Synthetic Methods

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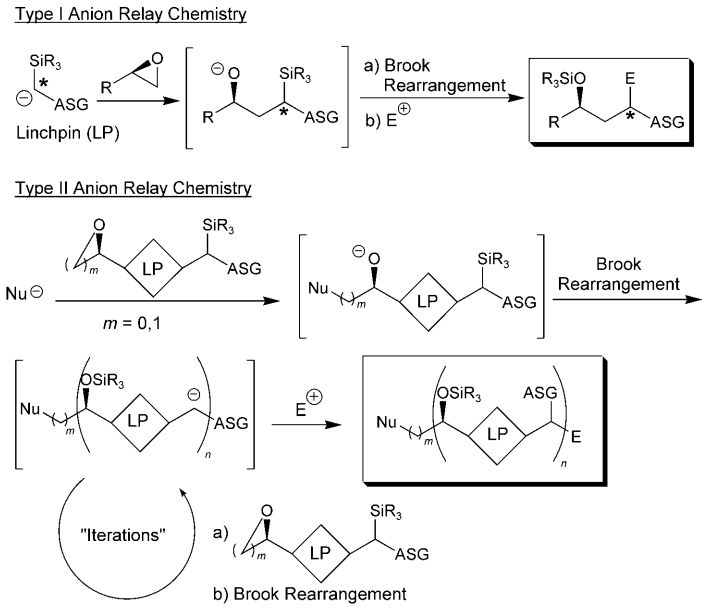
Ortho-TMS Benzaldehyde: An Effective Linchpin for Type II Anion Relay Chemistry (ARC)**

Amos B. Smith, III, Won-Suk Kim, and William M. Wuest*

Nature, with beautiful elegance, constructs natural products often in iterative fashion with both superb efficiency and exquisite stereochemical control.[1] For more than 100 years chemists have atempted to mimic the elegance of nature with laboratory syntheses. However, the shortcomings of many synthetic ventures lie in the multistep sequences, often leading to minimum structure augmentation, in conjunction with isolation and purification at each stage, leading to inefficient material advancement. Fortunately, multicomponent reactions[2] hold considerable promise of alleviating this inefficiency by orchestrating the conversion of simple starting materials, in a single (one-pot) operation, to advanced intermediates of high structural complexity without the need for multiple isolations and purifications.[3] Towards this end, we recently turned to the development of multicomponent reaction sequences exploiting anion relay chemistry (ARC).[4]

At the highest level, the ARC tactic can be divided into two processes involving anion migration, either through bonds or though space, the latter requiring the availability of a carrier to transport the negative charge. A simple example of a "through-bond" anion relay is the conjugate addition, through the π-system, with subsequent capture of the intermediate enolate. For "through-space" anion relay two possibilities exist involving σ-bonds (Type I and II ARC), the difference residing in the resulting locus of the transposed anion.

Type I ARC is defined as a multicomponent coupling (Scheme 1), wherein a linchpin nucleophile reacts with an electrophile to generate an oxyanion that subsequently transfers (or relays) the negative charge back to the initiating site, followed by reaction with a suitable electrophile. The Type II process entails reaction of a nucleophile with a bifunctional electrophilic linchpin to generate an anionic species that relays the negative charge to a different locus, whence it reacts with a second electrophile.



Scheme 1. Type I and II anion relay chemistry (ARC). ASG = anion stabilising group.

An important feature of the Type II ARC process is the potential for iteration with a sequential series of bifunctional linchpins, a process not dissimilar to living polymerization.[5]

In 1997, based on the early work by the groups of Matsuda,[6] Tietze,[7] and Oshima,[8] we introduced an example of the Type I ARC process involving mono-silyl dithianes,[9] which, in conjunction with a solvent-controlled Brook rearrangement,[10] led to the development of an effective three-component union protocol employing a wide variety of different second electrophiles. The utility of this process was subsequently demonstrated by completion of several natural product total syntheses, including (+)-spongistatins 1 and 2,[11] and more recently (−)-indolizidine 223AB and alkaloid (−)-205B, the latter two utilizing aziridine as the second electrophile.[12]

We extended the ARC concept, in 2006, to the Type II process, now employing bifunctional linchpins (see Figure 1 for examples, **1** and (−)-**2**), which, in conjunction with

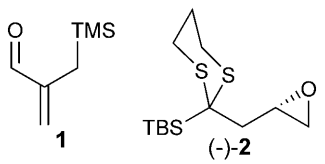


Figure 1. Type II ARC bifunctional linchpins utilized in natural product synthesis.

[*] A. B. Smith, III, W.-S. Kim, W. M. Wuest
Department of Chemistry
Penn Center for Molecular Discovery and Monell Chemical Senses Center
University of Pennsylvania, Philadelphia, PA 19104 (USA)
E-mail: smithab@sas.upenn.edu

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solvent-controlled Brook rearrangements, led to elaboration of a number of advanced intermediates utilized in the construction of a gorgonian sesquiterpene[4d] and the southern C(1)–C(25) fragment of the marine natural product spirastrellolide A.[4e]

The versatility of the Type II ARC tactic is, however, limited by the number of viable, readily available bifunctional linchpins that have been successfully implemented in the multicomponent tactic. Convinced of the considerable synthetic utility of the ARC tactic, we initiated a program to design, synthesize, and test the viability of several new bifunctional linchpins.[4] A central design element of any successful bifunctional linchpin comprises the appropriate placement of an electrophilic center relative to an anion stabilizing group (ASG), such that intramolecular anion transfer is both feasible and effective (Scheme 1).

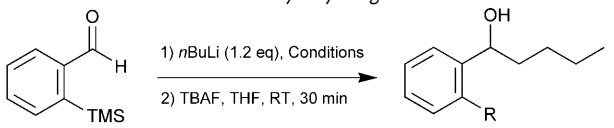
Building on our earlier successful incorporation of the dithiane,[9] nitrile,[4d] and allyl[4d] functionalities as ASGs in bifunctional linchpins, in conjunction with the recent work of Takeda,[13] Moser,[14] and Xian[15], we reasoned that *ortho*-TMS benzaldehyde (**3**, TMS = trimethylsilyl) held considerable promise as an effective linchpin for the Type II ARC process. Specifically, the early work of Moser and co-workers[14] demonstrated that strong electron-withdrawing groups, for example a chromium tricarbonyl moiety, are required to facilitate the Brook rearrangement in aryl systems. The precedent of Takeda and co-workers[13] further suggested that additives, such as copper(I), would facilitate the silyl-transfer process.

Accordingly, we explored a variety of reaction conditions, discovering that low temperature and a less-polar solvent than THF (−78 °C and Et_2O) comprise a prerequisite for success (Table 1). It was also evident that when either copper iodide or hexamethylphosphoramide (HMPA) were independently added, only minor amounts of the Brook-rearranged product (**5**) were isolated. However, when a 1:1 mixture of HMPA and THF containing 1.2 equivalents of CuI was added at −78 °C, silyl migration was complete within 30 min (Table 1, entry 7). Presumably, CuI, in conjunction with HMPA, promotes silyl transfer by stabilizing the resultant aryl carbanion.

With optimized Brook rearrangement conditions in hand, we explored the versatility of linchpin **3** in the Type II ARC process with a variety of electrophiles. A series of carbon- and heteroatom-based electrophiles proved viable, generating multicomponent products, **6a–g** and **7** in modest to good yields (Table 2). Of particular significance, a multicomponent palladium-mediated cross-coupling reaction proved feasible employing *n*BuLi, linchpin **3**, and vinyl bromide with 3 mol% $[Pd(PPh_3)_4]$ to furnish **6g**; the yield was 56% (Table 2, entry 8). To our knowledge, this result comprises the first report of a palladium-mediated Type II ARC process. Further studies are ongoing in our laboratory.

To investigate further the versatility of linchpin **3**, a series of nucleophiles were employed (Table 3). Addition of the lithium anions derived from methyl, allyl, vinyl, and phenyl

Table 1: Additive effects on the aryl-silyl migration.[a]

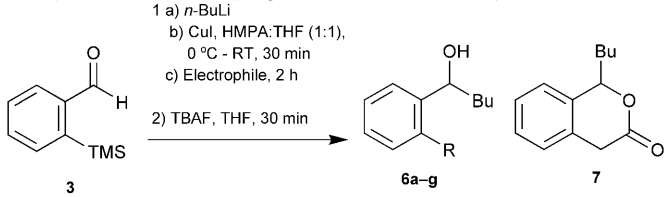


3 — **4**: R = TMS; **5**: R = H

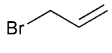
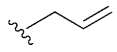
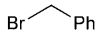
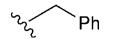
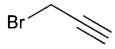
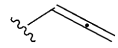
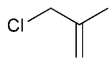
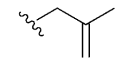
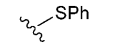
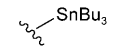
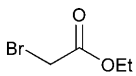
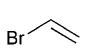
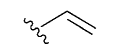
Entry	Solvent	Additive	Temperature/ Time	Yield **4** [%]	Yield **5** [%]
1	THF	–	−78 °C/30 min	87	0
2	Et_2O	–	−78 °C/30 min	88	0
3	Et_2O	–	0 °C/30 min	88	0
4	Et_2O	CuI (1.2 eq)	−78 °C/30 min then RT/1 h	73	< 5
5	Et_2O	HMPA:THF (1:1)	−78 °C/30 min then RT/1 h	46	24
6	Et_2O	CuI (0.6 eq), HMPA: Et_2O (1:1)	−78 °C/30 min then RT/30 min	0	52
7	Et_2O	CuI (1.2 eq), HMPA:THF (1:1)	−78 °C/30 min then RT/30 min	0	74

[a] TBAF = tetra-*n*-butylammonium fluoride, HMPA = hexamethylphosphoramide.

Table 2: Three-component linchpin coupling of *ortho*-TMS benzaldehyde with a series of electrophiles.



3 — **6a–g** — **7**

Entry	Electrophile	R	Product	Yield [%]
1			**6a**	69
2			**6b**	55
3			**6c**	58[a]
4			**6d**	64
5	PhS-SPh		**6e**	71
6	Bu_3SnCl		**6f**	65
7			**7**	50[b]
8			**6g**	56[c]

[a] propargyl bromide, 12 h; [b] 2% HCl in EtOH was used to deprotect the TMS group, 1 h; [c] vinyl bromide, 3 mol% $[Pd(PPh_3)_4]$, THF.

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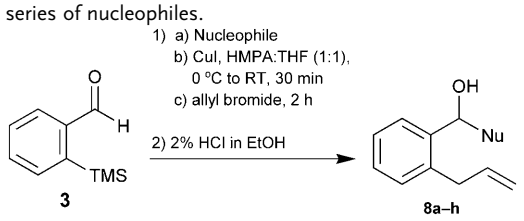
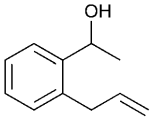
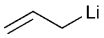
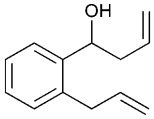
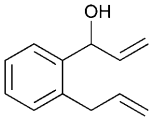
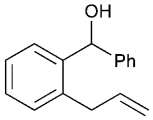
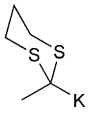
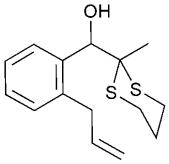
Table 3: Three-component linchpin coupling of *ortho*-TMS benzaldehyde with a series of nucleophiles.



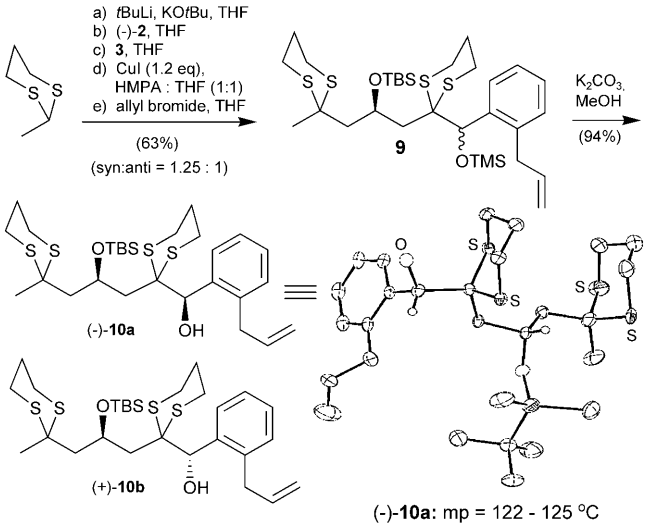
3 **8a–h**

Entry	Nucleophile	Product		Yield [%]
1	MeLi		**8a**	68
2			**8b**	66
3			**8c**	68
4	PhLi		**8d**	60
5			**8e**	78[a]

[a] *t*BuLi, KO*t*Bu, −78 °C, 30 min.

halides[16] as well as 2-methyl-1,3-dithiane[17] furnished **8a–e** with good efficiency (ca > 60%) after Brook rearrangement and subsequent allylation. Turning next to explore the Type II ARC process in an iterative manner, we applied the optimized Type II conditions to a four-component union sequence employing linchpins (−)-**2** and **3** (Scheme 2). Pleasingly, a 63% yield of the coupled product (**9**) was obtained, albeit, unsurprisingly, with poor diastereoselectivity (1.25:1) at the carbanol site. Removal of the TMS-group with methanolic potassium carbonate[18] followed by chromatographic separation of the resulting diastereomers furnished alcohols (−)-**10a** and (+)-**10b** with an overall yield of 59% from 2-methyl-1,3-dithiane. Single-crystal X-ray analysis defined the relative and absolute stereochemistry of (−)-**10a**, the latter by the anomalous dispersion technique. With both diastereomers of **10** secured, we advanced each isomer towards a "proof of concept" sequence for construction of "natural product-like" libraries.

Union of both alcohols (**10a**,**b**) with 4-pentenoic acid, followed by ring-closing metathesis (RCM), implementing the recent conditions reported by Grubbs and co-workers,[19] provided macrolides (−)-**12a** and (+)-**12b** in high yield (Scheme 3). It should be noted that a wide variety of commercially available acids or alkyl halides hold the promise



Scheme 2. Optimized four-component linchpin union implementing *ortho*-TMS benzaldehyde.

of a diverse series of macrolides and cyclic ethers, respectively. Removal of both dithiane moieties according to the Corey–Erickson protocol (NCS and $AgNO_3$ in MeCN:H_2O)[20] led to diketones (−)-**13a** and (+)-**13b** in 65 and 67% yields, which in turn were subjected to acid-mediated removal of the silyl groups[14] to provide the epimeric "natural product-like" targets. From the perspective of diversity-oriented synthesis, macrolactones (−)-**14a** and (+)-**14b** were constructed employing linchpins (−)-**2** and **3** in the Type II ARC process in 13% and 12% overall yield, respectively. Currently, we are testing this "proof of concept" sequence by exploiting a variety of nucleophiles, electrophiles, and acids with (−)-**2** and **3** to create an array of new "natural product-like" chemical entities (that is, those containing five points of diversity) for the NIH Roadmap Program.[21]

In summary, we have developed and implemented *ortho*-TMS benzaldehyde (**3**) as an effective bifunctional linchpin to expand the synthetic versatility of the Type II ARC tactic. In addition, we uncovered a palladium-mediated cross-coupling process applicable to the ARC tactic, the first of its kind. Finally, the synthesis of (−)-**14a** and (+)-**14b** comprises a "proof of concept" sequence to "natural product-like" compounds.

Experimental Section

9: KO*t*Bu (1.0 M in THF, 9.7 mL, 9.7 mmol, 1.26 equiv) and *t*BuLi (1.7 M in pentane, 5.7 mL, 9.7 mmol, 1.26 equiv) were added to a precooled (−78 °C) solution of 2-methyl-1,3-dithiane (1.24 g, 9.2 mmol, 1.2 equiv) in THF (15 mL). The resulting solution was stirred at −78 °C for 30 min, and a solution of epoxide (−)-**2** (2.24 g, 7.7 mmol, 1.0 equiv) in THF (15 mL) was added. The mixture was stirred for 20 min at −78 °C and then a solution of aldehyde **3** (1.64 g, 9.2 mmol, 1.2 equiv) in THF (15 mL) was added by cannula. After stirring for 30 min at −78 °C, the resulting solution was transferred by cannula to a mixture of CuI (142.6 mg, 0.75 mmol, 1.2 equiv) and

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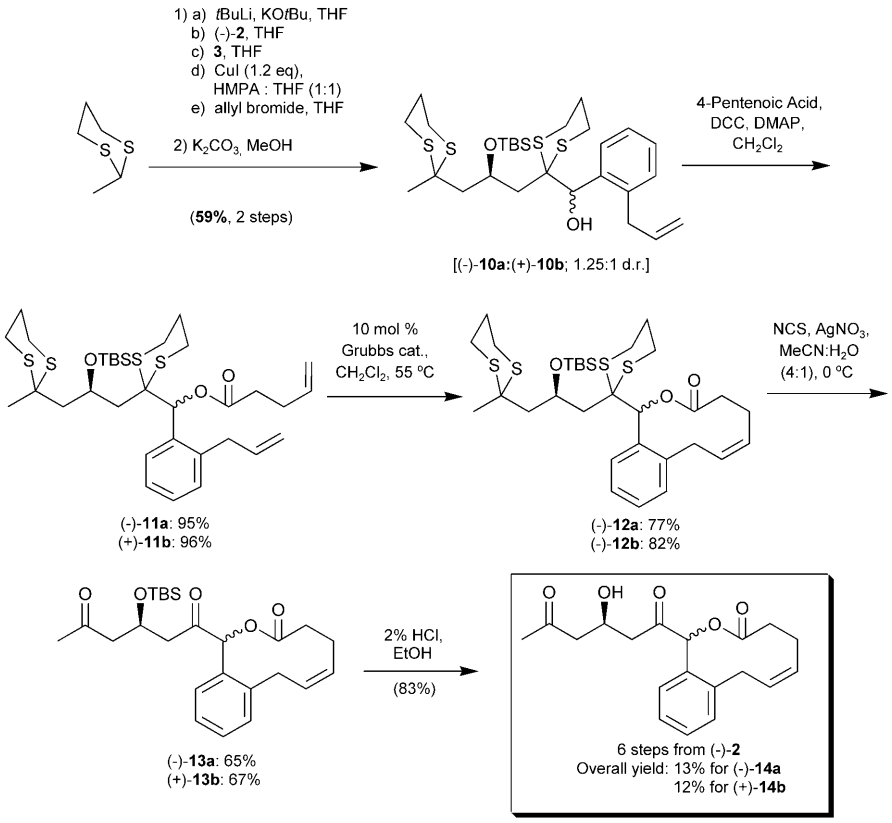

Scheme 3. "Proof of concept" library of "natural product-like" compounds utilizing type II ARC. DCC = dicyclohexylcarbodiimide, DMAP = 4-dimethylaminopyridine

HMPA/THF (10 mL/10 mL) at 0 °C, then warmed to ambient temperature and stirred for 30 min. Allyl bromide (2.0 mL, 23.1 mmol, 3.0 equiv) was next added at ambient temperature and after 1 h, the reaction was quenched with saturated aqueous NH_4Cl solution (100 mL). The resulting mixture was then extracted with Et_2O (100 mL × 3) and the organic layers were combined, washed with brine (100 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography on silica gel (Et_2O/hexane; 1/50), provided a 1.25:1 diastereomeric mixture of **9** (3.13 g, 4.87 mmol, 63 %) as pale yellow oil. R_f 0.8 (hexane/Et_2O = 10/1).

(−)-**10a**, (+)-**10b**: At ambient temperature, K_2CO_3 (4.17, 30.2 mmol, 10.0 equiv) was added to a methanolic (40 mL) solution of **9** (1.94 g, 3.02 mmol, 1.0 equiv) and stirred overnight. The reaction was diluted with H_2O (100 mL) and extracted with Et_2O (3 × 50 mL). The organic layers were combined, washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography on silica gel, (Et_2O/hexane; 1/10) provided two separable diastereomers (−)-**10a** as solid and (+)-**10b** as pale yellow oil (1.62 g, 2.84 mmol, 94 %). R_f 0.2 (hexane/Et_2O = 10/1).(−)-**10a**: $[\alpha]^{20}_D$ −0.90 deg cm^3 g^{-1} dm^{-1} (*c* 1.0 g cm^{-3} $CDCl_3$); R_f 0.2 (10:1 hexane/diethyl ether). IR (film) $\tilde{\nu}$ = 3434 (m), 2927 (s), 2855 (s), 1471 (m), 1254 (s), 1090 (s), 1028 (s), 775 cm^{-1} (s); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.78–7.76 (m, 1H), 7.25–7.22 (m, 2H), 7.17–7.16 (m, 1H), 6.04–5.96 (m, 1H), 5.29 (s, 1H), 5.09 (dd, *J* = 10.0 and 1.5 Hz, 1H), 5.03 (dd, *J* = 17.0 and 2.0 Hz, 1H), 4.59–4.55 (m, 1H), 3.81 (dd, *J* = 16.0 and 6.5 Hz, 1H), 3.63 (br, 1H), 3.55 (dd, *J* = 16.0 and 6.0 Hz, 1H), 3.12–3.06 (m, 1H), 3.03–2.94 (m, 2H), 2.85–2.62 (m, 6H), 2.44 (dd, *J* = 15.5 and 6.5 Hz, 1H), 2.05–1.81 (m, 6H), 1.73 (s, 3H), 0.83 (s, 9H), 0.12 (s, 3H), −0.04 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 138.9, 137.5, 137.0, 129.6, 129.5, 128.0, 125.6, 115.9, 73.3, 68.4, 58.3, 50.7, 48.5, 46.3, 37.9, 29.5, 27.6, 27.1, 26.7, 26.2, 26.1, 25.2, 24.0, 18.1, −3.35, −3.4 ppm; high resolution mass spectrum (ES$^+$) *m/z* 593.2061 [(*M* + Na)$^+$; calcd for $C_{28}H_{46}O_2S_4SiNa$: 593.2048]. (+)-**10b**: $[\alpha]^{20}_D$ +18.6 deg cm^3 g^{-1} dm^{-1} (*c* 0.5 g cm^{-3} $CDCl_3$); IR (film) $\tilde{\nu}$ = 3440 (m), 2952 (s), 2856 (s), 1468 (m), 1254 (s), 1092 (s), 1026 (s), 775 cm^{-1} (s); ^{1}H NMR (500 MHz, $CDCl_3$) δ = .75–7.74 (m, 1H), 7.26–7.20 (m, 2H), 7.18–7.17 (m, 1H), 6.04–5.96 (m, 1H), 5.26 (s, 1H), 5.09 (dd, *J* = 10.5 and 1.5 Hz, 1H), 5.04 (dd, *J* = 17.0 and 1.5 Hz, 1H), 4.60–4.56 (m, 1H), 3.92 (d, *J* = 3.5 Hz, 1H), 3.79 (dd, *J* = 16.0 and 6.5 Hz, 1H), 3.58 (dd, *J* = 16.0 and 6.5 Hz, 1H), 3.06–3.01 (m, 1H), 2.97–2.92 (m, 1H), 2.91–2.67 (m, 7H), 2.44 (dd, *J* = 15.5 and 5.0 Hz, 1H), 2.32 (dd, *J* = 15.5 and 6.0 Hz, 1H), 1.96 (dd, *J* = 8.0 and 3.5 Hz, 1H), 1.94–1.80 (m, 4H), 1.72 (s, 3H), 0.91 (s, 9H), 0.22 (s, 3H), 0.20 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 138.6, 137.5, 137.1, 129.6, 129.3, 127.8, 125.4, 116.0, 73.0, 68.9, 58.3, 49.9, 48.0, 45.0, 37.7, 29.3, 27.6, 27.0, 26.6, 26.2, 26.1, 25.1, 24.2, 18.1, −3.4 ppm; high resolution mass spectrum (ES$^+$) *m/z* 593.2049 [(*M* + Na)$^+$; calcd for $C_{28}H_{46}O_2S_4SiNa$: 593.2048].

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[1] a) D. E. Cane, C. T. Walsh, C. Khosla, *Science* **1998**, *282*, 63; b) C. T. Walsh. *ChemBioChem* **2002**, *3*, 125.
[2] A. Dömling, I. Ugi, *Angew. Chem.* **2000**, *112*, 3300; *Angew. Chem. Int. Ed.* **2000**, *39*, 3168.
[3] a) S. H. Bertz, *J. Am. Chem. Soc.* **1981**, *103*, 3599; b) S. H. Bertz, T. J. Sommer, *Chem. Commun.* **1997**, 2409; c) P. A. Wender, M. P. Croatt, B. Witulski, *Tetrahedron* **2006**, *62*, 7505, and references therein.
[4] a) A. B. Smith III, M. O. Duffey, *Synlett* **2004**, 1363; b) A. B. Smith III, M. Xian, *J. Am. Chem. Soc.* **2006**, *128*, 66; c) A. B. Smith III, M. Xian, W. S. Kim, D. S. Kim, *J. Am. Chem. Soc.* **2006**, *128*, 12368; d) A. B. Smith III, D. S. Kim, M. Xian, *Org. Lett.* **2007**, *9*, 3307; e) A. B. Smith III, D. S Kim, M. Xian, *Org. Lett.* **2007**, *9*, 3311.
[5] A. Hirao, S. Nakahama, *Acta Polym.* **1998**, *49*, 208.
[6] I. Matsuda, S. Murata, Y. Ishii, *J. Chem. Soc. Perkin Trans. 1* **1979**, *1*, 26.
[7] L. F. Tietze, H. Geissler, J. A. Gewart, U. Jakobi, *Synlett* **1994**, 511.
[8] H. Shinokubo, K. Miura, K. Oshima, K. Utimoto, *Tetrahedron* **1996**, *52*, 503.
[9] A. B. Smith III, A. M. Boldi, *J. Am. Chem. Soc.* **1997**, *119*, 6925.
[10] a) A. G. Brook, *J. Am. Chem. Soc.* **1958**, *80*, 1886; b) W. H. Moser, *Tetrahedron* **2001**, *57*, 2065.
[11] a) A. B. Smith III, V. A. Doughty, Q. Lin, L. Zhuang, M. D. McBriar, A. M. Boldi, W. H. Moser, N. Murase, K. Nakayama, M. Sobukawa, *Angew. Chem.* **2001**, *113*, 197; *Angew. Chem. Int. Ed.* **2001**, *40*, 191; b) A. B. Smith III, Q. Lin, V. A. Doughty, L. Zhuang, M. D. McBriar, J. K. Kerns, C. S. Brook, N. Murase, K.

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Nakayama, *Angew. Chem.* **2001**, *113*, 202; *Angew. Chem. Int. Ed.* **2001**, *40*, 196.
[12] a) A. B. Smith III, D. S. Kim, *Org. Lett.* **2004**, *6*, 1493; b) A. B. Smith III, D. S. Kim, *Org. Lett.* **2005**, *7*, 3247; c) A. B. Smith III, D. S. Kim, *J. Org. Chem.* **2006**, *71*, 2547.
[13] H. Taguchi, K. Takami, A. Tsubouchi, T. Takeda, *Tetrahedron Lett.* **2004**, *45*, 429.
[14] a) W. H. Moser, K. E. Endsley, J. T. Colyer, *Org. Lett.* **2000**, *2*, 717; b) W. H. Moser, J. Zhang, C. S. Lecher, T. L. Frazier, M. Pink, *Org. Lett.* **2002**, *4*, 1981,.
[15] N. O. Devarie-Baez, B. J. Shuhler, H. Wang, M. Xian, *Org. Lett.* **2007**, *9*, 4655.
[16] K. S. Dunne, S. E. Lee, V. Gouverneur, *J. Organomet. Chem.* **2006**, *691*, 5246.
[17] M. Schlosser, S. Strunk, *Tetrahedron Lett.* **1984**, *25*, 741.
[18] D. T. Hurst, A. G. McInnes, *Can. J. Chem.* **1965**, *43*, 2004.
[19] R. H. Grubbs, *Tetrahedron* **2004**, *60*, 7117; also see: H. E. Blackwell, D. J. O'Leary, A. K. Chatterjee, R. A. Washenfelder, D. A. Bussmann, R. H. Grubbs, *J. Am. Chem. Soc.* **2000**, *122*, 442.
[20] E. J. Corey, B. W. Erickson, *J. Org. Chem.* **1971**, *36*, 3553.
[21] D. M. Huryn, N. D. P. Cosford, *Annu. Rep. Med. Chem.* **2007**, *42*, 401; also see http://nihroadmap.nih.gov/.

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