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Alkynylation-Desilylation-Alkynylation-Cycloisomerization (ADAC) Three-Component Synthesis of 2,2‘-Biindolyls – Concise Synthesis of Tjipanazole I

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Dedication ((optional))

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Abstract: A sequentially Pd/Cu-catalyzed alkynylation-desilylation-alkynylation-cycloisomerization (ADAC) process in the sense of a consecutive three-component reaction using TIPS-butadiyne as a four carbon building block gives a rapid and efficient access to 2,2'-biindolyls in a one-pot fashion. This facile entry to unsymmetrically substituted title compounds has been employed in a concise two-step synthesis of the alga alkaloid tjipanazole I.

Multicomponent Reactions (MCR)[1] are characterized by the formation of more than two bonds from more than two compounds in a one-pot reaction. Consequently, this multifaceted reactivity based concept[2] has opened many avenues from reaction design[3] over natural product syntheses[4] and diversity-oriented syntheses[5] to sustainable organic syntheses[6] and application in medicinal chemistry.[7] MCR syntheses of heterocycles[8] are particularly attractive, because they provide many scaffolds for the development of lead structures in active pharmaceutical ingredients[9] and functional molecules for advanced photonic and electronic technologies.[10] MCR syntheses of heterocycles catalyzed or initiated by transition metal catalysis even more enhance the versatility of this highly efficient and efficacious concept.[11]

The 2,2'-biindolyl ligation (Figure 1) is present in indigoids, indolocarbazole and indolotryptoline alkaloids.[12]

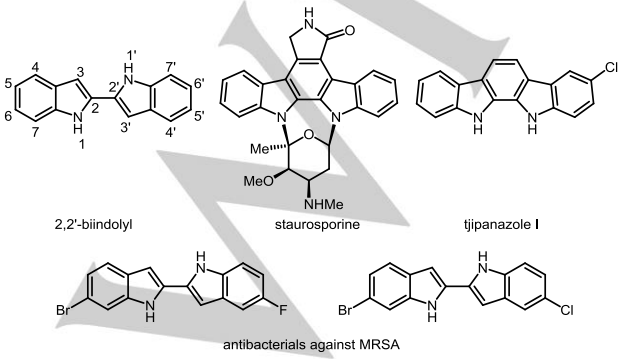

Figure 1. 2,2‘-Biindolyl, indolo[2,3-*a*]carbazole alkaloids staurosporine and tjipanazole I, and antibacterial MRSA-pyruvate kinase inhibitors.

Most prominently, staurosporine, an indolo[2,3-*a*]carbazole alkaloid, and related compounds reveal potent protein kinase inhibition,[13] which is particularly interesting for developing anticancer therapeutics.[14] Tjipanazole I, isolated from blue-green alga *Tolypothrix tjipanasensis*, turned out to show antifungal activity.[15] Interestingly, tjipanazole I is accessible in a straightforward cyclocondensation with 2,2-diethoxy-*N*,*N*-dimethylethylamine starting from an unsymmetrically substituted 2,2'-biindolyl.[16] Finally, unsymmetrically halogen substituted 2,2'-biindolyls have been shown to efficiently inhibit MRSA-pyruvate kinase with high antibacterial activity against *Staphylococcus aureus* ATCC 29213, however, without significant cytotoxicity in mammals.[17]

While symmetrically substituted 2,2'-biindolyls are accessible by Madelung cyclization of *N*-aryloxamides,[18] by cycloisomerization of 1,4-bis(*ortho*-aminoaryl)-1,3-butadiynes,[19] Ir-catalyzed cyclization of 2-ethynyl anilines,[20] or protecting group directed metal catalyzed homocoupling of indoles,[21] concise syntheses of unsymmetrically substituted 2,2'-biindolyl derivatives still remain a major challenge. Although 2-iodo indoles can be coupled to the title compounds by Pd-catalyzed coupling with stannanes (Stille coupling)[22] or boronic acids (Suzuki coupling),[23] often the starting materials have to be prepared in multistep reactions. In 2003 for the total syntheses of tjipanazoles B, D, E, and I, Davies and coworkers reported a robust multistep approach to 2,2'-biindolyls using an *ortho*-nitro toluene aldol-type condensation followed by Cadogan-Sundberg cyclization or Pd-catalyzed reductive cyclization.[16]

In recent years, starting with catalytic generation of alkynoyl intermediates as an entry to consecutive multicomponent syntheses of many classes of functional heterocycles[24] we became increasingly interested in sequentially Pd-catalyzed processes,[25] in particular for developing them for one-pot syntheses of heterocycles.[25e] Inspired by our one-pot coupling-cyclization synthesis of (aza)indoles[26] and the implementation of TIPS-butadiyne as an ideal C4-building block in sequentially catalyzed MCR-formations of triazole derivatives[27] we reasoned that unsymmetrically substituted 2,2'-biindolyls might be accessible in a one-pot fashion by sequential Sonogashira alkynylation with TIPS-butadiyne followed by base-catalyzed

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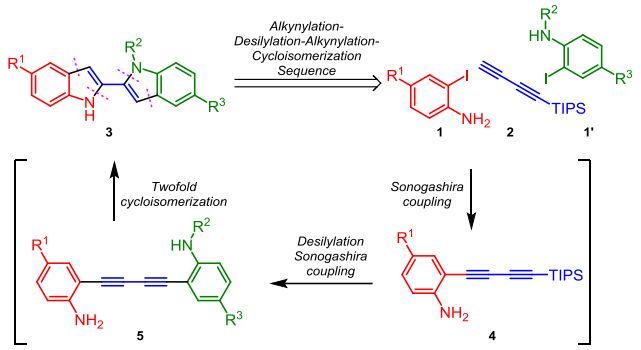
cycloisomerization in the sense of a MCR. Here, we communicate our first findings on a consecutive three-component alkynylation-desilylation-alkynylation-cycloisomerization (ADAC) synthesis of unsymmetrically substituted 2,2'-biindolyls.

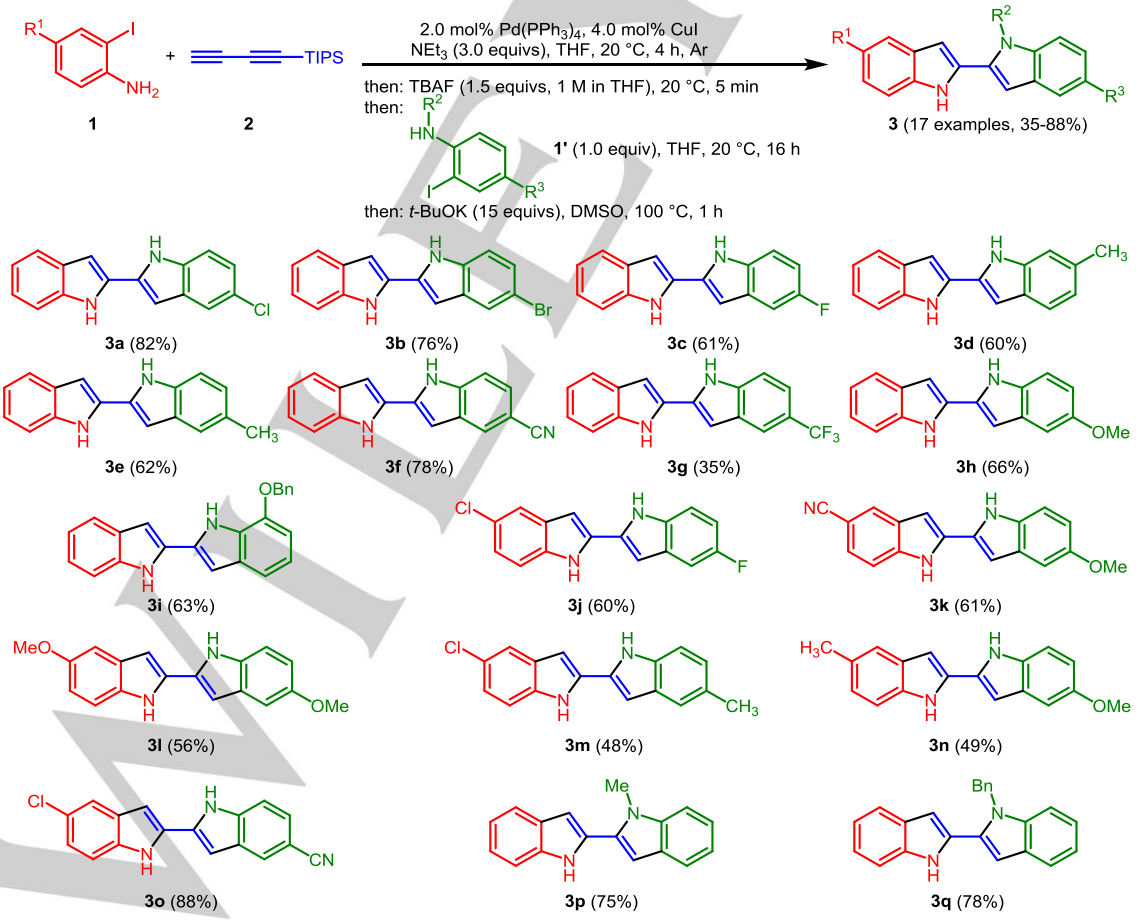
De novo ring formation starting from *ortho*-iodo anilines **1** (and **1'**) as versatile and readily available substrates is particularly attractive for devising a retrosynthetic analysis of 2,2'-biindolyls **3** (Scheme 1).



Scheme 1. Retrosynthetic analysis of unsymmetrically substituted 2,2'-biindolyls by one-pot alkynylation-desilylation-alkynylation-cycloisomerization (ADAC) sequence (TIPS = triisopropylsilyl).

The unsymmetrical nature of TIPS-protected butadiyne (**2**) allows the formation of unsymmetrically substituted diynes **4** and **5** by intermediate desilylation in a one-pot fashion. Based upon the catalytic generation of pentadiynones and pyrazolyl-triazoles thereof[27b] and 1*H*-1,2,3-triazol-4-yl-pyrrolo[2,3-*b*]pyridines,[27a] both in a consecutive one-pot fashion, the ADAC one-pot sequence was conceptualized to begin with an alkynylation of an *ortho*-iodo aniline **1** with TIPS-butadiyne (**2**) furnishing the coupled butadiyne **4**. Thereof, desilylation and alkynylation uniquely generate the unsymmetrically substituted butadiyne **5**, which in turn cycloisomerizes by two-fold base-mediated 5-*endo*-*dig* cyclization to furnish the title compounds **3**. The individual steps and their concatenation to a one-pot sequence were optimized to identify the most optimal reaction conditions (see Supporting Information).

With optimized conditions for the one-pot synthesis of 2,2'-biindolyl **3a** in hand we set out to check the scope of this novel consecutive three-component synthesis by varying the substitution pattern on the 2-iodo aniline derivatives **1**. The versatility of this process was illustrated by the synthesis of 17 examples in yields from 35 to 88% (Scheme 2).[28]



Scheme 2. Consecutive three-component alkynylation-desilylation-alkynylation-cycloisomerization (ADAC) synthesis of unsymmetrically substituted 2,2'-biindolyls.

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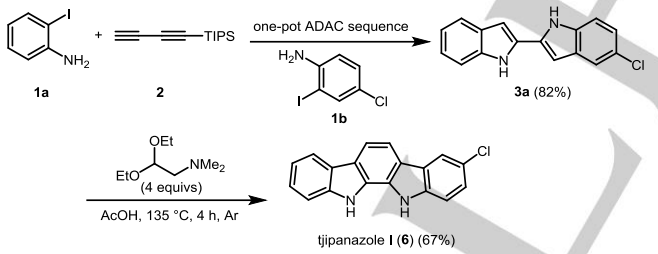
Taking into account that four new bonds and two rings are being formed in this one-pot process an average bond forming yield of 77-97%. Interestingly, the electronic nature of substituents on the aniline aryl ring of substrate **1** and **1'** can be electron-rich, electron-poor and even chloro and bromo substituents can be carried through the sequence uneventfully. *N*-Methyl and benzyl substituted anilines **1'** are also tolerated (see products **3p** and **3q**), which are perfectly suited for desymmetrizing applications in complex molecules synthesis. In this study, we primarily employed commercially available substituted anilines **1** and **1'**, yet, 2-iodo-5-methylaniline (**1e**) and 2-benzyloxy-6-iodoaniline (**1j**) were successfully employed to demonstrate the accessibility of substitution patterns at 7- and 6-positions in title molecules **3** (see products **3d** and **3i**). Most favorably, the three components are efficiently reacted in an almost equistoichiometric ratio to give the desired target compounds in good yield. It is noteworthy mentioning that an *N*-tosyl substituent is not tolerated, because it is cleaved under the strongly basic conditions of the terminal twofold-cycloisomerization.

The straightforward one-pot synthesis of the unsymmetrically substituted 2,2'-biindolyl **3a** encouraged us to apply it in the total synthesis of tjipanazole I applying Davies' final cyclization step.[16] Starting from 2-iodo aniline (**1a**), TIPS-butadiyne (**2**), and 4-chloro-2-iodoaniline (**1b**) 2,2'-biindolyl **3a** was obtained in 82% yield by three-component alkynylation-desilylation-alkynylation-cycloisomerization (ADAC) synthesis (Scheme 3). Then, compound **3a** was heated in acetic acid to 135 °C under argon atmosphere and over a period of 6 h every hour an equivalent of (dimethylamino)acetaldehyde diethylacetal (in total 4 equivalents) was added to the hot reaction mixture. After workup tjipanazole I (**6**) was isolated after flash chromatography in 67% yield. This concise synthesis furnishes tjipanazole I in 56% yield over two steps the highest reported yield, which is also more than twice of the combined yield of 27% of Davies' synthesis.



Scheme 3. Concise two-step synthesis of tjipanazole I by three-component alkynylation-desilylation-alkynylation-cycloisomerization (ADAC) synthesis (ADAC sequence: 2.0 mol% $Pd(PPh_3)_4$, 4.0 mol% CuI, NEt_3 (3.0 equivs), THF, 20 °C, 4 h, Ar; then: then: TBAF (1.5 equivs, 1 M in THF), 20 °C, 5 min; then: **1b** (1.0 equiv), THF, 20 °C, 16 h; then: *t*-BuOK (15 equivs), DMSO, 100 °C, 1 h) and subsequent cyclization with (dimethylamino)acetaldehyde diethylacetal).

In conclusion we have developed a concise one-pot synthesis of unsymmetrically substituted 2,2'-biindolyls in the sense of a consecutive three-component alkynylation-desilylation-alkynylation-cycloisomerization (ADAC) process taking advantage of TIPS-butadiyne as a four carbon building block, which can be unsymmetrically coupled by a sequentially Pd/Cu-catalyzed sequence. The scope of the substitution pattern of 2,2'-biindolyls is broad and allows exploration of potential therapeutics for the treatment of MRSA infections. Furthermore, this novel ADAC synthesis has successfully applied to a two-step synthesis of tjipanazole I in higher yield than the published three-step synthesis. Studies directed to expand the diversity oriented scope to complex functionalization of 2,2'-biindolyls, their use in alkaloid syntheses and evaluation of MRSA inhibition are currently underway.

Acknowledgements

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Keywords: Alkynylation • Cross-coupling • Copper • Indole • Palladium

[1] For leading monographies and reviews, see e.g. a) A. Dömling, I. Ugi, *Angew. Chem. Int. Ed.* **2000**, *39*, 3168-3210; b) Multi-component Reactions in Organic Synthesis J. Zhu, Q. Wang, M.-X. Wang, eds. Wiley-VHC, Weinheim, **2015**; c) G. H. Posner, *Chem. Rev.* **1986**, *86*, 831-844; d) L. F. Tietze, U. Beifuss, *Angew. Chem. Int. Ed.* **1993**, *32*, 131-163; e) L. F. Tietze, *Chem. Rev.* **1996**, *96*, 115-136.

[2] T. J. J. Müller In *Multicomponent Reactions 1. General Discussion and Reactions Involving a Carbonyl Compound as Electrophilic Component*, T. J. J. Müller, ed., Science of Synthesis Series, Georg Thieme Verlag KG, Stuttgart, **2014**, 5-27.

[3] B. Ganem, *Acc. Chem. Res.* **2009**, *42*, 463-472.

[4] B. B. Toure, D. G. Hall, *Chem. Rev.* **2009**, *109*, 4439-4486.

[5] a) J. E. Biggs-Houck, A. Younai, J. T. Shaw, *Curr. Opin. Chem. Biol.* **2010**, *14*, 371-382; b) E. Ruijter, R. Scheffelaar, R. V. A. Orru, *Angew. Chem. Int. Ed.* **2011**, *50*, 6234-6246.

[6] R. C. Cioc, E. Ruijter, R. V. A. Orru, *Green Chem.* **2014**, *16*, 2958-2975.

[7] P. Slobbe, E. Ruijter, R. V. A. Orru, *Med. Chem. Commun.* **2012**, *3*, 1189-1218.

[8] For general conceptional reviews, see e.g. a) B. Jiang, T. Rajale, W. Wever, S.-J. Tu, G. Li, *Chem. Asian J.* **2010**, *5*, 2318-2335; b) B. H. Rotstein, S. Zaretsky, V. Rai, A. K. Yudin, *Chem. Rev.* **2014**, *114*, 8323-8359.

[9] For recent reviews, highlighting the importance of multicomponent reactions in the synthesis of biologically active heterocycles, see e.g. a) D. Insuasty, J. Castillo, D. Becerra, H. Rojas, R. Abonia, *Molecules* **2020**, *25,* 505; b) A. P. Taylor, R. P. Robinson, Y. M. Fobian, D. C. Blakemore, L. H. Jones, O. Fadeyi, *Org. Biomol. Chem.* **2016**, *14*, 6611-6637; For reviews on MCR syntheses of priviledged heterocycles, see e. g. c) C. G. Neochoritis, T. Zhao, A. Dömling, *Chem. Rev.* **2019**, *119*, 1970-2042; d) T. L. Pavlovska, R. G. Redkin, V. V. Lipson, D. V. Atamanuk, *Mol. Divers.* **2016**, *20*, 299-344; e) M. Shiri, *Chem. Rev.* **2012**, *112*, 3508-3549; f) V. Estevez, M. Villacampa, J. Carlos Menendez, *Chem. Soc. Rev.* **2010**, *39*, 4402-4421.

[10] For reviews on multicomponent syntheses of functional chromophores, see e.g. a) L. Levi, T. J. J. Müller, *Chem. Soc. Rev.* **2016**, *45*, 2825-2846; b) L. Levi, T. J. J. Müller, *Eur. J. Org. Chem.* **2016**, 2907-2918; c) T. J. J. Müller, *Drug Discov. Today Technol.* **2018**, *29*, 19-26; d) F. K. Merkt, T. J. J. Müller, *Isr. J. Chem.* **2018**, *58*, 889-900.

[11] For lead references, see e.g. a) G. Balme, E. Bossharth, N. Monteiro, *Eur. J. Org. Chem.* **2003**, 4101-4111; b) D. M. D'Souza, T. J. J. Müller, *Chem. Soc. Rev.* **2007**, *36*, 1095-1108; For recent reviews, see e.g. c) S. Perrone, L. Troisi, A. Salomone, *Eur. J. Org. Chem.* **2019**, 4626-4643; d) R. M. Cherian, N. A. Harry, S. Saranya, K. R. Rohit, G. Anilkumar, *Asian J. Org. Chem.* **2019**, *8*, 197–233.

[12] M. Sato, S. Kishimoto, H. Noguchi, K. Watanabe, Bisindole. In *Comprehensive Natural Products III: Chemistry and Biology*, 3rd edition, Elsevier B. V., **2020**, Vol. 2, pp 467-485.

[13] T. Tamaoki, H. Nomoto, I. Takahashi, Y. Kato, M. Morimoto, F. Tomita, *Biochem. Biophys. Res. Commun.* **1986**, *135*, 397-402. DOI: 10.1016/0006-291X(86)90008-2.

[14] P. Cohen, *Nat. Rev. Drug Discov.* **2002**, *1*, 309-315.

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[15] R. Bonjouklian, T. A. Smitka, L. E. Doolin, R. M. Molloy, M. Debono, S. A. Shaffer, R. E. Moore, J. B. Stewart, G. M. L. Patterson, *Tetrahedron* **1991**, *47*, 7739-7750.

[16] J. T. Kuethe, A. Wong, I. W. Davies, *Org. Lett.* **2003**, *5*, 3721-3723.

[17] N. S. Kumar, E. M. Dullaghan, B. B. Finlay, H. Gong, N. E. Reiner, J. Jon Paul Selvam, L. M. Thorson, S. Campbell, N. Vitko, A. R. Richardson, R. Zoraghi, R. N. Young, *Bioorg. Med. Chem.* **2014**, *22*, 1708-1725.

[18] a) J. L. Wood, B. M. Stoltz, H.-J. Dietrich, D. A. Pflum, D. T. Petsch, *J. Am. Chem. Soc.* **1997**, *119*, 9641-9651; b) S. C. Pelly, C. J. Parkinson, W. A. L. van Otterlo, C. B. de Koning, *J. Org. Chem.* **2005**, *70*, 10474-10481.

[19] a) C. Koradin, W. Dohle, A. L. Rodriguez, B. Schmid, P. Knochel, *Tetrahedron* **2003**, *59*, 1571-1587; b) G. Abbiati, A. Arcadi, E. Beccalli, G. Bianchi, F. Marinelli, E. Rossi, *Tetrahedron* **2006**, *62*, 3033-3039; c) A. Arcadi, G. Bianchi, F. Marinelli, *Synthesis* **2004**, 610-618.

[20] E. Kumaran, W. Y. Fan, W. K. Leong, *Org. Lett.* **2014**, *16*, 1342-1345.

[21] a) A. García-Rubia, B. Urones, R. Gómez Arrayás, J. C. Carretero, *Chem. Eur. J.* **2010**, *16*, 9676-9685; b) J. Le, Y. Gao, Y. Ding, C. Jiang, *Tetrahedron Lett.* **2016**, *57*, 1728-1731; c) J. Bergman, N. Eklund, *Tetrahedron* **1980**, *36*, 1439-1443.

[22] R. L. Hudkins, J. L. Diebold, F. D. Marsh, *J. Org. Chem.* **1995**, *60*, 6218-6220.

[23] C. A. Merlic, Y. You, D. M. McInnes, A. L. Zechman, M. M. Miller, Q. Deng, *Tetrahedron* **2001**, *57*, 5199-5212.

[24] a) For reviews on the catalytic generation of alkynoyl intermediates and their application in consecutive multicomponent syntheses of heterocycles, see e.g. T. J. J. Müller, *Top. Heterocycl. Chem.* **2010**, *25*, 25-94; b) C. F. Gers-Panther, T. J. J. Müller, *Adv. Heterocycl. Chem.* **2016**, *120*, 67-98.

[25] For instructive reviews on sequentially catalyzed processes, see: a) D. E. Fogg, E. N. dos Santos, *Coord. Chem. Rev.* **2004**, *248*, 2365-2379; b) J.-C. Wasilke, S. J. Obrey, R. T. Baker, G. C. Bazan, *Chem. Rev.* **2005**, *105*, 1001-1020; c) A. Ajamian, J. L. Gleason, *Angew. Chem. Int. Ed.* **2004**, *43*, 3754-3760; d) T. J. J. Müller, In "Metal Catalyzed Cascade Reactions", T. J. J. Müller, ed., Springer Berlin/Heidelberg. *Top. Organomet. Chem.* **2006**, *19*, 149-205; e) T. Lessing, T. J. J. Müller, *Appl. Sci.* **2015**, *5*, 1803−1836.

[26] a) T. Lessing, F. Sterzenbach, T. J. J. Müller, *Synlett* **2015**, *26*, 1217-1221; b) T. Lessing, T. J. J. Müller, *Synlett* **2017**, *28*, 1743-1747; c) T. Lessing, T. J. J. Müller, *Chem. Heterocycl. Comp.* **2018**, *54*, 334-338.

[27] a) T. Lessing, H. van Mark, T. J. J. Müller, *Chem. Eur. J.* **2018**, *24*, 8974-8979; b) P. Niesobski, F. Klukas, H. Berens, G. Makhloufi, C. Janiak, T. J. J. Müller, *J. Org. Chem.* **2018**, *83*, 4851-4858.

[28] **Synthesis of 2,2'-biindolyl 3a (Typical procedure).** 2-Iodoaniline (**1a**) (110 mg, 0.50 mmol), $Pd(PPh_3)_4$ (11.6 mg, 10.0 μmol, 2.00 mol%), and CuI (3.80 mg, 20.0 μmol, 4.00 mol%) were placed in a screw-cap Schlenk tube with a magnetic stir bar under argon (three evacuation-argon flush cycles). Then, TIPS-butadiyne (**2**) (124 mg, 0.30 mmol), THF (1.0 mL), and triethylamine (152 mg, 1.50 mmol) were successively added. After stirring at room temp for 4 h TBAF (1 m in THF, 0.75 mL, 0.75 mmol) was added and after 5 min 4-chloro-2-iodoaniline (**1b**) (127 mg, 0.50 mmol) and THF (0.75 mL) were added to the reaction mixture. After stirring at room temp for 16 h KO^{t}Bu (842 mg, 7.50 mmol) and DMSO (2.50 mL) were added and the reaction mixture was stirred at 100 °C (oil bath) for 1 h. After cooling to room temp the reaction mixture was extracted with ethyl acetate (4 x 25.0 mL) and deionized water (2 x 25.0 mL). The aqueous layer was extracted with ethyl acetate (25.0 mL), and finally the combined organic layers were extracted with brine (25.0 mL) and dried (anhydrous sodium sulfate). After filtration the solvents were removed in vacuo. The crude product was adsorbed on Celite® and purified by chromatography on silica gel (*n*-hexane/ethyl acetate 3:1) to give the analytically pure 2,2'-biindolyl **3a** (110 mg**,** 82%) as a colorless solid, R_f = 0.37 (*n*-hexane/ethyl acetate 3:1), Mp 282-284 °C (dec.) (ref. 16: 275 °C (dec.). ^{1}H NMR (acetone-d_6, 300 MHz): δ 6.91–6.94 (m, 1 H), 6.95–6.98 (m, 1 H), 7.04 (t, *J* = 7.4 Hz, 1 H), 7.11 (dd, *J* = 8.6, 2.0 Hz, 1 H), 7.14 (t, *J* = 7.6 Hz, 1 H), 7.42 (t, *J* = 8.0 Hz, 2 H), 7.55–7.59 (m, 2 H), 10.75 (s, 1 H), 10.89 (s, 1 H). ^{13}C NMR (acetone-d_6, 151 MHz): δ 99.1 (CH), 100.1 (CH), 111.9 (CH), 113.1 (CH), 120.2 (CH), 120.7 (CH), 121.2 (CH), 122.8 (CH), 123.1 (CH), 125.7 (C_{quat}), 129.8 (C_{quat}), 131.1 (C_{quat}), 131.7 (C_{quat}), 134.1 (C_{quat}), 136.6 (C_{quat}), 138.3 (C_{quat}). MS (EI, 70 eV, *m*/*z* (%)): 268 ([^{37}Cl-M]$^+$, 31), 266 ([^{35}Cl-M]$^+$, 100), 231 ([M – Cl]$^+$, 100), 204 (21), 149 (15), 111 (18), 105 (15), 91 (42). HRMS (ESI) calcd. for [$C_{16}H_{11}{}^{35}ClN_2$ + H$^+$]: 267.0684; Found: 267.0682. Anal. calcd. for $C_{16}H_{11}ClN_2$ [266.7]: C 72.05, H 4.16, N 10.50; Found: C 72.04, H 4.10, N 10.21.

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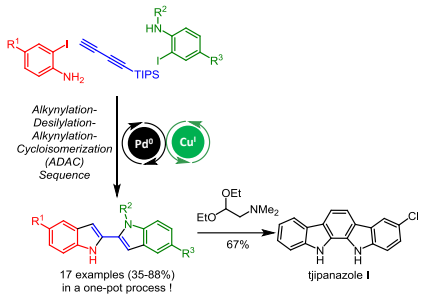

The sequentially Pd/Cu-catalyzed (ADAC) process uses TIPS-butadiyne as a four carbon building block and furnishes 2,2'-biindolyls in consecutive three-component synthesis. Thereby, the alga alkaloid tjipanazole I can be efficiently synthesized in an extremely concise fashion.

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