Cycloaddition

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

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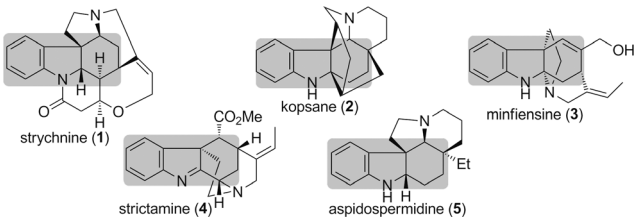
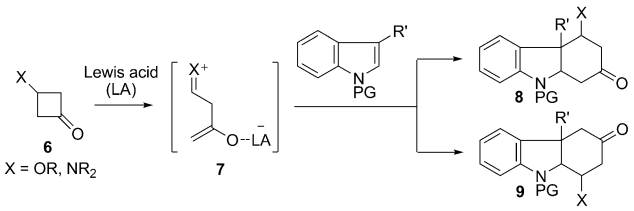
Hydrocarbazoles are found in the skeletons of many alkaloids, such as strychnine (**1**),[1] kopsane (**2**),[2] minfiensine (**3**),[3] strictamine (**4**),[4] and aspidospermidine (**5**; Scheme 1).



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

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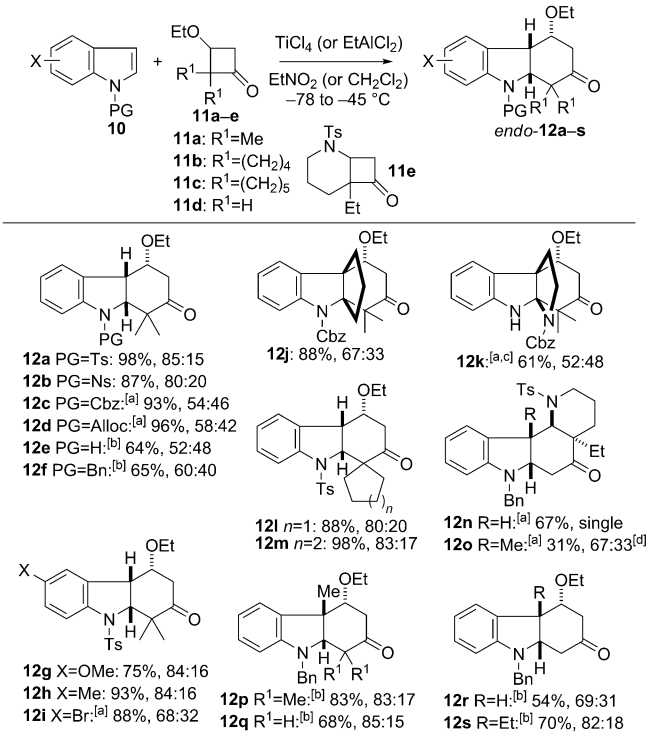
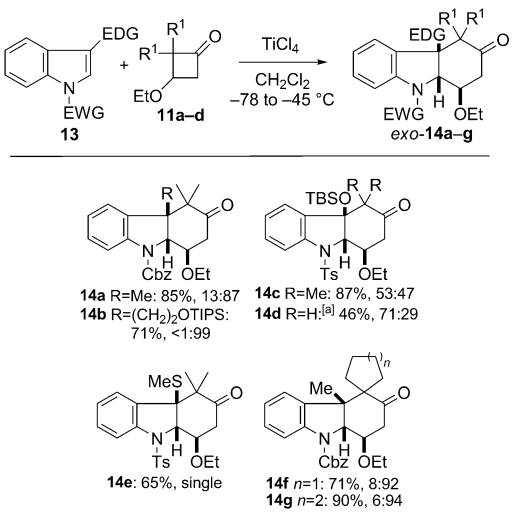


Scheme 3. Lewis acid promoted formal [4+2] cycloaddition of indoles **10** with cyclobutanones **11a–e** to give hexahydro-2-oxocarbazoles **12a–s**. $TiCl_4$ was used as the Lewis acid and $EtNO_2$ as the solvent unless otherwise mentioned.[14] The structures of the *endo* product, the yield of the 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**.

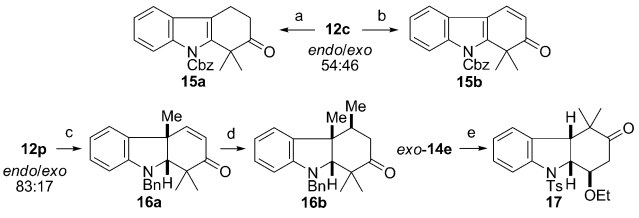
Interestingly, reversed regioselectivity of the cycloaddition was observed when an indole had an electron-donating group (EDG) at the 3-position and an EWG on the nitrogen atom (Scheme 4). Thus, *N*-benzyloxycarbonyl 3-alkyl indoles reacted with cyclobutanone **11a** to afford hexahydro-3-oxocarbazoles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



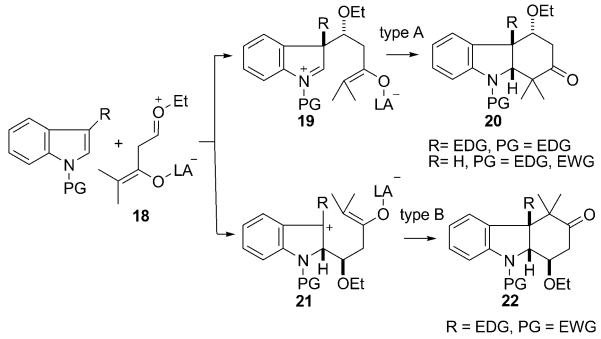
Scheme 4. Inverse regioselectivity in the formal [4+2] cycloaddition of 3-substituted indoles **13** with cyclobutanones **11a–d** to give hexahydro-3-oxocarbazoles **14a–g**. The structure of the *exo* product, the yield of the isolated product, and the *endo*/*exo* ratio are given.[14] The *endo*/*exo*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

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.

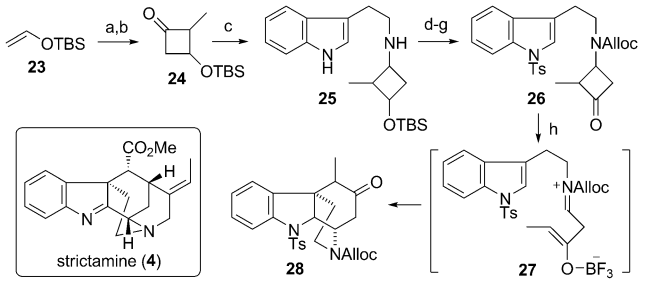
A proposed mechanism for the present cycloaddition is shown in Scheme 6. The zwitterion **18** generated from the cyclobutanone (in this case, **11a**) reacts with an indole to form an iminium intermediate **19**[17] or a benzylic carbocation **21**, which then cyclizes to **20** (cyclization type A) 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



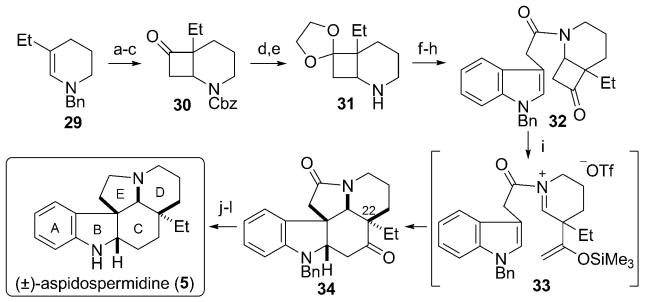
Scheme 5. Transformation of adducts **12c**,**p** and **14e**: a) Me_3SiOTf, CH_2Cl_2, 0 °C, 1 h, then room temperature, 1 h, 86%; b) 1) DDQ, toluene, reflux, 45 min; 2) Me_3SiOTf, CH_2Cl_2, 0 °C, 5 min, 80% (for two steps); c) 1) Me_3SiOTf, Et_3N, CH_2Cl_2, 0→15 °C, 1.5 h; 2) Me_3SiOTf, CH_2Cl_2, 0 °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.

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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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