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Review

Solid-phase organic synthesis of heterocyclic compounds

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Combinatorial chemistry has become an important tool in both drug discovery and chemical biology and its continued success is dependent, in part, on further advances in solid-phase organic synthesis (SPOS). This paper describes recent findings and a useful method for the synthesis of heterocycle and nitrogen heterocycle compounds. © Pesticide Science Society of Japan

Keywords: combinatorial chemistry, solid-phase organic synthesis (SPOS), heterocycle.

Introduction

The establishment of an efficient method of synthesizing heterocycles is required for the development of pharmaceuticals and agrochemicals, since many bioactive compounds have a heterocyclic ring. It is also necessary to prepare libraries of small organic compounds for investigations of function and the discovery of more bioactive compounds in pharmaceutical and agrochemical chemistry. Combinatorial and parallel synthetic methodologies provide the main driving force for the preparation of libraries for applications in the discovery of lead compounds and high-throughput medicinal chemistry within the pharmaceutical industry.[1–3] Many different formats of high-throughput chemistry are available and solid-phase organic synthesis (SPOS) plays a pivotal role allowing the convenient handling of large numbers of synthetic intermediates.[4,5]

Since the combinatorial chemistry first appeared in the early 1990s, the way drugs are discovered has changed dramatically. The SPOS strategy has been a strong tool for high throughput synthesis and combinatorial chemistry.[6–9] Synthetic intermediates are retained on the support and can be, therefore, quickly separated from the reaction mixture without extraction, concentration, and purification. SPOS is thus particularly advantageous for multi-step iterative synthesis. Various solid-phase automated synthesizers have been developed and are now commercially available. Even though several synthesizers for solution synthesis have been developed, automation is essentially easier in solid-phase synthesis than solution synthesis. In particular, the automated synthesis of peptides and oligonucleotides has allowed their facile and rapid preparation and greatly contributed to the elucidation of their functions. However, SPOS is not without its drawbacks since often extended development times are required to optimize new solid-phase chemical reactions. Actually, many laboratories have been engaged in the development of novel solid-phase linking strategies and chemical technologies. This paper describes recent findings in, and a useful method for, the synthesis of heterocycle and nitrogen heterocycle compounds.

1. Selenium-based solid-phase chemistry to include nitrogen-containing heterocycles

Nicolaou and co-workers have been engaged in the development of novel solid-phase linking strategies and chemical technologies aimed at the construction of discovery-oriented, natural product-like libraries.[10–12] Toward this end, several natural product-like templates have been tethered to a solid-support utilizing an intramolecular, selenium-mediated cycloaddition procedure. Encouraged by their success in developing chemistry and technology to produce natural product-like libraries of oxygen-containing heterocycles and carbocyclic frameworks[13–16] and due to the potential utility of such libraries in chemical biology investigations,[17,18] they sought to expand the scope of this selenium-based solid-phase chemistry to include nitrogen-containing heterocycles. Recently, they reported that *o*-allyl- and *o*-prenyl-anilines were cycloadded to afford a series of solid-supported indole and indoline scaffolds (**2**) using a polymer-bound selenenyl bromide resin (Scheme 1). These scaffolds were then functionalized and cleaved *via* four distinct methods, namely traceless reduction, radical cyclization, radical rearrangement, and oxidative elimination, to afford 2-methyl indolines, polycyclic indolines,

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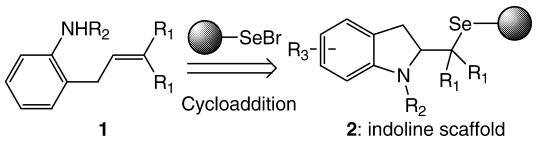


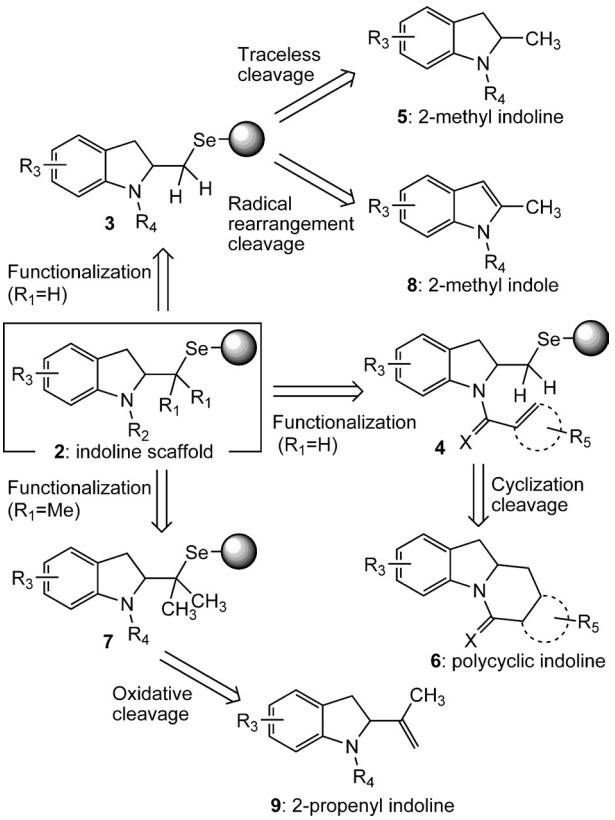
Scheme 1

2-methyl indoles, and 2-propenyl indolines.

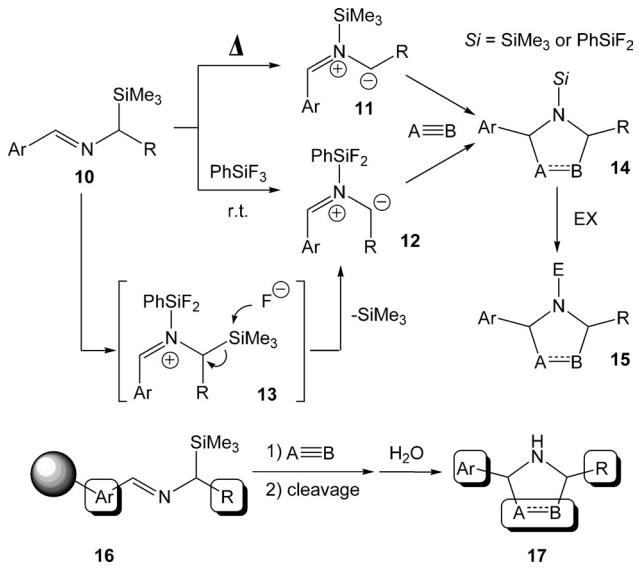
On the basis of their new findings, they reported the successful loading, functionalization, and cleavage of four novel classes of natural product-like templates, namely 2-methyl indoline (**5**), polycyclic indoline (**6**), 2-methyl indole (**8**), and 2-propenyl indoline (**9**) using selenium-based solid-phase chemistry. These technologies may prove useful in the synthesis of further combinatorial libraries of biologically relevant compounds for chemical biology studies and drug discovery purposes (Scheme 2).[19)]

2. *Generation and cycloaddition of polymer-supported azomethine ylides*

One of the most useful methods for the synthesis of diverse heterocyclic compounds involves 1,3-dipolar cycloaddition reactions.[20–26)] In a series of studies on the generation of 1,3-dipoles in solution phase, Komatsu and co-wokers discovered that azomethine ylides (**11** or **12**) can be generated from α-silylimines (**10**) by thermal 1,2-silatropy onto the imino nitrogen or by treatment with a trifluorosilane as a quaternization



Scheme 2



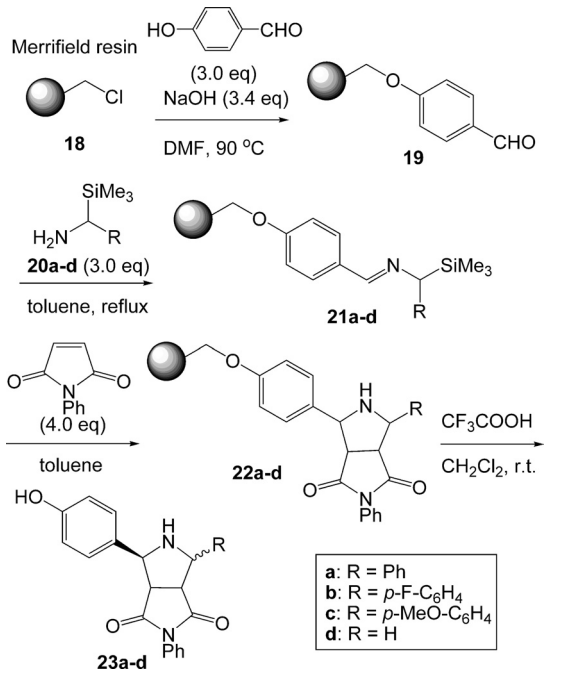
Scheme 3

and desilylation reagent (Scheme 3).[27)]

In the former method, no additives are required and the reactions can be performed under completely neutral conditions. In the latter method, a fluorosilane plays multiple functions and the reaction proceeds under mild conditions. These methods are based on the strong affinity between silicon and nitrogen or fluorine. The resulting *N*-silylated azomethine ylides (**11** or **12**) are quite useful species in terms of the simultaneous formation of two C-C bonds leading to *N*-unsubstituted and *N*-substituted heterocycles. By applying these 1,3-dipolar cycloaddition reactions to SPOS, they developed a novel solid-phase strategy for the synthesis of pyrrolidine and pyrrole derivatives from polymer-supported α-silylimines (**16**) by utilizing the characteristics of silicon.[28)] Polymer-supported azomethine ylides (**21**) were generated from the corresponding α-silylimines (**20**) by thermal 1,2-silatropy or by treatment with a trifluorosilane, and the resulting species were then reacted with dipolarophiles (Scheme 4). A modification of the linker led to a traceless solid-phase synthesis. They also demonstrated versatility in several steps, suggesting that these methods are potentially useful for the construction of a library of heterocycles.

3. *Named reaction on solid-phase for the synthesis of heterocycles*

The formation of C-C bonds is an important process in synthetic organic chemistry. Among a variety of methods reported to date, the Pictet–Spengler reaction[29–33)] is one that involves the acid-catalyzed condensation of an aldehyde with an aliphatic amine attached to a sufficiently reactive aromatic nucleus like **24** to form imine (**25**), which is often activated by acids. Endo cyclization between a carbon nucleophile of a sufficiently reactive aromatic moiety and the activated iminium ion results in a new C-C bond, forming a *N*-hetero-

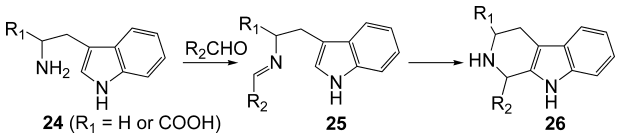


Scheme 4

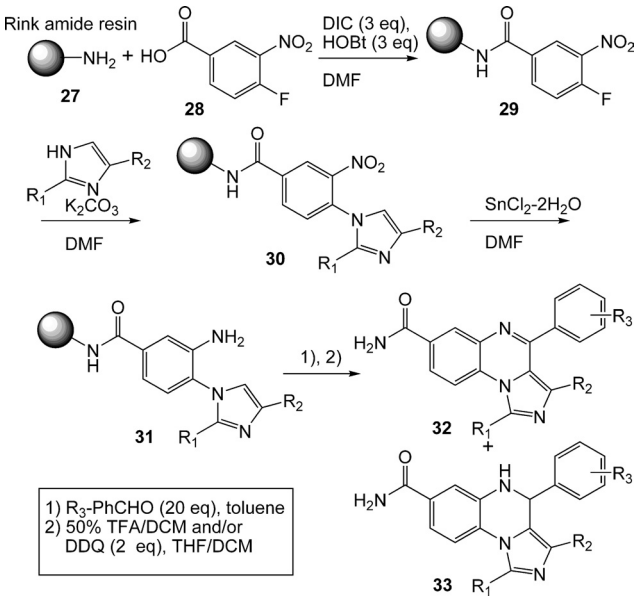
cyclic ring (**26**) (Scheme 5).

Kundu and co-workers have developed a modified solid-phase strategy for the Pictet–Spengler reaction involving an aromatic amine linked to N1 of imidazole (**31**) and an aldehyde (Scheme 6).[34] This method can be used for the generation of large libraries of imidazoquinoxaline-based compounds using an automated synthesizer. Their strategy also opens up possibilities for the design and synthesis of a variety of aryl or aliphatic amine substrates derived from an activated aromatic nucleus. Such amine can be used for the generation of heterocycles using the Pictet–Spengler reaction.

Pulici and co-workers reported the SPOS of oxazoles *via* a Robinson–Gabriel reaction of solid-supported-acylamino ketones.[35] Robinson–Gabriel is the name normally given to the cyclocondensation reaction of acylamino ketones. It is one of the first methods reported for the synthesis of oxazoles (Scheme 7),[36,37] and it has been accomplished only using rather harsh conditions involving a cyclodehydrating agent such as sulfuric acid, phosphorus pentachloride, phosphorus oxychloride, polyphosphoric acid, phosgene, or anhydrous hydrogen fluoride.[38,39] Pulici and co-workers were interested in developing a more general strategy to enable the synthesis of functionalized oxazoles carrying no memory of the original anchoring point. Their works involved, therefore, preparing



Scheme 5



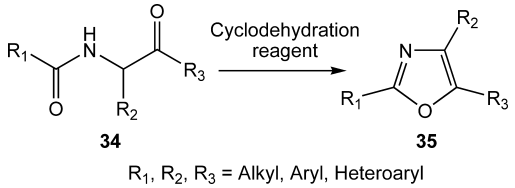
Scheme 6

an acylamino ketone bound to a suitable linker (**37**) by means of the only viable atom, that is, the nitrogen. Treatment with an appropriate dehydrating agent mediates a cyclative cleavage, releasing the expected product in solution (Scheme 8).

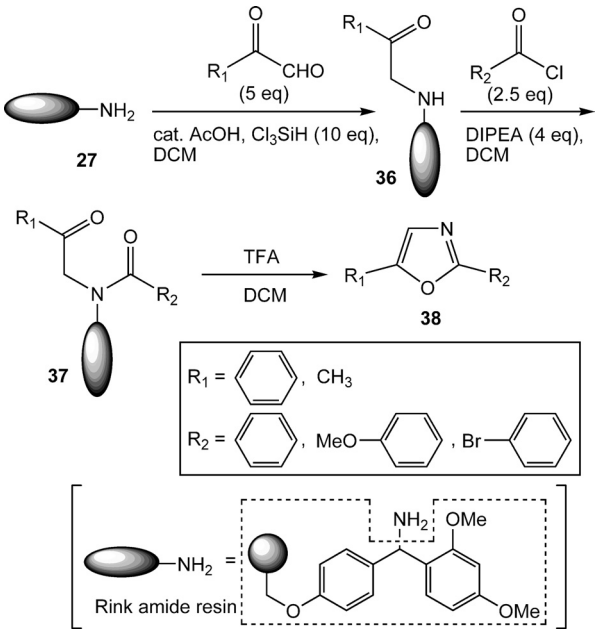
4. Solid-phase synthesis of tertiary amines by reduction of tertiary amides with $LiAlH_4$

Tertiary amines are an important class of compounds for drug discovery processes. It is well recognized that the reduction of primary and secondary amides affords the corresponding primary and secondary amines in good yields with $LiAlH_4$. The reduction of tertiary amides, however, generally gives secondary amines when the *N*-substituents are bulky.[40] In fact, the reduction of *N*-benzyl-*N*-phenylbenzamide (**39**) with $LiAlH_4$ in solution gave benzylphenylamine (**40**) as the sole product. Fukase and co-workers reported a novel solid-phase synthesis of tertiary amines through the reduction of *N*-aryl-*N*-benzylbenzamides with $LiAlH_4$.[41] Their method allows for the facile introduction of diversity with the use of commercially available amines and acyl chlorides.

As has been described, SPOS has proved to be useful for preparing libraries of small organic compounds, since it helps in both expediting the preparation and increasing the diversity of the molecules.[42,43] In addition, SPOS may enable new reactions which can not be effected by traditional solution



Scheme 7

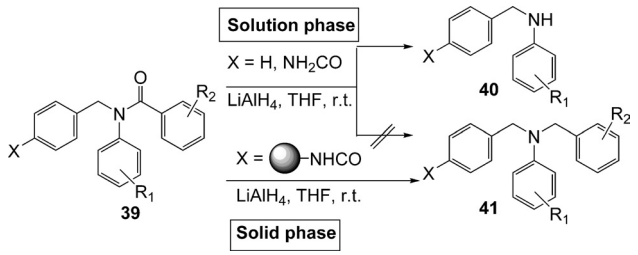


Scheme 8

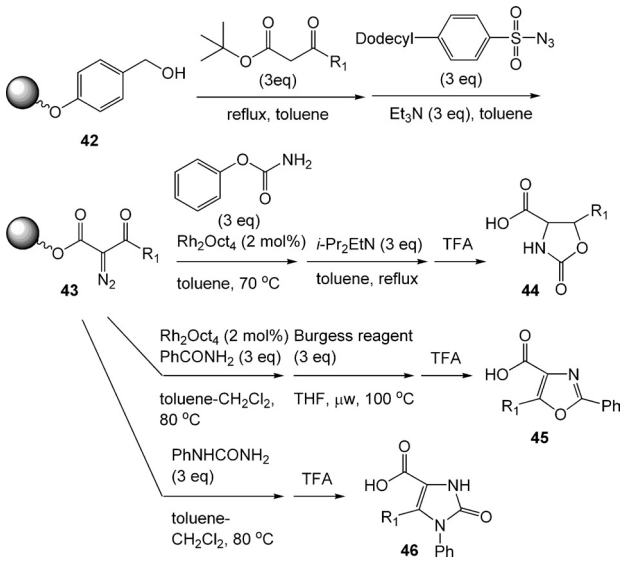
synthesis. But, reactions on a solid-support generally proceed slowly in comparison to those in solutions owing to the low rate of diffusion of reagents in polymer-supports. Fukase and co-workers, therefore, expected the reactivity of reagents to be controllable using solid-phase reaction conditions.[44] They found that tertiary amides (*N*-aryl-*N*-benzylbenzamides) (**39**) bound to a gel-type polystyrene support were reduced with $LiAlH_4$ to give tertiary amines, whereas the reduction of similar tertiary amides in solution generally gives secondary amines as main products.[41] Reduction with $LiAlH_4$ in solid-phase synthesis is additionally advantageous in that the inorganic salt formed by the reduction can be readily removed by just filtration and washing with aqueous acetic acid and aqueous methanol (Scheme 9).

5. *SPOS aimed at diversity-oriented synthesis (DOS)*

Janda and co-workers reported a novel and efficient N–H insertion-based strategy for the synthesis of oxazolones from diazocarbonyls.[45] In this paper, in order to synthesize oxazolone arrays using the solid-phase methodology, an alternative TFA labile linker strategy was developed. Wang resin-bound diazocarbonyl substrates were also shown to be of



Scheme 9



Scheme 10

great utility in the preparation of oxazoles and imidazolones. In the case of the oxazolones (**44**), the majority of the desired products were also isolated in excellent purity and good yield. In the case of the imidazolones (**46**), a primary urea was used as the insertion component, and the product from this reaction was treated with TFA to achieve both cyclizations to the imidazolone and cleavage from the resin in one pot. These highly useful intermediates were used for the synthesis of a series of heterocycle libraries, which were obtained from the resin using TFA cleavage. This work has centered on the application of polymer-bound α-diazo-β-ketoesters as key building blocks for the DOS[46] of a series of heterocycle libraries, including oxazoles,[47] indoles,[48] imidazolones and imidazoles,[49,50] and pyrazinones and pyrazines (Scheme 10).[51]

DOS is an emerging field involving the synthesis of combinatorial libraries of diverse small molecules for biological screening.[52] Rather than being directed toward a single biological target, DOS libraries can be used to identify new ligands for a variety of targets. Several different strategies for library design have been developed to target the biologically relevant regions of chemical structure space. DOS has provided powerful probes to investigate biological mechanisms and also served as a new driving force for advancing synthetic organic chemistry.[52]

References

1) B. A. Lorsbach and M. Kurth: *J. Chem. Rev.* **99**, 1549–1581 (1999), and references therein.
2) R. E. Sammelson and M. Kurth: *J. Chem. Rev.* **101**, 137–202 (2001), and references therein.
3) D. G. Hall, S. Manku and F. Wang: *J. Combust. Chem.* **3**, 125–150 (2001).
4) S. Kobayashi: *Chem. Soc. Rev.* **28**, 1–15 (1999).
5) R. E. Dolle: *J. Combust. Chem.* **2**, 383–433 (2000), and refer-

ences therein.
6) F. Balkenhohl, C. von dem Bussche-Hunnefeld, A. Lansky and C. Zechel: *Angew. Chem., Int. Ed.* **35**, 2288–2337 (1996).
7) D. F. Veber, F. H. Drake and M. Gowen: *Curr. Opin. Chem. Biol.* **1**, 151–156 (1997).
8) K. Gordon and S. Balasubramanian: *Curr. Opin. Drug Discovery Dev.* **2**, 342–349 (1999).
9) K. C. Nicolaou, R. Hanko and W. Hartwig (eds.): "Handbook of Combinatorial Chemistry," Vols. 1 and 2, Wiley-VCH, Weinheim, 2001.
10) K. C. Nicolaou, J. A. Pfefferkorn, A. J. Roecker, G.-Q. Cao, S. Barluenga and H. J. Mitchell: *J. Am. Chem. Soc.* **122**, 9939–9953 (2000).
11) K. C. Nicolaou, J. A. Pfefferkorn, H. J. Mitchell, A. J. Roecker, S. Barluenga, G.-Q. Cao, R. L. Affleck and J. E. Lillig: *J. Am. Chem. Soc.* **122**, 9954–9967 (2000).
12) K. C. Nicolaou, J. A. Pfefferkorn, S. Barluenga, H. J. Mitchell, A. J. Roecker and G.-Q. Cao: *J. Am. Chem. Soc.* **122**, 9968–9976 (2000).
13) K. C. Nicolaou, J. A. Pfefferkorn, G.-Q. Cao, S. Kim and J. Kessabi: *Org. Lett.* **1**, 807–810 (1999).
14) K. C. Nicolaou, J. A. Pfefferkorn and G.-Q. Cao: *Angew. Chem., Int. Ed.* **39**, 734–739 (2000).
15) K. C. Nicolaou, G.-Q. Cao and J. A. Pfefferkorn: *Angew. Chem., Int. Ed.* **39**, 739–743 (2000).
16) K. C. Nicolaou and J. A. Pfefferkorn: *Biopolymers* **60**, 171–193 (2001).
17) K. C. Nicolaou, J. A. Pfefferkorn, F. Schuler, A. J. Roecker and G.-Q. Cao: *Chem. Biol.* **7**, 979–992 (2000).
18) K. C. Nicolaou, A. J. Roecker, S. Barluenga, J. A. Pfefferkorn and G.-Q. Cao: *Chembiochem* **6**, 460–465 (2001).
19) K. C. Nicolaou, A. J. Roeckera, R. Hughesa, R. Summerena, J. A. Pfefferkorna and N. Winssingera: *Bioorg. Med. Chem.* **11**, 465–476 (2003).
20) R. Huisgen: "1,3-Dipolar Cycloaddition Chemistry," Vol. 1, ed. by A. Padwa, Wiley, New York, pp. 1–176, 1984, and references therein.
21) A. Nefzi, J. M. Ostresh and R. A. Houghten: *Chem. Rev*. **97**, 449–472 (1997), and references therein.
22) K.-I. Washizuka, K. Nagai, S. Minakata, I. Ryu and M. Komatsu: *Tetrahedron Lett.* **40**, 8849–8853 (1999), and references therein.
23) M. Komatsu, J. Choi, Y. Oderaotoshi and S. Minakata: *Tetrahedron Lett.* **42**, 9221–9223 (2001), and references therein.
24) W.-C. Cheng, M. Wong, M. M. Olmstead and M. J. Kurth: *Org. Lett.* **4**, 741–744 (2002).
25) Y.-J. Shang and Y.-G. Wang: *Tetrahedron Lett.* **43**, 2247–2249 (2002), and references therein.
26) G. Faita, M. Mella, A. Mortoni, A. Paio, P. Quadrelli and P. Seneci: *Eur. J. Org. Chem.* **7**, 1175–1183 (2002), and references therein.
27) M. Komatsu, H. Okada, T. Akaki, Y. Oderaotoshi and S. Minakata: *Org. Lett.* **4**, 3505–3508 (2002), and references therein.
28) H. Okada, T. Akaki, Y. Oderaotoshi, S. Minakata and M. Komatsu: *Tetrahedron* **59**, 197–205 (2003).
29) A. Pictet and T. Spengler: *Ber. Deutsch. Chem. Ges.* **44**, 2030–2036 (1911).
30) E. D. Cox and J. Cook: *Chem. Rev.* **95**, 1797–1842 (1995), and references therein.
31) R. Tsuji, M. Nakagawa and A. Nishida: *Tetrahedron: Asymmetry* **14**, 177–180 (2003), and references therein.
32) T. E. Nielsen, F. Dines and M. Meldal: *Curr. Opin. Drug Discovery* **6**, 801–814 (2003), and references therein.
33) J. Royer, M. Bonin and L. Micouin: *Chem. Rev.* **104**, 2311–2352 (2004), and references therein.
34) B. Kundu, D. Sawant and R. Chhabra: *J. Comb. Chem.* **7**, 317–321 (2005).
35) M. Pulici, F. Quartieri and E. R. Felder: *J. Comb. Chem.* **7**, 463–473 (2005).
36) S. Gabriel: *Chem. Ber.* **40**, 2647–2650 (1907).
37) J. Lister and R. Robinson: *J. Chem. Soc.* **101**, 1297–1315 (1913).
38) G. V. Boyd: "Comprehensive Heterocyclic Chemistry," Vol. 6, ed. by A. R. Katritzky and C. W. Rees, Pergamon Press, Oxford, pp. 177–234, 1984.
39) I. J. Turchi: "The Chemistry of Heterocyclic Compounds," Vol. 45, Wiley, New York, 1986.
40) B. C. Challis and J. A. Challis (eds.): "The Chemistry of Amides," John Wiley, New York, pp. 795–801, 1970.
41) H. Akamatsu, S. Kusumoto and K. Fukase: *Tetrahedron Lett.* **43**, 8867–8869 (2002).
42) G. C. Look, J. R. Schullek, C. P. Holmes, J. P. Chinn, E. M. Gordon and M. A. Gallop: *Bioorg. Med. Chem. Lett.* **6**, 707–712 (1996).
43) P. Wipf, A. Cunningham, R. L. Rich and J. S. Lazo: *Bioorg. Med. Chem. Lett.* **5**, 165–177 (1997).
44) M. Izumi, K. Fukase and S. Kusumoto: *Synlett* **9**, 1409–1416 (2002).
45) M. Yamashita, S.-H. Lee, G. Koch, J. Zimmermann, B. Clapham and K. D. Janda: *Tetrahedron Lett.* **46**, 5495–5498 (2005).
46) M. D. Burke and S. L. Schreiber: *Angew. Chem., Int. Ed.* **43**, 46–58 (2004).
47) B. Clapham, C. Spanka and K. D. Janda: *Org. Lett.* **3**, 2173–2176 (2001).
48) S.-H. Lee, B. Clapham, G. Koch, J. Zimmermann and K. D. Janda: *J. Comb. Chem.* **5**, 188–196 (2003).
49) S.-H. Lee, B. Clapham, G. Koch, J. Zimmermann and K. D. Janda: *Org. Lett.* **5**, 511–514 (2003).
50) S.-H. Lee, K. Yoshida, H. Matsushita, B. Clapham, G. Koch, J. Zimmerman and K. D. Janda: *J. Org. Chem.* **69**, 8829–8835 (2004).
51) H. Matsushita, S.-H. Lee, K. Yoshida, B. Clapham, G. Koch, J. Zimmermann and K. D. Janda: *Org. Lett.* **6**, 4627–4629 (2004).
52) D. S. Tan: *Nature Chem. Biol.* **1**, 74–84 (2005), and references therein.