Synthetic Methods

DOI: 10.1002/anie.200901299

Highly Substituted Furo[3,4-*d*][1,2]oxazines: Gold-Catalyzed Regiospecific and Diastereoselective 1,3-Dipolar Cycloaddition of 2-(1-Alkynyl)-2-alken-1-ones with Nitrones**

*Feng Liu, Yihua Yu, and Junliang Zhang**

Dedicated to Professor Li-Xin Dai on the occasion of his 85th birthday

Heterocyclic structures are core components of many natural products and man-made synthetic drugs. The design and synthesis of novel heterocyclic compounds with high efficiency is, therefore, highly desirable. 1,3-Dipolar cycloaddition reactions, which can provide rapid access to heterocyclic compounds in a convergent and efficient manner, have attracted the interest of many chemists.

Despite various metal-catalyzed methods developed for the synthesis of highly substituted furan compounds from various cyclic or acyclic precursors in past years,[1] it is still a challenge to efficiently assemble novel 3,4-fused bicyclic furans,[1j,2] especially from acyclic precursors. Furthermore, 1,2-oxazines are frequently found as structural skeletons in biologically active compounds[3] and as valuable synthetic building blocks in organic synthesis.[4] Among the many methods developed in past years to construct 1,2-oxazines,[5] the 1,3-dipolar [3+3] cycloaddition of nitrones[6] is a particularly effective one. For example, Kerr and co-workers[7] reported an efficient [3+3] cycloaddition of donor–acceptor cyclopropanes with nitrones leading to tetrahydro-1,2-oxazines under Lewis acid catalysis. The enantioselective version of this transformation was later accomplished by Sibi et al.[8a] and Tang and co-workers.[8b] Recently, Shintani, Hayashi, and co-workers[9] described an asymmetric and efficient palladium-catalyzed [3+3] cycloaddition of trimethylene methane derivatives with nitrones leading to 1,2-oxazines. Herein we report a gold(I)-catalyzed[13] 1,3-dipolar cycloaddition of 2-(1-alkynyl)-2-alken-1-ones with nitrones, which provides a practical, efficient, regiospecific, and highly diastereoselective route to novel heterobicyclic highly substituted furo[3,4-*d*]-[1,2]-oxazines.

During our research on the synthesis and reactivity of 2-(1-alkynyl)-2-alken-1-ones **1**,[10,11] we became interested in the metal-catalyzed 1,3-dipolar cycloaddition reaction of **1** with the nitrones **2**. We envisaged that this reaction might provide three different types of adducts (Figure 1): 1) isoxazolidines **3** by a 1,3-dipolar [3+2] cycloaddition of nitrones with the olefin moiety of **1**;[12] 2) 2,3-dihydroisoxazoles **4** by a 1,3-dipolar [3+2] cycloaddition of nitrones with the alkyne moiety of **1**; and 3) novel heterobicyclic furo[3,4-*d*]-[1,2]oxazines **5** by a 1,3-dipolar [3+3] cycloaddition (tandem double cyclizations) of nitrone with **1**.

We began by examining the cycloaddition reaction of ketone **1a** with nitrone **2a** in the presence of different metal catalysts (see Table 1 in the Supporting Information). After many attempts, we found that the reaction proceeded very well in CH_2Cl_2 at room temperature in the presence of 2.5 mol% of $Ph_3PAuOTf$; after a reaction time of 20 minutes (3*S**,8a*R**)-furo[3,4-*d*,*e*][1,2]oxazine **5aa** was isolated in 93% yield with a greater than 99:1 diastereoselectivity, which was determined by the ^1H NMR analysis of the crude product. In addition, the reaction was very clean and a [3+2] cycloadduct was not formed, indicating that this transformation is regiospecific and chemospecific. The configuration of **5aa** was confirmed by the single-crystal X-ray diffraction analysis.[14] Surprisingly, other commonly used metal catalysts such as $Sc(OTf)_3$, $Sn(OTf)_2$, $Cu(OTf)_2$, $Yb(OTf)_3$, $Y(OTf)_3$, $In(OTf)_3$, and $Ni(ClO_4)_2\cdot 6H_2O$ showed almost no catalytic activity, even at elevated reaction temperatures (40 °C). AgOTf and $AuCl_3$ also catalyzed this transformation but gave lower product yields. Changing to solvents such as MeCN, THF, or toluene failed to improve the reaction.

To determine the scope of this transformation, various ketones **1** were examined (Scheme 1). The reactions of both the cyclic substrates **1a–c** and acyclic substrates **1d–i** with various nitrones **2a–f** proceeded to afford the corresponding highly substituted furo[3,4-*d*][1,2]oxazines **5** in good to excellent yields with up to >99:1 diastereoselectivity (reaction time 30 min). The olefinic and cyclopropyl substitutents on **1b** and **1c**, respectively, did not affect the reaction. The R^1 and R^2 substitutents of **1** have larger effects on the diastereoselectivity of the reaction than the R^3 group of **1**. The configuration of the cycloadducts derived from acyclic

[*] F. Liu, Prof. Dr. J. Zhang
Shanghai Key Laboratory of Green Chemistry and Chemical Processes, Department of Chemistry
East China Normal University
3663 N. Zhongshan Road, Shanghai 200062 (P.R. China)
Fax: (+86) 21-6223-5039
E-mail: jlzhang@chem.ecnu.edu.cn
Prof. Y. Yu
Shanghai Key Laboratory of Magnetic Resonance
Department of Physics, East China Normal University (P.R. China)
Prof. Dr. J. Zhang
State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences
354 Fenglin Road, Shanghai 200032 (P.R. China)

[**] Financial support from the National Natural Science Foundation of China (20702015), the Science and Technology Commission of Shanghai Municipality (07DZ22937), Shanghai Shuguang Program (07SG27), Shanghai Pujiang Program (07pj14039), and Shanghai Leading Academic Discipline Project (B409) is greatly appreciated.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200901299.

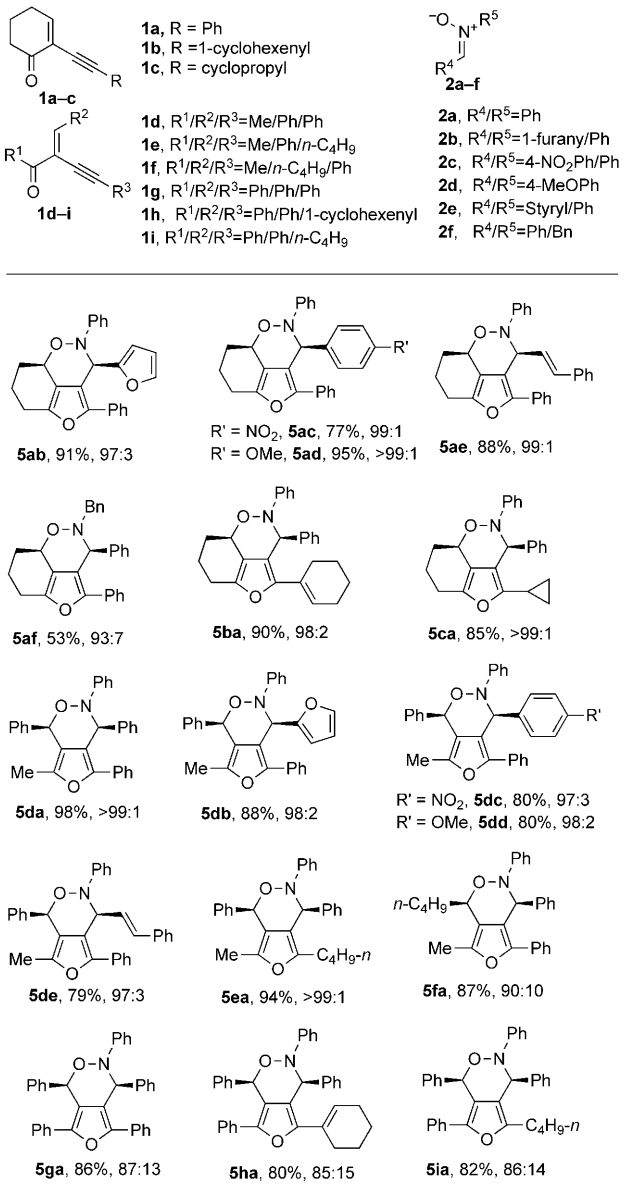
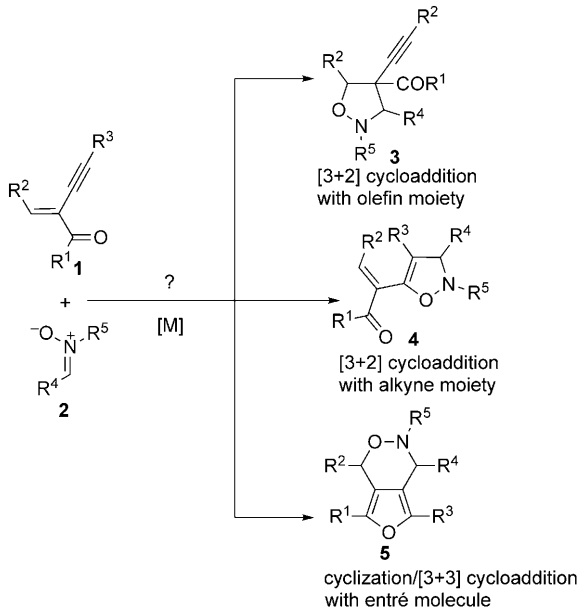


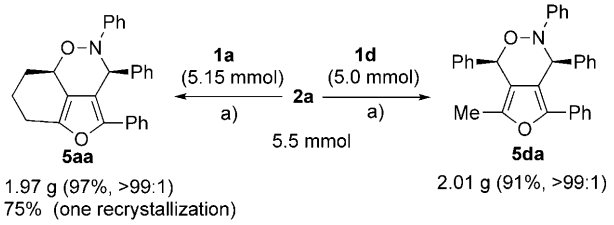
Figure 1. Gold(I)-catalyzed 1,3-dipolar [3+3] cycloaddition of 2-(1-alkynyl)-2-alken-1-ones **1** with nitrones **2**. The respective yields and diastereomeric ratios are given. Reaction conditions: **1** (0.4 mmol), nitrone **2** (0.44 mmol, 1.1 equiv), catalyst (2.5 mol%), CH_2Cl_2 (4 mL), RT, 10–30 min.

ketones **1d–i**, which may be different from cyclic ketones, was also confirmed by the X-ray crystallographic analysis of **5da**.[14]

Notably, the catalyst loading could be reduced to 0.2 mol% without any loss in the yield and diastereoselectivity on a 5 mmol scale reaction (Scheme 2). For example, the reactions of **2a** (5.5 mmol) with **1a** (5.15 mmol) or **1d** (5.0 mmol) was complete within 20 minutes to yield 1.97 grams of **5aa** (97% yield upon isolation; turnover number is about 500) or 2.01 grams of **5da** (91% yield upon isolation), respectively. Furthermore, a 75% yield of **5aa** could be obtained through only one simple recrystallization (CH_2Cl_2/hexanes) of the crude product, thereby making this transformation practical.

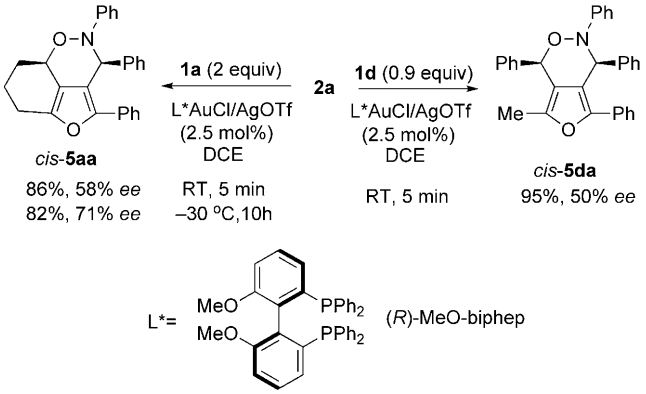


Scheme 1. Proposed metal-catalyzed cycloaddition of 2-(1-alkynyl)-2-alken-1-ones **1** with nitrones **2**.



Scheme 2. Cyclization of **1a** and **1d** with **2a** on a 5 mmol scale using only 0.2 mol% of the catalyst. Reaction conditions: a) $Ph_3PAuOTf$ (0.20 mol%), CH_2Cl_2, RT, 20 min.

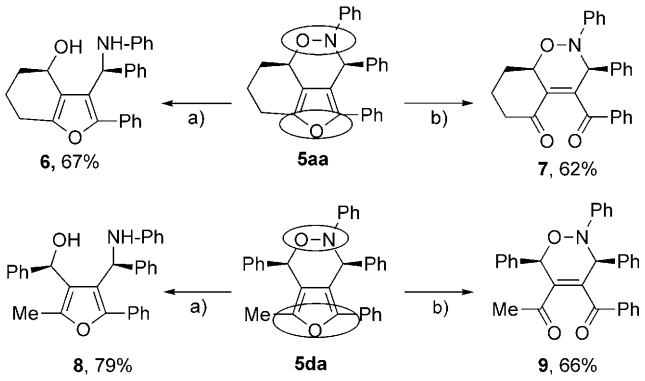
Our preliminary results (Scheme 3) showed that chiral the (*R*)-MeO-biphep-derived gold complex could be used as the asymmetric catalyst. The [3+3] cycloaddition reaction of **1a** with **2a** proceeded rapidly at room temperature to give the tricyclic product *cis*-**5aa** in 86% yield and 58% *ee* (71% *ee* at



Scheme 3. Asymmetric gold-catalyzed [3+3] cycloaddition. DCE = 1,2-dichloroethane, Tf = trifluoromethanesulfonyl.

−30°C; after one recrystallization: 98% *ee*). Furthermore, heterobicycle *cis*-**5da** could also be attained in 95% yield and 50% *ee* from the corresponding acyclic substrate **1d** and nitrone **2a** after reaction for five minutes at room temperature.

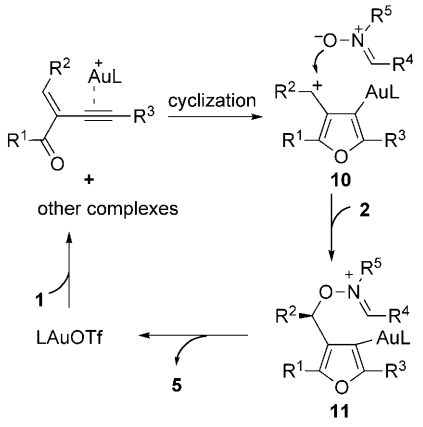
The synthetic utility of furo[3,4-*d*][1,2]oxazines was showcased by the selective additional transformations of the two representative products *cis*-**5aa** and *cis*-**5da** (Scheme 4). The



Scheme 4. Chemoselective ring-opening of furo[3,4-*d*][1,2]oxazines provides efficient access to highly functionalized furans or 1,2-oxazines. Reaction conditions: a) SmI_2, THF, 40°C; b) CAN, CH_3CN/H_2O 1:1, RT.

compounds *cis*-**5aa** and *cis*-**5da** were converted into functionalized tetrasubstituted amino alcohol containing furans **6** and **8**, respectively, by SmI_2-mediated reductive cleavage of the N–O bond.[15] Alternatively, the functionalized 1,2-oxazines **7** and **9** were obtained in moderate yields by treatment of *cis*-**5aa** and *cis*-**5da**, respectively, with cerium(IV) ammonium nitrate (CAN).[16]

A plausible stepwise reaction pathway for this gold(I)-catalyzed transformation is depicted in Scheme 5. The cationic gold(I) species first coordinates to ketone **1**, with subsequent cyclization to generate the furanyl gold complex **10**, which is rapidly trapped by the nucleophilc oxygen atom of the nitrone to afford intermediate **11**. Subsequent intramolecular cyclization would then yield product **5** as well as regenerate the gold catalyst.



Scheme 5. Plausible mechanism for this gold(I)-catalyzed transformation.

In summary, a gold(I)-catalyzed 1,3-dipolar [3+3] cycloaddition of 2-(1-alkynyl)-2-alken-1-ones with nitrones has been developed, providing a practical, regiospecific, and diastereoselective access to highly substituted fused heterobicyclic furo[3,4-*d*][1,2]oxazines under mild reaction conditions. The cycloadducts were obtained with moderate *ee* values by using (*R*)-MeO-biphep as the chiral ligand. Furthermore, the heterobicyclic products could be easily converted into furans or 3,6-dihydro-2*H*-1,2-oxazines in a chemoselective fashion.

Experimental Section

Typical procedure for furo[3,4-*d*][1,2]oxazine synthesis (see Table S1, entry 10 in the Supporting Information): A solution of $Ph_3PAuOTf$ (1 mL, 0.01M in CH_2Cl_2, 2.5 mol%) was added to a solution of 2-(1-alkynyl)-2-alken-1-one **1a** (78.5 mg, 0.40 mmol) and nitrone **2a** (86.7 mg, 0.44 mmol, 1.1 equiv) in CH_2Cl_2 (3 mL) at room temperature. The resulting mixture was stirred for 20 min and the reaction was complete as determined by TLC analysis. The reaction mixture was passed through a short silica gel column and then concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexanes/ethyl acetate 20:1) to afford the pure product **5aa** (146.4 mg) in 93% yield as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.37$ (d, $J = 7.5$ Hz, 2H), 7.24–7.16 (m, 4H), 7.11–6.89 (m, 9H), 5.95 (s, 1H), 5.16–5.09 (m, 1H), 2.86–2.78 (m, 2H), 2.30–2.23 (m, 2H), 1.97–1.98 (m, 1H), 1.64–1.50 ppm (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 148.62$, 147.00, 146.70, 137.06, 130.93, 129.39, 128.42, 128.28, 127.57, 127.39, 126.30, 123.90, 123.21, 122.39, 118.07, 117.59, 75.26, 66.01, 27.81, 23.14, 20.37 ppm; MS(EI): *m/z* (%): 393.3(M^+, 13.11); 43.1 (100), HRMS calcd for $C_{27}H_{23}NO_2$: 393.1729, found: 393.1730. For preparative procedures and spectroscopic data for all new compounds, see the Supporting Information.

Received: March 9, 2009
Revised: May 15, 2009
Published online: June 24, 2009

Keywords: chemoselectivity · cyclization · gold · regioselectivity · stereoselectivity

[1] For reviews, see: a) X. L. Hou, H. Y. Cheung, T. Y. Hon, P. L. Kwan, T. H. Lo, S. Y. Tong, H. N. C. Wong, *Tetrahedron* **1998**, *54*, 1955; b) B. A. Keay, *Chem. Soc. Rev.* **1999**, *28*, 209; c) T. L. Gilchrist, *J. Chem. Soc. Perkin Trans. 1* **1999**, 2849; d) S. F. Kirsch, *Org. Biomol. Chem.* **2006**, *4*, 2076; e) X. L. Hou, Z. Yang, K.-S. Yeung, H. N. C. Wong in *Progress in Heterocyclic Chemistry*, *Vol. 19* (Eds.: G. W. Gribble, J. Joule), Pergamon, Oxford, **2008**, pp. 176–207. For selected recent examples, see: f) Y. Liu, F. Song, Z. Song, M. Liu, B. Yan, *Org. Lett.* **2005**, *7*, 5409; g) A. W. Sromek, M. Rubina, V. Gevorgyan, *J. Am. Chem. Soc.* **2005**, *127*, 10500; h) A. S. Dudnik, V. Gevorgyan, *Angew. Chem.* **2007**, *119*, 5287; *Angew. Chem. Int. Ed.* **2007**, *46*, 5195; i) T. Schwier, A. W. Sromek, D. M. L. Yap, D. Chernyak, V. Gevorgyan, *J. Am. Chem. Soc.* **2007**, *129*, 9868; j) J. Zhang, H.-G. Schmalz, *Angew. Chem.* **2006**, *118*, 6856; *Angew. Chem. Int. Ed.* **2006**, *45*, 6704; k) G. Zhang, X. Huang, G. Li, L. Zhang, *J. Am. Chem. Soc.* **2008**, *130*, 1814; l) G. Li, X. Huang, L. Zhang, *J. Am. Chem. Soc.* **2008**, *130*, 6944.

[2] Only a very few examples on approach to 3–4 fused bicyclic furans have been reported, see: a) M. Suzuki, H. Ohtake, Y.

Kameya, N. Hamanaka, R. Noyori, *J. Org. Chem.* **1989**, *54*, 5292; b) M. E. Price, N. E. Schore, *J. Org. Chem.* **1989**, *54*, 2777; c) Y. Siqot, P. Frere, T. Nozdryn, J. Cousseau, M. Sallé, M. Jubauct, J. Orduna, J. Gařin, A. Gorgues, *Tetrahedron Lett.* **1997**, *38*, 1919.

[3] 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; c) Q.-S. Yu, X. Zhu, H. W. Holloway, N. F. Whittaker, A. Brossi, N. H. Greig, *J. Med. Chem.* **2002**, *45*, 3684; d) T. Katoh, E. Itoh, T. Yoshino, S. Terashima, *Tetrahedron* **1997**, *53*, 10229; e) T. C. Judd, R. M. Williams, *Angew. Chem.* **2002**, *114*, 4877; *Angew. Chem. Int. Ed.* **2002**, *41*, 4683; f) M. Suzuki, M. Kambe, H. Tokuyama, T. Fukuyama, *Angew. Chem.* **2002**, *114*, 4880; *Angew. Chem. Int. Ed.* **2002**, *41*, 4686.

[4] a) R. Pulz, A. Al-Harrasi, H.-U. Reißig, *Org. Lett.* **2002**, *4*, 2353; b) A. A. Tishkov, H. U. Reißig, S. Ioffe, *Synlett* **2002**, 863; c) M. Buchholz, H.-U. Reißig, *Eur. J. Org. Chem.* **2003**, 3524; d) A. Al-Harrasi, H.-U. Reißig, *Angew. Chem.* **2005**, *117*, 6383; *Angew. Chem. Int. Ed.* **2005**, *44*, 6227.

[5] For reviews on synthesis of 1,2-oxazines, see: a) T. L. Gilchrist, J. E. Wood in *Comprehensive Heterocyclic Chemistry II*, *Vol. 6*, Elsevier, Oxford, UK, **1996**, pp. 279 – 299 and 1177–1307; b) P. G. Tsoungas, *Heterocycles* **2002**, *57*, 1149; for the synthesis of 1,2-oxazines, see: c) S. C. Yoon, K. Kim, Y. J. Park, *J. Org. Chem.* **2001**, *66*, 7334; d) R. Pulz, S. Cicchi, A. Brandi, H.-U. Reißig, *Eur. J. Org. Chem.* **2003**, 1153; e) Y. Yamamoto, N. Momiyama, H. Yamamoto, *J. Am. Chem. Soc.* **2004**, *126*, 5962; f) S. Kumarn, D . M. Shaw, D. A. Longbottom, S. V. Ley, *Org. Lett.* **2005**, *7*, 4189; g) M. Helms, W. Schade, R. Pulz, T. Watanabe, A. Al-Harrasi, L. Fišera, I. Hlobilová, G. Zahn, H.-U. Reißig, *Eur. J. Org. Chem.* **2005**, 1003; h) S. Kumarn, D . M. Shaw, S. V. Ley, *Chem. Commun.* **2006**, 3211.

[6] For reviews on nitrone chemistry, see: a) R. C. F. Jones, J. N. Martin in *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products, The Chemistry of Heterocyclic Compounds*, *Vol. 59* (Eds.: A. Padwa, W. H. Pearson), Wiley, New York, **2002**, pp. 1 – 87; b) K. Rück-Braun, T. H. E. Freysoldt, F. Wierschem, *Chem. Soc. Rev.* **2005**, *34*, 507; c) F. Cardona, A. Goti, *Angew. Chem.* **2005**, *117*, 8042; *Angew. Chem. Int. Ed.* **2005**, *44*, 7832, and references cited therein.

[7] a) I. S. Young, M. A. Kerr, *Angew. Chem.* **2003**, *115*, 3131; *Angew. Chem. Int. Ed.* **2003**, *42*, 3023; b) M. D. Ganton, M. A. Kerr, *J. Org. Chem.* **2004**, *69*, 8554; for the total synthesis of (+)-phyllantidine and nakadomarin A from a cyclopropane, see: c) C. A. Carson, M. A. Kerr, *Angew. Chem.* **2006**, *118*, 6710; *Angew. Chem. Int. Ed.* **2006**, *45*, 6560; d) I. S. Young, M. A. Kerr, *J. Am. Chem. Soc.* **2007**, *129*, 1465.

[8] a) M. P. Sibi, Z. Ma, C. P. Jasperse, *J. Am. Chem. Soc.* **2005**, *127*, 5764; b) Y. B. Kang, X.-L. Sun, Y. Tang, *Angew. Chem.* **2007**, *119*, 3992; *Angew. Chem. Int. Ed.* **2007**, *46*, 3918.

[9] R. Shintani, S. Park, W.-L. Duan, T. Hayashi, *Angew. Chem.* **2007**, *119*, 6005; *Angew. Chem. Int. Ed.* **2007**, *46*, 5901.

[10] For work from our group, see: a) Y. Xiao, J. Zhang, *Angew. Chem.* **2008**, *120*, 1929; *Angew. Chem. Int. Ed.* **2008**, *47*, 1903; b) X. Yu, H. Ren, Y. Xiao, J. Zhang, *Chem. Eur. J.* **2008**, *14*, 8481; c) L. Fan, W. Zhao, W. Jiang, J. Zhang, *Chem. Eur. J.* **2008**, *14*, 9139; d) Y. Xiao, J. Zhang, *Chem. Commun.* **2009**, 3594.

[11] a) T. Yao, X. Zhang, R. C. Larock, *J. Am. Chem. Soc.* **2004**, *126*, 11164; b) T. Yao, X. Zhang, R. C. Larock, *J. Org. Chem.* **2005**, *70*, 7679; c) Y. Liu, S. Zhou, *Org. Lett.* **2005**, *7*, 4609; d) N. T. Patil, H. Wu, Y. Yamamoto, *J. Org. Chem.* **2005**, *70*, 4531.

[12] For a review on [3+2] cycloaddition of nitrone with olefin, see: a) P. N. Confalone, E. M. Huie, *Org. React.* **1988**, 36.

[13] For reviews on gold-catalyzed reactions published since **2008**, see: a) Z. Li, C. Brouwer, C. He, *Chem. Rev.* **2008**, *108*, 3239; b) A. Arcadi, *Chem. Rev.* **2008**, *108*, 3266; c) E. Jime'nez-Nu'n ~ ez, A. M. Echavarren, *Chem. Rev.* **2008**, *108*, 3326; d) D. J. Gorin, B. D. Sherry, F. D. Toste, *Chem. Rev.* **2008**, *108*, 3351; e) N. T. Patil, Y. Yamamoto, *Chem. Rev.* **2008**, *108*, 3395; f) R. A. Widenhoefer, *Chem. Eur. J.* **2008**, *14*, 5382; g) H. C. Shen, *Tetrahedron* **2008**, *64*, 3885; h) A. S. K. Hashmi, *Angew. Chem.* **2008**, *120*, 6856; *Angew. Chem. Int. Ed.* **2008**, *47*, 6754; i) N. Marion, S. P. Nolan, *Chem. Soc. Rev.* **2008**, *37*, 1776; j) A. S. K. Hashmi, M. Rudolph, *Chem. Soc. Rev.* **2008**, *37*, 1766; k) N. Bongers, N. Krause, *Angew. Chem.* **2008**, *120*, 2208; *Angew. Chem. Int. Ed.* **2008**, *47*, 2178.

[14] Please find the X-ray structures of **5aa** and **5da** in Figure 1 of the Supporting Information. CCDC 716897(**5aa**) and 716897(**5da**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[15] B. Bressel, B. Egart, A. Al-Harrasi, R. Pulz, H.-U. Reißig, I. Brüdgam, *Eur. J. Org. Chem.* **2008**, 467.

[16] L. Lepage, Y. Lepage, *Synthesis* **1983**, 1018.

