

This Provisional PDF corresponds to the article as it appeared upon acceptance and copyediting. Fully formatted PDF and full text (HTML) versions will be made available soon.

## Continuous flow based catch and release protocol for the synthesis of $\alpha$ -ketoesters

*Beilstein Journal of Organic Chemistry* 2009, **5**:23 doi:10.3762/bjoc.5.23

Alessandro Palmieri; Steven V. Ley - svl1000@cam.ac.uk; Anastasios Polyzos - tash.polyzos@csiro.au; Mark Ladlow; Ian R. Baxendale

**ISSN** 1860-5397

**Article type** Full Research Paper

**Submission date** 05 March 2009

**Acceptance date** 14 May 2009

**Publication date** 20 May 2009

**Guest Editor** A. Kirschning

**Article URL** <http://www.beilstein-journals.org/bjoc/content/5/1/23>

This peer-reviewed article was published immediately upon acceptance and copyediting. It can be downloaded, printed and distributed freely for any purposes (see copyright notice below).

Articles in *Beilstein Journal of Organic Chemistry* are listed in PubMed and archived at PubMed Central.

For information about publishing your research in *Beilstein Journal of Organic Chemistry* go to

<http://www.beilstein-journals.org/bjoc/submission/submissionOverview.htm>

# Continuous flow based catch and release protocol for the synthesis of $\alpha$ -ketoesters

Alessandro Palmieri<sup>1</sup>, Steven V. Ley<sup>\*1</sup>, Anastasios Polyzos<sup>1,2</sup>, Mark Ladlow<sup>3</sup> and  
Ian R. Baxendale<sup>1</sup>

Address: <sup>1</sup>Innovative Technology Centre (ACS), Department of Chemistry, University  
of Cambridge, Lensfield Road, Cambridge, CB2 1EW, United Kingdom; <sup>2</sup>CSIRO  
Molecular and Health Technologies, Bayview Avenue, Clayton South, Melbourne,  
Australia, 3169 and <sup>3</sup>Uniqsis, Shepreth, Cambridgeshire, SG8 6GB, United Kingdom

Email: Steven V. Ley - svl1000@cam.ac.uk

\* Corresponding author

## Abstract

Using a combination of commercially available mesofluidic flow equipment and tubes packed with immobilised reagents and scavengers, a new synthesis of  $\alpha$ -ketoesters is reported.

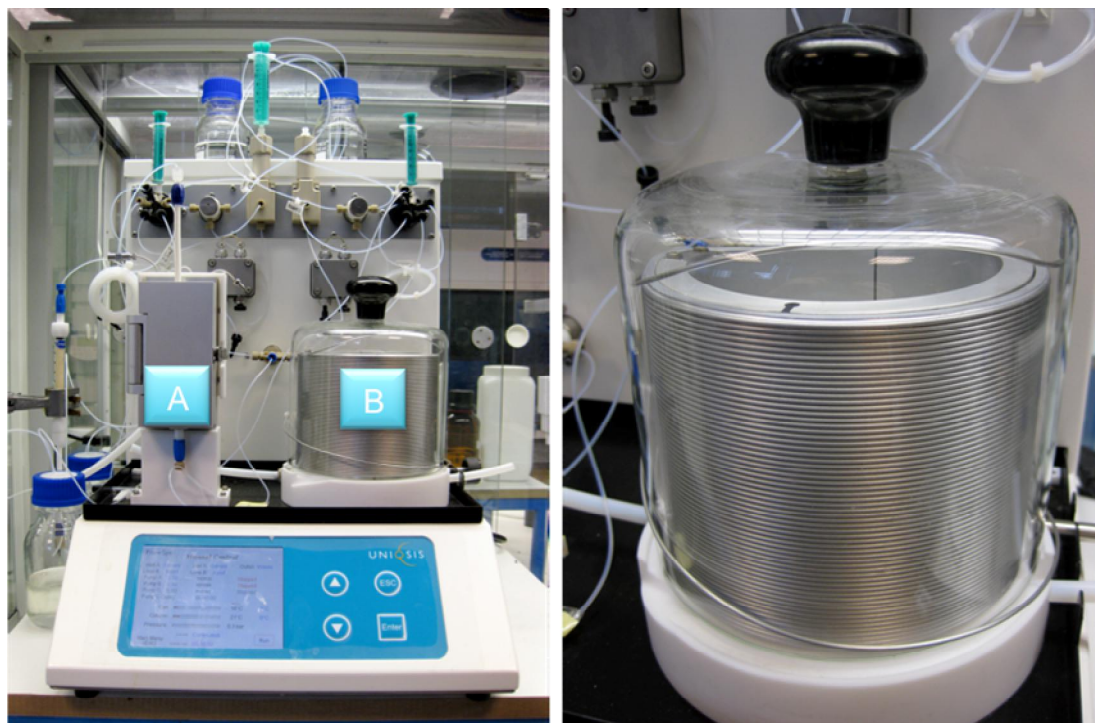
## Keywords

catch and release; flow synthesis;  $\alpha$ -ketoesters; mesoreactor; polymer supported reagents

## Introduction

Organic synthesis is changing rapidly owing to the discovery of processes that challenge current dogma and lead to the invention of new chemical reactions [1-2]. Likewise, new synthesis tools are impacting on the way we assemble molecules. Of these, flow chemistry technologies are becoming especially important [3-14]. For many years, our group [15-22] has been focussed on using immobilised systems [23-29] to more effectively and cleanly bring about chemical transformations, especially in multistep mode [17,30-37]. Given the success of these concepts, it is not surprising that we would want to adapt these principles to various flow-chemical synthesis platforms to bring about automated multistep chemical syntheses [38-54].

In this work we report the use of the Uniqsis FlowSyn™ continuous flow reactor [55] (Figure 1) to effect a flow-based preparation of  $\alpha$ -ketoesters. The key feature of this process is the application of a catch and release protocol [56-72], under the flow reaction conditions. Our choice of  $\alpha$ -ketoesters as products of the process was governed by their use as starting materials for various synthesis programmes [73-81] and as important products in their own right [82-88]. Common methods for the preparation of  $\alpha$ -ketoesters include the modified Dakin-West reaction [89] and the addition of a Grignard reagent to oxalates or oxalyl chlorides [90-92] together with a few alternative syntheses [93-99]. These procedures often suffer from drastic conditions, restricted selectivity and poor yields. Our flow-based approach delivers a new and general method for the preparation of  $\alpha$ -ketoesters, which proceeds under mild conditions, with good functional group tolerability and generates products in high purity.



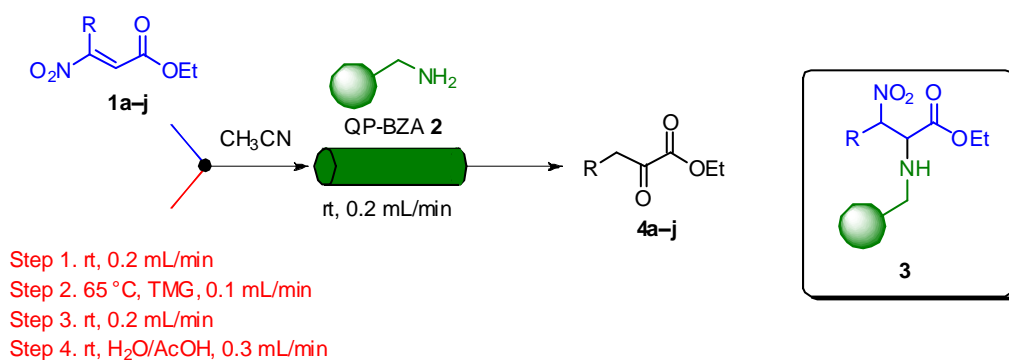
**Figure 1:** The Uniqsis FlowSyn™ continuous flow reactor comprising of a column holder and heating unit (A) and the reactor coil (B). A detailed image of the reactor coil is shown on the right.

## Results and Discussion

The experimental set up for these transformations involves the use of the Uniqsis FlowSyn™ device [55]. The fully integrated instrument employs a dual channel flow system, with each channel independently driven by a variable high-pressure piston pump. The starting materials and reagents are dispensed from sample loops (0.5-10 mL) and are united in a T-mixing piece and then passed into either a coil or column reactor (Figure 1). The column reactor utilises adjustable glass columns with variable internal diameter (1–1.5 cm) and range in volume from 6–83 mL (unpacked). The coil reactors are made from a selection of materials including PTFE, PEEK, stainless steel or Hastelloy® and accommodate volumes from 2–20 mL. The column reactor (Figure 1, A) can be heated up to 150 °C and the coil heater (Figure 1, B) up

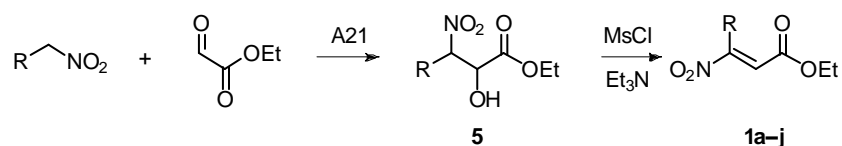
to 260 °C, over a range of flow rates between 0.01–20 mL/min, and can be configured for multistep or parallel operation. Exiting products can be collected as aliquots using an automated fraction collector for reaction optimisation or as a bulk sample for scale-up. In addition, product purification can be achieved as part of the overall flow process by in-line solid phase extraction (SPE) or alternatively by diverting the flow stream into an attached HPLC system [100].

A series of preliminary experiments was carried out on the flow equipment to profile the reaction in terms of optimum reaction temperature, concentration, residence time, solvent and stoichiometry. Following rapid screening of conditions, we fixed upon a set of reaction parameters for efficient synthesis of  $\alpha$ -ketoesters (Scheme 1). The overall reaction process proceeds in the flow apparatus *via* nitroolefinic esters **1** as substrates which are captured onto a benzylamine polymer **2** (QuadraPure™ QP-BZA polymer, loading 5.5 mmol/g, 4 equiv) to give **3** to effect product clean-up. In this way the immobilised species **3** can be washed and any solution phase impurities (resulting from the formation of the nitroolefinic ester – see later) are directed to waste (step 1). Next the column is treated with a flow stream of tetramethylguanidine (TMG; step 2) to cause elimination of nitrous acid and produce the corresponding enamino acid esters, which remains attached to the polymer support. Finally, after flow-washing (step 3), the solid supported species is hydrolysed, liberating  $\alpha$ -ketoester product **4** by flowing aqueous acetic acid (step 4) through the in-line column. The overall route constitutes a new flow chemistry example of the *catch-react-and-release* concept that we have used successfully in other synthesis programmes [101-103].



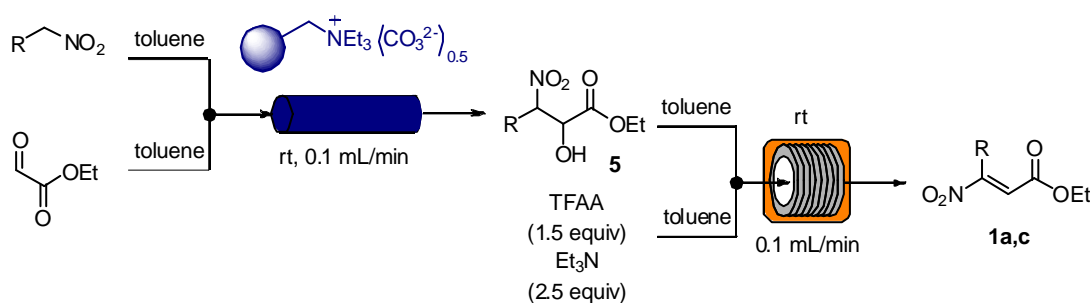
**Scheme 1:** General procedure for the flow synthesis of  $\alpha$ -ketoester products **4a–j**.

The nitroolefinic esters **1** were originally formed in a separate batch reaction from a Henry coupling of appropriate nitro compounds with ethyl glyoxalate over Amberlyst™ 21 (A21) resin to give the corresponding nitroalkanol **5** [104]. This was followed by treatment of **5** with methanesulfonyl chloride (MsCl) or trifluoroacetic anhydride (TFAA) to promote the base-catalysed dehydration, affording the nitroolefinic esters **1** (Scheme 2) [105]. As we have deliberately constructed this sequence for implementation in a continuous flow process, the intermediate nitroalkanols **5** were not isolated and the nitroolefinic esters were used without further purification. The average yield for the nitroolefins **1a–j** prepared as described in Scheme 2 was approximately 60% by LCMS. Impurities were readily removed following immobilisation of nitroolefinic esters **1** on the QP-BZA resin.



**Scheme 2:** General procedure for the batch synthesis of nitroolefinic esters **1a–j**.

In addition, the flow synthesis of two representative compounds was undertaken to allow for the complete generation of  $\alpha$ -ketoester products in flow from the starting nitroalkanes (Scheme 3). As shown in Table 1, we demonstrate that the synthesis of the nitroolefinic esters was achieved under flow conditions in a clean and effective fashion. Moreover, this synthesis demonstrates the first reported example of Henry reaction conducted in flow and we intend to elaborate on this important transformation in future studies.



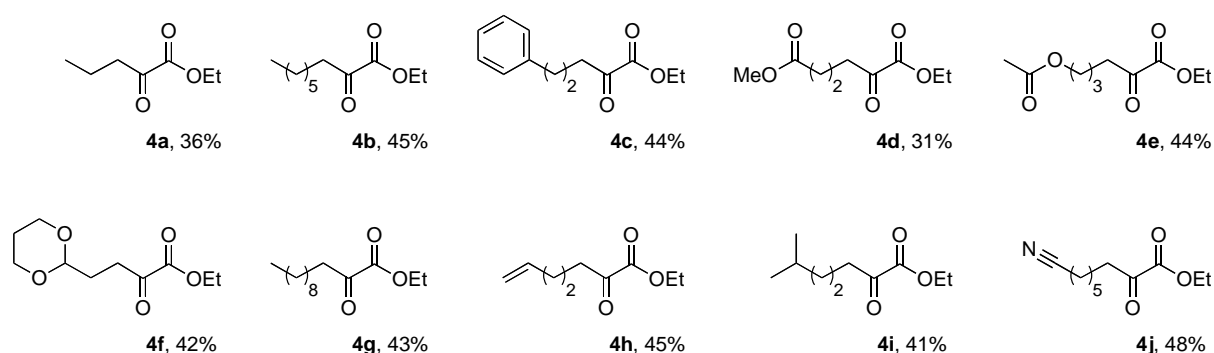
**Scheme 3:** General procedure for the flow synthesis of nitroolefinic esters **1a,c**.

**Table 1:** Nitroolefinic esters **1a,c** prepared under flow conditions (as described in Scheme 3).

Entry	1	Compound	Yield (%) <sup>a</sup>
1	<b>1a</b>		63
2	<b>1c</b>		55

<sup>a</sup>Isolated yields are shown.

Figure 2 illustrates the examples and yields of  $\alpha$ -ketoester products afforded by this new approach. While the list is not extensive, we have established that the process is tolerant of both aliphatic and aromatic substituted nitro-derivatives in the first step, and accommodates ester, acetate, acetal, nitrile and olefinic functionality in the final product. The process was reliable over several runs and consistently afforded very clean material ( $\geq 97\%$  by NMR). The yields while only moderate for the *overall process* still equate to an average step conversion of 68–78% per chemical iteration, given that the sequence is a multistep process (see Supporting Information for full experimental data).



**Figure 2:**  $\alpha$ -Ketoesters prepared and isolated yields.

## Conclusion

In conclusion, we have demonstrated the versatility of the Uniqsis FlowSyn™ unit to achieve multi-step organic synthesis under continuous flow-chemistry conditions. This was accomplished by adapting the device to incorporate immobilised reagents packed in flow tubes, enabling clean transformations without recourse to conventional product work-up or purification. The overall process delivers



synthetically useful  $\alpha$ -ketoester products in high purity from various nitroalkane inputs and paves the way for more extended reaction sequences.

## Supporting Information

Supporting Information File 1:

File Name: S1.doc

File Format: doc-file

Title: Supporting Information – Continuous flow based catch and release protocol for the synthesis of  $\alpha$ -ketoesters

## Acknowledgements

We gratefully acknowledge financial support from the EPSRC (to I. R. Baxendale), the BP endowment (to S. V. Ley), University of Camerino and MIUR-Italy (to A. Palmieri) and CSIRO Capability Development Fund (CDF) (to A. Polyzos).

## References

1. Ley, S. V.; Baxendale, I. R. *Nat. Rev. Drug Discovery* **2002**, *1*, 573–586.  
doi:10.1038/nrd871
2. Baxendale, I. R.; Hayward, J. J.; Ley, S. V.; Tranmer, G. K. *ChemMedChem* **2007**, *2*, 768–788. doi:10.1002/cmdc.200700008
3. Baxendale, I. R.; Pitts, M. R. *Chim. Oggi* **2006**, *24*(3), 41–45.
4. Baxendale, I. R.; Ley, S. V. Heterogeneous Reactions. In *New Avenues to Efficient Chemical Synthesis, Emerging Technologies*; Seeberger, P. H.; Blume, T., Eds.; Springer-Verlag: Berlin, Heidelberg, 2007; pp 151–185.

5. Baxendale, I. R.; Hayward, J. J.; Ley, S. V. *Comb. Chem. High Throughput Screening* **2007**, *10*, 802–836. doi:10.2174/138620707783220374
6. Baxendale, I. R.; Hayward, J. J.; Lanners, S.; Ley, S. V.; Smith, C. D. Heterogeneous Reactions. In *Microreactors in Organic Synthesis and Catalysis*; Wirth, T., Ed.; Wiley-VCH: Weinheim, 2008; Chapter 4.2, pp 84–122.
7. Jas, G.; Kirschning, A. *Chem.–Eur. J.* **2003**, *9*, 5708–5723. doi:10.1002/chem.200305212
8. Hodge, P. *Curr. Opin. Chem. Biol.* **2003**, *7*, 362–373. doi:10.1016/S1367-5931(03)00052-8
9. Jähnisch, K.; Hessel, V.; Löwe, H.; Baerns, M. *Angew. Chem.* **2004**, *116*, 410–451; doi:10.1002/ange.200300577  
*Angew. Chem., Int. Ed.* **2004**, *43*, 406–446. doi:10.1002/anie.200300577
10. Kirschning, A.; Solodenko, W.; Mennecke, K. *Chem.–Eur. J.* **2006**, *12*, 5972–5990. doi:10.1002/chem.200600236
11. Ahmed-Omer, B.; Brandt, J. C.; Wirth, T. *Org. Biomol. Chem.* **2007**, *5*, 733–740. doi:10.1039/b615072a
12. Mason, B. P.; Price, K. E.; Steinbacher, J. L.; Bogdan, A. R.; McQuade, D. T. *Chem. Rev.* **2007**, *107*, 2300–2318. doi:10.1021/cr050944c
13. Glasnov, V. T. N.; Kappe, C. O. *Macromol. Rapid Commun.* **2007**, *28*, 395–410. doi:10.1002/marc.200600665
14. Benito-López, F.; Egberink, R. J. M.; Reinhoudt, D. N.; Verboom, W. *Tetrahedron* **2008**, *64*, 10023–10040. doi:10.1016/j.tet.2008.07.108
15. Ley, S. V.; Baxendale, I. R.; Bream, R. N.; Jackson, P. S.; Leach, A. G.; Longbottom, D. A.; Nesi, M.; Scott, J. S.; Storer, R. I.; Taylor, S. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3815–4195. doi:10.1039/b006588i

16. Baxendale, I. R.; Lee, A.-L.; Ley, S. V. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1850–1857. doi:10.1039/b203388g
17. Baxendale, I. R.; Ernst, M.; Krahnert, W.-R.; Ley, S. V. *Synlett* **2002**, 1641–1644. doi:10.1055/s-2002-34249
18. Ley, S. V.; Baxendale, I. R. *Chem. Rec.* **2002**, 2, 377–388. doi:10.1002/tcr.10033
19. Baxendale, I. R.; Ley, S. V.; Nesi, M.; Piutti, C. *Tetrahedron* **2002**, 58, 6285–6304. doi:10.1016/S0040-4020(02)00628-2
20. Storer, R. I.; Takemoto, T.; Jackson, P. S.; Ley, S. V. *Angew. Chem.* **2003**, 115, 2625–2629; doi:10.1002/ange.200351413  
*Angew. Chem., Int. Ed.* **2003**, 42, 2521–2525. doi:10.1002/anie.200351413
21. Storer, R. I.; Takemoto, T.; Jackson, P. S.; Brown, D. S.; Baxendale, I. R.; Ley, S. V. *Chem.–Eur. J.* **2004**, 10, 2529–2547. doi:10.1002/chem.200305669
22. Baxendale, I. R.; Ley, S. V. *Ind. Eng. Chem. Res.* **2005**, 44, 8588–8592. doi:10.1021/ie048822i
23. Thompson, L. A. *Curr. Opin. Chem. Biol.* **2000**, 4, 324–337. doi:10.1016/S1367-5931(00)00096-X
24. Kobayashi, S. *Curr. Opin. Chem. Biol.* **2000**, 4, 338–345. doi:10.1016/S1367-5931(00)00097-1
25. Kirschning, A.; Monenschein, H.; Wittenberg, R. *Chem.–Eur. J.* **2000**, 6, 4445–4450. doi:10.1002/1521-3765(20001215)6:24<4445::AID-CHEM4445>3.0.CO;2-W
26. Kirschning, A.; Monenschein, H.; Wittenberg, R. *Angew. Chem.* **2001**, 113, 670–701; doi:10.1002/1521-3757(20010216)113:4<670::AID-ANGE6700>3.0.CO;2-G

- Angew. Chem., Int. Ed.* **2001**, *40*, 650–679. doi:10.1002/1521-3773(20010216)40:4<650::AID-ANIE6500>3.0.CO;2-C
27. Sherrington, D. C. *J. Polym. Sci., Part A: Polym. Chem.* **2001**, *39*, 2364–2377. doi:10.1002/pola.1213
28. Hodge, P. *Ind. Eng. Chem. Res.* **2005**, *44*, 8542–8553. doi:10.1021/ie040285e
29. Solinas, A.; Taddei, M. *Synthesis* **2007**, 2409–2453. doi:10.1055/s-2007-983806
30. Baxendale, I. R.; Ley, S. V. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1983–1986. doi:10.1016/S0960-894X(00)00383-8
31. Ley, S. V.; Baxendale, I. R.; Brusotti, G.; Caldarelli, M.; Massi, A.; Nesi, M. *Farmaco* **2002**, *57*, 321–330. doi:10.1016/S0014-827X(02)01210-7
32. Baxendale, I. R.; Brusotti, G.; Matsuoka, M.; Ley, S. V. *J. Chem. Soc., Perkin Trans. 1* **2002**, 143–154. doi:10.1039/b109482n
33. Baxendale, I. R.; Lee, A.-L.; Ley, S. V. *Synlett* **2002**, 516–518. doi:10.1055/s-2002-20483
34. Baxendale, I. R.; Ley, S. V.; Lumeras, W.; Nesi, M. *Comb. Chem. High Throughput Screening* **2002**, *5*, 197–199.
35. Baxendale, I. R.; Ley, S. V.; Sneddon, H. F. *Synlett* **2002**, 775–777. doi:10.1055/s-2002-25333
36. Baxendale, I. R.; Storer, R. I.; Ley, S. V. Supported Reagents and Scavengers in Multi-Step Organic Synthesis. In *Polymeric Materials in Organic Synthesis and Catalysis*; Buchmeiser, M. R., Ed.; Wiley-VCH: Weinheim, 2003; pp 53–136. doi:10.1002/3527601856.ch2
37. Baxendale, I. R.; Ley, S. V. *Curr. Org. Chem.* **2005**, *9*, 1521–1534. doi:10.2174/138527205774370513
38. Baxendale, I. R.; Deeley, J.; Griffiths-Jones, C. M.; Ley, S. V.; Saaby, S.; Tranmer, G. K. *Chem. Commun.* **2006**, 2566–2568. doi:10.1039/b600382f

39. Baumann, M.; Baxendale, I. R.; Ley, S. V.; Smith, C. D.; Tranmer, G. K. *Org. Lett.* **2006**, *8*, 5231–5234. doi:10.1021/ol061975c
40. Smith, C. J.; Iglesias-Sigüenza, F. J.; Baxendale, I. R.; Ley, S. V. *Org. Biomol. Chem.* **2007**, *5*, 2758–2761. doi:10.1039/b709043a
41. Smith, C. D.; Baxendale, I. R.; Lanners, S.; Hayward, J. J.; Smith, S. C.; Ley, S. V. *Org. Biomol. Chem.* **2007**, *5*, 1559–1561. doi:10.1039/b702995k
42. Hornung, C. H.; Mackley, M. R.; Baxendale, I. R.; Ley, S. V. *Org. Process Res. Dev.* **2007**, *11*, 399–405. doi:10.1021/op700015f
43. Baumann, M.; Baxendale, I. R.; Ley, S. V. *Synlett* **2008**, 2111–2114. doi:10.1055/s-2008-1078026
44. Baumann, M.; Baxendale, I. R.; Ley, S. V.; Nikbin, N.; Smith, C. D. *Org. Biomol. Chem.* **2008**, *6*, 1587–1593. doi:10.1039/b801634h
45. Baumann, M.; Baxendale, I. R.; Ley, S. V.; Nikbin, N.; Smith, C. D.; Tierney, J. P. *Org. Biomol. Chem.* **2008**, *6*, 1577–1586. doi:10.1039/b801631n
46. Baxendale, I. R.; Ley, S. V.; Smith, C. D.; Tamborini, L.; Voica, A.-F. *J. Comb. Chem.* **2008**, *10*, 851–857. doi:10.1021/cc800070a
47. Jas, G.; Kirschning, A. *Chem.–Eur. J.* **2003**, *9*, 5708–5723. doi:10.1002/chem.200305212
48. Bernstein, D.; France, S.; Wolfer, J.; Lectka, T. *Tetrahedron: Asymmetry* **2005**, *16*, 3481–3483. doi:10.1016/j.tetasy.2005.09.014
49. Bonfils, F.; Cazaux, I.; Hodge, P.; Caze, C. *Org. Biomol. Chem.* **2006**, *4*, 493–497. doi:10.1039/b515241k
50. Wiles, C.; Watts, P.; Haswell, S. J. *Tetrahedron Lett.* **2006**, *47*, 5261–5264. doi:10.1016/j.tetlet.2006.05.157
51. Dräger, G.; Kiss, C.; Kunz, U.; Kirschning, A. *Org. Biomol. Chem.* **2007**, *5*, 3657–3664. doi:10.1039/b712804e

52. Burguete, M. I.; Cornejo, A.; García-Verdugo, E.; Gil, M. J.; Luis, S. V.; Mayoral, J. A.; Martínez-Merino, V.; Sokolova, M. *J. Org. Chem.* **2007**, *72*, 4344–4350.  
doi:10.1021/jo070119r
53. Solodenko, W.; Jas, G.; Kunz, U.; Kirschning, A. *Synthesis* **2007**, 583–589.  
doi:10.1055/s-2007-965877
54. Odedra, A.; Geyer, K.; Gustafsson, T.; Gilmour, R.; Seeberger, P. H. *Chem. Commun.* **2008**, 3025–3027. doi:10.1039/b803715a
55. Uniqsis web site. <http://www.uniqsis.com> (accessed April 6, 2009)
56. Cohen, B. J.; Kraus, M. A.; Patchornik, A. *J. Am. Chem. Soc.* **1977**, *99*, 4165–4167. doi:10.1021/ja00454a050
57. Cohen, B. J.; Kraus, M. A.; Patchornik, A. *J. Am. Chem. Soc.* **1981**, *103*, 7620–7629. doi:10.1021/ja00415a034
58. Patchornik, A. In *Proc. IUPAC, I. U. P. A. C., Macromol. Symp., 28th, 1982*, University of Massachusetts, Amherst, July 12–16, 1982; IUPAC: Oxford, 1982; p 85.
59. Brown, S. D.; Armstrong, R. W. *J. Am. Chem. Soc.* **1996**, *118*, 6331–6332.  
doi:10.1021/ja961203j
60. Hu, Y.; Baudart, S.; Porco, J. A., Jr. *J. Org. Chem.* **1999**, *64*, 1049–1051.  
doi:10.1021/jo981874v
61. Studer, A.; Hadida, S.; Ferritto, R.; Kim, S.-Y.; Jeger, P.; Wipf, P.; Curran, D. P. *Science* **1997**, *275*, 823–826. doi:10.1126/science.275.5301.823
62. Flynn, D. L.; Crich, J. Z.; Devraj, R. V.; Hockerman, S. L.; Parlow, J. J.; South, M. S.; Woodard, S. *J. Am. Chem. Soc.* **1997**, *119*, 4874–4881.  
doi:10.1021/ja963462e
63. Curran, D. P. *Angew. Chem.* **1998**, *110*, 1230–1255; doi:10.1002/(SICI)1521-3757(19980504)110:9<1230::AID-ANGE1230>3.0.CO;2-Y

- Angew. Chem., Int. Ed.* **1998**, *37*, 1174–1196. doi:10.1002/(SICI)1521-3773(19980518)37:9<1174::AID-ANIE1174>3.0.CO;2-P
64. Bosanac, T.; Yang, J.; Wilcox, C. S. *Angew. Chem.* **2001**, *113*, 1927–1931; doi:10.1002/1521-3757(20010518)113:10<1927::AID-ANGE1927>3.0.CO;2-#  
*Angew. Chem., Int. Ed.* **2001**, *40*, 1875–1879. doi:10.1002/1521-3773(20010518)40:10<1875::AID-ANIE1875>3.0.CO;2-5
65. Ley, S. V.; Massi, A.; Rodríguez, F.; Horwell, D. C.; Lewthwaite, R. A.; Pritchard, M. C.; Reid, A. M. *Angew. Chem.* **2001**, *113*, 1088–1090; doi:10.1002/1521-3757(20010316)113:6<1088::AID-ANGE10880>3.0.CO;2-#  
*Angew. Chem., Int. Ed.* **2001**, *40*, 1053–1055. doi:10.1002/1521-3773(20010316)40:6<1053::AID-ANIE10530>3.0.CO;2-D
66. Galante, A.; Lhoste, P.; Sinou, D. *Tetrahedron Lett.* **2001**, *42*, 5425–5427. doi:10.1016/S0040-4039(01)01055-3
67. Yoshida, J.-i.; Itami, K. *Chem. Rev.* **2002**, *102*, 3693–3716. doi:10.1021/cr0103524
68. Dobbs, A. P.; McGregor-Johnson, C. *Tetrahedron Lett.* **2002**, *43*, 2807–2810. doi:10.1016/S0040-4039(02)00322-2
69. Lan, P.; Porco, J. A., Jr.; South, M. S.; Parlow, J. J. *J. Comb. Chem.* **2003**, *5*, 660–669. doi:10.1021/cc030028h
70. Siu, J.; Baxendale, I. R.; Lewthwaite, R. A.; Ley, S. V. *Org. Biomol. Chem.* **2005**, *3*, 3140–3160. doi:10.1039/b503778f
71. Curran, D. P.; Wang, X.; Zhang, Q. *J. Org. Chem.* **2005**, *70*, 3716–3719. doi:10.1021/jo050116j
72. Mothana, S.; Chahal, N.; Vanneste, S.; Hall, D. G. *J. Comb. Chem.* **2007**, *9*, 193–196. doi:10.1021/cc060149s

73. Audrain, H.; Thorhauge, J.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **2000**, *65*, 4487–4497. doi:10.1021/jo9918596
74. Peng, Z.-H.; Woerpel, K. A. *Org. Lett.* **2002**, *4*, 2945–2948.  
doi:10.1021/ol026343e
75. Yu, S.; Saenz, J.; Srirangam, J. K. *J. Org. Chem.* **2002**, *67*, 1699–1702.  
doi:10.1021/jo016131f
76. Griesbeck, A. G.; Bondock, S.; Lex, J. *Org. Biomol. Chem.* **2004**, *2*, 1113–1115.  
doi:10.1039/b401990c
77. Sun, Y.; Wan, X.; Wang, J.; Meng, Q.; Zhang, H.; Jiang, L.; Zhang, Z. *Org. Lett.* **2005**, *7*, 5425–5427. doi:10.1021/ol052212c
78. Zhang, W.; Shi, M. *Chem. Commun.* **2006**, 1218–1220. doi:10.1039/b516467b
79. Howard, B. E.; Woerpel, K. A. *Org. Lett.* **2007**, *9*, 4651–4653.  
doi:10.1021/ol702148x
80. Kratzer, R.; Nidetzky, B. *Chem. Commun.* **2007**, 1047–1049.  
doi:10.1039/b616475g
81. Ntaganda, R.; Milovic, T.; Tiburcio, J.; Thadani, A. N. *Chem. Commun.* **2008**, 4052–4054. doi:10.1039/b808302a
82. Peet, N. P.; Burkhart, J. P.; Angelastro, M. R.; Giroux, E. L.; Mehdi, S.; Bey, P.; Kolb, M.; Neises, B.; Schirlin, D. *J. Med. Chem.* **1990**, *33*, 394–407.  
doi:10.1021/jm00163a063
83. Patel, D. V.; Rielly-Gauvin, K.; Ryono, D. E.; Free, C. A.; Smith, S. A.; Petrillo, E. W., Jr. *J. Med. Chem.* **1993**, *36*, 2431–2447. doi:10.1021/jm00069a001
84. Li, Z.; Patil, G. S.; Golubski, Z. E.; Hori, H.; Tehrani, K.; Foreman, J. E.; Eveleth, D. D.; Bartus, R. T.; Powers, J. C. *J. Med. Chem.* **1993**, *36*, 3472–3480.  
doi:10.1021/jm00074a031



85. Koutek, B.; Prestwich, G. D.; Howlett, A. C.; Chin, S. A.; Salehani, D.; Akhavan, N.; Deutsch, D. G. *J. Biol. Chem.* **1994**, *269*, 22937–22940.
86. Conde-Frieboes, K.; Reynolds, L. J.; Lio, Y.-C.; Hale, M. R.; Wasserman, H. H.; Dennis, E. A. *J. Am. Chem. Soc.* **1996**, *118*, 5519–5525.  
doi:10.1021/ja953553w
87. Otto, H.-H.; Schirmeister, T. *Chem. Rev.* **1997**, *97*, 133–172.  
doi:10.1021/cr950025u
88. Choe, Y.; Brinen, L. S.; Price, M. S.; Engel, J. C.; Lange, M.; Grisostomi, C.; Weston, S. G.; Pallai, P. V.; Cheng, H.; Hardy, L. W.; Hartsough, D. S.; McMakin, M.; Tilton, R. F.; Baldino, C. M.; Craik, C. S. *Bioorg. Med. Chem.* **2005**, *13*, 2141–2156. doi:10.1016/j.bmc.2004.12.053
89. Buchanan, G. L. *Chem. Soc. Rev.* **1988**, *17*, 91–109.  
doi:10.1039/cs9881700091
90. Nimitz, J. S.; Mosher, H. S. *J. Org. Chem.* **1981**, *46*, 211–213.  
doi:10.1021/jo00314a057
91. Creary, X.; Mehrsheikh-Mohammadi, M. E. *J. Org. Chem.* **1986**, *51*, 2664–2668.  
doi:10.1021/jo00364a009
92. Babudri, F.; Fiandanese, V.; Marchese, G.; Punzi, A. *Tetrahedron* **1996**, *52*, 13513–13520. doi:10.1016/0040-4020(96)00805-8
93. Wasserman, H. H.; Ives, J. L. *J. Org. Chem.* **1985**, *50*, 3573–3580.  
doi:10.1021/jo00219a025
94. Bulman Page, P. C.; Rosenthal, S. *Tetrahedron Lett.* **1986**, *27*, 1947–1950.  
doi:10.1016/S0040-4039(00)84419-6
95. Sakakura, T.; Yamashita, H.; Kobayashi, T.-a.; Hayashi, T.; Tanaka, M. *J. Org. Chem.* **1987**, *52*, 5733–5740. doi:10.1021/jo00235a017

96. Wong, M.-K.; Yu, C.-W.; Yuen, W.-H.; Yang, D. *J. Org. Chem.* **2001**, *66*, 3606–3609. doi:10.1021/jo0015974
97. Li, L.-S.; Wu, Y.-L. *Tetrahedron Lett.* **2002**, *43*, 2427–2430. doi:10.1016/S0040-4039(02)00290-3
98. Ma, M.; Li, C.; Peng, L.; Xie, F.; Zhang, X.; Wang, J. *Tetrahedron Lett.* **2005**, *46*, 3927–3929. doi:10.1016/j.tetlet.2005.03.199
99. Shimizu, H.; Murakami, M. *Chem. Commun.* **2007**, 2855–2857. doi:10.1039/b704105e
100. Baxendale, I. R.; Griffiths-Jones, C. M.; Ley, S. V.; Tranmer, G. K. *Synlett* **2006**, 427–430. doi:10.1055/s-2006-926244
101. Baxendale, I. R.; Ley, S. V.; Smith, C. D.; Tranmer, G. K. *Chem. Commun.* **2006**, 4835–4837. doi:10.1039/b612197g
102. Smith, C. D.; Baxendale, I. R.; Tranmer, G. K.; Baumann, M.; Smith, S. C.; Lewthwaite, R. A.; Ley, S. V. *Org. Biomol. Chem.* **2007**, *5*, 1562–1568. doi:10.1039/b703033a
103. Griffiths-Jones, C. M.; Hopkin, M. D.; Jönsson, D.; Ley, S. V.; Tapolczay, D. J.; Vickerstaffe, E.; Ladlow, M. *J. Comb. Chem.* **2007**, *9*, 422–430. doi:10.1021/cc060152b
104. Ballini, R.; Bosica, G.; Forconi, P. *Tetrahedron* **1996**, *52*, 1677–1684. doi:10.1016/0040-4020(95)00996-5
105. Ballini, R.; Fiorini, D.; Palmieri, A. *Tetrahedron Lett.* **2004**, *45*, 7027–7029. doi:10.1016/j.tetlet.2004.07.141