tral data were completely identical with those reported in literature.[1b]

In conclusion, we have completed a highly efficient total synthesis of FR900482 (**1**). The present synthesis features a facile formation of *N*-hydroxybenzazocine by intramolecular reductive hydroxylamination and an ensuing facile construction of the hydroxylamine hemiacetal. The synthetic strategy described above should be applicable to the synthesis of analogues of FR900482 as well as of other benzazocine derivatives. Application of this approach to the synthesis of mitomycin C is currently under investigation in our laboratories.

Received: August 6, 2002 [Z19901]

[1] a) M. Iwami, S. Kiyoto, H. Terano, M. Kohsaka, H. Aoki, H. Imanaka, *J. Antibiot.* **1987**, *40*, 589; b) S. Kiyoto, T. Shibata, M. Yamashita, T. Komori, M. Okuhara, H. Terano, M. Kohsaka, H. Aoki, H. Imanaka, *J. Antibiot.* **1987**, *40*, 594; c) I. Uchida, S. Takase, H. Kayakiri, S. Kiyoto, M. Hashimoto, *J. Am. Chem. Soc.* **1987**, *109*, 4108.

[2] K. Shimomura, O. Hirai, T. Mizota, S. Matsumoto, J. Mori, F. Shibayama, H. Kikuchi, *J. Antibiot.* **1987**, *40*, 600.

[3] a) R. M. Williams, S. R. Rajski, S. B. Rollins, *Chem. Biol.* **1997**, *4*, 127; b) M. M. Paz, P. B. Hopkins, *J. Am. Chem. Soc.* **1997**, *119*, 5999; c) R. M. Williams, S. B. Rollins, S. R. Rajski, *J. Am. Chem. Soc.* **1998**, *120*, 2192.

[4] For representative examples, see: a) N. Yasuda, R. M. Williams, *Tetrahedron Lett.* **1989**, *30*, 3397; b) R. J. Jones, H. Rapoport, *J. Org. Chem.* **1990**, *55*, 1144; c) S. J. Miller, S. H. Kim, Z. R. Chen, R. H. Grubbs, *J. Am. Chem. Soc.* **1995**, *117*, 2108; d) H. J. Lim, G. A. Sulikowski, *Tetrahedron Lett.* **1996**, *37*, 5243; e) S. Mithani, D. M. Drew, E. H. Rydberg, N. J. Taylor, S. Mooibroek, G. I. Dmitrienko, *J. Am. Chem. Soc.* **1997**, *119*, 1159.

[5] a) T. Fukuyama, L. Xu, S. Goto, *J. Am. Chem. Soc.* **1992**, *114*, 383; b) J. M. Schkeryantz, S. J. Danishefsky, *J. Am. Chem. Soc.* **1995**, *117*, 4722.

[6] a) T. Katoh, E. Itoh, T. Yoshino, S. Terashima, *Tetrahedron* **1997**, *53*, 10229; b) T. Yoshino, Y. Nagata, E. Itoh, M. Hashimoto, T. Katoh, S. Terashima, *Tetrahedron* **1997**, *53*, 10239; c) T. Katoh, Y. Nagata, T. Yoshino, S. Nakatani, S. Terashima, *Tetrahedron* **1997**, *53*, 10253.

[7] I. M. Fellows, D. E. Kaelin, Jr., S. F. Martin, *J. Am. Chem. Soc.* **2000**, *122*, 10781.

[8] After submission of this manuscript, we learned that two groups have independently completed enantioselective total syntheses; see the previous communication: a) T. C. Jude, R. M. Williams, *Angew. Chem.* **2002**, *114*, 4877; *Angew. Chem. Int. Ed.* **2002**, *41*, 4683; and the following communication: b) R. Ducray, M. A. Ciufolini, *Angew. Chem.* **2002**, *114*, 4882; *Angew. Chem. Int. Ed.* **2002**, *41*, 4688.

[9] For an approach utilizing intramolecular [3+2] cycloaddition of nitrile oxide, see: M. Kambe, E. Arai, M. Suzuki, H. Tokuyama, T. Fukuyama, *Org. Lett.* **2001**, *3*, 2575.

[10] G. Pandey, M. Kapur, *Tetrahedron Lett.* **2000**, 41, 8821. Alternatively, we prepared **9** by a modified procedure: 2,3-di-*O*-isopropylidene-L-threitol, NaH, TBSCl, THF; cat. TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy, free radical), $PhI(OAc)_2$, CH_2Cl_2; dimethyl-1-diazo-2-oxopropylphosphonate, K_2CO_3, MeOH (S. Müller, B. Liepold, G. J. Roth, H. J. Bestmann, *Synlett* **1996**, 521).

[11] K. Sonogashira, Y. Tohda, N. Hagihara, *Tetrahedron Lett.* **1975**, *16*, 4467.

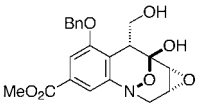
[12] The coupling reaction under typical conditions ($[PdCl_2(PPh_3)_2]$ and CuI in Et_3N) gave a considerable amount of the homocoupling by-product of the acetylene.

[13] T. Nakata, Y. Tani, M. Hatozaki, T. Oishi, *Chem. Pharm. Bull.* **1984**, 32, 1411.

[14] J. Hartung, S. Hünig, R. Kneuer, M. Schwarz, H. Wenner, *Synthesis* **1997**, 1433.

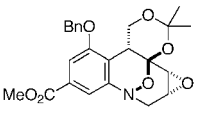
[15] Ketone **21** could be isolated when the reaction was quenched with NH_4Cl (1N) instead of HCl (1N), and its diastereomeric ratio was estimated by means of ^1H NMR spectroscopy. The structure of **21** was unambiguously confirmed by observation of NOE interactions between 7-H and 9-H.

[16] In addition to **22**, formation of a side product, which was tentatively assigned as hydroxylamine hemiacetal diastereomer **22′**, was observed. This mixture was subjected to the next acetonide formation without separation.



22'

[17] The ratio of **22**/**22′** was almost the same as that of **23** and a side product, which was tentatively assigned as **23′**. Furthermore, deprotection of the acetonide of **23** and **23′** under acidic conditions (HCl (1N) in THF, room temperature) gave only **22** and **22′**, respectively. These observations would indicate that neither epimerization of C7 nor interconversion of the hemiacetal diastereomers via the eight-membered ring ketone occurred during the acetonide formation.



23'

[18] T. Fukuyama, A. A. Laird, L. M. Hotchkiss, *Tetrahedron Lett.* **1985**, *26*, 6291.

[19] The aldehyde was protected as the dimethyl acetal to prevent reduction during hydrogenolysis of the phenolic benzyl ether.

Total Synthesis of (±)-FR66979**

Richard Ducray and Marco A. Ciufolini*

In the late 1980s, scientists at the Fujisawa Co. (Japan) unveiled a new class of antitumor agents with general structure **1** (Scheme 1).[1] These substances, denoted FR-66979 (**1a**) and FR-900482 (**1b**), are structurally related to the mitomycins (see mitomycin C (**2**)).[2] Indeed, the two families of anticancer agents possess comparable bioactivity[3] and are believed to act by a similar mechanism, yet FR-type compounds are less toxic than mitomycins, probably as a result of the absence of a quinoid nucleus.[4] Derivatives of **1b** are currently undergoing clinical trials.[5]

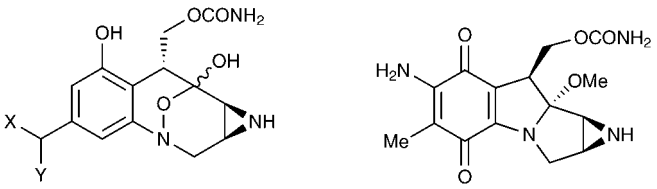
The biomedical potential and unusual architecture of compounds **1** have stimulated substantial interest at a

[*] Prof. Dr. M. A. Ciufolini, R. Ducray
Laboratoire de Synthèse et Méthodologie Organiques
CNRS UMR 5078
Université Claude Bernard Lyon 1
and
Écôle Supérieure de Chimie, Physique, Electronique de Lyon
43, Bd. du 11 Novembre 1918, 69622 Villeurbanne cedex (France)
Fax: (+33) 4-7243-2963
E-mail: ciufi@cpe.fr

[**] We thank the MENRT (doctoral fellowship to R.D.), the CNRS, and the Région Rhône-Alpes for support of our research. We are grateful to Ms. Laurence Rousset and Dr. Denis Bouchu for the mass spectral data, to Dr. Bernard Fenet for the NMR spectroscopic data. Finally, we thank the Fujisawa Co. for a gift of natural FR-66979. M.A.C. is the recipient of a Merck & Co. Academic Development Award.

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

  0044-8249/02/11424-4882 $ 20.00+.50/0

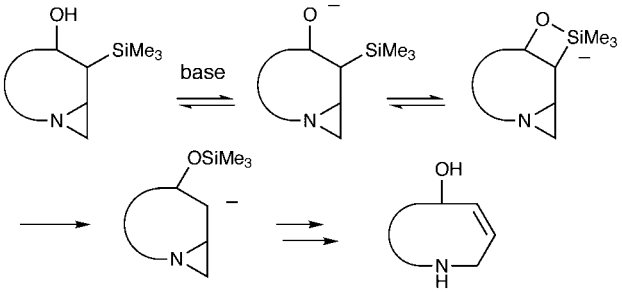


FR66979 **1a**: X = H; Y = OH
FR900482 **1b**: X, Y = O

mitomycin C **2**

Scheme 1. Structure of FR66979 (**1a**), FR900482 (**1b**), and mitomycin C (**2**).

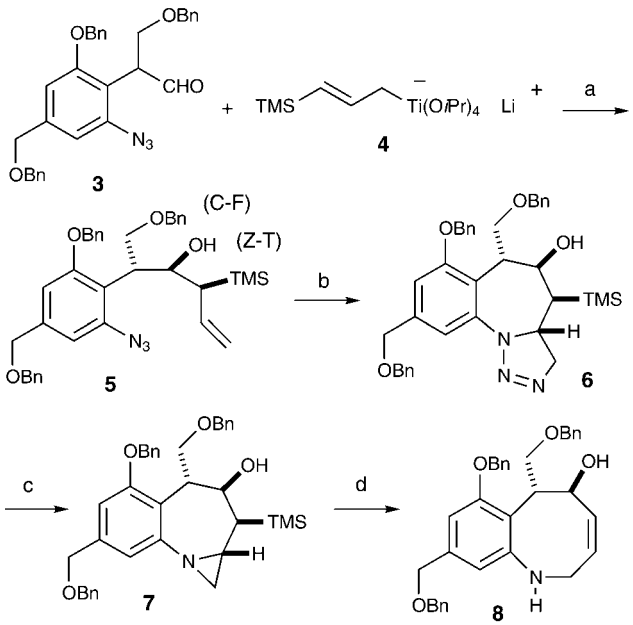
chemical level. In that respect, the fragile nature of these molecules and their problematic structural features have inspired the development of much innovative synthetic chemistry.[6,7] Our own involvement in this area[8] has recently produced a new method for benzazocene assembly through an unusual fragmentation of a silylated aziridine[9] orchestrated by a preliminary homo-Brook[10] transposition (Scheme 2). We describe herein a total synthesis of (±)-FR-66979 (**1a**), which showcases this new reaction as a key step.



Scheme 2. Presumed mechanism for the homo-Brook aziridine fragmentation.

Aldehyde (±)-**3**[11] reacted with the organometallic species arising through the interaction of lithiated allyltrimethylsilane and [Ti(*i*PrO)$_4$],[12] and represented simply in Scheme 3 as **4**, to furnish adduct **5** as a diastereomerically homogeneous product (by ^{1}H NMR spectroscopy). The relative configuration of this intermediate[13] suggests that the addition process occurred with essentially complete Cram–Felkin selectivity (see **5**, descriptor "C-F") within the manifold of a Zimmerman–Traxler-type cyclic transition state (descriptor "Z-T"). The simultaneous presence of an activated double bond (the allylsilane) and of a 1,3-dipole (the azido group) in **5** engendered a smooth intramolecular cycloaddition upon heating in toluene. Triazoline **6** thus emerged as a single diastereomer (by ^{1}H NMR spectroscopy). Brief photolysis of **6**[14] provided aziridine **7**,[13] which underwent a homo-Brook-triggered fragmentation to form benzazocenol **8**. This crucial eight-membered N-heterocycle was thus assembled in just four steps in a fully diastereocontrolled manner from readily available **3**.

Substances of the type **8** are known intermediates for the synthesis of FR900482 and of mitomycinoids,[6] except that their construction normally requires considerably longer sequences; hence, the interest of the new methodology. To



Scheme 3. Reagents and conditions: a) THF, −78 °C; b) toluene, 100 °C, 80 % over two steps; c) *hν*, THF, 77 %; d) *n*Bu$_4$NOH, DMF, −20 °C, 49 %. DMF = *N*,*N*-dimethylformamide.

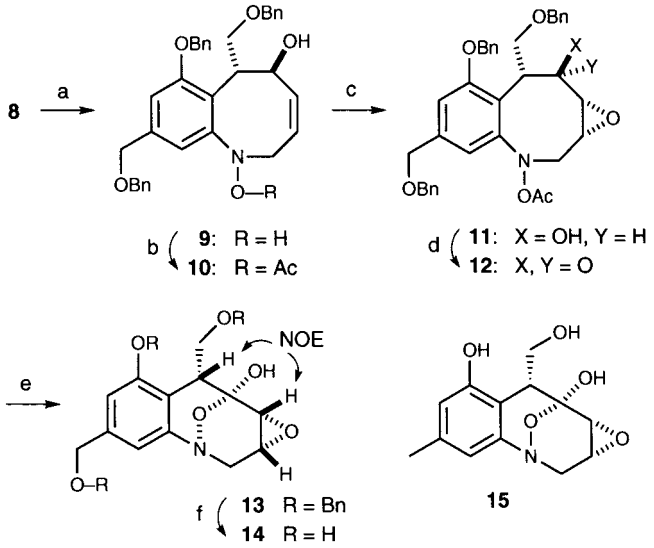
the best of our knowledge, only approaches that rely on olefin metathesis[7k] appear to be competitive with our aziridine fragmentation methodology for the creation of such medium-ring N-heterocycles.

Straightforward operations patterned after reported syntheses of **1b**[6a] advanced **8** to **11**, oxidation of which to ketone **12** was best carried out with TPAP–NMO.[15] Release of the hydroxylamine O-acetyl group precipitated transannular cyclization to **13**, which upon hydrogenolytic cleavage of all benzyl groups furnished **14**. The progress of the debenzylation step was carefully monitored to minimize formation of by-product **15** (Scheme 4). The latter is an interesting intermediate in its own right,[6h] but, of course, it is not useful for the pursuit of the total synthesis. The relative configuration of **13** and **14** was assigned as shown in Scheme 4 on the basis of an observed NOE interaction between the indicated protons (2D-NOESY).

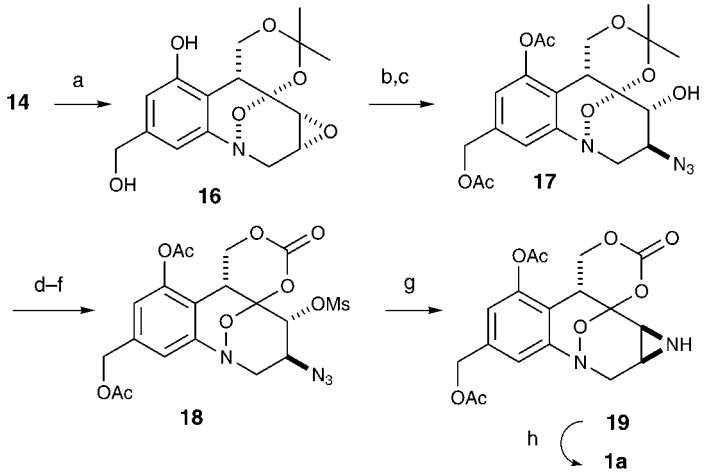
Tetraol **14** was elaborated to (±)-**1a** by a modification of known procedures,[6a,h] as detailed in Scheme 5. Selective acetonide formation led to **16**, which underwent regioselective azidolysis of the oxirane, followed by selective acetylation of primary and phenolic OH groups, to give **17**. Mesylation of the hindered, electronically deactivated secondary alcohol and exchange of the acetonide with a cyclic carbonate provided **18**.[16] Finally, sequential Staudinger-type aziridine formation and ammonolysis of both cyclic carbonate and acetate units in **19** produced the target (±)-**1a**, which was spectrally and chromatographically identical to authentic material.

In summary, the homo-Brook-mediated aziridine fragmentation avenue to medium-sized N-heterocycles can be used to prepare molecules of at least moderate complexity (e.g. **1a**). The applicability of the new method to the construction of other mitomycinoids, as well as further simplifications of the

  0044-8249/02/11424-4883 $ 20.00+.50/0



Scheme 4. Reagents and conditions: a) MCPBA, CH_2Cl_2, 0 °C; b) neat Ac_2O, room temperature, 87% over two steps; c) MCPBA, CH_2Cl_2, $NaHCO_3$, room temperature, 70%; d) cat. TPAP, NMO, CH_2Cl_2, molecular sieves (4 Å), room temperature, 83%; e) $N_2H_4{\cdot}H_2O$, MeOH, CH_2Cl_2, 100%; f) H_2 (1 atm), Pd/C, EtOAc, 97% crude. MCPBA = *m*-chloroperoxybenzoic acid, TPAP = tetrapropylammonium perruthenate, NMO = 4-methylmorpholine *N*-oxide.



Scheme 5. Reagents and conditions: a) 2-Methoxypropene, PPTS, DMF, room temperature, 83%; b) LiN_3, DMF, 100 °C, 67%; c) Ac_2O, K_2CO_3, THF, room temperature, 81%; d) MsCl, Et_3N, CH_2Cl_2, room temperature, 71%; e) TFA, CH_2Cl_2, room temperature; f) $COCl_2$, CH_2Cl_2, Et_3N, 0 °C, 28%; g) Ph_3P, *i*Pr_2NEt, aqueous THF (90%), 60 °C, 78%; h) NH_3, MeOH, room temperature, 40%. PPTS = pyridinium *p*-toluenesulfonate, Ms = methanesulfonyl, TFA = trifluoroacetic acid.

synthetic pathway, are currently under study and will be reported in due course.

Received: September 18, 2002 [Z50186]

[1] a) I. Uchida, S. Takase, H. Kayakiri, S. Kiyoto, M. Hashimoto, T. Tada, S. Koda, Y. Morimoto, *J. Am. Chem. Soc.* **1987**, *109*, 4108; b) H. Terano, S. Takase, J. Hosoda, M. Kohsaka, *J. Antibiot.* **1989**, *42*, 145.

[2] For a review, see: W. T. Bradner, *Cancer Treat. Rev.* **2001**, *27*, 35.

[3] K. Shimomura, O. Hirai, T. Mizota, S. Matsumoto, J. Mori, F. Shibayama, H. Kikuchi, *J. Antibiot.* **1987**, *40*, 600.

[4] a) T. Fukuyama, S. Goto, *Tetrahedron Lett.* **1989**, *30*, 6491; b) R. M. Williams, S. R. Rajski, *Tetrahedron Lett.* **1992**, *33*, 2929; c) R. M. Williams, S. R. Rajski, *Tetrahedron Lett.* **1993**, *34*, 7023; d) H. Huang, S. R. Rajski, R. M. Williams, P. B. Hopkins, *Tetrahedron Lett.* **1994**, *35*, 9669; e) J. Woo, S. T. Sigurdsson, P. B. Hopkins, *J. Am. Chem. Soc.* **1993**, *115*, 1199; f) H. Huang, T. K. Pratum, P. B. Hopkins, *J. Am. Chem. Soc.* **1994**, *116*, 2703; g) M. M. Paz, P. B. Hopkins, *Tetrahedron Lett.* **1997**, *38*, 343; h) M. M. Paz, P. B. Hopkins, *J. Am. Chem. Soc.* **1997**, *119*, 5999; i) R. M. Williams, S. R. Rajski, *Chem. Biol.* **1997**, *4*, 127; j) L. Beckerbauer, J. J. Tepe, R. A. Eastman, P. Mixter, R. M. Williams, R. Reeves, *Chem. Biol.* **2002**, *9*, 427; k) L. Beckerbauer, J. Tepe, J. Cullison, R. Reeves, R. M. Williams, *Chem. Biol.* **2000**, *7*, 805; l) R. M. Williams, S. R. Rajski, *J. Am. Chem. Soc.* **1998**, *120*, 2192; m) T. C. Judd, R. M. Williams, *Org. Lett.* **2002**, *4*, 3711.

[5] a) K. Shimomura, T. Manda, S. Mukumoto, K. Masuda, T. Nakamura, T. Mizota, S. Matsumoto, F. Nishigaki, T. Oku, J. Mori, F. Shibayama, *Cancer Res.* **1988**, *48*, 1166; b) T. Nakamura, K. Masuda, S. Matsumoto, T. Oku, T. Manda, J. Mori, K. Shimomura, *Jpn. J. Pharmacol.* **1989**, *49*, 317; c) K. Masuda, T. Nakamura, T. Mizota, J. Mori, K. Shimomura, *Cancer Res.* **1988**, *48*, 5172; d) K. Masuda, T. Nakamura, K. Shimomura, *J. Antibiot.* **1988**, *41*, 1497; e) Y. Naoe, M. Inami, S. Matsumoto, F. Nishigaki, S. Tsujimoto, I. Kawamura, K. Miyayasu, T. Manda, K. Shimomura, *Cancer Chemother. Pharmacol.* **1998**, *42*, 31; f) Y. Naoe, M. Inami, I. Kawamura, F. Nishigaki, S. Tsujimoto, S. Matsumoto, T. Manda, K. Shimomura, *Jpn. J. Cancer Res.* **1998**, *89*, 666; g) Y. Naoe, M. Inami, S. Takagaki, S. Matsumoto, I. Kawamura, F. Nishigaki, S. Tsujimoto, T. Manda, K. Shimomura, *Jpn. J. Cancer Res.* **1998**, *89*, 1047; h) Y. Naoe, M. Inami, S. Matsumoto, S. Takagaki, T. Fujiwara, S. Yamazaki, I. Kawamura, F. Nishigaki, S. Tsujimoto, T. Manda, K. Shimomura, *Jpn. J. Cancer Res.* **1998**, *89*, 1306; i) Y. Naoe, I. Kawamura, M. Inami, S. Matsumoto, F. Nishigaki, S. Tsujimoto, T. Manda, K. Shimomura, *Jpn. J. Cancer Res.* **1998**, *89*, 1318; j) M. Inami, I. Kawamura, S. Tsujimoto, F. Nishigaki, S. Matsumoto, Y. Naoe, Y. Sasakawa, M. Matsuo, T. Manda, T. Goto, *Cancer Lett.* **2002**, *181*, 39; k) M. Tomasz, R. Lipman, D. Chowdary, J. Pawlak, G. Verdine, K. Nakanishi, *Science* **1987**, *235*, 1204; l) M. Tomasz, *Chem. Biol.* **1995**, *2*, 575, and references therein.

[6] For total syntheses of **1b**, see: a) T. Fukuyama, L. Xu, S. Goto, *J. Am. Chem. Soc.* **1992**, *114*, 383; b) J. M. Schkeryantz, S. J. Danishefsky, *J. Am. Chem. Soc.* **1995**, *117*, 4722; c) T. Katoh, E. Itoh, T. Yoshino, S. Terashima, *Tetrahedron* **1997**, *53*, 10229; d) T. Yoshino, Y. Nagata, E. Itoh, M. Hashimoto, T. Katoh, S. Terashima, *Tetrahedron* **1997**, *53*, 10239; e) T. Katoh, Y. Nagata, T. Yoshino, S. Nakatani, S. Terashima, *Tetrahedron* **1997**, *53*, 10253; see also two previous communications: f) T. C. Judd, R. M. Williams, *Angew. Chem.* **2002**, *114*, 4877; *Angew. Chem. Int. Ed.* **2002**, *41*, 4683; g) M. Suzuki, M. Kambe, H. Tokuyama, T. Fukuyama, *Angew. Chem.* **2002**, *114*, 4882; *Angew. Chem. Int. Ed.* **2002**, *41*, 4688. We are grateful to Profs. Robert M. Williams and Tohru Fukuyama for informing us of their independent syntheses of FR-900482 and FR-66979 prior to submission of our work, and for agreeing to have our three papers appear consecutively in this issue of *Angewandte Chemie*.

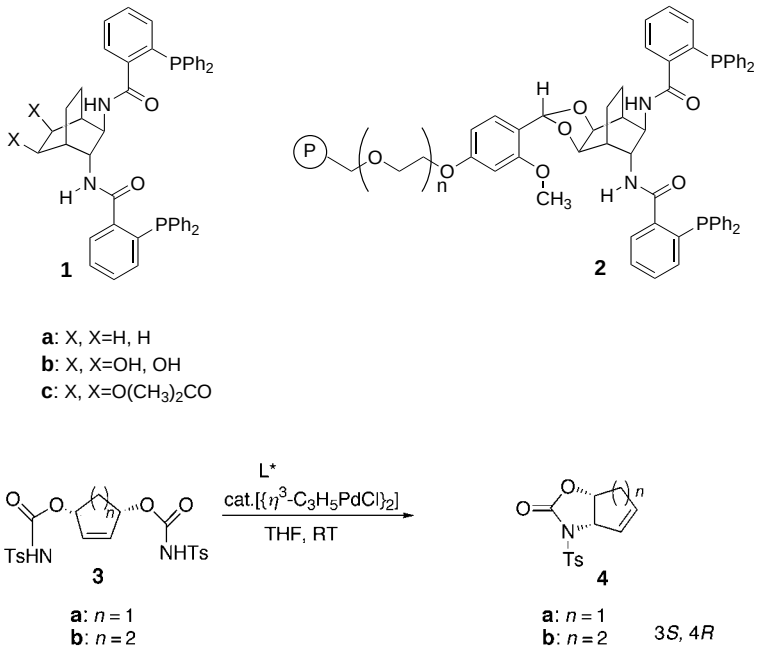
[7] For synthetic studies, see: a) N. Yasuda, R. M. Williams, *Tetrahedron Lett.* **1989**, *30*, 3397; b) R. J. Jones, H. Rapoport, *J. Org. Chem.* **1990**, *55*, 1144; c) S. J. Miller, S. H. Kim, Z. R. Chen, R. H. Grubbs, *J. Am. Chem. Soc.* **1995**, *117*, 2108; d) T. Katoh, E. Itoh, T. Yoshino, S. Terashima, *Tetrahedron Lett.* **1996**, *37*, 3471; e) T. Yoshino, Y. Nagata, E. Itoh, M. Hashimoto, T. Katoh, S. Terashima, *Tetrahedron Lett.* **1996**, *37*, 3475; f) T. Katoh, T. Yoshino, Y. Nagata, S. Nakatani, S. Terashima, *Tetrahedron Lett.* **1996**, *37*, 3479; g) H. J. Lim, G. A. Sulikowski, *Tetrahedron Lett.* **1996**, *37*, 5243; h) F. E. Ziegler, M. Belema, *J. Org. Chem.* **1997**, *62*, 1083; i) S. Mithani, D. M. Drew, E. H. Rydberg, N. J. Taylor, S. Mooibroek, G. I. Dmitrienko, *J. Am. Chem. Soc.* **1997**, *119*, 1159; j) W. Zhang, C. Wang, L. S. Jimenez, *Synth. Commun.* **2000**, *30*, 351; k) I. M. Fellows, D. E. Kaelin, Jr., S. F. Martin, *J. Am. Chem. Soc.* **2000**, *122*, 10781; l) M. Kambe, E. Arai, M. Suzuki, H. Tokuyama, T. Fukuyama, *Org. Lett.* **2001**, *3*, 2575.

[8] cf. a) M. A. Ciufolini, M. Chen. , D. P. Lovett, M. V. Deaton, *Tetrahedron Lett.* **1997**, *38*, 4355; b) M. A. Ciufolini, M. V. Deaton, S. Zhu, M. Chen, *Tetrahedron* **1997**, *53*, 16299.

[9] R. Ducray, N. Cramer, M. A. Ciufolini, *Tetrahedron Lett.* **2001**, *42*, 9175.

  0044-8249/02/11424-4884 $ 20.00+.50/0

[10] a) P. F. Hudrlik, A. M. Hudrlik, A. K. Kulkarni, *J. Am. Chem. Soc.* **1982**, *104*, 6809; b) P. F. Hudrlik, P. E. Holmes, A. M. Hudrlik, *Tetrahedron Lett.* **1988**, *29*, 6395.
[11] Prepared from the corresponding, known 2-(2-nitroaryl)-propanediol (see compound **24** in reference [7k]), readily available in > 10-g batches, by: a) H_2, Raney Ni; b) HONO/NaN_3; c) BnBr, NaH (facile monobenzylation); d) IBX, DMSO, 53% overall yield; Bn = benzyl, IBX = *o*-iodoxylbenzoic acid, DMSO = dimethyl sulfoxide.
[12] M. T. Reetz, R. Steinbach, J. Westermann, R. Peter, B. Wenderoth, *Chem. Ber.* **1985**, *118*, 1441.
[13] The relative configuration of this intermediate was inferred from the X-ray crystal structure of compound **7**.
[14] This photolysis reaction occurred most efficiently when a Sylvania 250-W suntanning lamp was used as the light source (water-cooled pyrex reactor). A standard Hanovia lamp produced less satisfactory results.
[15] S. V. Ley, J. Norman, W. P. Griffith, S. P. Marsden, *Synthesis* **1994**, 639.
[16] The relative configuration of the bridged system of this substance was not determined.



Polymer-Supported C_2-Symmetric Ligands for Palladium-Catalyzed Asymmetric Allylic Alkylation Reactions**

Barry M. Trost,* Zhengying Pan, Jorge Zambrano, and Christof Kujat

Development of immobilized ligands/catalysts for asymmetric synthesis is a rapidly growing field.[1] Because of palladium's broad applications in organic synthesis,[2] many types of supported ligands have been reported for allylic,[3] alkylation,[4] amination, and cross-coupling reactions.[5] However, there are surprisingly few successful polymer-bound ligands for palladium-catalyzed asymmetric allylic alkylations.[6,7] In the late 1970s, we demonstrated the use of polymer-bound phosphane ligands in Pd-catalyzed transformations.[8] We here report a competent, easily prepared, recyclable chiral ligand for asymmetric allylic alkylation (AAA) reactions.

Initially, we examined the supported ligand **2**, which was derived from the rigid bicyclic templates **1**[9] to minimize any perturbation of the chiral pocket. The supported ligand **2** formed readily by reacting the diol **1b** with ArgoGel-CHO catalyzed by *p*-toluenesulfonic acid (TsOH) in dichloromethane. Cyclization of the bisurethane **3a** to the oxazolidin-2-one **4a**[10,11] was examined as the test reaction [Eq. (1)]. As a baseline, the reaction was performed in normal solution phase with the simple ligands **1a** and **1b**. Table 1, entries 1 and 2, reveals the effectiveness of this class of ligands. It is somewhat surprising that a small dip in enantiomeric excess (*ee*) occurs on introducing electronegative oxygen atoms into the remote bridge (91 to 87% *ee*). The supported ligand **2** was effective in performing the reaction but there was a more significant drop in enantiomeric excess (Table 1, entry 3) although it was still reasonable. Simply decanting the reaction mixture from the solid support and washing the beads with fresh THF prepared the beads for the next cycle. No additional palladium was loaded after the initial charge. The yield dipped in the second cycle but subsequently stabilized at 60 ± 5%. Thus, the supported catalyst was quite robust remaining highly active even after seven cycles (Table 1, entries 3–9). The enantiomeric excess also remained quite constant through most of the cycles at 70 ± 1%. In earlier experiments with normal solution ligands, addition of triethylamine led to a significant enhance-

Table 1. First-generation bicyclic ligands.[a]

Entry	Ligand	Run	Yield of **4a** [%]	*ee*[b] [%]
1[c]	**1a**	–[d]	69	91
2[c]	**1c**	–[d]	79	87
3	**2**	1	81	73
4	**2**	2	74	71
5	**2**	3	70	70
6	**2**	4	63	71
7	**2**	5	63	69
8	**2**	6	60	70
9	**2**	7	66	69
10	**2**	–[d]	78	68

[a] All reactions were performed with 10 mol% [{η^3-C_3H_5PdCl}$_2$] and 25 mol% ligand in THF at room temperature; the vessel was shaken for mixing unless otherwise indicated. [b] Determined by chiral HPLC in an AD chiralpak column. [c] Performed with 2.5 mol% [{η^3-C_3H_5PdCl}$_2$], 7.5 mol% ligand in THF at room temperature with normal magnetic stirring for mixing. [d] Not applicable. [e] Triethylamine added.

[*] Prof. B. M. Trost, Z. Pan, J. Zambrano, C. Kujat
Department of Chemistry
Stanford University
Stanford, CA 94305-5080 (USA)
Fax: (+1) 650-725-0259
E-mail: bmtrost@stanford.edu

[**] We thank the National Science Foundation and the National Institute of Health, General Medical Sciences (GM13598), for their generous support of our programs. We thank Argonaut Technologies for a generous gift of ArgoGel resins.

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