S. Leonce, P. Renard, A. Pierre, G. Atassi, *J. Nat. Prod.* **1998**, *61*, 982 – 986.
[10] a) G. K. Hughes, F. N. Lakey, J. R. Price, L. J. Webb, *Nature* **1948**, *162*, 223 – 224; b) R. T. Dorr, J. D. Liddil, D. D. Von Hoff, M. Soble, C. K. Osborne, *Cancer Res.* **1989**, *49*, 340 – 344, and references therein.
[11] a) L. A. Sorbera, P. Leeson, J. Castaner, *Drugs Future* **1999**, *24*, 235 – 245; b) Y. Kashman, K. R. Gustafson, R. W. Fuller, J. H. Cardellina II, J. B. McMahon, M. J. Currens, R. W. Buckheit, Jr., S. H. Hughes, G. M. Cragg, M. R. Boyd, *J. Med. Chem.* **1992**, *35*, 2735 – 2743; c) Z.-Q. Xu, M. G. Hollingshead, S. Borgel, C. Elder, A. Khilevich, M. T. Flavin, *Bioorg. Med. Chem. Lett.* **1999**, *9*, 133 – 138, and references therein.
[12] a) N. Fang, J. E. Casida, *Proc. Natl. Acad. Sci. USA* **1998**, *95*, 3380 – 3384; b) N. Fang, J. E. Casida, *J. Natl. Prod.* **1999**, *62*, 205 – 210; c) M. Kaouadji, A. Agban, A. M. Mariotte, M. Tissut, *J. Nat. Prod.* **1986**, *49*, 281 – 285.
[13] A. C. Whyte, J. B. Gloer, D. T. Wicklow, P. F. Dowd, *J. Nat. Prod.* **1996**, *59*, 1093 – 1095.
[14] a) M. Takasugi, S. Nagao, S. Ueno, T. Masamune, A. Shirata, K. Takahashi, *Chem. Lett*. **1978**, 1239 – 1240; b) A. Shirata, K. Takahashi, M. Takasugi, S. Nagao, S. Ishikawa, S. Ueno, L. Munoz, T. Masamune, *Sanshi Shikenjo Hokoku* **1983**, *28*, 793 – 806.
[15] For a solution precedent of selenium-mediated 6-*exo*-trig cyclizations of *ortho*-prenylated phenols and related systems, see a) D. L. J. Clive, G. Chittattu, N. J. Curtis, W. A. Kiel, C. K. Wong, *J. Chem. Soc. Chem. Commun.* **1977**, 725 – 727; b) P. B. Anzeveno, *J. Org. Chem*. **1979**, *44*, 2578 – 2580; c) K. C. Nicolaou, Z. Lysenko, *J. Am. Chem. Soc.* **1977**, *99*, 3185 – 3187.
[16] All *ortho*-prenylated phenols employed were prepared in one of three ways: a) Friedel – Crafts-type alkylation, see F. Bohlmann, U. Buhmann, *Chem. Ber.* **1972**, *105*, 863 – 873; see also L. Jurd, K. Stevens, G. Manners, *Tetrahedron Lett.* **1971**, *25*, 2275 – 2278; b) anionic alkylation, see R. W. Bates, C. J. Gabel, *Tetrahedron Lett.* **1993**, *34*, 3547 – 3550; c) aromatic Claisen rearrangement, see F. Bohlmann, E. Vorwerk, *Chem. Ber.* **1980**, *113*, 261 – 266; also see D. Bell, M. R. Davies, G. R. Geen, I. S. Mann, *Synthesis* **1995**, 707 – 712.
[17] S. P. Hollinshead, *Tetrahedron Lett.* **1996**, *37*, 9157 – 9160.
[18] a) K. C. Nicolaou, X.-Y. Xiao, Z. Parandoosh, A. Senyei, M. P. Nova, *Angew. Chem*. **1995**, *107*, 2476 – 2479; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2289 – 2291; b) E. J. Moran, S. Sarshar, J. F. Cargill, M. J. M. Shahbaz, A. Lio, A. M. M. Mjalli, R. W. Armstrong, *J. Am. Chem. Soc*. **1995**, *117*, 10787 – 10788.
[19] We thank Mr. Rick Brown of Discovery Partners International (DPI) for a generous gift of IRORI MicroKans (K.C.N. is an advisor of DPI).
[20] IRORI microreactors were not applicable for the synthesis of compounds **1**, **2**, **55**, and **62** because of the high reaction temperature (165 °C) required. All other compounds (**56** – **61** and **63** – **68**) were synthesized using IRORI microreactor split-and-pool technology.[18, 19]
[21] a) Wittig reaction: H. Ishii, K. Kenmotsu, W. Dopke, T. Harayama, *Chem. Pharm. Bull*. **1992**, *40*, 1770 – 1772; b) β-ketoester reaction: J.-R. Yang, M. E. Langmuir, *J. Heterocycl. Chem.* **1991**, *28*, 1177 – 1180; see also T. Besson, G. Coudert, G. Guillaumet, *J. Heterocycl. Chem*. **1991**, *28*, 1517 – 1523.
[22] R. X. Tan, J.-L. Wolfender, L. X. Zhang, W. G. Ma, N. Fuzzati, A. Marston, K. Hostettmann, *Phytochemistry* **1996**, *42*, 1305 – 1313.
[23] K. Takai, K. Nitta, K. Utimoto, *J. Am. Chem. Soc.* **1986**, *108*, 7408 – 7410.
[24] Yields of reactions performed on the resin were estimated by oxidatively cleaving a portion of the resin after each step and determining the conversion by ^{1}H NMR analysis.
[25] Recent review: C. L. Kingsbury, S. J. Mehrman, J. M. Takacs, *Curr. Org. Chem.* **1999**, *3*, 497 – 555.
[26] T. G. Mayer, B. Kratzer, R. R. Schmidt, *Angew. Chem*. **1994**, *106*, 2289 – 2293; *Angew. Chem. Int. Ed. Engl*. **1994**, *33*, 2177 – 2181.
[27] R. R. Schmidt, J. Michel, *Angew. Chem*. **1980**, *92*, 763 – 764; *Angew. Chem. Int. Ed. Engl.* **1980**, *9*, 731 – 732.

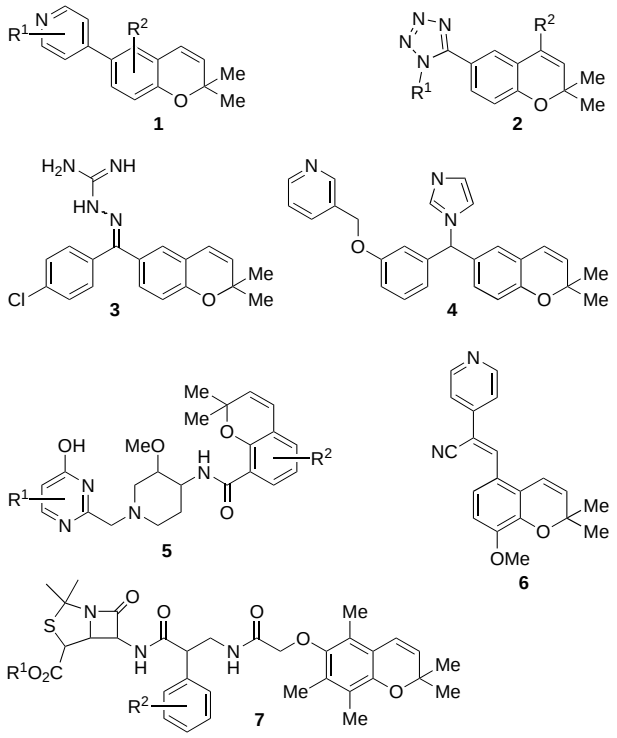
Selenium-Based Solid-Phase Synthesis of Benzopyrans II: Applications to Combinatorial Synthesis of Medicinally Relevant Small Organic Molecules**

K. C. Nicolaou,* Guo-Qiang Cao, and Jeffrey A. Pfefferkorn

In the preceding communication we described a novel selenium-based simultaneous cyclization and loading (cyclo-loading) strategy for the solid-phase combinatorial synthesis of natural products containing the 2,2-dimethylbenzopyran moiety.[1] Given the vast number and diverse biological activities of these benzopyran natural products, it is reasonable to consider whether this structural motif might be of value in the construction of designed pharmaceutical agents, particularly since natural-product-based mechanistic investigations have revealed that such structures interact with a variety of protein and nucleic acid cellular targets.[2] Not surprisingly, a search of the patent literature revealed a host of pharmaceutical ligands that contain the 2,2-dimethylbenzopyran skeleton (Scheme 1). Among these are the potassium-channel activators **1** and **2**,[3] aldosterone biosynthesis inhibitors **3** and **4**,[4] 5-hydroxytryptamine-3 receptor antagonist **5**,[5] phosphodiesterase IV inhibitor **6**,[6] and the ampicillin-derived antibacterial agent **7**.[7] However, in spite of the potential utility of this substituted benzopyran motif in ligand design, only a limited number of solid-phase methods for its construction has been reported.[8] Hence we investigated whether our current cyclo-loading approach might be a useful tool in medicinal chemistry for future combinatorial investigations of this class of compounds. Since structures **1** – **7**, unlike the natural products previously described, are structurally quite diverse and possess a variety of heteroatom functionalities, we sought to effect the solid-phase functionalization of several of the previously described resin-bound benzopyrans[1] with various heteroatom-based functional groups in order to produce scaffolds embodying their structural features. Herein we describe the synthesis of several representative scaffolds as well as a solid-phase synthesis of androsterone biosynthesis inhibitor **4** (Scheme 1) and a small library of analogues using radiofrequency

[*] Prof. Dr. K. C. Nicolaou, Dr. G.-Q. Cao, J. A. Pfefferkorn
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
and
Department of Chemistry and Biochemistry
University of California San Diego
9500 Gilman Drive, La Jolla, CA 92093 (USA)
E-mail: kcn@scripps.edu

[**] We are indebted to Nicolas Winssinger for advice and preparation of the selenium bromide resin employed in these studies. Financial support for this work was provided by The Skaggs Institute for Chemical Biology, the National Institutes of Health (USA), the Department of Defense (fellowship to J.A.P.), and grants from Abbott, Amgen, Boehringer-Ingelheim, GlaxoWellcome, Hoffmann-LaRoche, DuPont, Merck, Novartis, Pfizer, and Schering Plough.

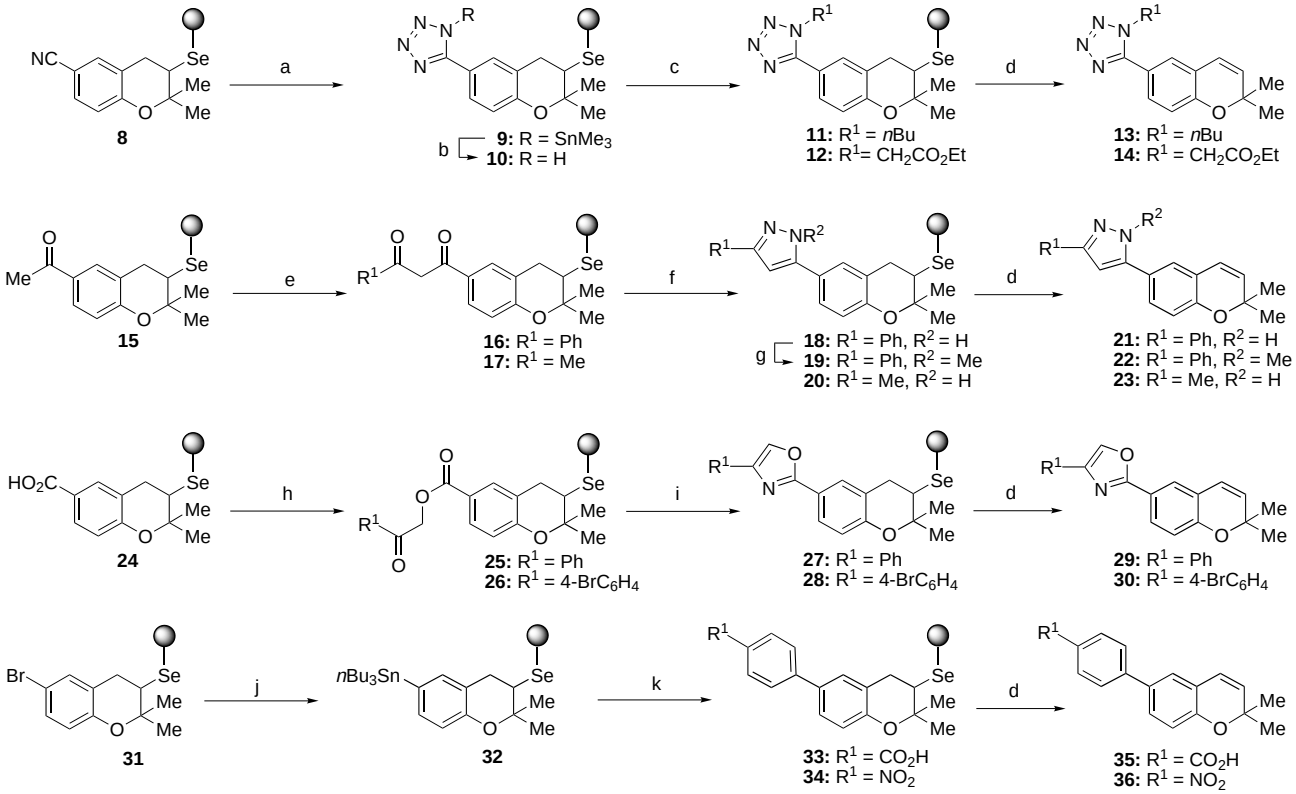


Scheme 1. Representative examples of potential pharmaceutical candidates incorporating the 2,2-dimethylbenzopyran moiety.

directed split-and-pool technology[9] as an illustration of the wide applicability and efficiency of this strategy.

The initial focus of these efforts was on the construction of several aromatic and heteroaromatic substituted benzopyrans resembling the core structures of the potassium-channel activators **1** and **2** (Scheme 1).[3] Four prototypes (**13**, **21**, **29**, and **35**, Scheme 2) were constructed, each synthesis commencing from a different resin-bound benzopyran platform (**8**, **15**, **24**, and **31**, respectively). Thus, tetrazoles **13** and **14** were constructed from cyanide **8** by treatment with azidotrimethylstannane at 100 °C to give stannylated tetrazole **9**, which was hydrolyzed with TFA (for abreviations of reagents and protecting groups see legends in schemes) to provide **10** in quantitative yield[10] over two steps.[11] Derivatization of tetrazole **10** was accomplished through alkylation by treatment with an appropriate alkyl halide and Et_3N at 80 °C to give **11** and **12** in 85 and 87 % yields, respectively.[12] These tetrazoles were then subjected to standard oxidative release conditions (H_2O_2)[1] to afford **13** and **14** in 52 and 65 % yields, respectively, based on **8**.

In the second example, acetophenone **15** was converted into pyrazoles **21**–**23** (Scheme 2) by initial conversion of the methyl ketone functionality into the corresponding β-dicarbonyl system through formation of an enolate with LHMDS followed by quenching with an appropriate acyl cyanide to afford **16** and **17** in 87 and 75 % yields, respectively.



Scheme 2. Solid-phase synthesis of heterocyclic and aryl-substituted 2,2-dimethylbenzopyrans: a) azidotrimethyltin (5.0 equiv), toluene, 110 °C, 12 h, 100 %; b) TFA (2.0 equiv), THF:H_2O (10:1), 25 °C, 2 h, 100 %; c) R^1Br (10.0 equiv), Et_3N (20.0 equiv), MeCN, 80 °C, 12 h, 85–87 %; d) H_2O_2 (10.0 equiv), THF, 25 °C, 30 min, **13** (52 %), **14** (65 %), **21** (65 %), **22** (58 %), **23** (49 %), **29** (42 %), **30** (46 %), **35** (62 %), **36** (75 %); e) LHMDS (3.0 equiv), $R^1C(O)CN$, THF, −78 → 0 °C, 1 h, 88–75 %; f) hydrazine hydrate (10.0 equiv), AcOH (0.01 equiv), THF:MeOH (2:1), 65 °C, 3 h, 87–65 %; g) MeI (10.0 equiv), NaH (5.0 equiv), THF, 40 °C, 12 h, 95 %; h) $R^1C(O)CH_2Br$ (10.0 equiv), DBU (20.0 equiv), DMF, 80 °C, 12 h, 100 %; i) acetamide (10.0 equiv), $BF_3 \cdot Et_2O$ (1.0 equiv), xylenes, 140 °C, 48 h, 50–55 %; j) *n*BuLi (10.0 equiv), THF, −78 °C, 2 h; then, nBu_3SnCl (15.0 equiv), THF, −78 → 0 °C, 1 h, ca. 100 %; k) $[Pd_2dba_3P(2\text{-furyl})_3]$ (0.05 equiv), 4-$R^1C_6H_4I$ (5.0 equiv), DMF, 100 °C, 12 h, 85–90 %. TFA = trifluoroacetic acid, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

  0044-8249/00/11204-0756 $ 17.50+.50/0

Condensation of **16** and **17** with hydrazine hydrate and catalytic amounts of acetic acid gave resin-bound pyrazoles **18** and **20** in 87 and 65% yields, respectively.[13] These pyrazoles could also be further derivatized through alkylation as demonstrated by the conversion of **18**→**19** upon treatment with MeI/NaH in DMF at 60°C. Finally, the constructed heterocycles were cleaved from the resin under oxidative conditions to afford **21**–**23** in 65, 58, and 49% overall yields, respectively, based on **15**.[14]

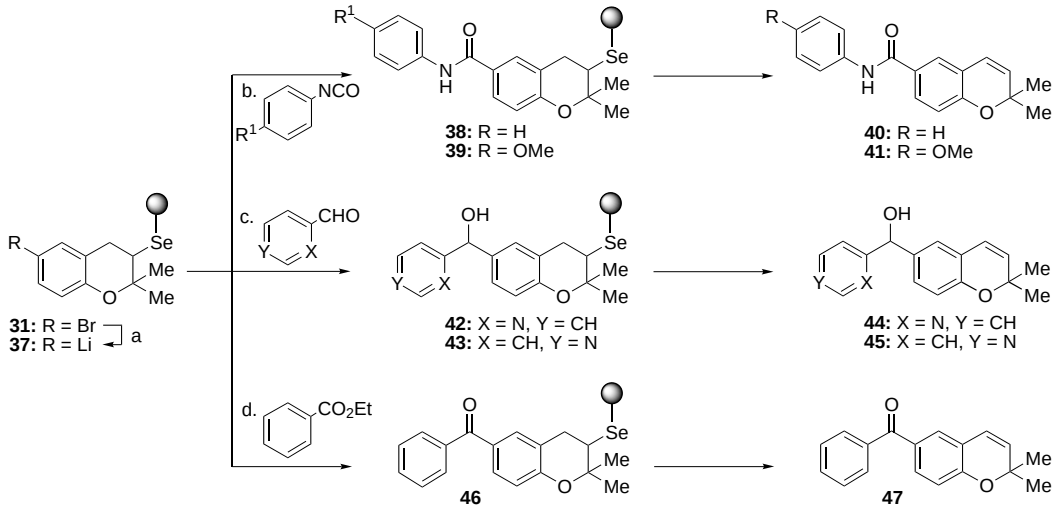
The third example involved conversion of benzoic acid **24** into oxazoles **29** and **30** (Scheme 2). Hence, alkylation of **24** was effected by treatment with several α-bromo ketones and DBU in DMF at 80°C to afford **25** and **26** in quantitative yields. Heterocycle formation was accomplished by treatment of **25** and **26** with acetamide and $BF_3 \cdot Et_2O$ in xylenes at 140°C[15] to give **27** and **28** (50 and 55% yields, respectively), which were then cleaved under standard oxidative conditions to afford oxazoles **29** and **30** in 42 and 46% yields over three steps based on **24**.

In the fourth example bromobenzopyran **31** was converted into the corresponding tri-*n*-butylstannane **32** through a halogen–metal exchange with *n*BuLi at −78°C followed by quenching with nBu_3SnCl (Scheme 2).[16] Tri-*n*-butylstannane **32** was then treated with several aryl iodides under palladium(0)-catalyzed coupling conditions[17] to afford structures **33** (90%) and **34** (85%), which were subsequently cleaved to give **35** and **36** in excellent yields and purities. Interestingly, while these electron-deficient aryl iodides coupled quite effectively, attempts to employ either unsubstituted or electron-rich aryl iodides resulted, so far, in only low yields of the desired coupling products.

The facility of the latter halogen–metal exchange prompted us to consider additional reaction manifolds of the resin-bound lithiobenzopyran (derived from **31**) for the construction of other potentially useful substituted benzopyran structures, particularly amides, alcohols, and benzophenones (for example, **40**, **44**, and **47**, Scheme 3).[16] Bromobenzopyran **31** was once again converted into the corresponding lithium anion and then treated with a series of electrophiles. For example, the quenching of **37** with aryl isocyanates led to amides **38** and **39** in yields greater than 95%. The addition of aromatic aldehydes followed by warming to 25°C provided access to benzylic alcohols **42** and **43** in 90 and 88% yields, respectively, whereas quenching with ethyl benzoate allowed direct access to benzophenones such as **46** in 82% yield.

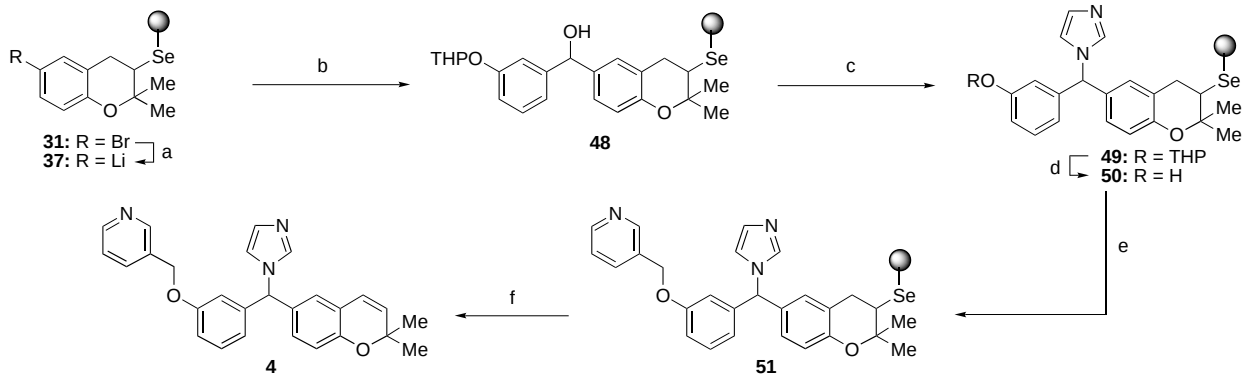
As a final illustration of how the current benzopyran cycloaddition-loading strategy could be useful in expediting drug discovery efforts, we set out to demonstrate a solid-phase synthesis of aldosterone biosynthesis inhibitor **4**[4] along with a small library. The initial synthesis of **4** commenced with the described halogen–metal exchange of **31** (Scheme 4) to give **37**, which was then treated with 3-(THPO)-benzaldehyde and allowed to warm from −78 to 25°C over 12 h to afford **48** in 99% yield over two steps. The benzylic alcohol of **48** was then displaced with imidazole employing standard Mitsunobu conditions to afford tetracycle **49** in 85% yield. After removal of the THP protecting group, phenol **50** was treated with 3-pyridylmethanol under Mitsunobu conditions to afford **51** (95% yield) from which the targeted compound **4** was released by treatment with H_2O_2 (75% yield over six steps based on **31**). Application of this route using IRORI MicroKans and radiofrequency encoded split-and-pool technology[9] allowed for the construction of a small library of related compounds (**57**–**64**, Scheme 5).[18] In general, the lithio species (**37**, Scheme 5) was treated with aromatic aldehydes to furnish alcohols **52**, which underwent Mitsunobu reaction with a variety of amines (R^3NH) to give structures **53**. Substrates containing a THP-protected phenol were then deprotected and the phenolic hydroxyl groups were reacted with benzyl alcohols (R^5OH) under Mitsunobu conditions to give structures **55**, which were subsequently oxidatively cleaved to provide benzopyrans **57**–**64**.

The chemistry described in this and the preceding communication[1] demonstrate the versatility and applicability of a

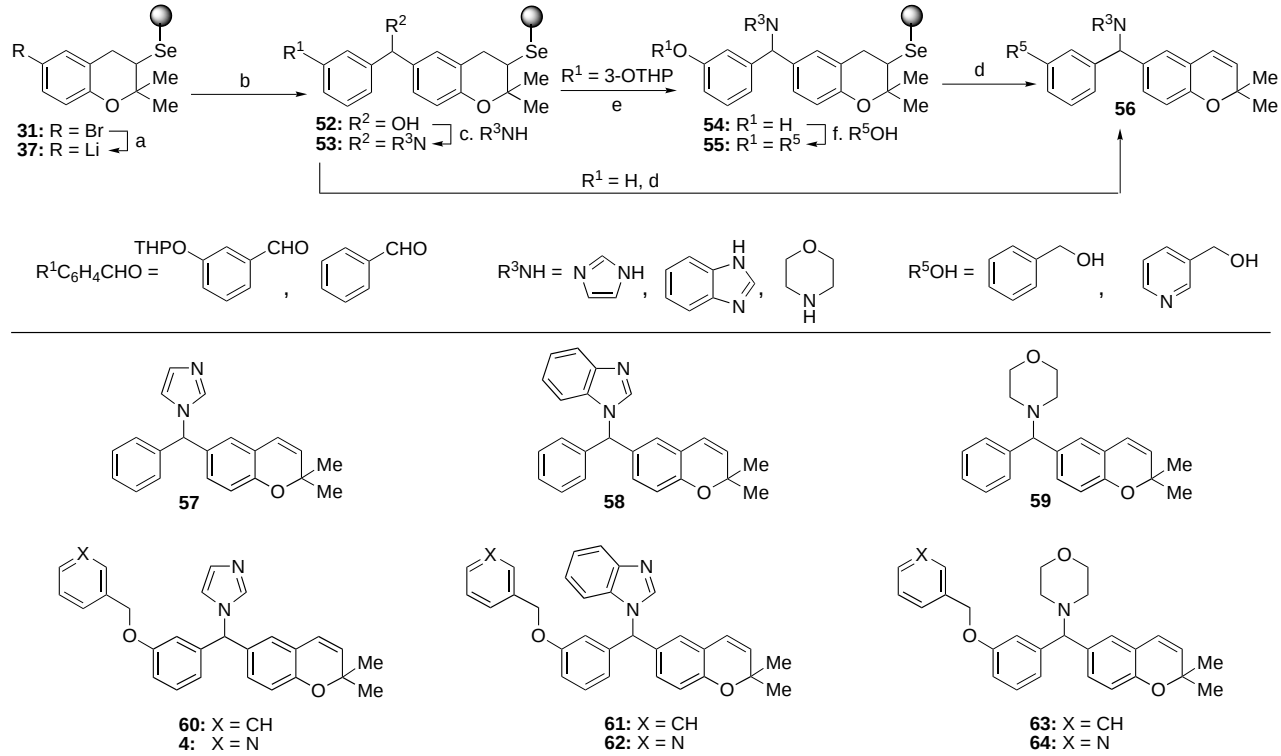


Scheme 3. Solid-phase synthesis of substituted 2,2-dimethylbenzopyrans: a) *n*BuLi (10.0 equiv, 1.6 M in hexane), THF, −78°C, 2 h; b) phenyl isocyanate (15.0 equiv), −78→25°C, 30 min, 90–95% over two steps; c) aryl aldehyde (15.0 equiv), −78→25°C, 12 h, 88–90% over two steps; d) ethyl benzoate (15.0 equiv), −78→25°C, 30 min, 85% over two steps; e) H_2O_2 (10.0 equiv), THF, 25°C, 30 min.

  0044-8249/00/11204-0757 $ 17.50+.50/0



Scheme 4. Solid-phase synthesis of the aldosterone biosynthesis inhibitor **4**: a) *n*BuLi (10.0 equiv, 1.6 M in hexane), THF, −78 °C, 2 h; b) 3-(THPO)-C_6H_4-CHO (20.0 equiv), THF, −78 →25 °C, 12 h, 99% over two steps; c) Ph_3P (10.0 equiv), DEAD (10.0 equiv), imidazole (20.0 equiv), CH_2Cl_2, 0 →25 °C, 48 h, 85%; d) $TsOH \cdot H_2O$ (1.0 equiv), THF:MeOH (10:1), 25 °C, 2 h, 100%; e) Ph_3P (20.0 equiv), DEAD (20.0 equiv), 3-pyridylmethanol (20.0 equiv), CH_2Cl_2, 25 °C, 20 h, 95%; f) H_2O_2 (10.0 equiv), THF, 25 °C, 15 min, 75% over six steps based on **31**. DEAD = diethyl azodicarboxylate, $TsOH \cdot H_2O$ = *p*-toluenesulfonic acid monohydrate.



Scheme 5. Solid-phase radiofrequency encoded split-and-pool synthesis of structural analogues (**58**–**65**) of aldosterone biosynthesis inhibitor **4**. Reagents and conditions: a) *n*BuLi (10.0 equiv, 1.6 M in hexane), THF, −78 °C, 2 h; b) $R^1C_6H_4CHO$ (10.0–20.0 equiv), THF, −78 →25 °C, 12 h, 80–90% over two steps; c) Ph_3P (10.0 equiv), DEAD (10.0 equiv), R^3NH (20.0 equiv), CH_2Cl_2, 0 →25 °C, 48 h, 75–85%; d) H_2O_2 (10.0 equiv), THF, 25 °C, 15 min; e) $TsOH \cdot H_2O$ (1.0 equiv), THF:MeOH (10:1), 25 °C, 2 h, (ca. 100%); f) Ph_3P (20.0 equiv), DEAD (20.0 equiv), R^5OH (20.0 equiv), CH_2Cl_2, 25 °C, 20 h, 90–95%.

new solid-phase, seamless linking strategy for the rapid construction of complex structures. The reported selenium-based method makes use of both the loading and cleavage steps to impart complexity and functionality into the target molecules and can be used to produce both natural products and designed molecules efficiently and in a specific or combinatorial fashion. The practical nature of the steps involved, the fact that no selenium compounds are released into the solution phase, and the high efficiency and purity in which the final products are obtained should make the reported strategy a favorite method for combinatorial synthesis to be applied in chemical biology studies and the drug discovery process.

Received: September 16, 1999 [Z 14024]

[1] K. C. Nicolaou, J. A. Pfefferkorn, G.-Q. Cao, *Angew. Chem.* **2000**, *112*, 748–753; *Angew. Chem. Int. Ed.* **2000**, *39*, 734–739.

[2] For examples, see a) A. A. L. Gunatilaka, D. G. I. Kingston, E. M. K. Wijeratne, B. M. R. Bandara, G. A. Hofmann, R. K. Johnson, *J. Nat. Prod.* **1994**, *57*, 518–520; b) M. J. Currens, R. J. Gulakowski, J. M.

  0044-8249/00/11204-0758 $ 17.50+.50/0

Mariner, R. A. Moran, R. W. Buckheit, Jr., K. R. Gustafson, J. B. McMahon, M. R. Boyd, *J. Pharmacol. Exp. Ther.* **1996**, *279*, 645 – 651; c) N. Fang, J. E. Casida, *Proc. Natl. Acad. Sci. USA* **1998**, *95*, 3380 – 3384; d) R. T. Dorr, J. D. Liddil, D. D. Von Hoff, M. Soble, C. K. Osborne, *Cancer Res.* **1989**, *49*, 340 – 344.

[3] a) A. R. Mackenzie, S. M. Monaghan (Pfizer Research and Development Co.), WO-A 9420491 [*Chem. Abstr.* **1994**, *123*, 55885]; b) P. W. Manley (Sandoz Ltd., Switzerland), US-A 5574049 [*Chem. Abstr.* **1996**, *126*, 47104].

[4] R. M. Soll, P. J. Dollings, R. D. Mitchell, D. A. Hafner, *Eur. J. Med. Chem.* **1994**, *29*, 223 – 232.

[5] V. Daele, G. H. Paul, J. P. R. Marie, V. Laerhoven, W. J. Carolus, WO-A 9412494 [*Chem. Abstr.* **1994**, *121*, 99834].

[6] B. Gutterer, D. Flockerzi, H. Amschler, W.-R. Ulrich, T. Bar, T. Martin, A. Hatzelmann, H. Boss, R. Beume, D. Hafner, H.-P. Kley (Byk Gulden Lomberg Chemische Fabrik Gmbh, Germany), EP-B 819689 [*Chem. Abstr.* **1998**, *128*, 140610].

[7] (Eisai Co., Ltd., Japan), JP-A 78 – 146098 [*Chem. Abstr.* **1980**, *93*, 204640].

[8] a) Y. Wang, T.-N. Huang, *Tetrahedron Lett.* **1998**, *39*, 9605 – 9608; b) D. Craig, M. J. Robson, S. J. Shaw, *Synlett* **1998**, 1381 – 1383.

[9] a) K. C. Nicolaou, X.-Y. Xiao, Z. Parandoosh, A. Senyei, M. P. Nova, *Angew. Chem.* **1995**, *107*, 2476 – 2479; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2289 – 2291; b) E. J. Moran, S. Sarshar, J. F. Cargill, M. J. M. Shahbaz, A. Lio, A. M. M. Mjalli, R. W. Armstrong, *J. Am. Chem. Soc.* **1995**, *117*, 10787 – 10788.

[10] Yields of reactions performed on the resin were estimated by oxidatively cleaving a portion of the resin after each step and determining the conversion by ^{1}H NMR spectroscopic analysis.

[11] J. V. Duncia, M. E. Pierce, J. B. Santella III, *J. Org. Chem.* **1991**, *56*, 2395 – 2400.

[12] P. M. O'Brien, D. R. Sliskovic, J. A. Picard, H. T. Lee, C. F. Purchase II, B. D. Roth, A. D. White, M. Anderson, S. B. Mueller, T. Bocan, R. Bousley, K. L. Hamelehle, R. Homan, P. Lee, B. R. Krause, J. F. Reindal, R. L. Stanfield, D. Turluck, *J. Med. Chem.* **1996**, *39*, 2354 – 2366.

[13] A. U. Siddiqui, U. M. Rao, M. Srinivas, A. H. Siddiqui, *Org. Proc. Proced. Int.* **1992**, *24*, 355 – 358.

[14] Inspection of the ^{1}H NMR spectrum of **19** after cleavage revealed that the starting pyrazole **18** was formed as a 1:1 mixture of isomers.

[15] W. Huang, J. Pei, B. Chen, W. Pei, X. Ye, *Tetrahedron* **1996**, *52*, 10131 – 10136.

[16] C. Z. Ding, *Synth. Commun.* **1996**, *26*, 4267 – 4273.

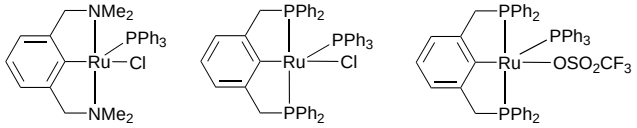
[17] V. Farina, S. I. Hauck, *Synlett* **1991**, 157 – 159.

[18] We thank Mr. Rick Brown of Discovery Partners International (DPI) for a generous gift of IRORI MicroKans (K.C.N. is an advisor to DPI).

Hydrogen-Transfer Catalysis with Pincer-Aryl Ruthenium(II) Complexes**

Paulo Dani, Thomas Karlen, Robert A. Gossage, Serafino Gladiali, and Gerard van Koten*

Complexes of pincerlike aryl ligands such as **1** – **3** belong to a new class of homogeneous catalytic systems that contain a stable metal – carbon σ bond.[1, 2a] Such organometallic complexes have already been used in a number of metal-mediated organic transformations, for example, dehydrogenation,[2a] asymmetric allylic alkylation,[2b] asymmetric aldol condensation,[2c,d] Heck reactions,[1b] atom-transfer radical polymerization (ATRP), and Kharasch addition (ATRA).[2e,f] Additionally, the terdentate pincer ligand stabilizes complexes with unusual geometries or oxidation states.[2f–i]



1 **2** **3**

Reduction by means of hydrogen-transfer reactions has recently attracted much attention because of its practical simplicity and potential use at ambient pressure.[3] Furthermore, the use of an alternative source of hydrogen may result in different reactivity patterns.[4] Coordination complexes containing bidentate ligands are normally used as catalysts in hydrogen-transfer reactions.[3] Herein we report that the pincer-type arylruthenium(II) complexes **1** – **3**,[5] containing the monoanionic, terdentate bis(amino)aryl $[C_6H_3(CH_2NMe_2)_2\text{-}2,6]^-$ (NCN) and bis(phosphanyl)aryl $[C_6H_3(CH_2PPh_2)_2\text{-}2,6]^-$ (PCP) ligands, are highly active catalysts for the reduction of various ketones to the corresponding alcohols with *i*PrOH as the hydrogen source and KOH as the promoter [Eq. (1)]. Representative types of ketones were chosen to evaluate the performance of **1** – **3** in such processes. Dialkyl (aliphatic and cyclic), alkyl aryl, and diaryl ketones were all

[*] Prof. Dr. G. van Koten, P. Dani, Dr. T. Karlen
Debye Institute, Department of Metal-Mediated Synthesis
Utrecht University, Padualaan 8
3584 CH, Utrecht (The Netherlands)
Fax: (+31) 30-2523615
E-mail: g.vankoten@chem.uu.nl

Dr. R. A. Gossage
Department of Chemistry, Acadia University
Wolfville, Nova Scotia, BOP 1X0 (Canada)

Prof. Dr. S. Gladiali
Dipartimento di Chimica, Universita′ di Sassari
Via Vienna 2-07100, Sassari (Italy)

[**] This work was financially supported by the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), Brazil (P.D.), the Swiss National Science Foundation and CIBA-GEIGY-Jubiläums-Stiftung (T.K.), and the Council for Chemical Sciences of the Netherlands Organization for Scientific Research (CW-NWO). Support by COST Chemistry Action D12 10009/98: "Organic Transformations: Selective Processes and Asymmetric Catalysis" is gratefully acknowledged.