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Asymmetric C2−C3 Cyclopentannulation of the Indole Ring

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The indoline ring is regarded as a privileged structure because this skeleton is found as a substructure in a huge number of alkaloids (e.g., penitrem and kopsane alkaloids) and natural products.[1,2] Therefore, several efficient methodologies have recently been developed for accessing the indoline unit by C−C and/or C−N bond-formation reactions.[3] On the other hand, because of the ready accessibility of indole heterocycles, strategies based on the reactivity of the indole C2═C3 double bond appear as a highly attractive procedure. However, reports on the direct transformation of indoles into indoline derivatives have been scarce. Thus, Zhang and co-workers have reported the intramolecular gold- and platinum-catalyzed cyclization of 3-substituted indoles to 2,3-indoline-fused cyclobutane[4] and cyclopentene derivatives.[5] Moreover, the [4 + 2] cyclization reaction of indole toward an Au-containing 1,4-dipole, leading to a complex 2,3-indoline-fused cyclohexane structure, has been achieved by Zhang et al.[6] The groups of Kerr[7] and Pagenkopf[8] have reported the synthesis of 2,3-cyclopentanoindolines by the [3 + 2] cyclization of indoles with 1,1-cyclopropane diesters and 2-methoxy-1-cyclopropane esters, respectively. Despite the high relevance of the indoline heterocycles, protocols for their enantioselective preparation remain very limited, as illustrated in Figure 1. While the metal-catalyzed or -mediated cyclization of aniline derivatives[9−11] and the reaction of fluorinated imines with alkylsulfinyl arene[12] have been demonstrated to be highly useful, a unique example involving structural modification of the indole nucleus has been reported.[13−15] Thus, Trost et al.[13] have developed the synthesis of annelated indolines by the Pd-catalyzed allylation of conveniently C3-substituted indoles followed by cyclization through C2.

Within this scenario, we report herein that indole heterocycles themselves can be transformed with complete selectivity into dihydrocyclopenta[*b*]indolones by [3 + 2] cyclization with alkynyl Fischer carbene complexes. The investigation of this synthetic route to fused indolines was stimulated by the easy cyclization of unsaturated (methoxy)carbene complexes and simple enamines.[16]

First, we examined the reaction of tungsten alkynyl(methoxy)-carbene complexes with 1-substituted and 1,3-disubstituted indoles. Disappointingly, unidentified complex mixtures along with low yields of Michael-type adducts were obtained. Since the 2-methylindoline subunit is well-recognized as an important feature of drug candidates,[17] the 2-methylindole derivatives **1** were then tested and found to work satisfactorily (Scheme 1, Table 1). Thus, stirring a 1:1 mixture of 1,2-dimethylindole and carbene complex **2** (R^4 = Ph) in THF (60 °C, 15 h) followed by cooling to room temperature and purification (solvent removal and column chromatography) produced the *cis*-indolinone **4a** in 55% yield. Similarly, *N*-benzyl- and *N*-allyl-substituted indoles afforded the corresponding cycloadducts **4b** and **4c** in 73−79% yield. Interestingly, it was observed not only that *N*-unsubstituted indoles do undergo C3 Michael addition to the highly electrophilic carbene complex but also that the cycloadducts **4d** and **4e** were formed even more

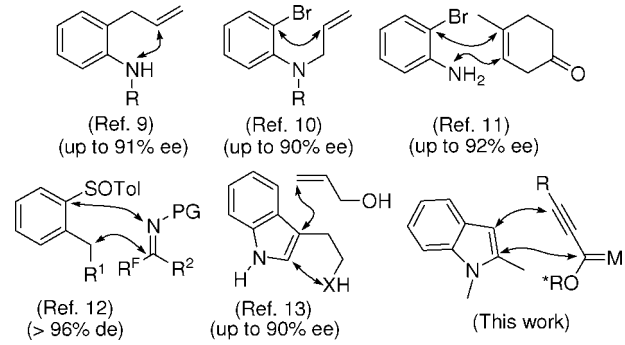
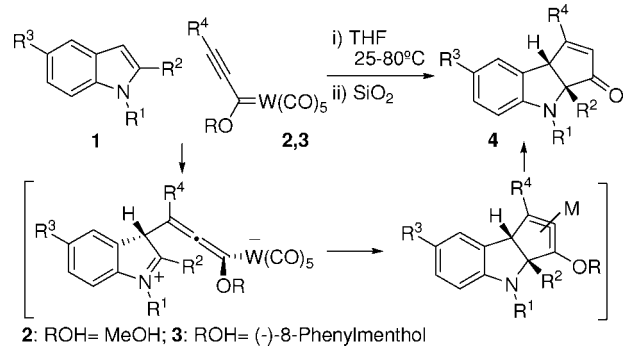


Figure 1. Routes to enantioenriched indolines.

Scheme 1. Synthesis of *cis*-Indolinones **4**



2: ROH= MeOH; **3**: ROH= (-)-8-Phenylmenthol

efficiently (83−86% yield). Preliminary studies reveal that the reaction works well for 5-substituted indoles (R^3 = Me, OMe, Br) as well as for aromatic- and aliphatic-substituted alkynylcarbenes (R^4 = aryl, cyclopropyl). Moreover, replacing the 2-methylindole (R^2 = Me) with 2-phenylindole (R^2 = Ph) also produces the expected indoline **4j** in satisfactory yield. The [3 + 2] cyclization is assumed to occur stepwise by conjugate addition and cyclization, in accordance with the general behavior of alkynylcarbene complexes,[16,18,19] and is followed by hydrolysis under chromatographic conditions.

At this point, the ready access to chiral nonracemic alkynyl(alkoxy)carbene complexes **3**, as recently developed in our group,[18] made apparent an attempt at the enantioselective synthesis of enantioenriched indolines. Thus, the indole derivatives **1** were treated with the alkynyl(alkoxy)carbenes **3** derived from (−)-8-phenylmenthol at 60−80 °C (THF, 20−48 h) (Scheme 1, Table 1). Despite the fact that the reaction was found to be somewhat more sluggish and to produce lower yields than when the (methoxy)carbene complexes **2** were used, the resulting cycloadducts **4** showed extremely high enantiomeric purity. Thus, the yields were in the 45−70% range, and the enantiomeric excess was in most instances >99% according to the HPLC analyses. The structure of (−)-**4f** was determined by an X-ray analysis.

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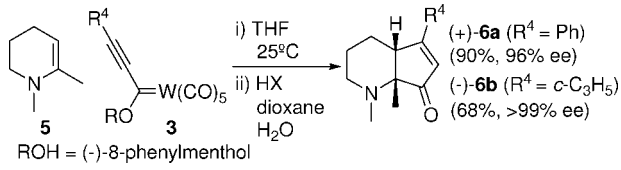
Table 1. *cis*-Indolinones **4a**−**j**

R^1	R^2	R^3	R^4	**4** (% yield[a])	*T* (°C)/*t* (h)	ee (%)[b]
Me	Me	H	Ph	(±)-**4a** (55)	60/15	
				(+)-**4a** (50)	60/22	97
Bn	Me	OMe	Ph	(±)-**4b** (79)	60/12	
allyl	Me	Me	4-CF_3−C_6H_4	(±)-**4c** (73)	25/14	
				(+)-**4c** (62)	60/20	>99
H	Me	H	Ph	(±)-**4d** (86)	60/6	
				(+)-**4d** (69)	60/40	>99
H	Me	OMe	Ph	(±)-**4e** (83)	25/22	
				(+)-**4e** (70)	60/24	>99
				(+)-**4e** (75)	60/20	96[c]
H	Me	Br	Ph	(±)-**4f** (83)	60/24	
				(−)-**4f** (52)	80/48	>99
H	Me	Br	4-Cl−C_6H_5	(±)-**4g** (69)	60/16	
				(+)-**4g** (45)	80/34	
H	Me	OMe	4-CF_3−C_6H_4	(±)-**4h** (91)	25/15	>99
H	Me	OMe	*c*-C_3H_5	(±)-**4i** (73)	25/15	
				(−)-**4i** (67)	60/27	>99
H	Ph	H	4-CF_3−C_6H_4	(±)-**4j** (75)	60/12	

[a] Isolated yield. [b] Determined via chiral HPLC analysis. [c] Using the carbene complex derived from (−)-menthol.

Scheme 2. Synthesis of Cyclopenta[*b*]pyridinones **6**



Although its efficiency as a chiral auxiliary is in general much lower than that of 8-phenylmenthol, menthol itself was tested, since both enantiomers are commercially available at low prices. It was greatly surprising that the reaction of 5-methoxy-2-methylindole and the phenylethynylcarbene derived from (−)-menthol (THF, 60 °C, 20 h) provided the indolinone **4e** in 75% yield with an ee as high as 96% [see the second entry for (+)-**4e** in Table 1].

The particular capability of these chiral carbene complexes for asymmetric induction also proved to be effective toward the cyclic enamine 1,6-dimethyl-1,2,3,4-tetrahydropyridine **5**. Thus, as shown in Scheme 2, treatment of **5** with the (−)-8-phenylmenthol carbene complexes **3** (R^4 = Ph, *c*-C_3H_5) in THF (25 °C, 6−20 h) followed by hydrolysis (HCl or TFA in dioxane−water) resulted in the formation of the cyclopenta[*b*]pyridin-7-ones **6** in good yield and very high enantioselectivity [(+)-**6a**: R^4 = Ph, 90% yield, 96% ee; (−)-**6b**: R^4 = *c*-C_3H_5, 68% yield, >99% ee).[20,21] An X-ray analysis of the corresponding dimethyl ammonium salt (−)-**8** derived from cycloadduct (−)-**6b** and MeI confirmed the structure.

In conclusion, the first asymmetric carbocyclization of the indole ring through the C2═C3 bond has been accomplished. This process is experimentally simple and efficient (moderate yields and excellent enantioselectivity) and proves the potential of chiral alkynylcarbene complexes in enantioselective cyclization reactions.[22] In addition, it has been shown that the process is not restricted to the indole ring but that related substrates, such as cyclic α-methylenamines, produce the corresponding annulation in higher yields and similar enantioselectivities. Importantly, the efficiency of menthol, an inexpensive chiral auxiliary available as either antipode, is excellent (≥96% ee). The densely functionalized cyclopentenone ring generated, along with the presence of an angular methyl group, is noteworthy and would allow further functionalization and growing to access more complex target molecules.

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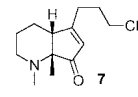
Supporting Information Available: Experimental procedures; spectral and analytical data for compounds **4a**−**j**, **5**, **6a**, **6b**, **7**, and **8**; and CIF files for (−)-**4f** and (−)-**8**. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Dewick. P. M. *Medicinal Natural Products: A Biosynthetic Approach*, 2nd ed.; John Wiley: New York, 2002.
(2) Recently their utility as sensitizers in organic dye−sensitizer ionic liquid-based solar cells has been reported. See: Kuang, D.; Uchida, S.; Humphry-Baker, R.; Zakeeruddin, S. M.; Grätzel, M. *Angew. Chem., Int. Ed* **2008**, *47*, 1923.
(3) For formation of the N−C7a bond, see: (a) Li, J.-J.; Mei, T.-S.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2008**, *47*, 6452. For formation of the C3−C3a bond, see: (b) Wipf, P.; Maciejewski, J. P. *Org. Lett.* **2008**, *10*, 4383. (c) Watanabe, T.; Oishi, S.; Fujii, N.; Ohno, H. *Org. Lett.* **2008**, *10*, 1759. For formation of the N−C3 and N−C7a bonds, see: (d) Minatti, A.; Buchwald, S. L. *Org. Lett.* **2008**, *10*, 2721. For formation of the N−C7a and C3−C3a bonds, see: (e) Gilmore, C. D.; Allan, K. M.; Stolz, B. M. *J. Am. Chem. Soc.* **2008**, *130*, 1558. (f) Thansandote, P.; Raemy, M.; Rudolph, A.; Lautens, M. *Org. Lett.* **2007**, *9*, 5255. For formation of the N−C7a and C2−C3 bonds, see: (g) Viswanathan, R.; Smith, C. R.; Prabhakaran, E. N.; Johnston, J. N. *J. Org. Chem.* **2008**, *73*, 3040.
(4) Zhang, L. *J. Am. Chem. Soc.* **2005**, *127*, 16804.
(5) Zhang, G.; Catalano, V. J.; Zhang, L. *J. Am. Chem. Soc.* **2007**, *129*, 11358.
(6) Zhang, G.; Huang, X.; Li, G.; Zhang, L. *J. Am. Chem. Soc.* **2008**, *130*, 1814.
(7) England, D. B.; Kuss, T. D. O.; Keddy, R. G.; Kerr, M. A. *J. Org. Chem.* **2001**, *66*, 4704.
(8) Bajtos, B.; Yu, M.; Zhao, H.; Pagenkopf, B. L. *J. Am. Chem. Soc.* **2007**, *129*, 9631.
(9) Yip, K.-T.; Yang, M.; Law, K.-L.; Zhu, N.-Y.; Yang, D. *J. Am. Chem. Soc.* **2006**, *128*, 3130.
(10) Sanz Gil, G.; Groth, U. M. *J. Am. Chem. Soc.* **2000**, *122*, 6789.
(11) Hyde, A. M.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 177.
(12) García Ruano, J. L.; Alemán, J.; Catalán, S.; Marcos, V.; Monteagudo, S.; Parra, A.; del Pozo, C.; Fustero, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 7941.
(13) Trost, B. M.; Quancard, J. *J. Am. Chem. Soc.* **2006**, *128*, 6314.
(14) For the catalytic asymmetric hydrogenation of substituted indoles, see: Kuwano, R.; Sato, K.; Kurokawa, T.; Karube, D.; Ito, Y. *J. Am. Chem. Soc.* **2000**, *122*, 7614.
(15) Access to enantiopure indolines has been recently accomplished by kinetic resolution. See: Arp, F. O.; Fu, G. C. *J. Am. Chem. Soc.* **2006**, *128*, 14264.
(16) (a) Barluenga, J.; Ballesteros, A.; Bernardo de la Rúa, R.; Santamaría, J.; Rubio, E.; Tomás, M. *J. Am. Chem. Soc.* **2003**, *125*, 1834. (b) Barluenga, J.; Tomás, M.; Ballesteros, A.; Santamaría, J.; Brillet, C.; García-Granda, S.; Piñera-Nicolás, A.; Vázquez, J. T. *J. Am. Chem. Soc.* **1999**, *121*, 4516. (c) Aumann, R.; Kössmeier, M.; Mück-Lichtenfeld, C.; Zippel, F. *Eur. J. Org. Chem.* **2000**, 37. (d) Aumann, R.; Meyer, A. G.; Fröhlich, R. *Organometallics* **1996**, *15*, 5018. (e) Meyer, A. G.; Aumann, R. *Synlett* **1995**, 1011.
(17) Nicolaou, K. C.; Roecker, A. J.; Pfefferkorn, J. A.; Cao, G.-Q. *J. Am. Chem. Soc.* **2000**, *122*, 2966.
(18) Barluenga, J.; Bernardo de la Rúa, R.; de Sáa, D.; Ballesteros, A.; Tomás, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4981.
(19) As one referee pointed out, a reaction pathway involving the allenyltungsten-to-propargyltungsten rearrangement followed by cyclization cannot be ruled out.
(20) In the case of **6a**, the primary fused alkoxycyclopentadiene cycloadduct was isolated prior to hydrolysis (d.e. ≈ 96% by ^{1}H NMR).
(21) The hydrolysis of cycloadduct **6b** with HCl/AcOH caused cyclopropane ring cleavage, affording compound (+)-**7** in 58% yield and >99% ee.



(22) The [4 + 2] cycloaddition toward 1-azadienes represents the sole precedent for these metal carbene reagents in enantioselective synthesis. See ref 18.

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