

Isoindoles and dihydroisoquinolines by gold-catalyzed intramolecular hydroamination of alkynes

Daniel Kadzimirsz, Dirk Hildebrandt, Klaus Merz and Gerald Dyker*

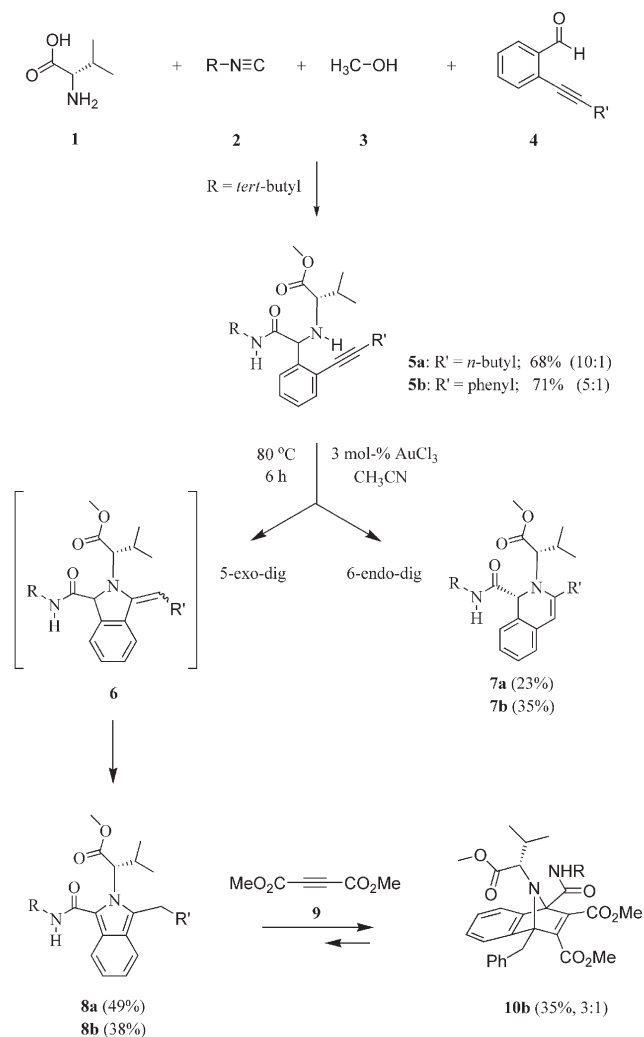
Received (in Cambridge, UK) 11th November 2005, Accepted 19th December 2005

First published as an Advance Article on the web 12th January 2006

DOI: 10.1039/b516017k

The title compounds are enantioselectively synthesized in just two preparative steps, making use of the Ugi-four-component reaction with an amino acid as chiral component, followed by a gold-catalyzed hydroamination.

Gold-catalyzed reactions have emerged as powerful and highly selective tools for organic synthesis in recent years:¹ obviously gold



Scheme 1 Combination of Ugi reaction, hydroamination and Diels-Alder reaction.

Fakultät für Chemie, Ruhr-Universität Bochum, Universitätsstrasse 150, D-44780, Bochum, Germany. E-mail: Gerald.Dyker@rub.de; Fax: +49 (0)234/32-14353; Tel: +49 (0)234/32-24551

complexes exhibit a high reactivity as rather soft Lewis-acids, especially in terms of alkyne activation for nucleophilic attacks,² enabling these processes to proceed under very moderate reaction conditions. As part of our ongoing studies on gold-catalyzed annelation reactions³ we envisioned that a two step sequence of the Ugi-four-component reaction⁴ with a gold-catalyzed cyclization should offer a fascinating opportunity to build up chiral heterocycles with a high degree of complexity.

According to this general idea we applied L-valine (**1**) as chiral amine component and benzaldehydes **4**⁵ as source of the alkyne moiety. The condensation process of the four reaction components **1–4** proceeds somewhat sluggishly at room temperature within 6 to 9 days, building up the highly functionalized amines **5**, finally with satisfactory yield and diastereoselectivity (Scheme 1).

The hydroamination⁶ succeeded with just 3 mol-% gold chloride as catalyst in acetonitrile at 80 °C with overall yields above 70%: the dihydroisoquinolines **7** obviously are the result of a 6-*endo*-dig cyclization, whereas the isoindoles **8** derive from the 5-*exo*-dig products **6**, which of course isomerize under aromatization under the acidic reaction conditions.

Alkynes **5** were applied as purified main diastereomers and gave **7a** and **7b** as single diastereomers according to TLC and NMR, thus indicating configurational stability under the acidic reaction conditions. In crystals of **7b** there are two independent molecules with identical configurations in the unit cell. Knowing the absolute configuration of the L-valine chiral centres to be *S* our X-ray structure analysis of **7b** (Fig. 1) then established that the other chiral centres have the *R*-configuration.⁷

To our knowledge **8a** and **8b** are the first examples of chiral isoindoles, prompting us to test the face selectivity of the Diels-Alder reaction of **8b** with acetylene dicarboxylic acid dimethyl ester

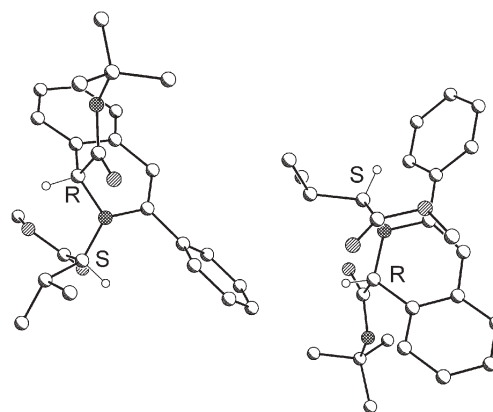


Fig. 1 Structure of the chiral isoquinoline **7b** in the crystal.

9. As the result we obtained a 3 : 1 mixture of the diastereomers of **10b** as an oily product: further separation and purification failed because of partial decomposition during flash chromatography. In test tube experiments also the Diels–Alder reactions with *N*-methyl and *N*-4-tolyl maleimides were examined: the resulting cycloadducts were even more sensitive than **10b**, clearly undergoing retro-Diels–Alder reaction at room temperature on silica. The retro reaction obviously profits from the electronic stabilization of isoindoles **8** by the amide substituent, which is part of the conjugated donor–acceptor system with the isoindole nitrogen. Normally retro-Diels–Alder reactions of isoindole adducts take place at much more elevated temperatures.⁸

In summary, the combination of Ugi reaction and gold catalysis offers a valuable opportunity for building up chiral dihydroisoquinolines and isoindoles, which are highly functionalized and of interest for further stereoselective transformations.

We gratefully acknowledge financial support from Fonds der Chemischen Industrie and the Deutsche Forschungsgemeinschaft (DFG-project DY 12/7-2).

Notes and references

- For reviews on gold catalysis, see: (a) G. Dyker, *Angew. Chem.*, 2000, **112**, 4407; G. Dyker, *Angew. Chem., Int. Ed.*, 2000, **39**, 4237; (b) A. S. K. Hashmi, *Gold Bull.*, 2004, **37**, 51; (c) A. Hoffmann-Röder and N. Krause, *Org. Biomol. Chem.*, 2005, **3**, 387; (d) A. S. K. Hashmi, *Angew. Chem., Int. Ed.*, 2005, **54**, 6990.
- Current examples of gold catalyzed reactions of alkynes: (a) Y. Luo and C. J. Li, *Chem. Commun.*, 2004, 1930; (b) Z. Shi and C. He, *J. Am. Chem. Soc.*, 2004, **126**, 13596; (c) S. T. Staben, J. J. Kennedy-Smith and F. D. Toste, *Angew. Chem., Int. Ed.*, 2004, **43**, 5350; (d) X. Yao and C.-J. Li, *J. Am. Chem. Soc.*, 2004, **126**, 6884; (e) A. S. K. Hashmi, M. Rudolph, J. P. Weyrauch, M. Wölflle, W. Frey and J. W. Bats, *Angew. Chem.*, 2005, **117**, 2858; A. S. K. Hashmi, M. Rudolph, J. P. Weyrauch, M. Wölflle, W. Frey and J. W. Bats, *Angew. Chem., Int. Ed.*, 2005, **44**, 2798; (f) Y. Harrak, C. Blaszykowski, M. Bernard, K. Cariou, E. Mainetti, V. Mouries, A.-L. Dhimane, L. Fensterbank and M. Malacria, *J. Am. Chem. Soc.*, 2004, **126**, 8656; (g) C. Nieto-Oberhuber, M. P. Muñoz, E. Buñuel, C. Nevado, D. J. Cárdenas and A. M. Echavarren, *Angew. Chem.*, 2004, **116**, 2456; C. Nieto-Oberhuber, M. P. Muñoz, E. Buñuel, C. Nevado, D. J. Cárdenas and A. M. Echavarren, *Angew. Chem., Int. Ed.*, 2004, **43**, 2402; (h) M. R. Luzung, J. P. Markham and F. D. Toste, *J. Am. Chem. Soc.*, 2004, **126**, 10858; (i) V. Mamane, T. Gress, H. Krause and A. Fürstner, *J. Am. Chem. Soc.*, 2004, **126**, 8654; (j) K. Miki, T. Yokoi, F. Nishino, Y. Kato, Y. Washitake, K. Ohe and S. Uemura, *J. Org. Chem.*, 2004, **69**, 1557; (k) T. Yao, X. Zhang and R. C. Larock, *J. Am. Chem. Soc.*, 2004, **126**, 11164; (l) S. Antonietti, E. Genin, V. Michelet and J. P. Genêt, *J. Am. Chem. Soc.*, 2005, **127**, 9976; (m) N. Asao, K. Sato, Menggenbateer and Y. Yamamoto, *J. Org. Chem.*, 2005, **70**, 3682; (n) L. Zhang and S. A. Kozmin, *J. Am. Chem. Soc.*, 2005, **127**, 6962; (o) C.-G. Yang and C. He, *J. Am. Chem. Soc.*, 2005, **127**, 6966; (p) J. Zhu, N. P. Grigoriadis, J. P. Lee and J. A. Porco, Jr., *J. Am. Chem. Soc.*, 2005, **127**, 9342; (q) J. P. Markham, S. T. Staben and F. D. Toste, *J. Am. Chem. Soc.*, 2005, **127**, 9708; (r) A. S. K. Hashmi and P. Sinha, *Adv. Synth. Catal.*, 2004, **346**, 432; (s) A. S. K. Hashmi, M. Rudolph, J. P. Weyrauch, M. Wölflle, W. Frey and J. W. Bats, *Angew. Chem., Int. Ed.*, 2005, **44**, 2798.
- (a) G. Dyker, D. Hildebrandt, J. Liu and K. Merz, *Angew. Chem.*, 2003, **115**, 4536; G. Dyker, D. Hildebrandt, J. Liu and K. Merz, *Angew. Chem., Int. Ed.*, 2003, **42**, 4399; (b) G. Dyker and D. Hildebrandt, *J. Org. Chem.*, 2005, **70**, 6093.
- (a) I. Ugi, S. Lohberger, R. Karl, B. M. Trost, I. Fleming and C. H. Heathcock, The Passerini and Ugi reaction, in *Comprehensive Organic Chemistry*, Vol. 2, Ch. 4.6, pp. 1083–1109, Pergamon Press, Oxford, 1991; (b) A. Demharter, W. Hörl, E. Herdtweck and I. Ugi, *Angew. Chem.*, 1996, **108**, 185; A. Demharter, W. Hörl, E. Herdtweck and I. Ugi, *Angew. Chem., Int. Ed.*, 1996, **35**, 173; (c) A. Dömling and I. Ugi, *Angew. Chem.*, 2000, **112**, 3301–3344; A. Dömling and I. Ugi, *Angew. Chem., Int. Ed.*, 2000, **39**, 3168; (d) I. Ugi, W. Hörl, C. Hanusch-Kompa, T. Schmid and E. Herdtweck, *Heterocycles*, 1998, **47**, 965; (e) G. Dyker, *Angew. Chem.*, 1997, **109**, 1777; G. Dyker, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 1700; (f) G. Dyker, K. Breitenstein and G. Henkel, *Tetrahedron: Asymmetry*, 2002, **13**, 1929.
- (a) K. Sonogashira, Y. Tohda and N. Hagihara, *Tetrahedron Lett.*, 1975, **50**, 4467; (b) S. Thorand and N. Krause, *J. Org. Chem.*, 1998, **63**, 8551; (c) G. Dyker, W. Stirner and G. Henkel, *Eur. J. Org. Chem.*, 2000, 1433.
- Some current articles on hydroamination: (a) T. E. Müller, M. Grosche, E. Herdtweck, A.-K. Pleier, E. Walter and Y.-K. Yan, *Organometallics*, 2000, **19**, 170; (b) E. Mizushima, T. Hayashi and M. Tanaka, *Org. Lett.*, 2003, **5**, 3349; (c) G. B. Bajracharya, Z. Huo and Y. Yamamoto, *J. Org. Chem.*, 2005, **70**, 4883; (d) Y. Luo, Z. Li and C.-J. Li, *Org. Lett.*, 2005, **7**, 2675.
- G. M. Sheldrick, *SHELXTL-97*, University of Göttingen, 1997. *Crystal data for 7b*: C₂₆H₃₂N₂O₃, M = 420.54, triclinic, space group P1, *a* = 9.187(14), *b* = 11.389(18), *c* = 12.80(2) Å, α = 105.30(13), β = 93.62(10), γ = 105.23(8)°, *V* = 1234(3) Å³, *Z* = 2, $2\theta_{\max}$ = 50°, 5711 measured reflections, 512 parameters, μ = 0.074 mm⁻¹, *R*1 = 0.0509 for 2835 observed reflections (*I* > 2σ(*I*)), *wR*2 = 0.1214 for all reflections; The intensity data were collected on a Bruker-axis-SMART 1000 diffractometer (Mo-K α radiation, λ = 0.71707 Å, *T* = 203 K). The structure was solved by direct methods and refined by full matrix least squares using SHELXTL-97. All non-hydrogen atoms were refined using anisotropic thermal parameters; hydrogen atoms were included by use of a riding model and fixed isotropic thermal parameters. CCDC 289676. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b516017k.
- (a) P. Sohar, F. Miklos, A. Csampai and G. Stajer, *J. Chem. Soc., Perkin Trans. 1*, 2001, **5**, 558; (b) R. P. Kreher and N. Kohl, *Angew. Chem.*, 1984, **96**, 507; R. P. Kreher and N. Kohl, *Angew. Chem., Int. Ed.*, 1984, **23**, 517; (c) D. E. Remy and F. H. Bissett, *J. Org. Chem.*, 1978, **43**, 4469; (d) J. Bornstein, D. E. Remy and J. E. Shields, *J. Chem. Soc., Chem. Commun.*, 1972, **20**, 1149.