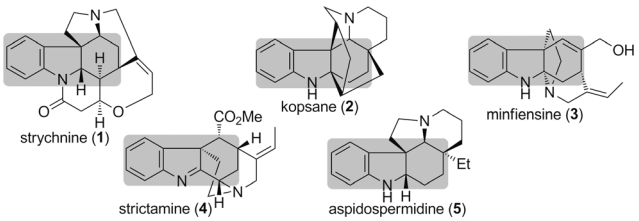
Cycloaddition

DOI: 10.1002/anie.201206734

Regioselective Inter- and Intramolecular Formal [4+2] Cycloaddition of Cyclobutanones with Indoles and Total Synthesis of (±)-Aspidospermidine**

Mizuki Kawano, Takaaki Kiuchi, Shoko Negishi, Hiroyuki Tanaka, Takaya Hoshikawa, Jun-ichi Matsuo, and Hiroyuki Ishibashi*

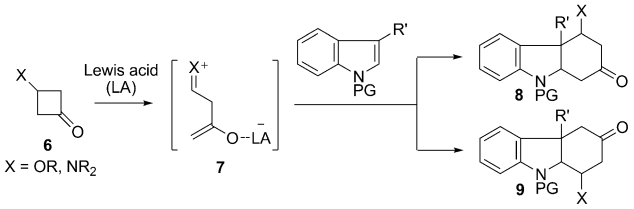
Hydrocarbazoles are found in the skeletons of many alkaloids, such as strychnine (**1**),[1] kopsane (**2**),[2] minfiensine (**3**),[3] strictamine (**4**),[4] and aspidospermidine (**5**; Scheme 1).



Scheme 1. Selected natural products with a hydrocarbazole skeleton.

Alkaloids and synthetic small molecules[5] with a hydrocarbazole structure exhibit a broad range of important bioactivities.[6] For the synthesis of structurally diverse and complex hydrocarbazoles, [4+2] cycloaddition to the C2–C3 positions of indoles has high synthetic potential, since two covalent bonds are formed in one step without the preintroduction of special substituents (e.g., a vinyl group[3e,7]) on the indole. Such [4+2] cycloadditions of indoles are categorized into three types of Diels–Alder reaction (DAR): 1) normal-electron-demand DARs, in which strongly electron-deficient indoles that contain two electron-withdrawing groups at their 1- and 3-positions are used,[8] 2) inverse-electron-demand DARs[9] of highly electron-poor dienes, such as 1,2,4,5-tetrazine,[9b,c] and 3) DARs of photochemically induced radical cations with triarylpyrylium salts.[10] In all of these DARs,[11] the combination of indoles and enophiles (4π donors) is restricted, and it is also difficult to change the regioselectivity of the cycloaddition. Therefore, the development of a general, efficient, and conceptually new strategy for the synthesis of structurally diverse hydrocarbazoles still remains important and challenging.

We describe herein the first example of a Lewis acid promoted formal [4+2] cycloaddition of cyclobutanones **6** with indoles (Scheme 2). This reaction enables the selective



Scheme 2. Formal [4+2] cycloaddition between indoles and 3-donor-substituted cyclobutanones **6**. PG = protecting group.

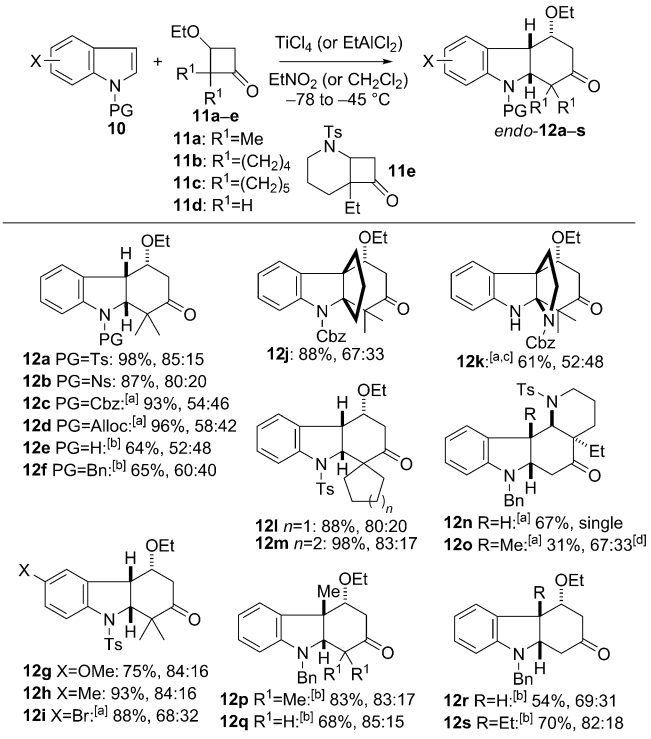
synthesis of both of the two possible regioisomeric hydrocarbazoles **8** and **9**. Thus, we found that the zwitterionic intermediate **7**, which was formed by the activation of 3-donor-substituted cyclobutanones[12] with a Lewis acid,[13] reacted efficiently with indoles to give the corresponding hydrocarbazoles (**8** or **9**). A special activating group on the indole nucleus was not required, and a variety of indoles underwent the reaction, both in an intermolecular and in an intramolecular manner. The synthesis of a substructure of strictamine (**4**) and the total synthesis of (±)-aspidospermidine (**5**) by intramolecular cycloaddition reactions are also described herein.

The screening of Lewis acids for a formal [4+2] cycloaddition of indoles **10a–f** with cyclobutanone **11a** revealed that $TiCl_4$ was a suitable Lewis acid for indoles **10a–d** with an electron-withdrawing group (EWG) as the N-protecting group, whereas the use of $EtAlCl_2$ led to the formation of adducts **12e,f** in good yields from the reactive indoles **10e,f** (Scheme 3).[14] Notably, the cycloaddition of indole **10e** without an N-protecting group proceeded smoothly to give **12e**. We tested dichloromethane, toluene, and nitroethane as solvents and found that the use of nitroethane led to better yields of the cycloadducts derived from the *N*-arenesulfonylindoles **10a,b** and reactive indoles **10e,f**, whereas dichloromethane was suitable for the reaction of the *N*-alkoxycarbonylindoles **10c,d**.[14] Good *endo*/*exo* selectivities were observed in the reactions of *N*-arenesulfonylindoles, whereas almost equal amounts of the *endo* and *exo* adducts were obtained in other cases. As described below, the removal of

[*] M. Kawano, T. Kiuchi, S. Negishi, H. Tanaka, T. Hoshikawa, Prof. Dr. J. Matsuo, Prof. Dr. H. Ishibashi
School of Pharmaceutical Sciences
Institute of Medical, Pharmaceutical, and Health Sciences
Kanazawa University
Kakuma-machi, Kanazawa 920-1192 (Japan)
E-mail: jimatsuo@p.kanazawa-u.ac.jp

[**] We thank Prof. Shuhei Fujinami (Kanazawa University) for X-ray crystallographic analysis and Mio Hashizume for technical assistance. This study was partially supported by the Kurata Memorial Hitachi Science and Technology Foundation and JSPS KAKENHI Grant Number 24590007.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201206734.

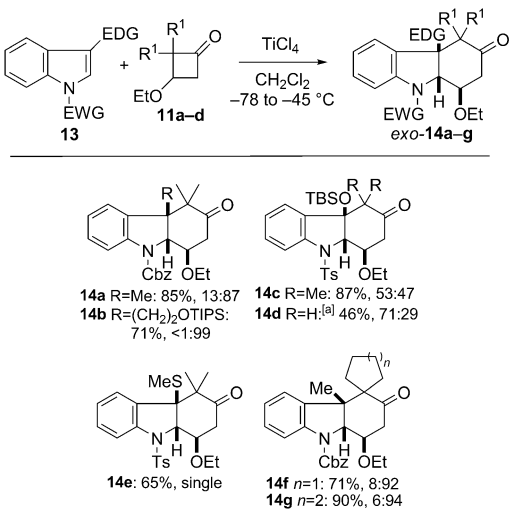


Scheme 3. Lewis acid promoted formal [4+2] cycloaddition of indoles **10** with cyclobutanones **11a–e** to give hexahydro-2-oxocarbazoles **12a–s**. $TiCl_4$ was used as the Lewis acid and $EtNO_2$ as the solvent unless otherwise mentioned.[14] The structures of the *endo* product, the yield of the isolated product, and the *endo*/*exo* ratio are given. [a] CH_2Cl_2 was used instead of $EtNO_2$. [b] $EtAlCl_2$ was used instead of $TiCl_4$. [c] Et_2AlCl was used as the Lewis acid. [d] For details about the configuration, see the Supporting Information. Ts = *p*-toluenesulfonyl, Ns = *o*-nitrobenzenesulfonyl, Cbz = benzyloxycarbonyl, Alloc = allyloxycarbonyl, Bn = benzyl.

the ethoxy group in cycloadducts **12** was straightforward. The stereostructure of *exo*-**12c** as a representative *exo* adduct was determined unambiguously by X-ray crystallography, whereas that of an *endo* adduct was determined by NOE experiments.[14]

Indoles bearing a methoxy, methyl, or bromo group at the 5-position reacted with **11a** to give the corresponding cycloadducts **12g–i** in good to high yields (Scheme 3). The propeller-like cycloadducts **12j**,**k** were obtained from indoles fused with a five-membered ring. Structures similar to those of **12j** and **12k** are found in kopsane (**2**) and minfiensine (**3**), respectively. The mild Lewis acid Et_2AlCl was used for the synthesis of **12k**, because the starting indole **10k** and the product **12k** were labile under strongly acidic conditions. Spirocyclobutanones **11b**,**c** with a cyclopentane or cyclohexane ring reacted efficiently to afford spirocycloadducts **12l**,**m**. The bicyclic cyclobutanone **11e** reacted with *N*-benzylindoles to give the tetracyclic products **12n** (in 67% yield as a single diastereomer) and **12o** (in 31% yield as a 67:33 mixture of diastereomers).[15] This result suggests that the cyclobutanone ring of **11e** was cleaved selectively to form the zwitterionic intermediate with the less substituted enolate.[13a] Finally, cyclobutanone **11d** with no alkyl substituents at the α position to the carbonyl group reacted with *N*-benzylindoles to afford compounds **12q–s**.

Interestingly, reversed regioselectivity of the cycloaddition was observed when an indole had an electron-donating group (EDG) at the 3-position and an EWG on the nitrogen atom (Scheme 4). Thus, *N*-benzyloxycarbonyl 3-alkyl indoles reacted with cyclobutanone **11a** to afford hexahydro-3-

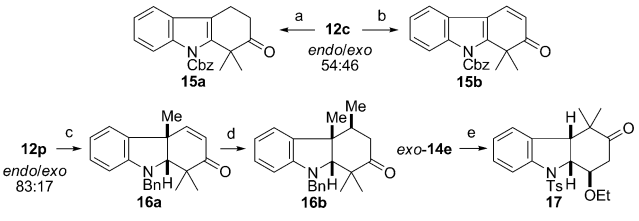


Scheme 4. Inverse regioselectivity in the formal [4+2] cycloaddition of 3-substituted indoles **13** with cyclobutanones **11a–d** to give hexahydro-3-oxocarbazoles **14a–g**. The structure of the *exo* product, the yield of the isolated product, and the *endo*/*exo* ratio are given.[14] The *endo*/*exo* ratio was determined by ^1H NMR spectroscopy. [a] $EtAlCl_2$ was used instead of $TiCl_4$. TBS = *tert*-butyldimethylsilyl, TIPS = triisopropylsilyl.

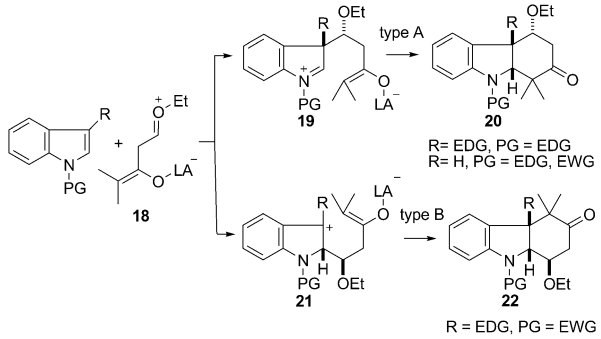
oxocarbazoles **14a**,**b** without formation of the regioisomeric hexahydro-2-oxocarbazoles **12**. 3-*tert*-Butyldimethylsilyloxy- or 3-methylthio-substituted *N*-*p*-toluenesulfonylindoles also reacted with **11a**,**d** to give hexahydro-3-oxocarbazoles **14c–e**.[16] Two contiguous quaternary carbon centers were constructed efficiently in the formation of spiro compounds **14f**,**g** through the cycloaddition of spirocyclobutanones **11b**,**c**.

A diastereomeric mixture of **12c** (*endo*/*exo* 54:46) was transformed smoothly into **15a** by the Me_3SiOTf-promoted elimination of ethanol and isomerization (Scheme 5). The oxidation of **12c** with DDQ, followed by treatment with Me_3SiOTf, gave enone **15b** in 80% yield over the two steps. The conjugate addition of Me_2CuLi to enone **16a**, which was prepared from **12p**, proceeded stereoselectively to afford **16b**. The methylthio group of *exo*-**14e** was removed with Raney nickel at a low temperature to give **17**. Thus, we could synthesize both of the two possible regioisomers **12a** and **17** selectively by our cycloaddition approach.

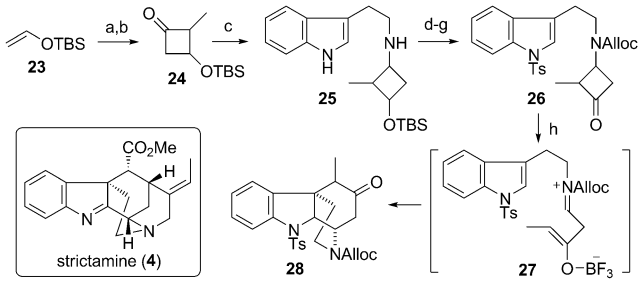
A proposed mechanism for the present cycloaddition is shown in Scheme 6. The zwitterion **18** generated from the cyclobutanone (in this case, **11a**) reacts with an indole to form an iminium intermediate **19**[17] or a benzylic carbocation **21**, which then cyclizes to **20** (cyclization type A) or **22** (cyclization type B), respectively.[18] When PG is an electron-donating group, such as a benzyl group, **19** is formed because the electron-donating group stabilizes the iminium cation. On the



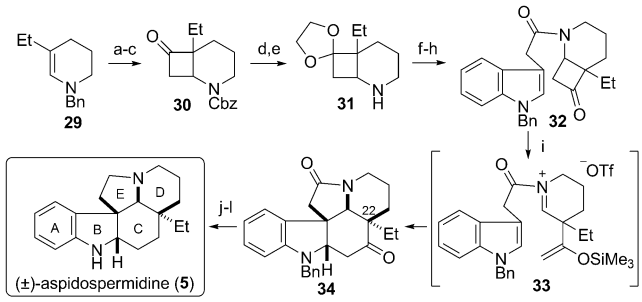
Scheme 5. Transformation of adducts **12c**,**p** and **14e**: a) Me_3SiOTf, CH_2Cl_2, 0 °C, 1 h, then room temperature, 1 h, 86%; b) 1) DDQ, toluene, reflux, 45 min; 2) Me_3SiOTf, CH_2Cl_2, 0 °C, 5 min, 80% (for two steps); c) 1) Me_3SiOTf, Et_3N, CH_2Cl_2, 0→15 °C, 1.5 h; 2) Me_3SiOTf, CH_2Cl_2, 0 °C→RT, 1 h, 83% (for two steps); d) Me_2CuLi, $BF_3{\cdot}Et_2O$, Et_2O/THF, −78→0 °C, 3.5 h, 92%, single diastereomer; e) Raney nickel, EtOH/THF, −20 °C, 1 h, 70%, d.r. 90:10. DDQ = 2,3-dichloro-5,6-dicyano-*p*-benzoquinone, Tf = trifluoromethanesulfonyl.



Scheme 6. Proposed mechanism for the formal [4+2] cycloaddition of 3-ethoxycyclobutanones with indoles.



Scheme 7. Synthesis of a substructure of **4**: a) 2,2-dichloropropanoyl chloride, Zn, Et_2O, room temperature, 2 h; b) Zn/Cu, NH_4Cl, MeOH, room temperature, 1 h, 60% (for two steps), d.r. 66:34; c) tryptamine, $NaBH(OAc)_3$, CH_2Cl_2, room temperature, 14 h, quantitative; d) AllocCl, 10% aqueous Na_2CO_3, Et_2O, room temperature, 12 h, 87%; e) TsCl, NaOH, TBHSA, CH_2Cl_2, room temperature, 5 h, quantitative; f) TBAF, AcOH, THF, room temperature, 24 h; g) DMP, CH_2Cl_2, room temperature, 4 h, 80% (for two steps), d.r. 83:17; h) $BF_3{\cdot}Et_2O$, CH_2Cl_2, room temperature, 2 h, 87%, d.r. 65:35. TBHSA = tetrabutylammonium hydrogen sulfate, TBAF = tetrabutylammonium fluoride, DMP = Dess–Martin periodinane.



Scheme 8. Total synthesis of (±)-**5**: a) CbzCl, CH_2Cl_2, room temperature, 15 h, 99%; b) Zn/Cu, $Cl_3C(C{=}O)Cl$, Et_2O, sonication, 0 °C, 0.5 h, then room temperature, 14 h; c) Zn/Cu, NH_4Cl, MeOH, room temperature, 2 h, 85% (for two steps); d) ethylene glycol, $TsOH/H_2O$, benzene, reflux, 12 h, 95%; e) H_2, Pd/C, EtOH, room temperature, 3 h, quantitative; f) 3-indoleacetic acid, EDC, 0 °C, 5 h, 89%; g) BnBr, NaH, DMF, room temperature, 2.5 h, 95%; h) 1 N HCl, EtOH, reflux, 3 h, 93%; i) Me_3SiOTf, toluene, reflux, 10 min, 46% (+ C22 epimer, 32%); j) $N_2H_4{\cdot}H_2O$, Na, $(CH_2OH)_2$, 160–210 °C, 18 h; k) $LiAlH_4$, THF, room temperature, 1 h, 71% (for two steps); l) H_2, $Pd(OH)_2$, EtOH, room temperature, 46 h, 93%. EDC = 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride.

other hand, the presence of an electron-withdrawing group on the nitrogen atom to disfavor **19** (compare **12p** and **14a**) and an electron-donating R group to favor **21** (compare **12c** and **14a**) promotes type B cyclization.

An intramolecular cyclization between a cyclobutanone and an indole was employed for the synthesis of a substructure **28** of (±)-strictamine (**4**; Scheme 7).[19] Compound **26**, the indole nitrogen atom of which was protected with an electron-withdrawing group (Ts), was used for the intramolecular formal [4+2] cycloaddition, since type-B cyclization was expected to give **28**. A [2+2] cycloaddition between the TBS enol ether **23** and methyl chloro ketene was followed by reductive removal of the chloro group with a zinc–copper couple to give cyclobutanone **24**. The reductive amination of **24** with tryptamine afforded **25**, the secondary amino group and indole nitrogen atom of which were protected with an Alloc and a Ts group, respectively. Deprotection and oxidation of the hydroxy group gave the cycloaddition precursor **26**. The key intramolecular [4+2] cycloaddition of **26** proceeded smoothly in the presence of the Lewis acid $BF_3{\cdot}Et_2O$, and the desired product **28** was obtained in 87% yield. It was assumed that an intermediate **27** was formed by regioselective ring cleavage[13a] of the α-methylcyclobutanone ring of **26** and that type-B intramolecular addition then gave **28**.

We used a type-A intramolecular cyclization for the total synthesis of (±)-aspidospermidine (**5**;[20] Scheme 8).[21] The *N*-benzyl group of enamine **29**, which was readily prepared in five steps according to a procedure described by Norman and Heathcock,[22] was exchanged for an *N*-Cbz group by treatment with benzyloxycarbonyl chloride.[23] A [2+2] cycloaddition with dichloroketene, followed by reductive dechlorination, gave cyclobutanone **30** in 85% yield over two steps. Protection of the carbonyl group of cyclobutanone **30** as an acetal and removal of the *N*-Cbz group afforded the piperidine derivative **31**. It was necessary to protect the carbonyl group of **30** because the 3-aminocyclobutanone that should be formed by removal of the *N*-Cbz group of **30** was too unstable to be isolated. Amine **31** was coupled with 3-indoleacetic acid to give the corresponding amide, the indole nitrogen atom of which was protected with a benzyl group. Hydrolysis of the acetal group then gave the cycloaddition

precursor **32**.[24] After extensive screening of Lewis acids and optimization of the reaction conditions, the intramolecular [4+2] cycloaddition of **32** proceeded to give the desired pentacyclic compound **34** in 46% yield along with the C22 epimer of **34** (32%). The cyclobutanone ring of **32** was cleaved regioselectively as observed for the bicyclic cyclobutanone **11e**, and an intramolecular type-A cyclization of **33** gave **34**. Wolff–Kishner reduction[20i,25] of **34**, followed by reduction of the amide group with $LiAlH_4$ and removal of the *N*-Bn group with $Pd(OH)_2$,[20k] gave (±)-**5**. Notably, in this synthesis, the C and E rings of **5**, with an angular C22 ethyl substituent, were constructed in a single step.

In conclusion, we have developed a new formal [4+2] cycloaddition between indoles and cyclobutanones that can proceed in both an intra- and an intermolecular manner, and we have shown that cyclobutanones were excellent four-carbon-atom donors for various indoles. The regioselectivity of the cycloaddition was controlled by the indole substituents, and it was demonstrated that the two possible regioisomers of a cycloaddition product could be synthesized selectively. The wide reaction scope and unique orientation control were applied to the synthesis of a tetracyclic substructure of (±)-strictamine (**4**) and the total synthesis of (±)-aspidospermidine (**5**). We believe that this regioselective method offers rapid and reliable access to structurally diverse hydrocarbazoles from abundant indoles.

Received: August 20, 2012
Revised: October 30, 2012
Published online: November 26, 2012

Keywords: alkaloids · cycloaddition · Lewis acids · regioselectivity · total synthesis

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[14] See the Supporting Information for details.

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[16] An attempted cycloaddition of **11e** with 3-*tert*-butyldimethylsilyloxy-substituted *N*-*p*-toluenesulfonylindole did not proceed.

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