carbon has been removed by an oxidation process in the example presented here, which would suggest, that only stable oxides or oxidation-resistant compositions could be obtained following this pathway. However, carbon can also be removed by other reactions, such as high-temperature hydrogenation, which should allow the synthesis of compounds which are not stable against oxidation.

Experimental Section

Materials: The following materials, tetraethylorthosilicate (TEOS, 98%, Aldrich), furfuryl alcohol (98%, Fluka), trimethylbenzene (THB, 98%, Aldrich), and hydrochloric acid 37%, were used as received without further purification.

Synthesis of SBA-15: The synthesis of the SBA-15 was performed following published procedures[10] by first heating the reaction mixture at 40 °C for 4 h, followed by aging at 80 °C for 24 h. The filtered samples were calcined at 550 °C for 5 h with a heating rate of 1 °C min^{-1} to the final temperature. To improve the carburization, the SBA-15 (12 g) was stirred for 12 h in a solution of $AlCl_3$ (2 g) in ethanol, collected by filtration, and washed with ethanol.

Synthesis of CMK-3: CMK-3 was synthesized by the incipient wetness technique to introduce furfuryl alcohol into the pores of SBA-15 following two different procedures: 1) furfuryl alcohol was introduced as received in the channels of SBA-15, followed by carbonization of the infiltrated furfuryl alcohol with a heating rate of 1 °C min^{-1} from 80–150 °C, where the sample was kept at 150 °C for 3 h, then the temperature was increased from 150 °C to 300 °C at a rate of 1 °C min^{-1}, and, finally, the temperature was increased to 850 °C with a rate of 5 °C min^{-1} and maintained at this temperature for 4 h. 2) furfuryl alcohol, diluted with ethanol or TMB was introduced into SBA-15 and then carbonized following the procedure outlined in 1).

Synthesis of NCS-1: Under vigorous agitation CMK-3 (0.15 g) was impregnated drop by drop with TEOS (0.15 mL), then one drop of HCl solution (pH 1) was added under vigorous agitation. After 10 min, the sample was put into a box oven at 40 °C for 3 h and then at 80 °C for 3 h. Subsequently, the sample was removed, cooled, and the impregnation was repeated until the desired amount of TEOS (typically corresponding to a silica loading of 60%) was introduced. The sample was then heated to 700 °C in flowing nitrogen as described in the text, then calcined in a box furnace at 550 °C for 5 h in air with the heating rate of 1 °C min^{-1} to the final temperature. After that treatment, a white powder was obtained in a yield of typically 1.5–2 g SiO_2 g^{-1} CMK-3, depending on the pore volume of the CMK-3 starting material.

Characterization: Low-angle X-ray diffraction patterns were recorded with a Stoe STADI P diffractometer in the Bragg–Brentano (reflection) geometry. The step width was 0.02° 2θ at an acquisition time of 8 s per step.

Nitrogen adsorption isotherms were measured with an ASAP 2010 adsorption analyzer (Micromeritics) at liquid nitrogen temperature. Prior to the measurements, all samples were degassed at a temperature of 250 °C for at least 3 h. Pore sizes and pore-size-distribution curves were calculated from the adsorption branch, since calculation from the desorption branch might be influenced by network percolation effects and the instability of the meniscus at $p/p_0 = 0.42$.

TEM images were obtained with a HF2000 electron microscope from Hitachi equipped with a cold field emission gun. The acceleration voltage was 200 kV. Samples were prepared dry on a lacey carbon grid.

Received: June 19, 2002 [Z19566]

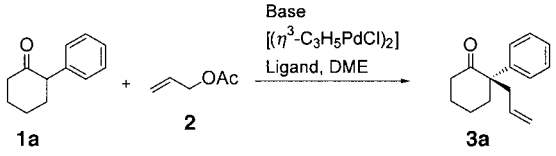
[1] S. A. Johnson, E. S. Brigham, P. J. Olivier, T. E. Mallouk, *Chem. Mater.* **1999**, *9*, 2448–2458.
[2] R. Joo, S. H. Jun, *J. Phys. Chem. B* **1999**, *103*, 7743–7746.
[3] J. Lee, S. Yoo, T. Hyeon, S. M. Oh, K. B. Kim, *Chem. Commun.* **1999**, 2177–2178.
[4] F. Schüth, *Stud. Surf. Sci. Catal.* **2001**, *135*, 1–13.
[5] for a survey, see: A. Stein, *Microporous Mesoporous Mater.* **2001**, *44–45*, 227–239.
[6] C. J. H. Jacobsen, C. Madsen, J. Houzvicka, I. Schmidt, A. Carlsson, *J. Am. Chem. Soc.* **2000**, *122*, 7116–7117.
[7] M. Schwickardi, W. Schmidt, F. Schüth, *Chem. Mater.* in print.
[8] H. J. Shin, R. Ryoo, M. Kruk, M. Jaroniec, *Chem. Commun.* **2001**, 349–350.
[9] Z. Liu, O. Terasaki, T. Oshuna, K. Hiraga, H. J. Shin, R. Ryoo, *ChemPhysChem* **2001**, *2*, 229–231.
[10] D. Zhao, J. Feng, Q. Huo, N. Melosh, G. H. Fredrickson, B. F. Chmelka, G. D. Stucky, *Science* **1998**, *279*, 548–552.
[11] J. Sauer, F. Marlow, F. Schüth, *Phys. Chem. Chem. Phys.* **2001**, *3*, 5579–5583.

Palladium-Catalyzed Asymmetric Allylic Alkylation of α-Aryl Ketones**

Barry M. Trost,* Gretchen M. Schroeder, and Jesper Kristensen

The generation of quatenary chiral centers through catalytic asymmetric alkylation of ketone enolates has been the subject of investigation in recent years.[1] The palladium-catalyzed asymmetric allylic alkylation (AAA) of prochiral nucleophiles represents one such strategy for the creation of quaternary chiral centers.[2] Given the success of stabilized nucleophiles such as β-ketoesters in palladium-catalyzed AAA[3,4] we inquired whether simple ketone enolates, perhaps the most important class of nucleophiles, would function. Previously, we reported the AAA of α'-blocked α-alkylcycloalkanones.[3a] Herein we report the palladium-catalyzed AAA of a series of α'-unblocked enolates: aryl ketone enolates.

Initial studies examined the reaction of 2-phenylcyclohexanone (**1a**) with allyl acetate (**2**) using the conditions developed in our previous work with α'-blocked α-alkylcycloalkanones: 2 equivalents of LDA, 1 equivalent of trimethyltin chloride, 2.5% [(η^3-$C_3H_5PdCl)_2$], and 5% **L$_{ST}$** in DME as solvent [Eq. (1)]. Unfortunately, under these standard



(1)

[*] Prof. B. M. Trost, G. M. Schroeder, J. Kristensen
Department of Chemistry
Stanford University
Stanford, CA 94305-5080
Fax: (+1) 650-725-0002
E-mail: bmtrost@stanford.edu

[**] We thank the National Science Foundation and the National Institutes of Health, General Medical Sciences Grant GM13598, for their generous support of our programs. G.M.S. has been supported in part by fellowhips form the NSF, the Organic Division of the American Chemical Society, and the Achievement Rewards for College Scientists Foundations. Mass spectra was provided by the Mass Spectrometry Regional Center of the University of California—San Francisco supported by the NIH Divisdion of Research Resources. We thank Chirotech (now Dow) for their generous gifts of ligands.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

  0044-8249/02/4118-3492 $ 20.00+.50/0

conditions, the allylated product **3a** was generated with a very poor *ee* value. We therefore sought to re-optimize the palladium-catalyzed AAA for this class of nucleophile by first varying the counterion of the enolate in the absence of any additional additive such as trimethyltin chloride (Table 1). The potassium enolate gave the best *ee* value with the standard ligand $\mathbf{L_{ST}}$ (Table 1, entry 3 versus entries 1 and 2). Since the largest counterion gave the best *ee* value, we

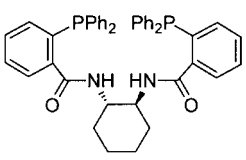
Table 1. Selected optimization studies of the AAA of 2-phenylcyclohexanone.[a]

Entry	Base (1.1 equiv)	Ligand	Yield [%][b]	*ee* [%][c]
1	LDA	$\mathbf{L_{ST}}$	96	28
2	NaH	$\mathbf{L_{ST}}$	75	28
3	KH	$\mathbf{L_{ST}}$	46	42
4	LDA	$\mathbf{L_N}$	46	32
5	NaH	$\mathbf{L_N}$	93	84
6	KH	$\mathbf{L_N}$	55	53

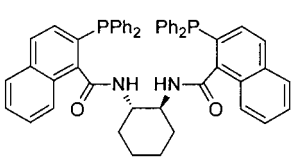
[a] All reactions were performed using DME as solvent (0.18 M), 2.5 equiv $[(\eta^3\text{-}C_3H_5PdCl)_2]$, and 5% ligand at room temperature. [b] Yield of isolated product. [c] Determined by HPLC on a chiral stationary phase.

thought that perhaps the *ee* value could be further improved by enhancing the steric interactions between the nucleophile and the ligand through the use of a more sterically demanding ligand such as naphthyl-derived ligand $\mathbf{L_N}$. With this ligand, the lithium enolate still appeared to be too small (entry 4), the potassium enolate was perhaps a bit too large (entry 6), and the sodium enolate gave the best fit of the approaching nucleophile with its counterion into the chiral pocket to give ketone **3** in 93% yield and 84% *ee*. To summarize, the use of 1.1 equivalents of sodium 1,1,1,3,3,3-hexamethyldisilazone (NaHMDS) as base, 1,2-dimethoxyethane (DME) as solvent, 2.5% $[(\eta^3\text{-}C_3H_5PdCl)_2]$ as the palladium source, and 5% $\mathbf{L_N}$ as the chiral ligand became the standard conditions for alkylating α-aryl ketones.

Next, the scope of the reaction was examined. The reaction was found to be general in terms of the ring size and the aryl substituent on the nucleophile. As shown in Table 2, six- (entry 1), seven- (entry 2), and eight-membered (entry 3) cycloalkanones all gave products with gave good *ee* values. A variety of aryl groups were tolerated. For example, the sterically bulky naphthylcyclohexanone **1d**[5] (entry 4) and biphenylcyclohexanone **1e**[6] (entry 5) gave their respective allylated products in 89% *ee*. Importantly, electron-rich and electron-poor aromatic substrates both functioned well. Thus, methoxy-substituted ($\sigma_p = -0.27$) aryl ketone **1f**[7] and flouride-substituted ($\sigma_p = +0.06$) aryl ketone **1g**[8] gave the alkylated products in 84% and 90% *ee*, respectively. Interestingly, the methoxy-bearing naphthalene ring ketone **1h** (entry 8) gave the best *ee* value.

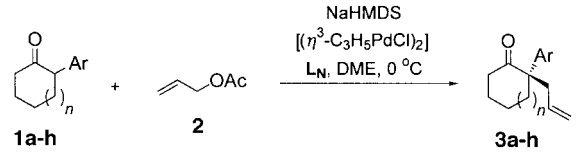


(*S*,*S*)-$\mathbf{L_{ST}}$



(*S*,*S*)-$\mathbf{L_N}$

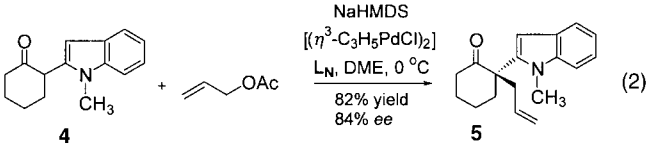
Table 2. Examples of the Pd-catalyzed AAA of aryl ketones.[a]



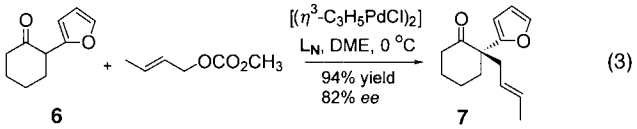
Entry	*n*	Ar	Yield [%][b]	*ee* [%][c]
1	1	**a**	90	88
2	2	**b**	90	83
3	3	**c**	89	84
4	1	**d**	82	89
5	1	Ph **e**	95	89
6	1	OCH_3 **f**	92	84
7	1	F **g**	77	90
8	1	**h** OCH_3	84	92

[a] All reactions were performed using DME as solvent (0.18 M), 1.1 equivalents of NaHMDS as base, 2.5% $[(\eta^3\text{-}C_3H_5PdCl)_2]$, and 5% $\mathbf{L_N}$ at 0 °C.

Two heterocycles have also been alkylated as shown in Equations (2) and (3). Furan **6** shows that the reaction is not



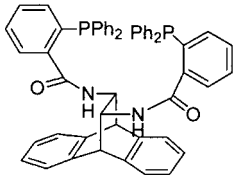
(2)



(3)

limited to allyl acetate as an electrophile. Other electrophiles can function equally well.

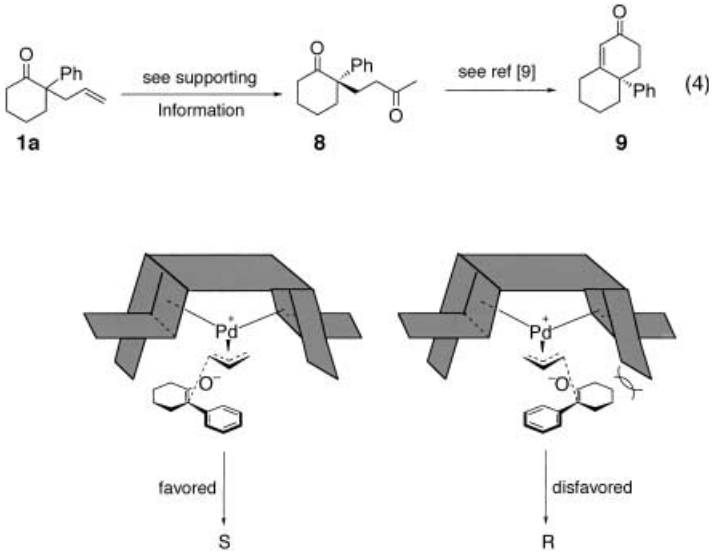
The absolute configuration has been determined in the case of 2-phenylcyclohexanone by comparison of the optical rotation of diketone **8** to that reported in the literature [Eq. (4)].[9] Thus, the (*S*,*S*)-naphthyl ligand gives the stereochemistry illustrated and is consistent with the mnemonic developed in our group (Scheme 1). The absolute configuration of the other examples were assigned by analogy. Diketone **8** has itself been cyclized to give enone **9.** Thus, this methodology can give access to enantioenriched polycycles in which the ring junction is substituted with an aryl group.



(*S*,*S*)-$\mathbf{L_A}$

The impact of the orientation of the aryl group with respect to the

  0044-8249/02/4118-3493 $ 20.00+.50/0

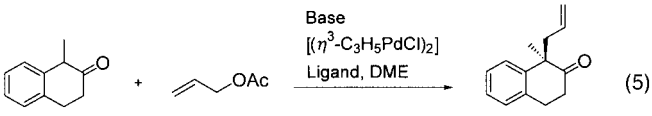


Scheme 1. Rationale for chiral recognition.

enolate was explored by using the conformationally rigid β-tetralone. Unfortunately, the conditions developed for 2-phenylcyclohexanone gave poor *ee* values (20%) with 1-methyl-2-tetralone (**10**). Therefore we investigated new conditions for this class of nucleophile (Table 3). The *ee* value obtained using the standard ligand $\mathbf{L_{ST}}$ (entries 1–4) was found to vary dramatically with the base: with LDA, the *ee* value was −33%, whereas with cesium carbonate the *ee* value was 45%, a total change of 78%. Such a remarkable effect clearly indicates the importance of the structure of the ion pair which constitutes the nucleophile rather than the simple enolate. The same trend was observed with naphthyl-derived ligand $\mathbf{L_N}$ (entries 4–5). The ligand was then varied, and gratifyingly, the anthracene-derived ligand $\mathbf{L_A}$, which has a larger bite angle than $\mathbf{L_{ST}}$ and $\mathbf{L_N}$ and can therefore better embrace the substrate, was found to give ketone **11**[10] in 93% yield and 90% *ee*.

The absolute configuration of allylated tetralone **11** was established by the synthesis of the known pyrrolidine-fused tetralin **13**, a family of molecules that has attracted attention

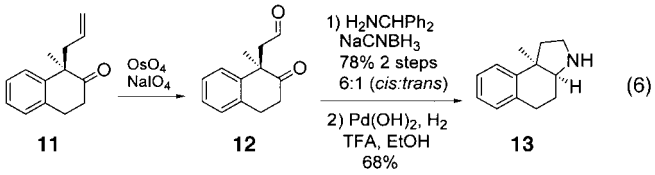
Table 3. Pd-catalyzed AAA of 1-methyl-2-tetralone (**10**).[a]



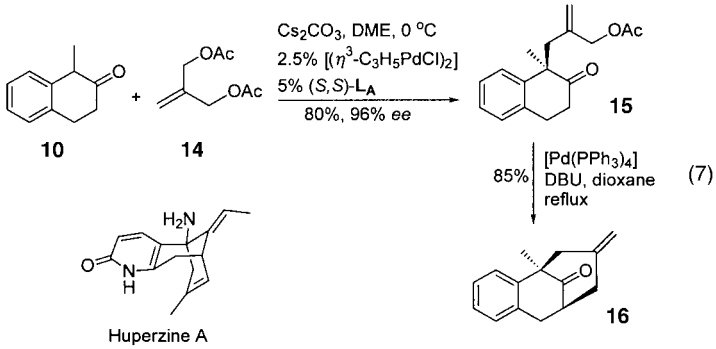
Entry	Base (1.1 equiv)	Ligand	Yield [%][b]	*ee* [%][c]
1	LDA	$\mathbf{L_{ST}}$	90	−33
2	NaHMDS	$\mathbf{L_{ST}}$	79	−23
3	KHMDS	$\mathbf{L_{ST}}$	83	15
4	Cs_2CO_3	$\mathbf{L_{ST}}$	91	45
5	LDA	$\mathbf{L_N}$	93	−1
6	Cs_2CO_3	$\mathbf{L_N}$	91	41
7	Cs_2CO_3	$\mathbf{L_A}$	93	90

[a] All reactions were performed using DME as solvent (0.18 M), 1.1 equivalents of base, 2.5% [$(\eta^3$-$C_3H_5PdCl)_2$], and 5% *S*,*S* ligand at 0°C. [b] Yield of isolated product. [c] Determined by HPLC on a chiral stationary phase. A negative sign indicates the absolute stereochemistry to be opposite to that depicted in **11.**

due to their serotonin and dopamine agonist activity.[11,12] To this end, the terminal olefin of tetralone **11** was oxidatively cleaved to give unstable keto aldehyde **12**. Aldehyde **12** was reductively aminated with benzhydrylamine and then the tertiary amine was deprotected by hydrogenation with Pearlman's catalyst to give aminotetralin **13**. Thus,(*S*,*S*)-anthracene ligand $\mathbf{L_A}$ gives the stereochemistry shown in Equation (6)



and allows for a concise, enantioselective synthesis of aminotetralin **13**. Performing the alkylation with the allyl bisacetate **14** gave **15** in good yield. Sequential cyclization using an



achiral Pd catalyst and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) provided tricycle **16**, whose *ee* value was established to be an excellent 96%. Thus, this method may provide an asymmetric synthesis of huperzine A,[15] an alkaloid with potent activity as an inhibitor of acetylcholinesterase.

To conclude, a variety of aryl ketones can be alkylated asymmetrically in a catalytic manner to generate quaternary chiral centers. These results confirm the broad compatibility of ketone enolates with the palladium-catalyzed AAA.[13] A strong correlation between the size of the enolate cation and the size of the chiral pocket is observed. The ease of access to the aryl ketones by the Buchwald–Hartwig Pd-catalyzed arylation[13] as well as by more classical routes and the utility of the allyl and substituted allyl groups for further elaboration impart great synthetic potential to this method. The alkylation of β-tetralone gives enantioenriched products that are versatile building blocks for the synthesis of diterpenes, steroids, and quassinoids.[14] The utility of these products is illustrated in the synthesis of aminotetralin **13** and a model system for huperzine A,[15] an alkaloid with potent activity as an inhibitor of acetylcholinesterase.[15] As a consequence of the success of ketone enolates in the palladium-catalyzed AAA, the investigation of even less stabilized nucleophiles is currently underway in our laboratories.

Received: June 17, 2002 [Z19543]

[1] J. Christoffers, A. Mann, *Angew. Chem.* **2001**, *113*, 4725; *Angew. Chem. Int. Ed.* **2001**, *40*, 4591; E. J. Corey, *Angew. Chem.* **1998**, *110*,

  0044-8249/02/4118-3494 $ 20.00+.50/0

402; *Angew. Chem. Int. Ed.* **1998**, *37*, 388; R. Noyori, *Asymmetric Catalysis in Organic Synthesis*, Wiley, New York, **1994**; K. Fuji, *Chem. Rev.* **1993**, *93*, 2037.

[2] For reviews of the palladium-catalyzed asymmetric allylic alkylation, see B. M. Trost, D. L. Van Vranken, *Chem. Rev.* **1996**, *96*, 395; A. Heumann, M. Reglier, *Tetrahedron* **1995**, *51*, 975; T. Hayashi in *Catalytic Asymmetric Synthesis* (Ed.: I. Ojima), VCH, New York, **1993**; M. Sawamura, Y. Ito, *Chem. Rev.* **1992**, *92*, 857; J. C. Fiaud, In *Metal-Promoted Selectivity in Organic Synthesis* (Eds.: M. Graziani, A. J. Hubert, A. F. Noels), Kluwer Academic, Dordrecht, **1991**; G. Consiglio, R. M. Waymouth, *Chem. Rev.* **1989**, *89*, 257.

[3] a) B. M. Trost, G. M. Schroeder, *J. Am. Chem. Soc.* **1999**, *121*, 6759; b) B. M. Trost, R. Radinov, E. M. Grenzer, *J. Am. Chem. Soc.* **1997**, *119*, 7879.

[4] S.-L. You, X.-L. Hou, L.-X. Dai, X.-Z. Zhu, *Org. Lett.* **2001**, *3*, 149, and references therein; T. Hayashi, K. Kanehira, T. Hagihara, M. Kumada, *J. Org. Chem.* **1988**, *53*, 113.

[5] K. Ishihara, S. Nakamura, M. Kaneeda, H. Yamamoto, *J. Am. Chem. Soc.* **1996**, *118*, 12854 – 12855.

[6] T. Ohwada, K. Okabe, T. Ohta, K. Shudo, *Tetrahedron* **1990**, *46*, 7539 – 7555.

[7] W. Vaccaro, C. Amore, J. Berger, R. Burrier, J. Clader, H. Davis, M. Domalski, T. Fevig, B. Salisbury, R. Sher, *J. Med. Chem.* **1996**, *39*, 1704 – 1719.

[8] Du Pont de Nemours and Co., FR 2283681 **1976**; DE 2539907 **1976**.

[9] W. Nerinckx, M. Vandewalle, *Tetrahedron: Asymmetry* **1990**, *1*, 265.

[10] B. B. Snider, B. M. Cole, *J. Org. Chem.* **1995**, *60*, 5376.

[11] A. P. Degnan, A. I. Meyers, *J. Org. Chem.* **2000**, *65*, 3503, and references therein.

[12] C.-H. Lin, S. R. Haadsman-Svensson, A. Lahti, R. B. McCall, M. F. Piercey, K. D. Schreur, P. F. Von Voigtlander, M. W. Smith, C. G. Chidester, *J. Med. Chem.* **1993**, *36*, 1053; M. Takeda, M. Konda, Y. Honma, H. Inoue, S. Saito, H. Kugita, S. Nurimoto, G. Hayashi, *J. Med. Chem.* **1975**, *18*, 697.

[13] The compatibility of ketone enolates with palladium has also been demonstrated in the palladium-catalyzed arylation of ketone enolates. This method also provides an alternative catalytic asymmetric route to quaternary centers bearing an aryl group, see T. Hamada, A. Chieffi, J. Arhman, S. L. Buchwald, *J. Am. Chem. Soc.* **2002**, *124*, 1261; J. M. Fox, X. Huang, A. Chieffi, S. L. Buchwald, *J. Am. Chem. Soc.* **2000**, *122*, 1360; M. Kawatsura, J. F. Hartwig, *J. Am. Chem. Soc.* **1999**, *121*, 1473; J. Ahman, J. P. Wolfe, M. V. Troutman, M. Palucki, S. L. Buchwald, *J. Am. Chem. Soc* **1998**, *120*, 1918; M. Palucki, S. L. Buchwald, *J. Am. Chem. Soc.* **1997**, *119*, 11108.

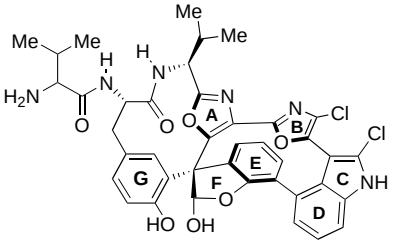
[14] K. Shishido, K. Goto, S. Miyoshi, Y. Takaishi, M. Shibuya, *J. Org. Chem.* **1994**, *59*, 406; C. K.-F. Chiu, S. V. Govindan, P. L. Fuchs, *J. Org. Chem.* **1994**, *59*, 311; W. Nerinckx, M. Vandewalle, *Tetrahedron: Asymmetry* **1990**, *1*, 265; R. H. Burnell, J.-M. DuFour, *Can. J. Chem.* **1987**, *65*, 21; T. Volpe, G. Revial, M. Pfau, J. d'Angelo, *Tetrahedron Lett.* **1987**, *28*, 2367, and references therein.

[15] C. Chassaing, A. Haudrechy, Y. Langlois, *Tetrahedron Lett.* **2000**, *41*, 785; A. Haudrechy, C. Chassaing, C. Riche, Y. Langlois, *Tetrahedron* **2000**, *56*, 3181; S. Kaneko, T. Yoshino, T. Katoh, S. Terashima, *Tetrahedron* **1998**, *54*, 5471; X.-C. He, B. Wang, D. Bai, *Tetrahedron Lett.* **1998**, *39*, 411; A. P. Kozikowski, Y. Xia, E. R. Reddy, W. Tuckmantel, I. Hanin, X. C. Tang, *J. Org. Chem.* **1991**, *56*, 4636; T. Hayashi, K. Kaneshira, T. Hagihara, M. Kumada, *J. Org. Chem.* **1988**, *53*, 113; see also D. L. Bai, X. C. Tang, X. C. He, *Curr. Med. Chem.* **2000**, *7*, 355. For analogues, see P. Camps, E. Gómez, D. Muñoz-Torrero, M. Arnó, *Tetrahedron: Asymmetry* **2001**, *12*, 2909.

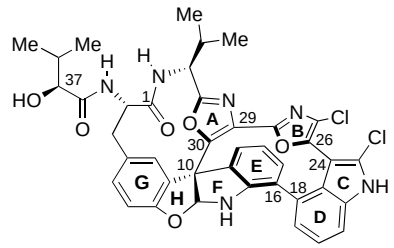
Total Synthesis of Diazonamide A**

K. C. Nicolaou,* Marco Bella, David Y.-K. Chen, Xianhai Huang, Taotao Ling, and Scott A. Snyder

In 1991, Fenical and co-workers reported structure **1** for diazonamide A, a marine natural product which had been isolated from the colonial ascidian *diazona angulata*.[1] A



1: original structure of diazonamide A



2: revised structure of diazonamide A

decade later, Harran and his group synthesized the proposed structure **1** only to prove that it was in error, and advanced structure **2** for diazonamide A instead.[2] In the intervening time, numerous efforts directed at the total synthesis of **1** had been reported;[3–13] no research activities related to the newly proposed structure **2** have yet been disclosed. The appeal of diazonamide A (**2**) stems both from its biological activity (cytotoxicity against several tumor cell lines with IC_{50} values $< 15\ ng\,mL^{-1}$) and its highly strained and unprecedented

[*] Prof. Dr. K. C. Nicolaou, Dr. M. Bella, Dr. D. Y.-K. Chen, Dr. X. Huang, Dr. T. Ling, S. A. Snyder
Department of Chemistry and The Skaggs Institute for Chemical Biology
The Scripps Research Institute
10550 North Torrey Pines Road, La Jolla, CA 92037 (USA)
Fax: (+1) 858-784-2469
E-mail: kcn@scripps.edu
and
Department of Chemistry and Biochemistry
University of California, San Diego
9500 Gilman Drive, La Jolla, CA 92093 (USA)

[**] We thank Dr. D. H. Huang and Dr. G. Siuzdak for NMR spectroscopic and mass spectrometric assistance, respectively. We also wish to acknowledge Mr. William R. Webb for his expertise in obtaining low-resolution mass spectral data. We thank Dr. Paraskevi Giannakakou and Aurora O'Brate of the Winship Cancer Institute, Emory University School of Medicine, for the biological assays. Financial support for this work was provided by The Skaggs Institute for Chemical Biology, American BioScience, the National Institutes of Health (USA), predoctoral fellowships from the National Science Foundation and Pfizer (S.A.S.), and postdoctoral fellowships from The Skaggs Institute for Research (M.B., X.H., and T.L.).

  0044-8249/02/4118-3495 $ 20.00+.50/0