzyl ester functionality. To reduce the reaction time we used polar-protic solvents such as ethanol instead of THF. The succinimide esters (–COOSu) are known to undergo cross esterification in alcohol solvents; therefore the stability of *N*-hydroxy succinimide (NHS) ester functionality of compound **2a** in EtOH at room temperature was verified. Under the present reaction conditions (EtOH solvent and Pd catalyst at room temperature) the activated ester was found to be stable for 12 h. Ethanolysis of compound **2a** was observed at elevated temperatures as well as when the reaction time was more than 12 h. This suggests that EtOH can be utilized for the reaction at room temperature provided the reaction is complete within 10–12 h.



Scheme 1. Typical example for the conversion of azide to carboxamide.

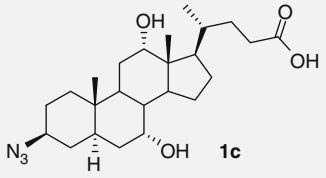
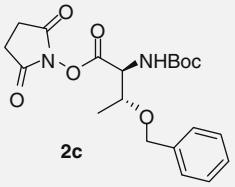
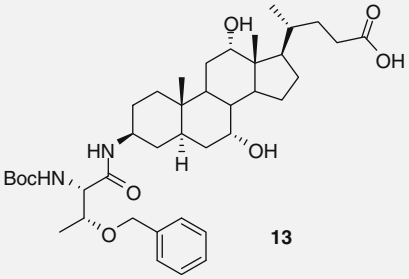
The first trial experiment for the amidation of benzyl azide **1a** with Boc-Gly-OSu **2a** in EtOH at 25 °C using H_2 balloon and $Pd/BaSO_4$ catalysis produced the desired amide **3** within 30 min (entry 1).[17] In a similar fashion, the reaction time for the synthesis of

Table 1
Single-step reductive transformation of azides to carboxamides using pre-formed activated carboxylic acids

Entry	Azide	NHS ester	Product	Catalyst[a]	Yield
1	 **1a**	 **2a**	 **3**	A B	89/86[b] 91
2	 **1a**	 **2b**	 **4**	A B	85/83[b] 87
3	 **1a**	 **2c**	 **5**	A B	82/82[b] 81
4	 **1a**	 **2d**	 **6**	A	86/79[b]
5	 **1a**	 **2d**	 **7**	B	81
6	 **1b**	 **2a**	 **8**	A B	85 84
7	 **1a**	 **2e**	 **9**	A B	88 87
8	 **1b**	 **2e**	 **10**	A B	77 80
9	 **1a**	 **2f**	 **11**	A B	87 83
10	 **1c**	 **2a**	 **12**	A B	79 76

(*continued on next page*)

Table 1 (*continued*)

Entry	Azide	NHS ester	Product	Catalyst[a]	Yield
11	 **1c**	 **2c**	 **13**	A B	73 70

[a] A—Palladium, 5 wt % on barium sulfate; B—Palladium, 5 wt % on calcium carbonate (purchased from Aldrich and used as received).
[b] Yields for the reactions carried out in THF (reaction time: 18 h), all other yields are for the reactions carried out in EtOH (reaction time: 30 min).

carboxamides **4** and **5** in ethanol was drastically reduced to 30 min, compared to the 18 h required for the reaction to be complete in THF. Even using this modified protocol, we could not realize the synthesis of the desired carboxamide **7**, compound **6** being formed instead from **2d** in 86% yield (entry 4). After surveying several catalytic systems for this transformation the best result was achieved using Lindlar catalyst[18] ($Pd/CaCO_3$) in EtOH.[17]

In a typical experimental procedure, benzyl azide **1a** treated with Boc-Asp(OBzl)-OSu **2d** in EtOH at 25 °C using H_2 balloon and $Pd/CaCO_3$ catalysis produced the desired amide **7** in 81% yield within 30 min (entry 5). The successful result obtained with substrate **2d** encouraged us to investigate the scope of the procedure. Thus, the simplicity, remarkable chemoselectivity, and mildness of this catalytic transformation were exhaustively studied with compounds bearing different sensitive functional groups such as benzyl ethers (entries 3 and 11), olefins (entries 6 and 8), and benzyl carbamates (entries 7 and 8) all of which survived the hydrogenolytic conditions to give the corresponding carboxamides. In particular, synthesis of compound **10** (entry 8) was realized when the azide-bearing olefin **1b** and the NHS ester **2e** bearing an *N*-Cbz protecting group were exposed to the present modified protocol. As expected, the azide was smoothly converted into the corresponding carboxamide **10** in excellent yield (80%) without affecting the carbon–carbon double bond and *N*-Cbz protecting group. In the context of our current research,[10] the generality of this protocol was demonstrated by the high yielding synthesis of peptide **11** (entry 9) and steroidal carboxamides **12** as well as **13** (entries 10 and 11, respectively). This also suggested that the method is tolerant to the presence of free carboxylic acids.

In the present Letter, we have demonstrated a new, robust, and efficient 'one-pot' chemoselective protocol for the preparation of carboxamides. Using this protocol, carboxamides were obtained in high yields from azides on reaction with the corresponding pre-formed activated carboxylic acids in a single-step reductive transformation using hydrogen atmosphere (balloon pressure) under $Pd/BaSO_4$ or $Pd/CaCO_3$ catalysis. The simplicity and remarkable chemoselectivity of this catalytic transformation were studied with compounds bearing different sensitive functional groups such as benzyl ethers, olefins, benzyl carbamates, and benzyl esters which remained untouched.

Acknowledgments

S.N.B. thanks the University Grant Commission (UGC, New Delhi) for the Senior Research Fellowship. D.B.S. thanks Embassy of France in India, New Delhi, for a Sandwich Thesis Scholarship. Emeritus Scientist Scheme awarded to B.G.H. by the CSIR, New Delhi, is gratefully acknowledged.

Supplementary data

Supplementary data (general experimental methods, analytical data for compounds **4**–**13**, selected ^1H, ^{13}C NMR and DEPT spectra) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.05.066.

References and notes

1. (a) Scriven, E. F. V.; Turnbull, K. *Chem. Rev.* **1988**, *88*, 298–368; (b) Amantini, D.; Fringuelli, F.; Pizzo, F.; Vaccaro, L. *Org. Prep. Proc. Int.* **2002**, *34*, 111–147.
2. Montalbetti, C. A. G. N.; Falque, V. *Tetrahedron* **2005**, *61*, 10827–10852.
3. (a) Garcia, J.; Urpf, F.; Vilarrasa, J. *Tetrahedron Lett.* **1984**, *25*, 4841–4844; (b) Inazu, T.; Kobayashi, K. *Synlett* **1993**, 869–870; (c) Bosch, I.; Urpi, F.; Vilarrasa, J. *J. Chem. Soc., Chem. Commun.* **1995**, 91–92; (d) Maunier, V.; Boullanger, P.; Lafont, D. *J. Carbohydr. Chem.* **1997**, *16*, 231–235; (e) Mizuno, M.; Haneda, K.; Iguchi, R.; Muramoto, I.; Kawakami, T.; Aimoto, S.; Yamamoto, K.; Inazu, T. *J. Am. Chem. Soc.* **1999**, *121*, 284–290; (f) Saxon, E.; Armstrong, J. I.; Bertozzi, C. R. *Org. Lett.* **2000**, *2*, 2141–2143; (g) Boullanger, P.; Maunier, V.; Lafont, D. *Carbohydr. Res.* **2000**, *324*, 97–106; (h) Damkaci, F.; DeShong, P. *J. Am. Chem. Soc.* **2003**, *125*, 4408–4409; (i) Bures, J.; Martin, M.; Urpi, F.; Vilarrasa, J. *J. Org. Chem.* **2009**, *74*, 2203–2206.
4. Ghosh, S. K.; Verma, R.; Ghosh, U.; Mamdapur, V. R. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 1705–1711.
5. Knapp, S.; Darout, E. *Org. Lett.* **2005**, *7*, 203–206.
6. Wu, X.; Hu, L. *J. Org. Chem.* **2007**, *72*, 765–774.
7. Kolawski, R. V.; Shangguan, N.; Sauers, R. R.; Williams, L. J. *J. Am. Chem. Soc.* **2006**, *128*, 5695–5702.
8. Barlett, K. N.; Kolakowski, R. V.; Katukojvala, S.; Williams, L. J. *Org. Lett.* **2006**, *8*, 823–826.
9. Nilsson, B. L.; Kiessling, L. L.; Raines, R. T. *Org. Lett.* **2000**, *2*, 1939–1941.
10. Bavikar, S. N.; Salunke, D. B.; Hazra, B. G.; Pore, V. S.; Dodd, R. H.; Thierry, J.; Shirazi, F.; Deshpande, M. V.; Srinath, K.; Chattopadhyay, S. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 5512–5517.
11. (a) Sugimoto, T.; Wada, Y.; Yamamura, S.; Ueda, M. *Tetrahedron* **2001**, *57*, 9817–9825; (b) Ballard, T. E.; Richards, J. J.; Aquino, A.; Reed, C. S.; Melander, C. *J. Org. Chem.* **2009**, *74*, 1755–1758.
12. Saito, S.; Nakajima, M.; Inaba, M.; Moriwake, T. *Tetrahedron Lett.* **1989**, *30*, 837–838.
13. Reddy, P. G.; Pratap, T. V.; Kumar, G. D. K.; Mohanty, S. K.; Baskaran, S. *Eur. J. Org. Chem.* **2002**, 3740–3743.
14. Kotsuki, H.; Ohishi, T.; Araki, T. *Tetrahedron Lett.* **1997**, *38*, 2129–2132.
15. Chandrasekhar, S.; Chandraiah, L.; Reddy, C. R.; Reddy, M. V. *Chem. Lett.* **2000**, 780–781.
16. Chandrasekhar, S.; Babu, B. N.; Reddy, C. R. *Tetrahedron Lett.* **2003**, *44*, 2057–2059.
17. *Typical experimental procedure*: Compound **3**: Palladium (5 wt % on barium sulfate or 5 wt % on calcium carbonate, poisoned with lead: 30 mg, 15% by wt) was added to a stirred solution of Boc-Gly-OSu **2a** (200 mg, 0.73 mmol) and benzyl azide **1a** (108 μL, 0.87 mmol) in EtOH (5 mL). The reaction flask was evacuated and flushed with hydrogen gas. The resulting mixture was stirred (stirring rate of ~500 RPM, to maintain the uniformity of the suspension) under a hydrogen atmosphere (balloon) at 25 °C for 30 min. After completion of the reaction, the catalyst was filtered through a pad of Celite, the filter cake was washed with EtOH (20 mL), and the filtrate was concentrated under reduced pressure. This crude product was dissolved in EtOAc (100 mL) washed with 10% citric acid (2 × 10 mL), 20% $NaHCO_3$ (2 × 10 mL), cold water (2 × 10 mL), brine (10 mL), and was dried over Na_2SO_4. The residue was purified by chromatography on silica gel (100–200 mesh) using 2% MeOH/CH_2Cl_2 to afford compound **3** as a white solid (176 mg, 91% yield); mp 65–66 °C (lit.[19] mp 64–68 °C); Anal. Calcd for $C_{14}H_{20}N_2O_3$: C, 63.62; H, 7.63; N, 10.60.

Found: C, 63.84; H, 7.51; N, 10.97; IR ν_{max} (Nujol) 3308, 1703, 1658, 1530 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.41 (s, 9H), 3.82 (d, 2H, J = 6 Hz), 4.45 (d, 2H, J = 6 Hz), 5.30 (br s, 1H), 6.67 (br s, 1H), 7.24–7.37 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 28.1 (3C), 43.1, 44.2, 80.0, 127.3, 127.5 (2C), 128.5 (2C), 137.9, 156.1, 169.5; MS (LCMS) m/z 265.23 $[M+H]^+$, 287.21 $[M+Na]^+$.

18. Selective hydrogenation of azides in presence of double bond and carbonyl group was earlier demonstrated using Lindlar catalyst. Corey, E. J.; Nicolaou, K. C.; Balanson, R. D.; Machida, Y. *Synthesis* **1975**, 590–591.
19. Jeganathan, A.; Richardson, S. K.; Mani, R. S.; Haley, B. E.; Watt, D. S. *J. Org. Chem.* **1986**, *51*, 5362–5367.