Alkaloids

DOI: 10.1002/anie.200801793

Synthesis of Marine Alkaloids from the Oroidin Family**

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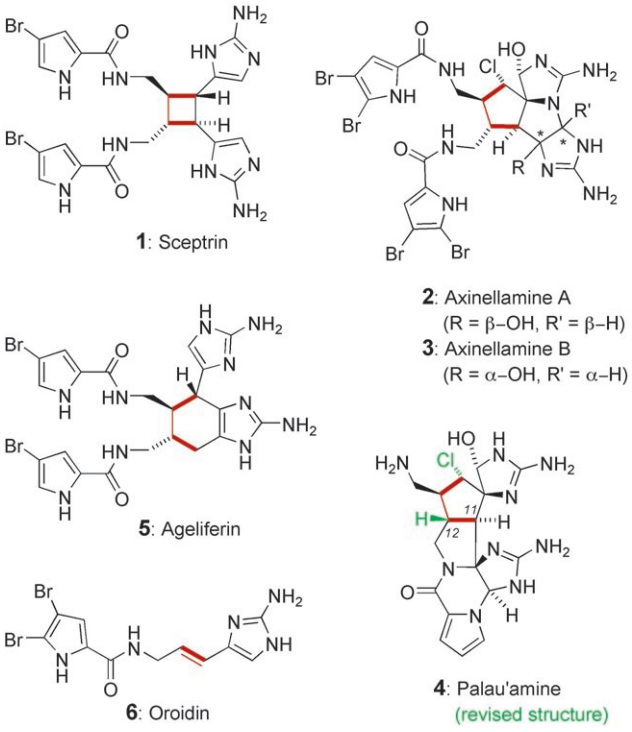
alkaloids · natural products · oroidin · synthetic methods · total synthesis

Polyheterocyclic, nitrogen-rich alkaloids probably rank among the most challenging synthetic targets in organic synthesis. In this regard the oroidin class of alkaloids has received much attention recently (Scheme 1),[1] among them sceptrin (**1**), the axinellamines (**2** and **3**), palau'amine (**4**), and ageliferin (**5**). These marine natural products arise from one precursor, the rather inconspicuous pyrrolo-imidazole alkene oroidin (**6**) first identified in 1971.[2] Dimerization of **6** and consecutive functionalizations are currently believed to give rise to this impressive array of densely functionalized, highly oxidized, polycyclic oroidin alkaloids.[1e,3] The similarity of these molecules and their often simultaneous occurrence is indicative of common biosynthetic pathways, and furthermore suggests the generation of a divergent natural product compound "library" from one simple precursor.[4]



Scheme 1. Selected oroidin alkaloids of marine origin. Oroidin-derived central bonds are highlighted in red.

Until lately, palau'amine (**4**) did not fit well into this unifying picture, mostly for stereochemical reasons. In the original work the junction of the two five-membered rings had been assigned as *cis*.[5] However, thorough spectroscopic investigation[6,1e] was recently complemented by synthesis (vide infra),[7] which likewise suggested the C-11/C-12 ring fusion in **4** to be in the thermodynamically less stable *trans* configuration (as shown in Scheme 1). This structural revision now makes palau'amine a full member of the oroidin alkaloid group and raises hope that integrative strategies for their total synthesis might be developed in the near future.

All these pyrrole–imidazole alkaloids feature a four-, five-, or six-membered central carbocyclic ring and an individual connectivity of the pendant side chain heterocycles. These unique patterns have stimulated many synthetic efforts and led to distinct solutions for each of the scaffolds (Scheme 2).[8] In one early hypothesis on the biosynthesis, the six-membered ring of the ageliferins **7** was proposed to arise from a [4 2] cycloaddition.[3a] This was implemented in synthesis first by Ohta et al. (**8**→**7**).[9] A Mn^{III}-promoted radical cascade annulation from the imidazolone **9** was developed by Chen and Tan.[10] In their total synthesis of **5**, Baran et al. successfully implemented a double ring-enlargement of the four-membered-ring precursor sceptrin (**1**) to **5** under high-temperature conditions.[11] The sceptrin scaffold **10** itself has been elaborated by [2+2] photocycloadditions, for instance from (*E*)-1,4-dichloro-2-butene and maleic anhydride[12] or by fragmentation of the photochemically accessible oxaquadricyclane **11**.[13]

The biggest challenge is probably posed by the fully substituted five-membered-ring scaffolds **12** present in the axinellamines and palau'amines. For these, biomimetic linear assembly, ring enlargements of four-membered sceptrin-like precursor **10**, or oxidative ring contractions of six-membered

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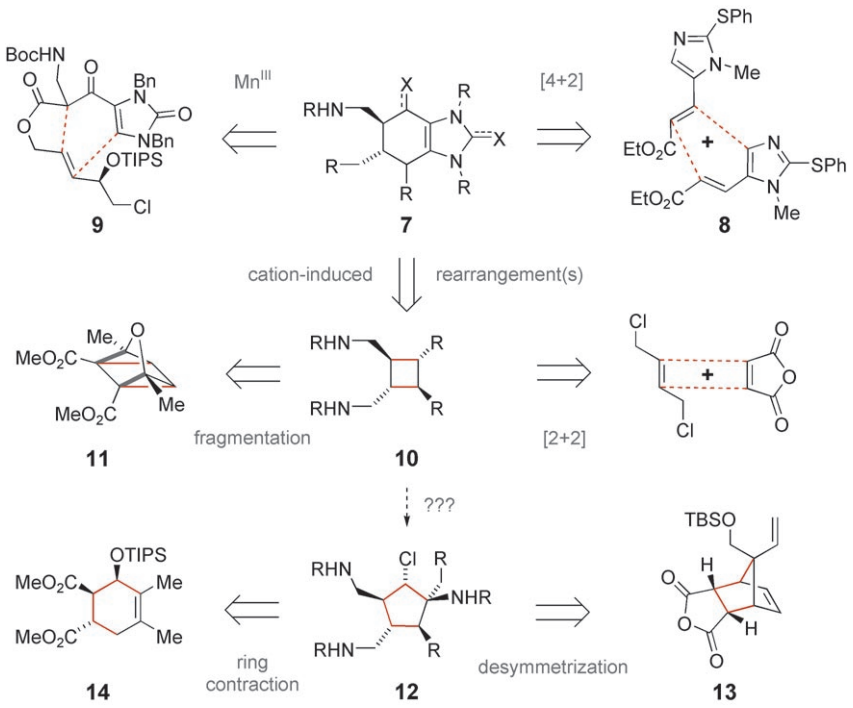
[**] Research by the authors was supported by the Deutsche Forschungsgemeinschaft (Emmy-Noether young investigator grants AR493-1 and -2 to H.D.A.) and the Fonds der Chemischen Industrie.

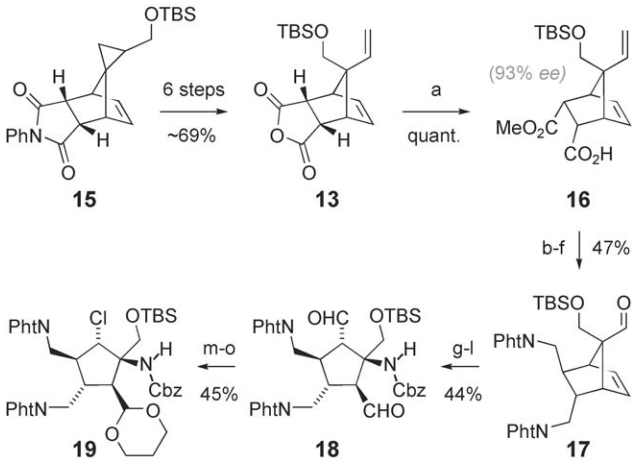


Scheme 2. Some synthetic routes to the related core structures of the oroidin alkaloids. Bn = benzyl, Boc = *tert*-butoxycarbonyl, TIPS = triisopropylsilyl, TBS = *tert*-butyldimethylsilyl.

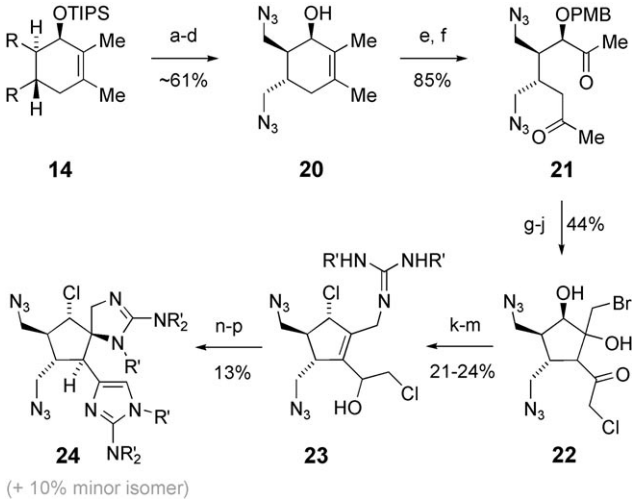
ageliferin-like precursors **7** have been proposed.[1,3] While the ring-enlargement **10**→**12** still waits to be realized experimentally, ring-contractions **7**→**12** have been executed with considerable success.[14] However, "abiotic" syntheses of scaffolds **12** have proven to be tantamount.[1] For instance, Carreira et al. already reported the first enantioselective synthesis of the axinellamine core **12** by desymmetrization of anhydride **13** in 2000.[15] Recently, Baran et al. completed the first total synthesis of axinellamines[16] (**2**, **3**) in racemic form by using a ring contraction of the cyclohexene **14**.[17]

Starting point for the enantioselective synthesis[15] of **19** was the readily available Diels–Alder adduct **15** (Scheme 3), which was converted to the sterically more congested anhydride **13** in six steps. Desymmetrization of *meso*-**13** to the chiral monoester **16** was achieved in 93% *ee* by using the method of Bolm et al.,[18] and epimerization of the more acidic ester α-CH group followed by reduction, introduction of the nitrogen substituents by Mitsunobu displacement, and chemoselective degradation of the vinyl group, provided aldehyde **17**. A third nitrogen atom was now introduced by oxidation of **17** and Curtius degradation, and ozonolysis of the alkene followed by thermodynamically driven epimerization delivered the all-*trans* dialdehyde **18**. The aldehyde group proximal to the carbamate nitrogen atom could now be regioselectively converted into its monoacetal, and degradation of a Barton ester derived from the remaining aldehyde function installed the secondary chloride **19** stereoselectively. Overall, 21 steps gave access to the axinellamine scaffold **19** with complete stereocontrol in 6.4% yield from **15**.[15]

The first completed total synthesis of the axinellamines[16] followed a very straightforward approach (Scheme 4). First, the racemic Diels–Alder product **14** was elaborated to diazide **20** in four standard transformations.[17] Re-installation of a PMB protecting group on the secondary alcohol and ozonolysis provided diketone **21**, which was α,ω-dibrominated via the bis-silylenol ether. Intramolecular aldol addition under solvent-free conditions, exchange of the most reactive bromide for a more stable chloride, and deprotection gave diol **22**. To install the third stereogenic substituent, the tertiary hydroxy group had to be eliminated and the secondary hydroxy group displaced by Cl^-, which was achieved in a one-pot reaction with SO_2Cl_2. Regioselective displacement of the bromide substituents with protected guanidine was then achieved after Luche reduction of the enone carbonyl (→**23**). Upon reoxidation to the enone, spirocyclization occurred, but high temperatures were found to be essential to favor the correct diastereomer (1.3:1). The 2-aminoimidazole was then introduced by displacement and in situ condensation with Boc-guanidine, and spirocycle **24** could be purified after derivatization (Boc_2O). Only 16 steps were required to generate the protected axinellamine precursor **24** from **14** with two heterocycles already installed (overall yield 0.7%).

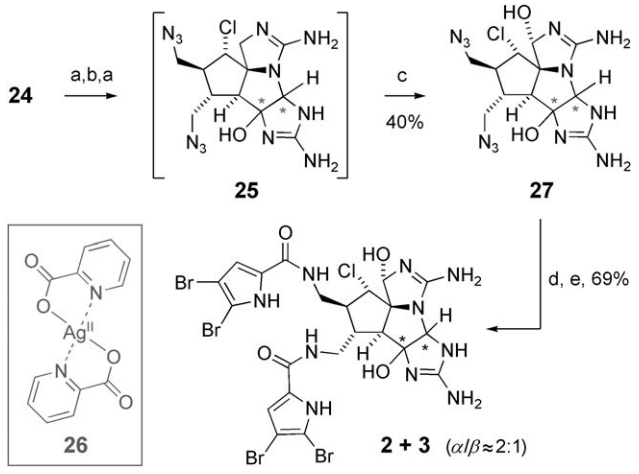


Scheme 3. Enantioselective synthesis of the axinellamine core (Carreira et al.).[15] a) Quinine, MeOH, CCl_4, toluene; b) lithium diisopropylamide, Et_2O; c) $LiAlH_4$, Et_2O; d) phthalimide, DEAD, PPh_3; e) 5% OsO_4·$(DHQD)_2Pyr$, NMO, THF/H_2O; f) $NaIO_4$, K_2CO_3, THF/H_2O; g) $NaClO_2$, DMSO, *t*BuOH/H_2O; h) $(COCl)_2$, CH_2Cl_2; i) NaN_3, DMSO; j) benzene, reflux; k) LiOBn, THF; l) O_3, CH_2Cl_2, then PPh_3, K_2CO_3; m) 1,3-propanediol, PPTS, Et_2O; n) $KMnO_4$, *t*BuOH/H_2O; o) thiopyridine-*N*-oxide, EDC, DMAP, CCl_4. PhtN = phthalimido, Cbz = benzyloxycarbonyl, DEAD = diethylazodicarboxylate, $(DHQD)_2Pyr$ = hydroquinidine-2,5-diphenyl-4,6-pyrimidindiyl diether, NMO = 4-methylmorpholine-*N*-oxide, PPTS = pyridinium-*p*-toluenesulfonate, EDC = *N*′-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide, DMAP = 4-dimethylaminopyridine.



Scheme 4. Diastereoselective synthesis of the axinellamine core (Baran et al.).[16,17] a) $LiAlH_4$, THF; b) MsCl, pyridine; c) NaN_3, DMF, 100 °C; d) TBAF; e) PMBCl, NaH, DMF; f) O_3, MeOH; g) TMSOTf, $EtNiPr_2$, then NBS; h) SiO_2, no solvent, 47 °C; i) LiCl, DMF; j) 10% TFA; k) SO_2Cl_2, 2,6-lutidine, CH_2Cl_2; l) $NaBH_4$, $CeCl_3$, MeOH; m) *N*,*N*′-bis-Boc-guanidine, DBU, DMF; n) IBX, benzene, reflux; o) Boc-guanidine, THF, reflux; p) Boc_2O, NEt_3, cat. DMAP, CH_2Cl_2. R = COOMe, R′ = Boc, PMB = *para*-methoxybenzyl, MsCl = methylsulfonyl chloride, TBAF = tetrabutylammonium fluoride, TMS = trimethylsilyl, NBS = *N*-bromosuccinimide, TFA = trifluoroacetic acid, DBU = 1,8-diazabicyclo-[5.4.0]undec-7-ene, IBX = *o*-iodoxybenzoic acid.

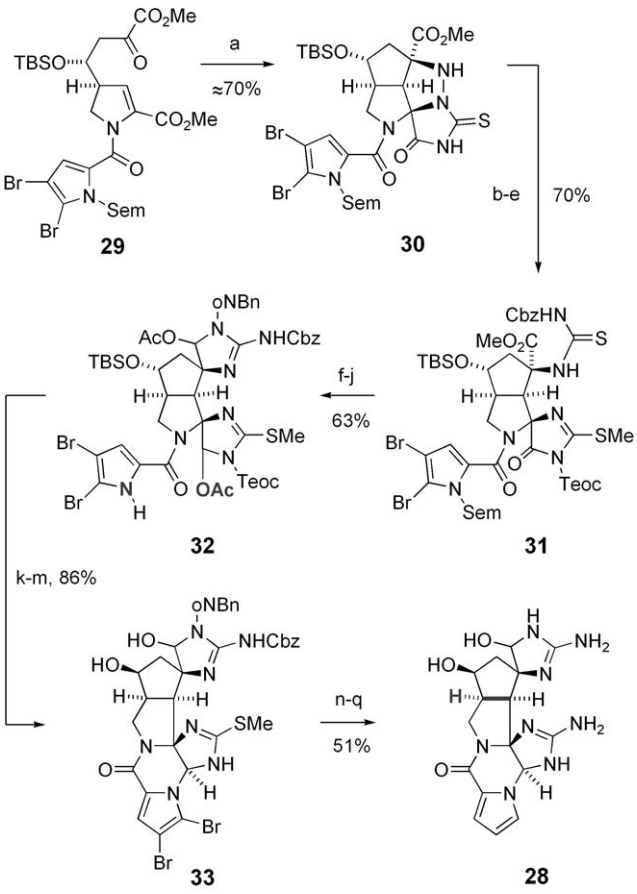
Only two oxidations now separated **24** from the axinellamide target connectivity (Scheme 5).[16] Baran et al. realized that the imidazole double bond might be selectively oxidized,[1c] and indeed found that after Boc deprotection of **24** the respective diol could be formed by DMDO, which on treatment with TFA condensed to aminal **25**. It can be speculated that in the aqueous reaction medium unwanted oxidations of the nitrogen atoms are suppressed by protonation.



Scheme 5. Completion of the axinellamine total synthesis (Baran et al.).[16] a) 67% TFA; b) DMDO, H_2O, 0 °C, c) **26**, H_2O, 50 °C; d) 1,3-propanedithiol, NEt_3, MeOH; e) 4,5-dibromopyrrole-2-yl-trichloromethyl ketone, $EtNiPr_2$, DMF, 45 °C. DMDO = 2,2-dimethyldioxirane.

The same in situ protection probably helped with the following transformation as well: The regioselective oxidation with the Ag^{II} complex **26**, which gave tetracycle **27** in only four steps and 40% yield from **24**. While it is not uncommon that methylene groups α to nitrogen atoms can be oxidized, the regioselectivity and control of overoxidation in this polyfunctionalized scaffold remains breathtaking! The axinellamides **2** and **3** were then swiftly reached by reduction of the azide groups followed by acylation with suitable pyrrole building blocks. The first total synthesis of **2** and **3** was thereby completed in 22 steps from **14** (overall yield 0.2%).

What remains to be solved is the palau'amine problem. Overman et al. recently provided synthetic material proving the newly assigned stereochemistry of **4** (Scheme 6). Key to the synthesis[7b] of the *epi*-palau'amine scaffold **28** was a distinctive bicyclization, which was achieved by an intramolecular 1,3-dipolar cycloaddition, to give the tetracycle **30** from the dihydropyrrole **29** in 70% yield.[7a] This elegant transformation fixed three contiguous stereocenters, two of



Scheme 6. Synthesis of the fully elaborated *epi*-palau'amine scaffold (Overman et al.).[7] a) Thiosemicarbazide, EtOH, 110 °C; b) SmI_2, THF/MeOH; c) MeI, $EtNiPr_2$, DMAP, CH_2Cl_2; d) TeocCl, $EtNiPr_2$, CH_2Cl_2; e) Cbz-NCS, CH_2Cl_2; f) EDC, oNBn-NH_2, $EtNiPr_2$, CH_2Cl_2; g) 10% TFA; h) TeocCl, $EtNiPr_2$, CH_2Cl_2; i) $NaBH_4$, MeOH/THF; j) Ac_2O, pyridine, DMAP; k) TBAF, THF; l) IBX, DMSO; m) $NaBH_4$, MeOH, 0 °C; n) mCPBA, CH_2Cl_2; o) NH_3, CH_2Cl_2, −78 °C; p) *hν*, dioxane; q) H_2, Pd/C, aq dioxane. Sem = 2-(trimethylsilyl)ethoxymethyl, Teoc = trimethylsilylethyloxycarbonyl, oNBn = *ortho*-nitrobenzyl, NCS = *N*-chlorosuccinimide, mCPBA = m-chloroperoxybenzoic acid.

them quaternary. Cleavage of the assisting N–N bond, thiohydantoin protection, and amine acylation provided the thiourea **31**, which was transformed into the protected imidazolone, doubly reduced, and protected to give the bisaminal **32**. The use of TBAF induced the removal of the Teoc- and TBS protecting groups and closure of the ketopiperazine ring as well, and inversion of the secondary alcohol by an oxidation–reduction sequence provided the hemiaminal **33**. Conversion of the isothiourea into the guanidine and deprotection yielded the *cis*-configured compound **28** in 17 steps and 14% total yield from **29** (ca. 31 steps and 2.4% yield from monoprotected 2-butene-diol), which was found by NMR spectroscopy to differ significantly from palau'amine (**4**). Nevertheless, this synthesis is characterized by thorough optimization and consecutive elegant buildup of the difficult heterocycles, and should be instrumental for future total synthesis efforts.

The oroidin alkaloids have helped to revitalize and advance heterocyclic chemistry by providing a stimulus for new chemical developments and elegant methodology.[1] With the stereochemical assignment of palau'amine (**4**) now proven, and the first total synthesis of the axinellamines (**2** and **3**) completed, the stage is set for new developments. Late-stage oxidations such as innovatively used by Baran et al. provide great opportunities for designing new synthesis routes and for the generation of complexity from common precursors. Indeed, exciting developments in C–H activation lend credit to the notion that such methods might become even more useful and broadly applicable in the future.[19] It is tangible that the findings highlighted here mark a beginning for many more future discoveries in this field.

Published online: May 30, 2008

[1] Some reviews: a) H.-D. Arndt, U. Koert in *Organic Synthesis Highlights 4* (Ed.: H.-G. Schmalz), Wiley-VCH, Weinheim, **2000**, pp. 241–250; b) H. Hoffmann, T. Lindel, *Synthesis* **2003**, 1753–1783; c) H. Du, Y. He, R. Sivappa, C. J. Lovely, *Synlett* **2006**, 965–992; d) S. M. Weinreb, *Nat. Prod. Rep.* **2007**, *24*, 931–948; e) M. Köck, A. Grube, I. B. Seiple, P. S. Baran, *Angew. Chem.* **2007**, *119*, 6706–6714; *Angew. Chem. Int. Ed.* **2007**, *46*, 6586–6594.

[2] S. Forenza, L. Minale, R. Riccio, E. Fattorusso, *J. Chem. Soc. D* **1971**, 1129–1130.

[3] a) R. Kinnel, H.-P. Gehrken, R. Swali, G. Skoporowski, P. J. Scheurer, *J. Org. Chem.* **1998**, *63*, 3281–3286; b) A. Al-Mourabit, P. Potier, *Eur. J. Org. Chem.* **2001**, 237–243; c) H. Garrido-Hernandez, M. Nakadai, M. Vimolratana, Q. Li, T. Doundolakis, P. G. Harran, *Angew. Chem.* **2005**, *117*, 775–779; *Angew. Chem. Int. Ed.* **2005**, *44*, 765–769.

[4] a) F. C. Schröder, J. J. Farmer, A. B. Attygale, S. R. Smedley, T. Eisner, J. Meinwald, *Science* **1998**, *281*, 428–431; b) R. Breinbauer, I. Vetter, H. Waldmann, *Angew. Chem.* **2002**, *114*, 3002–3015; *Angew. Chem. Int. Ed.* **2002**, *41*, 2878–2890; c) E. Gravel, E. Poupon, *Eur. J. Org. Chem.* **2008**, 27–42.

[5] R. B. Kinnel, H.-P. Gehrken, P. J. Scheurer, *J. Am. Chem. Soc.* **1993**, *115*, 3376–3377; see also ref. [3a].

[6] A. Grube, M. Köck, *Angew. Chem.* **2007**, *119*, 2372–2376; *Angew. Chem. Int. Ed.* **2007**, *46*, 2320–2324.

[7] a) J. D. Katz, L. E. Overman, *Tetrahedron* **2004**, *60*, 9559–9586; b) B. A. Lanman, L. E. Overman, R. Paulini, N. S. White, *J. Am. Chem. Soc.* **2007**, *129*, 12896–12900.

[8] For more complete coverage see refs. [1].

[9] I. Kawasaki, N. Sakaguchi, N. Fukushima, N. Fujioka, F. Nikaido, M. Yamashita, S. Ohta, *Tetrahedron Lett.* **2002**, *43*, 4377–4380.

[10] X. Tan, C. Chen, *Angew. Chem.* **2006**, *118*, 4451–4454; *Angew. Chem. Int. Ed.* **2006**, *45*, 4345–4348.

[11] a) P. S. Baran, D. P. O'Malley, A. L. Zografos, *Angew. Chem.* **2004**, *116*, 2728–2731; *Angew. Chem. Int. Ed.* **2004**, *43*, 2674–2677; b) B. H. Northrop, D. P. O'Malley, A. L. Zografos, P. S. Baran, K. N. Houk, *Angew. Chem.* **2006**, *118*, 4232–4236; *Angew. Chem. Int. Ed.* **2006**, *45*, 4126–4130.

[12] V. B. Birman, X.-T. Jiang, *Org. Lett.* **2004**, *6*, 2369–2371.

[13] a) P. S. Baran, A. L. Zografos, D. P. O'Malley, *J. Am. Chem. Soc.* **2004**, *126*, 3726–3727; b) D. P. O'Malley, K. Li, M. Maue, A. L. Zografos, P. S. Baran, *J. Am. Chem. Soc.* **2007**, *129*, 4762–4775.

[14] a) A. S. Dilley, D. Romo, *Org. Lett.* **2001**, *3*, 1535–1538; b) C. J. Lovely, H. Du, Y. He, H. V. Rasika-Dias, *Org. Lett.* **2004**, *6*, 735–738; c) see also refs. [1b] and [3c].

[15] J. T. Starr, G. Koch, E. M. Carreira, *J. Am. Chem. Soc.* **2000**, *122*, 8793–8794.

[16] D. O'Malley, J. Yamaguchi, I. S. Young, I. B. Seiple, P. S. Baran, *Angew. Chem.* **2008**, *120*, 3637–3639; *Angew. Chem. Int. Ed.* **2008**, *47*, 3581–3583.

[17] J. Yamaguchi, I. B. Seiple, I. S. Young, D. P. O'Malley, M. Maue, P. S. Baran, *Angew. Chem.* **2008**, *120*, 3634–3636; *Angew. Chem. Int. Ed.* **2008**, *47*, 3578–3580.

[18] C. Bolm, A. Gerlach, C. L. Dinter, *Synlett* **1999**, 195–196.

[19] A recent highlight: M. Christmann, *Angew. Chem.* **2008**, *120*, 2780–2783; *Angew. Chem. Int. Ed.* **2008**, *47*, 2740–2742.

