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Alkoxyacetyl (AAc) group as a useful linker for organic synthesis on poly(ethylene glycol) support

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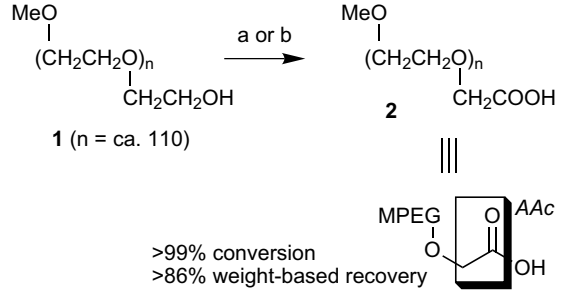
Abstract—An alkoxyacetyl group (AAc) group was found to be an efficient linker for high-throughput synthesis of small molecules on a soluble polymer support. The linker allows high-yield loading of alcohols and phenols either by conventional carbodiimide-mediated esterification or transesterification using $Yb(OTf)_3$. Chemoselective cleavage to release small molecules is attained also by $Yb(OTf)_3$ or $TMSCHN_2$. The preparation, protocols for loading and releasing of small molecules, and an application to the Ugi four-component coupling reaction are reported.

Poly(ethylene glycol) (PEG) was reported in 1972 by Bayer and Mutter as a support for peptide synthesis.[1] Much later on in the 1990s, the usefulness of the support was reinvestigated and found to really raise the efficiency for the preparation of small molecules.[2,3] The significant merit is brought by the unique physical properties of PEG; it is generally soluble to typical solvents such as $CHCl_3$, CH_2Cl_2, MeOH, water, and so on, whereas it is insoluble to ethers such as diethyl ether and *tert*-butyl methyl ether to form precipitates. Since then, the support has often been used especially in the field of carbohydrate chemistry.[4–8] On the other hand, this technology has been paid attention from the viewpoint of high-throughput synthesis of small molecules.[9] To attach small molecules on the PEG support, several linkers have been reported so far; succinate ester,[7] *p*-alkoxybenzyl ether,[5] arylsulfonamide,[3] dioxyxylyl diether (DOX),[4] alkyl silyl ether,[6] and formyl acetal linker.[8] As a part of our ongoing program directed toward chemical genetics studies,[10] we have found an alkoxyacetyl (AAc) linker is simple but useful to synthesize small molecules on the PEG support. In this letter, we report our preliminary results on the use of the AAc linker to load and release small molecules as well as to perform chemical reactions on the PEG support.

We used poly(ethylene glycol) monomethyl ether (MPEG-OH, **1**, average MW = 5000, 0.200 mmol/g)[11,12] as the starting material. The preparation of poly(ethylene glycol) monomethyl ether carboxylic acid (MPEG-O-AAc-OH, **2**)[13] was first attempted by alkylation of **1** with bromoacetic acid in the presence of Na metal or NaH in THF.[14] These reactions, however, did not give **2** cleanly, and only a messy reaction mixture was obtained. We then tried oxidation of **1** via two pathways as shown in Scheme 1. One is a direct oxidation to the carboxylic acid by Jones oxidation (CrO_3, H_2SO_4, acetone, rt)[15] and the other is a stepwise oxidation via an aldehyde (2,2,6,6-tetramethyl-1,1-piperidinyloxy (TEMPO) and (bis(acetoxy)iodo)benzene (BAIB)[16] followed by $NaClO_2$).[17] After extraction followed by precipitative purification using diethyl ether, both approaches were



Scheme 1. Reagents and conditions: (a) Jones oxidation, 0 °C → rt, 1.5 h. (b) TEMPO, BAIB, CH_3CN–H_2O, rt, 2 h; then $NaClO_2$, *t*BuOH–H_2O, rt, 4 h.

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found to give **2** successfully in quantitative conversion (0.199 mmol/g)[12,18] with more than 86% recovery.[19]

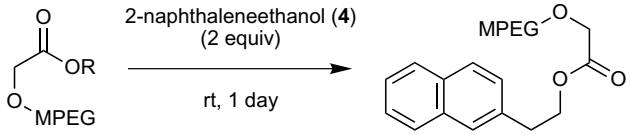
Condensation of chemically pure MPEG-O-AAc-OH **2** with 2-naphthaleneethanol (**4**) was next attempted under several conditions (Table 1). All reactions were carried out at rt for 1 day using 30 mg (ca. 12 μmol) of **2** and 2 mg (ca. 24 μmol, 2 equiv) of **4** except for run 6 where a methyl ester **3** was used. At first, carbodiimide-mediated acylation was attempted. When DCC was used in combination with DMAP, acylation was found to proceed only in 27% conversion yield as judged from the ^{1}H NMR spectrum after purification by gel-permeation column chromatography (GPC) on Sephadex G-25 (run 1). The conversion yield was improved to 70% by the use of water-soluble carbodiimide in place of DCC (run 2). Addition of HOBt was strongly effective for quantitative conversion to give **5** (run 3).[20] For polymer **2**, Vedejs' procedure using Bu_3P[21] or the Mitsunobu reaction (DEAD and Ph_3P)[22] gave **5** in moderate yields (runs 4 and 5). Ytterbium(III) trifluoromethanesulfonate ($Yb(OTf)_3$) is known to catalyze transesterification of methoxyacetates.[23,24] When methyl ester **3**, prepared from **2** and $TMSCHN_2$ in quantitative conversion, was treated with 5 equiv of 2-naphthaleneethanol (**4**) in the presence of 0.3 equiv of $Yb(OTf)_3$ and MS4A, the reaction certainly proceeded to provide **5** in 86% conversion yield (run 6). Because the applicability of this reaction was found to be limited to simple, primary alcohols from our independent studies, the protocol shown in run 3 was used for further studies.

With optimized acylation conditions in hand, loading of a variety of alcohols was next examined. At first, primary alcohols including hydroxyaldehyde (**6** and **7**) and glucose derivatives (**8**–**10**) were acylated with **2** (Fig. 1), and the reactions were found to proceed in high conversion yields (>91%) in 1 day. For secondary alcohols, the reaction gave the products generally in moderate yields (64–77% for **11**–**14**) except for sterically crowded (35% for **15**) and less crowded ones (>99% for **16**). Acylation of tertiary alcohols is sluggish, because 1-adamantanol was not acylated at all under these reaction conditions and **2** was completely recovered (data not shown). With this procedure, phenol is also acylated quantitatively unless electron-withdrawing groups are present at the *o*- or *p*-position (**17**–**20**).

Mild conditions other than strongly acidic or basic ones to cleave the AAc functionality for releasing small molecules on this platform were next explored using **5** of 0.193 mmol/g (Table 2).[12] At the outset, it was found that $Yb(OTf)_3$ worked as a catalyst also for this purpose well (run 1). Thus, 0.3 equiv of this catalyst in anhydrous MeOH at rt cleanly cleaved the AAc linker after 2 h. The reaction mixture was directly subjected to GPC to give MPEG-O-AAc-OMe **3** and 2-naphthaleneethanol (**4**) in 97% and 95% yield, respectively. Transesterification was also effected by the use of $TMSCHN_2$ in hexane–MeOH (run 2). With a large excess amount (20 equiv) of this reagent, both components **3** and **4** were isolated in high yields (>99% for **3** and 97% for **4**) after concentration followed by GPC. This reaction is apparently induced by a nucleophilic attack of MeOH to the ester carboxyl group as judged from the following experimental results; when deuterated methanol (CD_3OD) was used for a solvent, MPEG-O-AAc-OCD_3 was produced cleanly. For high-throughput parallel cleavage of small molecules aiming for library construction, the latter procedure would be advantageous over the former because the reagents are volatile; the procedure allows isolating the small molecules by removing **3** through simple precipitation using diethyl ether.

As described above, the procedures for loading and releasing small molecules via the AAc linker were established well. Our concern next moved to chemical reactions on this platform. This was demonstrated by applying Ugi 4-components coupling (4CC) reaction[25] to **21** of 0.194 mmol/g.[12] Two sets of reactions were carried out with large excess (20 equiv) of amine, isocyanide, and carboxylic acid in MeOH at rt (Scheme 2). After 1 day, the MPEG-bound Ugi products **22** and **24** were isolated by GPC and/or precipitation from diethyl

Table 1. Esterification of naphthaleneethanol **4** under various conditions



2 (R = H)
3 (R = Me)

Run	Polymer	Conditions (equiv)	Conversion yield[a,b] (%)
1	**2**	DCC (1.5), DMAP (0.1), CH_2Cl_2	27
2	**2**	EDC·HCl (1.5), DMAP (0.1), CH_2Cl_2	70
3	**2**	DIC (5), HOB*t* (0.15), DMAP (0.17), pyridine (5), DMF, CH_2Cl_2	>99
4	**2**	DIC (1.5), Bu_3P (0.1), CH_2Cl_2	50
5	**2**	DEAD (5), Ph_3P (5), benzene	65
6[c]	**3**	$Yb(OTf)_3$ (0.3), MS4A, CH_2Cl_2	86

[a] Yields were determined by ^{1}H NMR.
[b] Weight-based recovery was >95% in all runs.
[c] The reaction was carried out with 5 equiv of **4** for 4.5 h.

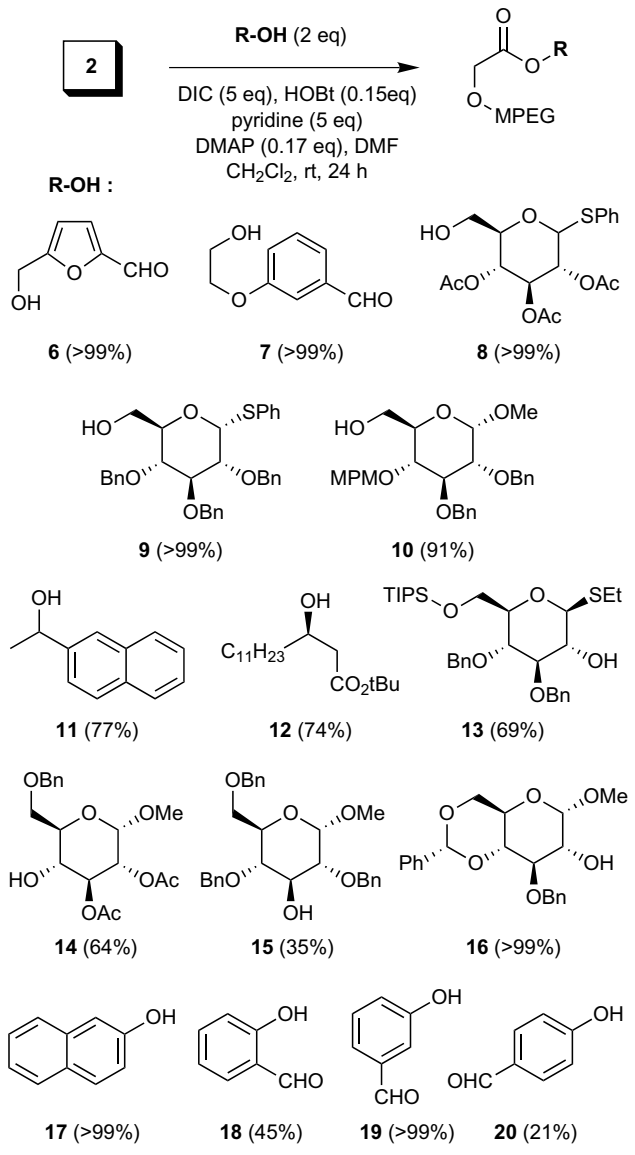
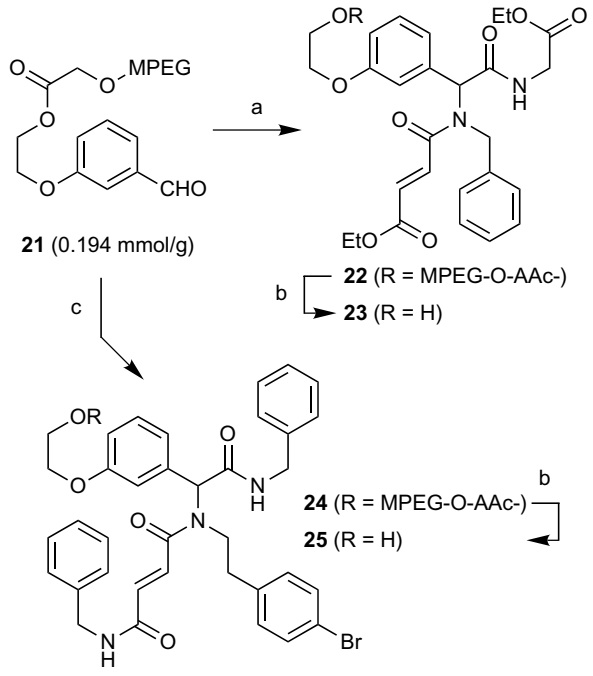


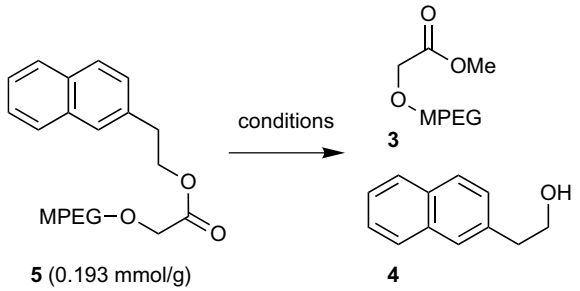
Figure 1. Structure and the loading yield for alcohols and phenols under conditions using DIC-HOBt-DMAP-pyridine in DMF and CH_2Cl_2.

ether. Weight-based recovery for **22** and **24** was 93% and 96% yields, respectively, most of the weight loss for which can be attributed to the precipitation operation. The conversion yields were satisfactorily 91% for **22** and 85% for **24**, as judged from the ^1H NMR spectra. In both cases, the ^1H NMR spectra of MPEG-bound Ugi 4CC products (**22** and **24**) showed no significant amount of contaminated small molecule reagents such as the amine, carboxylic acid, and isocyanide; only the presence of an unreacted aldehyde functionality and the Ugi 4CC product was recognized.



Scheme 2. Reagents and conditions: (a) benzylamine (20 equiv), ethyl isocyanoacetate (20 equiv), monoethyl fumarate (20 equiv), MeOH, rt, 1 day, 91% conversion yield. (b) $Yb(OTf)_3$ (0.3 equiv), MeOH, rt, 4 h, 96% (for **23**) and 97% (for **25**) yield. (c) 4-bromophenethylamine (20 equiv), benzyl isocyanide (20 equiv), fumaric acid monobenzyl amide (20 equiv), MeOH, rt, 1 day, 85% conversion yield.

Table 2. Cleavage of ester function of **5** (0.193 mmol/g) to release small molecule **4**



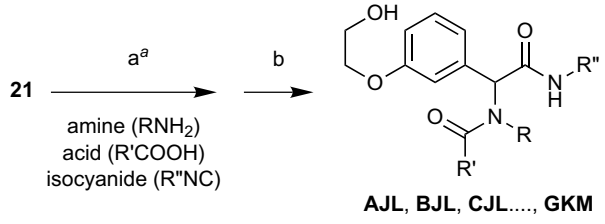
Run	Conditions (equiv)	Yield for **3**[a] (%)	Yield for **4** (%)
1	$Yb(OTf)_3$ (0.3), MeOH, rt, 2 h	97	95
2	$TMSCHN_2$ (20), hexane, MeOH, 0 °C → rt, 6 h	>99	97

[a] Isolated yield.

Cleavage of the AAc linker to release the Ugi 4CC products was attempted next. This was effected by applying $Yb(OTf)_3$ in MeOH at rt for 4 h. After purification either by GPC or silica-gel flash column chromatography, **23** and **25** were provided in 76% and 73% yields, respectively, for two steps from **21**. Calculated from these experiments, cleavage yield was evaluated to be 96% (**23**) and 97% (**25**) satisfactorily. Although it was unfortunately found that the conditions using volatile $TMSCHN_2$ in MeOH were not effective in this case as it caused decomposition of the product, no significant decomposition was detected at all in the present cleavage under the conditions using $Yb(OTf)_3$ in MeOH. It should also be noted that the cleavage reagent, $Yb(OTf)_3$, catalyzes the transesterification of the ethyl ester functionalities of **22** as well. The side reaction was, however, suppressed to be <10% under short reaction time (4 h) and thus *we achieved the selective cleavage of the AAc functionality*. Based on these protocols, we have successfully prepared 26 Ugi 4CC products of 28–92% purity on this platform (Scheme 3).

Though the Ugi 4CC reaction is a convenient and powerful diversity-generating reaction, it is often difficult to cleanly isolate the desired product by chromatographic separation especially when excess reagents are used to raise the conversion yield. An efficient purification is, however, readily realized in the present study by using the soluble MPEG polymer associated with the AAc linker as shown above and hence this is the apparent merit of this platform. In addition, release of the small molecules from the platform is effected rapidly under mild conditions using $Yb(OTf)_3$ catalyst without significantly losing the purity. By using this platform, a larger size of the compound library for the Ugi 4CC reaction is under construction in our laboratory.

In summary, we have shown in this paper an alkoxyacetyl (AAc) group is a useful linker for the MPEG support, which can load and release small molecules under mild conditions efficiently. Preparing Ugi 4CC products on this platform further showed the usefulness. From these results we believe the platform would be applicable not only to construction of small molecule libraries but also to rapid synthesis of hit compounds found from biological screening in chemical genetics studies.



	L		M	
A[b]	**AJL** 86%	**AKL** 83%	**AJM** 72%	**AKM**(23) 90%
B	**BJL** 68%	**BKL** 75%	**BJM** 74%	**BKM** 84%
C	**CJL** 70%	**CKL** 78%	**CJM** 57%	**CKM** 74%
D	**DJL** (25) 85%	**DKL** 85%	**DJM** 75%	**DKM** 83%
E	**EJL** 38%	**EKL** 69%	**EJM** 25%	**EKM** 53%
F	**FJL** <10%	**FKL** 52%	**FJM** 32%	**FKM**[c] 55%
G	**GJL** 85%	**GKL** 46%	**GJM** <10%	**GKM** 55%
	J	K	J	K

Scheme 3. Reagents and conditions: (a) MeOH, rt, 1 day, then GPC. (b) $Yb(OTf)_3$ (0.3 equiv), MeOH, rt, 4 h, then GPC. Abbreviations are as follows. A = benzylamine, B = 4-chlorobenzylamine, C = 4-methoxybenzylamine, D = 4-bromophenethylamine, E = octylamine, F = 2-aminoethanol, G = 3-aminopropanol, J = fumaric acid monobenzyl amide, K = monoethyl fumarate, L = benzyl isocyanide, M = ethyl isocyanoacetate. Obtained as a dimethyl ester.

Acknowledgements

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References and notes

1. Bayer, E.; Mutter, M. *Nature* **1972**, *237*, 512–513.
2. Whitfield, D. M.; Douglas, S. P.; Krepinsky, J. J. *Tetrahedron Lett.* **1992**, *33*, 6795–6798; Douglas, S. P.; Whitfield, D. M.; Krepinsky, J. J. *J. Am. Chem. Soc.* **1991**, *113*, 5095–5097.
3. Han, H. S.; Wolfe, M. M.; Brenner, S.; Janda, K. D. *Proc. Natl. Acad. Sci. U.S.A.* **1995**, *92*, 6419–6423.
4. Douglas, S. P.; Whitfield, D. M.; Krepinsky, J. J. *J. Am. Chem. Soc.* **1995**, *117*, 2116–2117; Mehta, S.; Whitfield, D. *Tetrahedron Lett.* **1998**, *39*, 5907–5910; Yan, F. Y.; Wakarchuk, W. W.; Gilbert, M.; Richards, J. C.; Whitfield, D. M. *Carbohydr. Res.* **2000**, *328*, 3–16; Schmidt, D.; Thiem *J. Chem. Commun.* **2000**, 1919–1920.
5. Ito, Y.; Kanie, O.; Ogawa, T. *Angew. Chem., Int. Ed.* **1996**, *35*, 2510–2512; Ito, Y.; Ogawa, T. *J. Am. Chem. Soc.* **1997**, *119*, 5562–5566; Manabe, S.; Ito, Y.; Ogawa, T. *Synlett* **1998**, 628–630; Zhu, T.; Boons, G. J. *Tetrahedron: Asymmetry* **2000**, *11*, 199–205.
6. Jesberger, M.; Jaunzems, J.; Jung, A.; Jas, G.; Schonberger, A.; Kirschning, A. *Synlett* **2000**, 1289–1293.
7. Ross, A. J.; Ivanova, I. A.; Higson, A. P.; Nikolaev, A. V. *Tetrahedron Lett.* **2000**, *41*, 2449–2452.
8. Oikawa, M.; Tanaka, T.; Kusumoto, S.; Sasaki, M. *Tetrahedron Lett.* **2004**, *45*, 787–790.
9. Gravert, D. J.; Janda, K. D. *Chem. Rev.* **1997**, *97*, 489–509; Wentworth, P.; Janda, K. D. *Chem. Commun.* **1999**, 1917–1924.
10. Oikawa, M.; Kiuchi, M.; Vance, J. M.; Schreiber, S. L.; Tallarico, J. A. *44th Tennen Yuki Kagobutsu Toronkai Koen Yoshishu*, **2002**, 599–604.

11. Purchased from Aldrich Co. (catalog No. 20251-7).
12. Density of functional groups of this platform was calculated from the theoretical average molecular weight, 5000 (1), 5014 (2), 5028 (3), 5168 (5), and 5162 (21).
13. Compound **2** can be commercially available from Nektar Therapeutics as its derivatives such as a *N*-hydroxysuccinimide ester for PEGylation of proteins. The AAc linker has, however, never been directly used as a linker for the PEG support probably because mild cleavage protocol had not been available, see Ref. 19.
14. Nakatsuji, Y.; Kawamura, N.; Okahara, M. *Synthesis* **1981**, 42–44; Hypolite, C. L.; McLernon, T. L.; Adams, D. N.; Chapman, K. E.; Herbert, C. B.; Huang, C. C.; Distefano, M. D.; Hu, W. S. *Bioconjugate Chem.* **1997**, *8*, 658–663.
15. Lele, B. S.; Kulkarni, M. G. *J. Appl. Polym. Sci.* **1998**, *70*, 883–890.
16. DeMico, A.; Margarita, R.; Parlanti, L.; Vescovi, A.; Piancatelli, G. *J. Org. Chem.* **1997**, *62*, 6974–6977; Epp, J. B.; Widlanski, T. S. *J. Org. Chem.* **1999**, *64*, 293–295.
17. Kraus, G. A.; Taschner, M. J. *J. Org. Chem.* **1980**, *45*, 1175–1176; Dalcanale, E.; Montanari, F. *J. Org. Chem.* **1986**, *51*, 567–569.
18. In this research, conversion yields were determined by ^{1}H NMR using methoxy group of MPEG and methylene group of AAc linker as standards. Recovery yields are based on its weight.
19. Zier, A.; Ryan, D.; Mutter, M. *Tetrahedron Lett.* **1994**, *35*, 1039–1042; Bremen, U.; Gais, H. J. *Tetrahedron: Asymmetry* **1996**, *7*, 3063–3066; Jung, K. W.; Zhao, X. Y.; Janda, K. D. *Tetrahedron Lett.* **1996**, *37*, 6491–6494; Jung, K. W.; Zhao, X. Y.; Janda, K. D. *Tetrahedron* **1997**, *53*, 6645–6652; Greenwald, R. B.; Choe, Y. H.; Wu, D. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 577–580.
20. Routledge, A.; Abell, C.; Balasubramanian, S. *Synlett* **1997**, 61–62.
21. Vedejs, E.; Bennett, N. S.; Conn, L. M.; Diver, S. T.; Gingras, M.; Lin, S.; Oliver, P. A.; Peterson, M. J. *J. Org. Chem.* **1993**, *58*, 7286–7288.
22. Mitsunobu, O. *Synthesis* **1981**, 1–28.
23. Hanamoto, T.; Sugimoto, Y.; Yokoyama, Y.; Inanaga, J. *J. Org. Chem.* **1996**, *61*, 4491–4492.
24. For another example of cleavage of esters using Lewis acid catalyst, see: Kajiro, H.; Mitamura, S.; Mori, A.; Hiyama, T. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 1553–1560.
25. Domling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3169–3210.