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Platinum-Catalyzed Tandem Indole Annulation/Arylation for the Synthesis of Diindolylmethanes and Indolo[3,2-*b*]carbazoles

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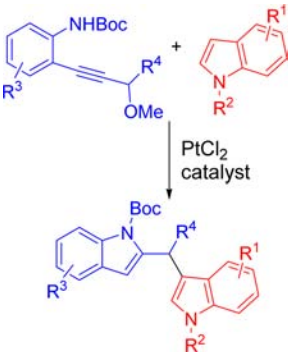
ABSTRACT



Various diindolylmethanes were prepared from propargylic ethers and substituted indoles via a platinum-catalyzed tandem indole annulation/arylation cascade. The resulting diindolylmethanes could be converted to natural product malassezin by formylation or indolo[3,2-*b*]carbazoles by cyclization.

Indole is one of the most abundant heterocycles in bioactive natural products and pharmaceutical agents. Not surprisingly, numerous efforts have been devoted to the preparation of indoles from a diverse range of starting materials.[1,2] Most previous efforts, however, have focused on indole annulation alone.[1] The efficiency of the synthesis can be increased significantly if the event of indole annulation is coupled with other transformations in a cascade manner. We recently developed a tandem indole annulation/(4 + 3) cycloaddition for the construction of both indole and a seven-membered ring simultaneously in the synthesis of cyclohepta[*b*]indoles.[3] We herein report a synthesis of diindolylmethanes via a platinum-catalyzed indole annulation/arylation cascade as a continuation of efforts in this area.

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(1) For recent reviews on indole synthesis, see: (a) Barluenga, J.; Rodriguez, F.; Fananas, F. J. *Chem.—Asian J.* **2009**, *4*, 1036. (b) Taber, D. F.; Tirunahari, P. K. *Tetrahedron* **2011**, *67*, 7195. (c) Vicente, R. *Org. Biomol. Chem.* **2011**, *9*, 6469. (d) Platon, M.; Amardeil, R.; Djakovitch, L.; Hierso, J.-C. *Chem. Soc. Rev.* **2012**, *41*, 3929.

(2) For recent examples of indole annulations, see: (a) Cui, X.; Li, J.; Fu, Y.; Liu, L.; Guo, Q.-X. *Tetrahedron Lett.* **2008**, *49*, 3458. (b) Oda, Y.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2012**, *14*, 664. (c) Ackermann, L.; Lygin, A. V. *Org. Lett.* **2012**, *14*, 764. (d) Inamoto, K.; Asano, N.; Nakamura, Y.; Yonemoto, M.; Kondo, Y. *Org. Lett.* **2012**, *14*, 2622. (e) Xia, X.-F.; Wang, N.; Zhang, L.-L.; Song, X.-R.; Liu, X.-Y.; Liang, Y.-M. *J. Org. Chem.* **2012**, *77*, 9163. (f) Song, W.; Ackermann, L. *Chem. Commun.* **2013**, *49*, 6638.

(3) (a) Shu, D.; Song, W.; Li, X.; Tang, W. *Angew. Chem., Int. Ed.* **2013**, *52*, 3237. For a synthesis of cyclohepta[*b*]indoles by a different type of (4 + 3) cycloaddition, see: (b) Han, X.; Li, H.; Hughes, R. P.; Wu, J. *Angew. Chem., Int. Ed.* **2012**, *51*, 10390.

(4) (a) Wille, G.; Mayser, P.; Thoma, W.; Monsees, T.; Baumgart, A.; Schmitz, H. J.; Schrenk, D.; Polborn, K.; Steglich, W. *Bioorg. Med. Chem.* **2001**, *9*, 955. (b) Kramer, H. J.; Podobinska, M.; Bartsch, A.; Battmann, A.; Thoma, W.; Bernd, A.; Kummer, W.; Irlinger, B.; Steglich, W.; Mayser, P. *ChemBioChem* **2005**, *6*, 860.

(5) Wahlstrom, N.; Romero, I.; Bergman, J. *Eur. J. Org. Chem.* **2004**, 2593.

10.1021/ol4018408

Diindolylmethanes are present in not only natural products such as malassezin[4] but also important precursors for other naturally occurring heterocycles such as indolocarbazoles **2** and **3a**–**3f**[5] shown in Figure 1.[6] Malassezin, ICZ, and FICZ are potent agonists of aryl hydrocarbon receptor (AhR), which is best known for mediating the toxicity of dioxin and related environmental toxins.[7] Recent studies showed that AhR also played a critical role in immune cell differentiation,[8] promoting intestinal immune function,[9] and the development of prostate.[10] It has been demonstrated that selective AhR modulators inhibit prostate tumor metastasis[11] and have antiasthmatic effects[12] in animal models. Indolo[3,2-*b*]carbazoles are also an important class of organic electroluminescent compounds.[6,13]

Rearrangement of the symmetrical 3,3′-diindolylmethanes to 2,3-diindolylmethanes could be realized using iodine as the catalyst.[14] Low yields, however, were observed when substituted indoles were employed as the substrates. Synthesis of nonsymmetric 2,3-diindolylmethanes requires the joining of two different indoles in multiple steps.[15]

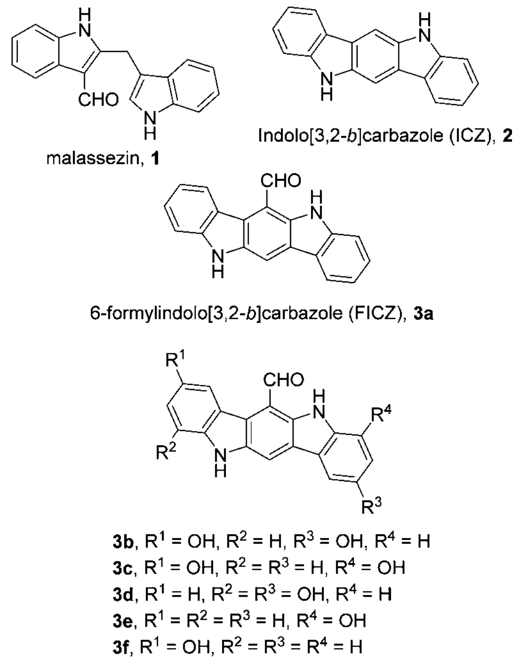
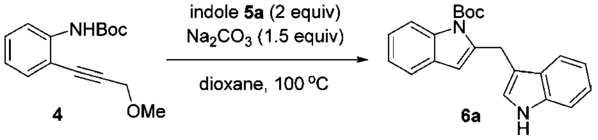


Figure 1. Diindolylmethanes and indolo[3,2-*b*]carbazoles.

A metal carbene intermediate was generated from annulation of propargylic ether **4** and trapped previously by a diene in a (4 + 3) cycloaddition.[3a] We envisioned that this metal carbene intermediate could also be trapped by other nucleophiles. In the presence of another indole, diindolylmethanes could then be prepared conveniently. We first examined the conditions that were employed previously (entries 1 and 2, Table 1). We were pleased to find that both Pt- and Rh-complexes promoted the formation of 2,3′-diindolylmethane product **6a**, though the former provided a higher yield. A slightly lower yield was obtained with a lower catalyst loading (entry 3). The electron-poor phosphine ligand was proven to be critical in the previous indole annulation/(4 + 3) cycloaddition cascade. In the case of indole annulation/arylation to form diindolylmethanes, using PtCl$_2$ alone as the catalyst appeared to be sufficient (entry 4). The yield again became slightly lower if the amount of catalyst was lowered to 5 mol % (entry 5). Other metal complexes did not produce any desired product (entries 6–10).

Table 1. Screening of Catalysts and Conditions[a]



entry	conditions	yield (%)
1	PtCl$_2$ (10 mol %), P(C$_6$F$_5$)$_3$ (20 mol %)	84
2	[Rh(CO)$_2$Cl]$_2$ (10 mol %), P[OCH(CF$_3$)$_2$]$_3$ (20 mol %)	56
3	PtCl$_2$ (5 mol %), P(C$_6$F$_5$)$_3$ (10 mol %)	77
4	PtCl$_2$ (10 mol %)	83[b]
5	PtCl$_2$ (5 mol %)	76
6	AgBF$_4$ (10 mol %)	0
7	AgOTf (10 mol %)	0
8	CuOTf (10 mol %)	0
9	AgOTf (10 mol %), P(C$_6$F$_5$)$_3$ (20 mol %)	0
10	CuOTf (10 mol %), P(C$_6$F$_5$)$_3$ (20 mol %)	0

[a] Unless noted otherwise, the yield of **6a** was determined by ^{1}H NMR of crude product. [b] Isolated yield.

The scope of different indoles was examined for this tandem indole annulation/arylation cascade using propargylic ether **4** as the starting material (Table 2).

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(6) (a) Knolker, H. J.; Reddy, K. R. *Chem. Rev.* **2002**, *102*, 4303. (b) Schmidt, A. W.; Reddy, K. R.; Knoelker, H.-J. *Chem. Rev.* **2012**, *112*, 3193.

(7) Denison, M. S.; Soshilov, A. A.; He, G.; Degroot, D. E.; Zhao, B. *Toxicol. Sci.* **2011**, *124*, 1.

(8) (a) Quintana, F. J.; Basso, A. S.; Iglesias, A. H.; Korn, T.; Farez, M. F.; Bettelli, E.; Caccamo, M.; Oukka, M.; Weiner, H. L. *Nature* **2008**, *453*, 65. (b) Stevens, E. A.; Mezrich, J. D.; Bradfield, C. A. *Immunology* **2009**, *127*, 299.

(9) (a) Li, Y.; Innocentin, S.; Withers, D. R.; Roberts, N. A.; Gallagher, A. R.; Grigorieva, E. F.; Wilhelm, C.; Veldhoen, M. *Cell* **2011**, *147*, 629. (b) Kiss, E. A.; Vonarbourg, C.; Kopfmann, S.; Hobeika, E.; Finke, D.; Esser, C.; Diefenbach, A. *Science* **2011**, *334*, 1561.

(10) Mehta, V.; Vezina, C. M. *Differentiation* **2011**, *82*, 211.

(11) Fritz, W. A.; Lin, T.-M.; Safe, S.; Moore, R. W.; Peterson, R. E. *Biochem. Pharmacol.* **2009**, *77*, 1151.

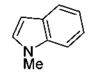
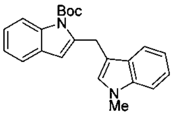
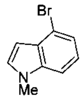
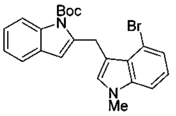
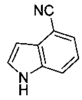
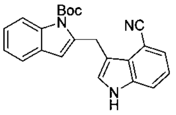
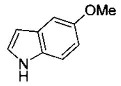
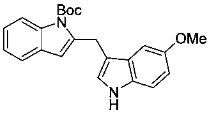
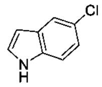
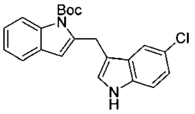
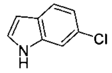
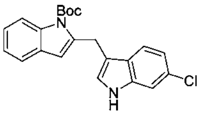
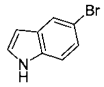
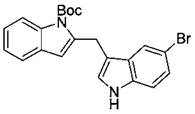
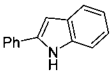
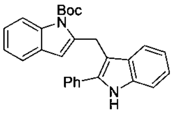
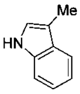
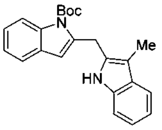
(12) Jeong, K.-T.; Hwang, S.-J.; Oh, G.-S.; Park, J.-H. *Int. Immunopharmacol.* **2012**, *13*, 377.

(13) (a) Gu, R.; Robeyns, K.; Van Meervelt, L.; Toppet, S.; Dehaen, W. *Org. Biomol. Chem.* **2008**, *6*, 2484. (b) Boudreault, P. L. T.; Wakim, S.; Tang, M. L.; Tao, Y.; Bao, Z. A.; Leclerc, M. *J. Mater. Chem.* **2009**, *19*, 2921.

(14) (a) Gu, R.; Hameurlaine, A.; Dehaen, W. *Synlett* **2006**, 1535. (b) Gu, R.; Hameurlaine, A.; Dehaen, W. *J. Org. Chem.* **2007**, *72*, 7207.

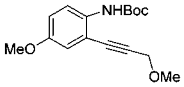
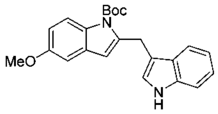
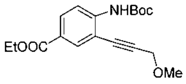
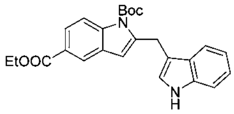
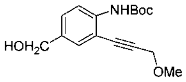
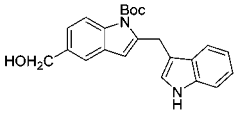
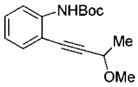
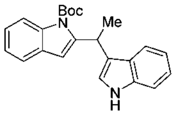
(15) (a) Tholander, J.; Bergman, J. *Tetrahedron Lett.* **1998**, *39*, 1619. (b) Tholander, J.; Bergman, J. *Tetrahedron* **1999**, *55*, 6243. (c) Wahlstrom, N.; Stensland, B.; Bergman, J. *Synthesis* **2004**, 1187.

Table 2. Scope of Indoles for Pt-Catalyzed Tandem Indole Annulation/Arylation of Propargylic Ether **4**[a]

indole substrates	products	yield(%)[b]
5b 	**6b** 	88
5c 	**6c** 	68
5d 	**6d** 	81
5e 	**6e** 	77
5f 	**6f** 	84
5g 	**6g** 	85
5h 	**6h** 	82
5i 	**6i** 	80
5j 	**6j** 	60

[a] Conditions: **4** (1 equiv), indole **5** (2 equiv), $PtCl_2$ (10 mol %), Na_2CO_3 (1.5 equiv), 100 °C, dioxane. [b] Isolated yield.

Table 3. Scope of Aniline and Propargylic Ether for Pt-Catalyzed Tandem Indole Annulation/Arylation[a]

indole substrates	products	yield[b]
7a 	**8a** 	77%
7b 	**8b** 	62%
7c 	**8c** 	55%
7d 	**8d** 	70%

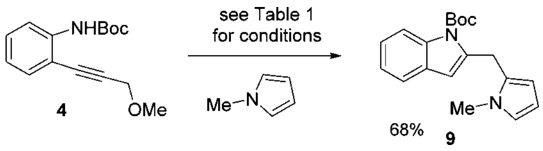
[a] See Table 1 for conditions. [b] Isolated yield.

N-Methyl indole **5b** afforded a high yield of the 2,3′-diindolyl methane product **6b**. The yield became 20% lower for 4-Br substituted *N*-methylindole **5c**. Interestingly, the 4-cyano substituted indole **5d** did not interfere with the efficiency of the tandem reaction. The indole annulation/arylation reaction could also tolerate electron-donating methoxy or halogen substituents on the 5- or 6-position of the indole (e.g., **5e**, **5f**, **5g**, and **5h**).

We then studied the effect of the substituent on the 2- and 3-position of indole **5**. With a 2-phenyl substituent on indole **5i**, the yield of product **6i** is comparable to **6a**. When the intrinsic more reactive 3-position of the indole is blocked in substrate **5j**, 2,2′-diindolylmethane was obtained in 60% yield.

The scope of aniline and propargylic ether was also investigated with different substituents (Table 3). We focused on the *para*-position of the aniline to examine how the change of pK_a of the aniline influenced the efficiency of the reaction. To our delight, anilines with either an electron-donating methoxy group or an electron-withdrawing ester group on the *para*-position participated in the tandem reaction. Aniline **7a** with an electron-donating *para* methoxy group provided a higher yield of the desired product than the one with a *para* electron-withdrawing group (**7b**). A moderate 55% yield was observed when aniline **7c** with a free hydroxyl group was employed as the substrate. Secondary propargylic ether **7d** could also participate in the tandem reaction and afford diindolylethane **8d**.

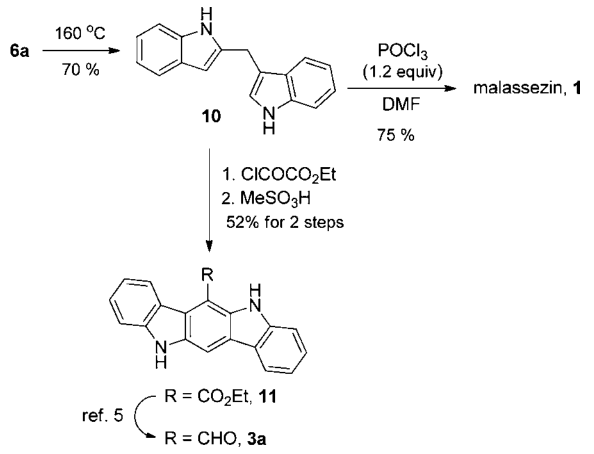
We next examined nucleophiles besides indoles. We were pleased to find that *N*-methylpyrrole could also serve as the nucleophile and product **9** was isolated in 68% yield (eq 1). We previously reported that various substituted furans underwent tandem indole annulation/(4 + 3) cycloaddition with substrate **4**.[3] When 1,3-dimethoxybenzene or thiophene was employed, a complex mixture was obtained.



(1)

To demonstrate the utility of the Pt-catalyzed indole annulation/arylation method, we finished the synthesis of natural product malassezin and a formal synthesis of natural product FICZ as shown in Scheme 1. Removal of the Boc-protecting group in product **6a** under thermal conditions yielded diindolylmethane **10**, which could

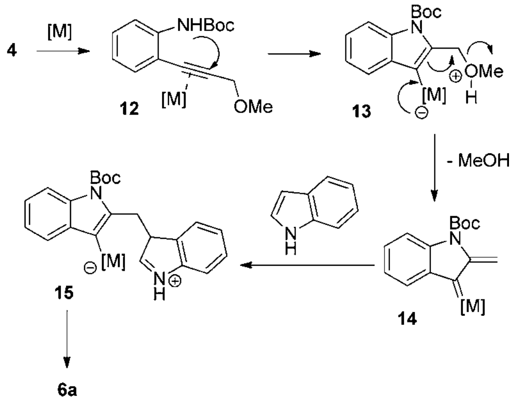
Scheme 1. Synthesis of Malassezin and FICZ



undergo formylation to afford natural product malassezin **1**.[4a] Acylation of diindolylmethane **10** followed by acid-mediated cyclization produced indolo[3,2-*b*]carbazole **11**, which has been converted to natural product FICZ **3a** through a known sequence of reduction and oxidation.[5] The spectroscopic data of compounds **1**, **10**, and **11** are all in accordance with literature.[17] The structure of 2,3′-diindolylmethane **6a** is then further confirmed.

The proposed mechanism for the indole annulation/arylation is shown in Scheme 2. After the coordination of the metal catalyst to propargylic ether **4**, 5-endo-cyclization of metal complex **12** will lead to the formation of indole intermediate **13**. Elimination of a methanol can then produce metal carbene intermediate **14**, which has been proposed previously by us and others.[3a,16] This electrophilic metal carbene is then captured by an indole nucleophile to form adduct **15**. Protonation and rearomatization can then lead to final diindolylmethane product **6a**. A (3 + 2) cycloaddition between metal carbene **14** and vinyl ethers has been reported.[16a] In our case, we did not observe any (3 + 2) cycloaddition product between metal carbene **14** and indole.

Scheme 2. Proposed Mechamism



In summary, we have developed an efficient method for the synthesis of various highly substituted 2,3′-diindolylmethanes. The indole annulation event is accompanied by the coupling of two indole units. An electrophilic platinum carbene intermediate was proposed to be involved in this cascade reaction. We also demonstrated that the method could be applied to the synthesis of natural products malassezin and indolo[3,2-*b*]carbazoles.

Acknowledgment. We thank the NIH (R01GM088285) and the University of Wisconsin for financial support.

Supporting Information Available. ^{1}H NMR, ^{13}C NMR, IR, HRMS for starting materials and products. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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(16) (a) Saito, K.; Sogou, H.; Suga, T.; Kusama, H.; Iwasawa, N. *J. Am. Chem. Soc.* **2011**, *133*, 689. (b) Allegretti, P. A.; Ferreira, E. M. *Org. Lett.* **2011**, *13*, 5924. (c) Allegretti, P. A.; Ferreira, E. M. *Chem. Sci* **2013**, *4*, 1053.

(17) See Supporting Information for details.