Tetrahedron Letters 175 (2026) 155919

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis of aza- and aza-carba-pterocarpens by electrophilic amination of arene C−H bonds

Jannik Eckert, Lisa Marx, Tobias Sauter, Rafael Valentin, Andreas Speicher *

Institute for Organic Chemistry, Saarland University, Campus C4.2, 66123 Saarbruecken, Germany

ARTICLE INFO

Keywords:
Heterocycles
Pterocarpens
Chromenes
Amination
Cross coupling

ABSTRACT

Tetracyclic fused heterocycles of the aza-pterocarpen type are attracting increasing interest due to their various biological activities. We present a novel and straightforward synthesis of representative aza- and aza-carba-pterocarpens. For the first time, the Grignard-induced electrophilic amination of arene C−H bonds starting with o-nitrobiaryls was applied to this type of compound.

Introduction

Pterocarpans, tetracyclic fused heterocycles of the dihydrobenzofuro [3,2-*c*]chromene type, are an abundant subclass of isoflavonoids [1]. The most prominent representative, Medicarpin (**1**), is found in a wide range of legumes (*Medicago* sp.) [2]. Numerous studies have reported its biological activities, including plant protective fungicidal or antibacterial properties [3,4]. The compound is also active against other microbes, including bacteria [5], and can induce apoptosis in human lung fibroblasts and peripheral lymphocytes [6]. We reported the first isolation and synthesis of the chromenoindole type 11a-aza-pterocarpan (**3**), found in roots of *Robinia pseudoacacia* (black locust) [7]. This compound exhibits moderate antineoplastic activity against HL-60 leukemia cell lines. Although not yet found in nature, related aza-carba-pterocarpens (e.g. **4**) were synthesized by Angerer et al., which inhibited the growth of breast cancer tumors in rats [8]. *N*-Tosyl-aza-carbapterocarpans (e.g. **5**) were prepared by Rennó, Buarque et al. to synthesize new antineoplastic and antiparasitic drug candidates (Fig. 1) [9]. For an overview of the biological activities and syntheses of various pterocarpan-type compounds see Ref. [10,11].

During our initial synthesis of natural aza-pterocarpan **3** and its dihydrochromenoindole analog **2**, we found that the unsubstituted skeleton of **2** was prepared by Buu-Hoï [12] via the traditional Fischer indole method. Besides the low yield (15 %), this route is impractical for synthesizing substituted derivatives, such as **2**, due to the need for specific chromanones as starting materials and the lack of regioselectivity in indole ring formation.

Although we were unsuccessful with some proposed concepts for synthesizing condensed heterocyclic indole derivatives of type **2** [13−16], we succeeded with an Ullmann coupling–Reissert cyclization strategy to synthesize natural aza-pterocarpan **3** via the aza-pterocarpen precursor **2** (Scheme 1a) [7]. To overcome the poor water solubility of medicarpin derivatives Koketsu et al. also synthesized **3** (and its HCl salt) via a Heck aza-arylation approach (Scheme 1b) [17]. Fan et al. [18] used an intramolecular Pd-catalyzed aryl-aryl coupling approach for less substituted derivatives. More recently, Brown et al. synthesized **3** through a nickel-catalyzed dearomative arylboration of indoles followed by Matteson homologation and cyclization [19]. High stereoselectivity was observed using an *N*-Boc-proline-protected indole precursor (Scheme 1c). Very recently, Bansal et al. reported a pentafluorophenol-catalyzed regioselective annulation synthesizing 7-aryl substituted dihydrochromeno indoles. The basic tetracyclic compound, however, was not accessible (Scheme 1d) [20].

Results and discussion

The growing interest in the aza- and carba-pterocarpan scaffolds prompted us to develop an alternative route. In 2014, Ess, Kürti et al. reported on the synthesis of a series of fused *N*-heterocycles via transition-metal-free electrophilic amination of arene C−H bonds [21]. Some types failed to cyclize, and neither aza- nor aza-carba-pterocarpans were discussed.

Electrophilic amination has become a significant research area in organic synthesis due to the importance of nitrogen in bioactive

* Corresponding author.
E-mail address: anspeich@mx.uni-saarland.de (A. Speicher).

https://doi.org/10.1016/j.tetlet.2025.155919
Received 11 September 2025; Received in revised form 5 November 2025; Accepted 2 December 2025
Available online 3 December 2025

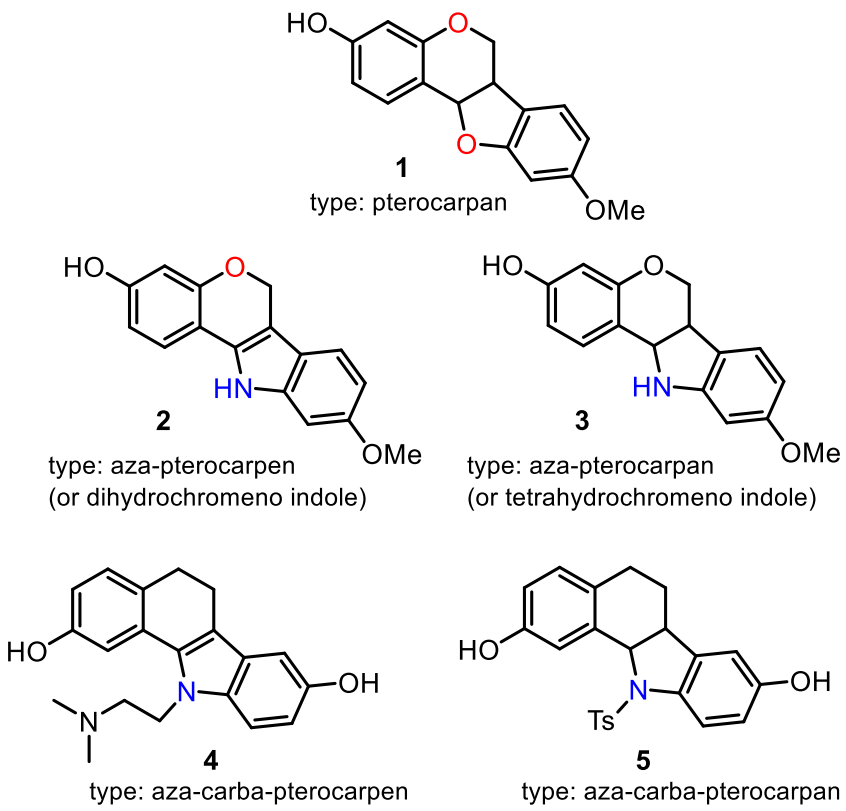


Fig. 1. Chemical compounds of the pterocarpan family.

molecules, pharmaceutical agents, and organic functional materials [22,23]. Electrophilic aminations involve an umpolung strategy and *O*-benzoylhydroxylamines (R_2N-OBz) have received the most attention and have been used in various aminations, particularly in transition-metal-catalyzed reactions [24]. Transition-metal-free concepts, however, were developed as an environmentally friendly alternative [25].

In addition to electrophilic amination concepts for the hydroamination, aminoboration and carboamination of alkenes or alkynes [26], the electrophilic arene $C(sp^2) - H$ amination strategy provides potential access to heterocyclic motifs [27,28]. Umpolung of imines can also be useful in this area [29].

Kürti's electrophilic amination strategy is based on a surprising carbazole formation rather than simple biaryl formation when *o*-nitrobiaryls are reacted with an excess of PhMgBr (Scheme 2) [30]. Possible mechanistic pathways have been investigated (Scheme 3) [31,32].

Our concept for synthesizing type **2** aza-pterocarpens is based on 3-(2-nitrophenyl)-2*H*-chromenes **6** as previously unknown amination precursors. They could be obtained via benzo[*b*]pyran anellation by alkylation of o-hydroxybenzyl triphenylphosphonium salts **8** with α-halogenated carbonyl compounds **9** (Scheme 2, route a) [33]. For type **4** aza-carba-pterocarpens, 3-(2-nitrophenyl)-1,2-dihydronaphthalene precursors **7** could be obtained via decarboxylative cross-coupling [34–37] of alkenyl halides **10** with o-nitrobenzoic acids **11** according to the Goosens procedure [38] (route b).

To test our concept, we started with commercially available compounds **12** and **13**. The original procedure (NaOMe in toluene at reflux) for the *p*-nitro analog of **14** [33] yielded no more than 10 % yield. However, the K_2CO_3/crown ether protocol [39] for the desired alkylation/Wittig sequence afforded the 3-(*o*-nitrophenyl)-2*H*-chromene **14** in high yield (Scheme 3). We were delighted to find that the subsequent Grignard-induced amination using four equivalents of PhMgBr was efficient, providing a novel access to the aza-pterocarpen basic system **15** (Scheme 3).

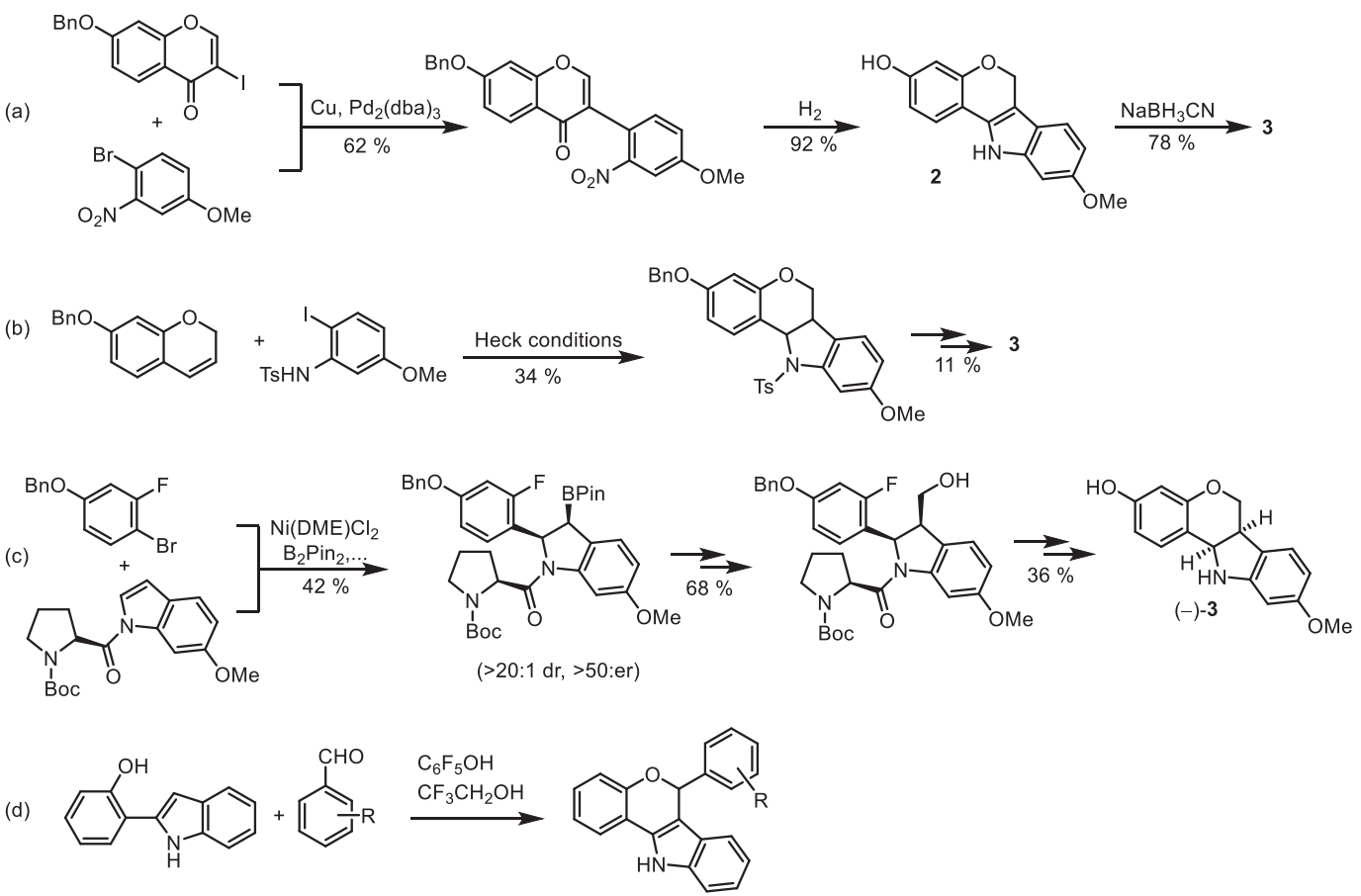
To synthesize the substituted natural aza-pterocarpene **2**, a suitable *o*-nitroacetophenone **19** was prepared using an improved three-step sequence. First, 1-bromo-4-methoxy-2-nitrobenzene **16** underwent Sonogashira coupling with trimethylsilyl acetylene to form compound **17** [40]. Then hydrolysis to **18** [41] and bromination of the methyl ketone yielded **19** [42].

Bromoacetophenone **19** was then reacted with the freshly prepared *o*-hydroxy phosphonium salt **20**, obtained via a known three-step synthesis [43,44]. The low yield of the chromene fusion reaction was attributed to the phosphonium salt's tendency to decompose easily. Using alternative protecting groups did not overcome this issue. However, the subsequent electrophilic amination, as the core reaction, was successful with a good yield (Scheme 4). Since the acetyl protecting group was a Grignard reagent consumer, four equivalents were now used instead of three in the original procedure (Scheme 4) [21]. Afterwards, this modification also increased the yield of the synthesis of **15** (see Scheme 3).

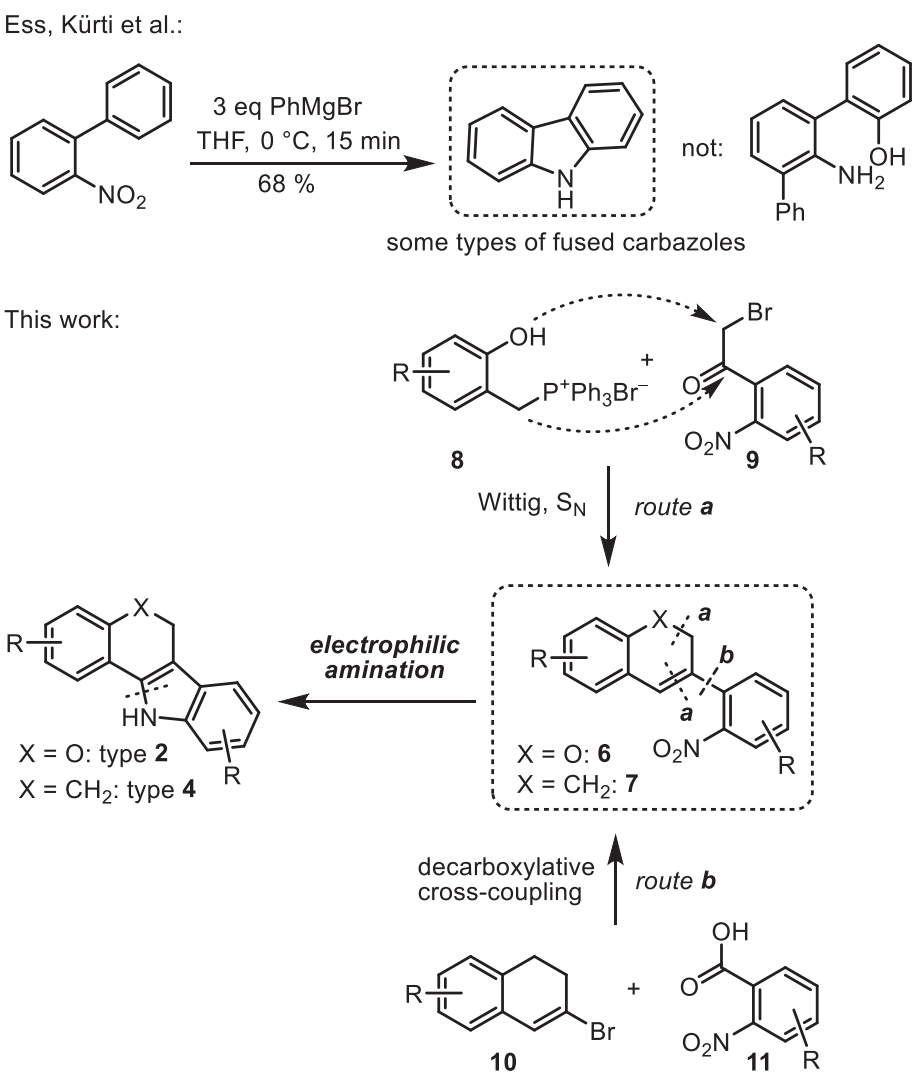
To synthesize representative aza-carba-pterocarpens (see Scheme 2, route b) we first prepared tetralone derivatives **22** according to a known procedure [45]. These compounds were then reacted with potassium salts **23** of commercially available o-nitrobenzoic acids according to a modified Gooßen procedure [46]. Then, our improved amination protocol was efficient once more, providing novel access also to the aza-carba-pterocarpens **7a-d** (Scheme 5). Note that compounds **7** are air-sensitive and slowly form the naphthalene derivatives **25** [47].

The high flexibility of the aza-carba-pterocarpens syntheses depicted in Scheme 5 inspired us to develop an alternative approach for aza-

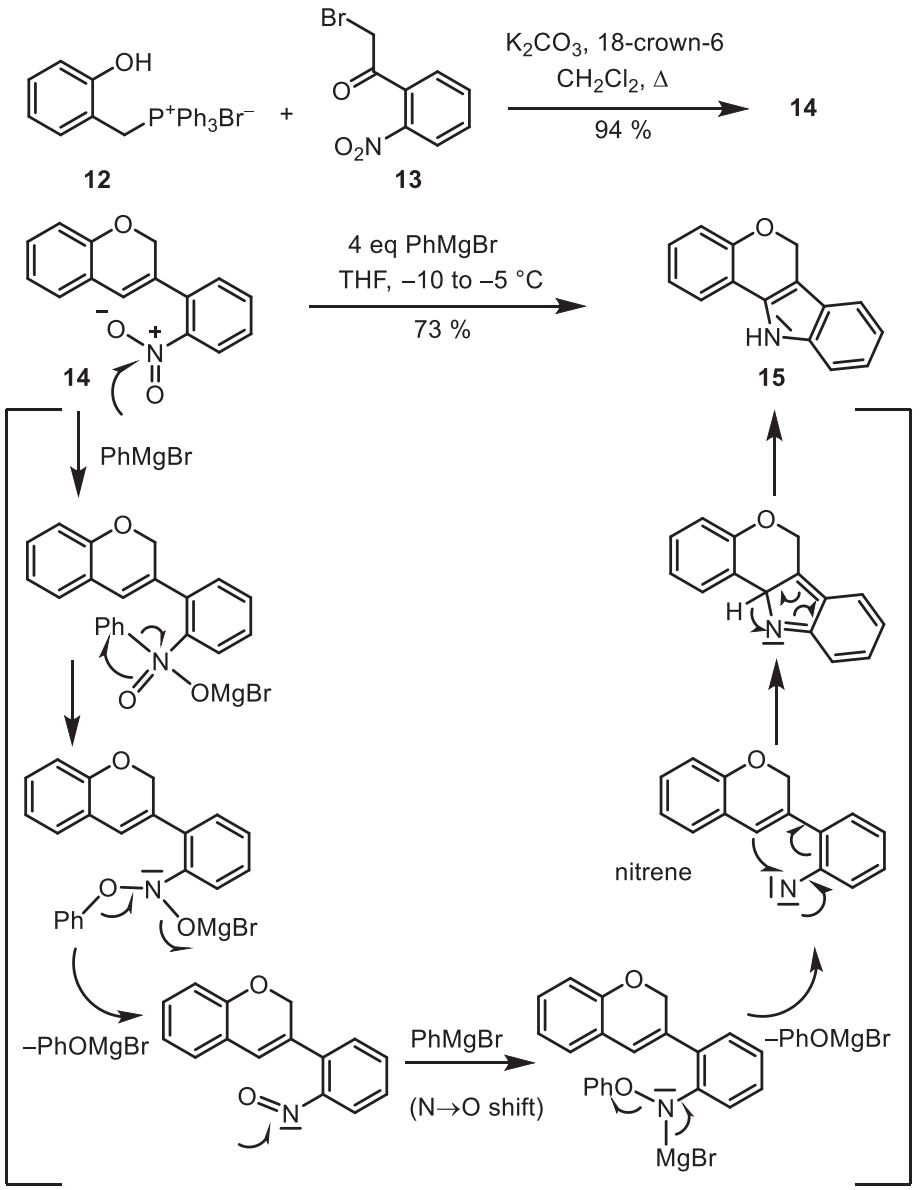
Previous work:



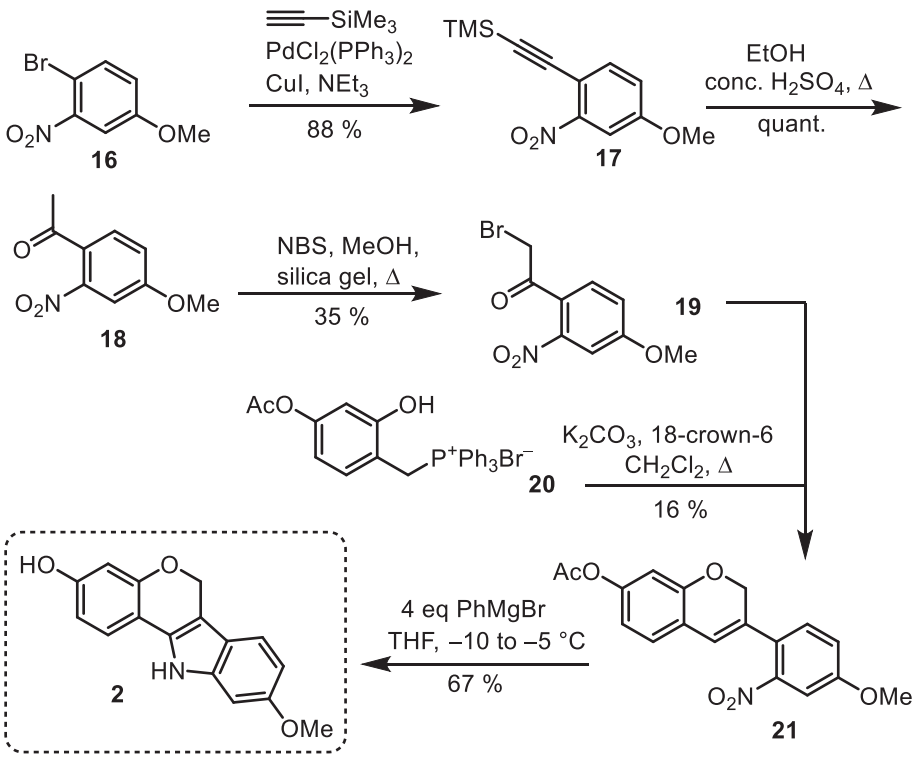
Scheme 1. Syntheses of the aza-pterocarpan **2**



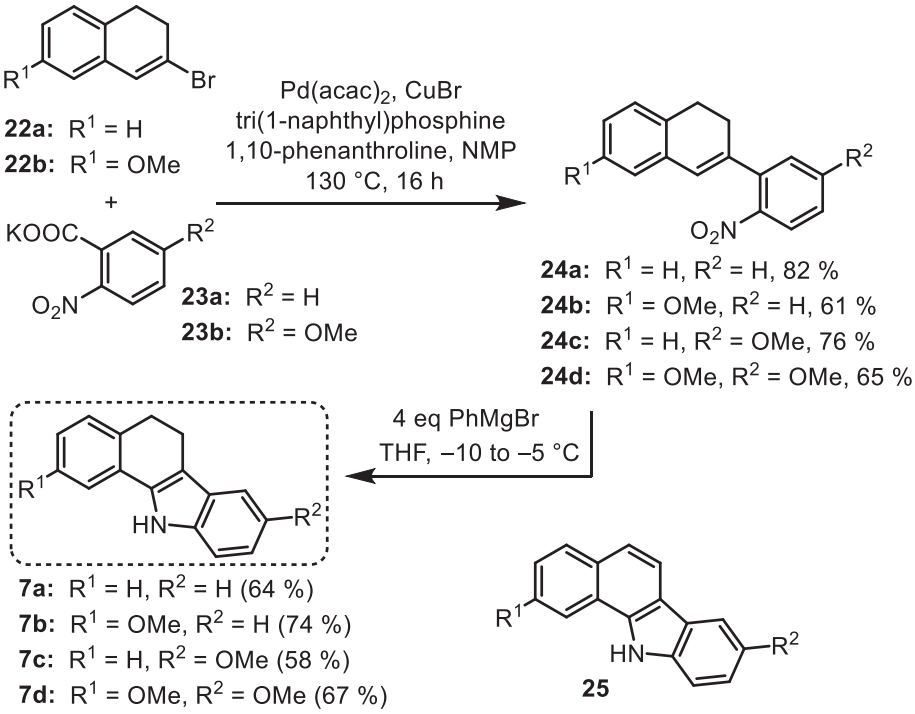
Scheme 2. New strategy of synthesis for pterocarpan framework



Scheme 3. Synthesis of the non-substituted aza-pterocarpen **15** and proposed mechanistic pathway



Scheme 4. Synthesis of the aza-pterocarpen **2**

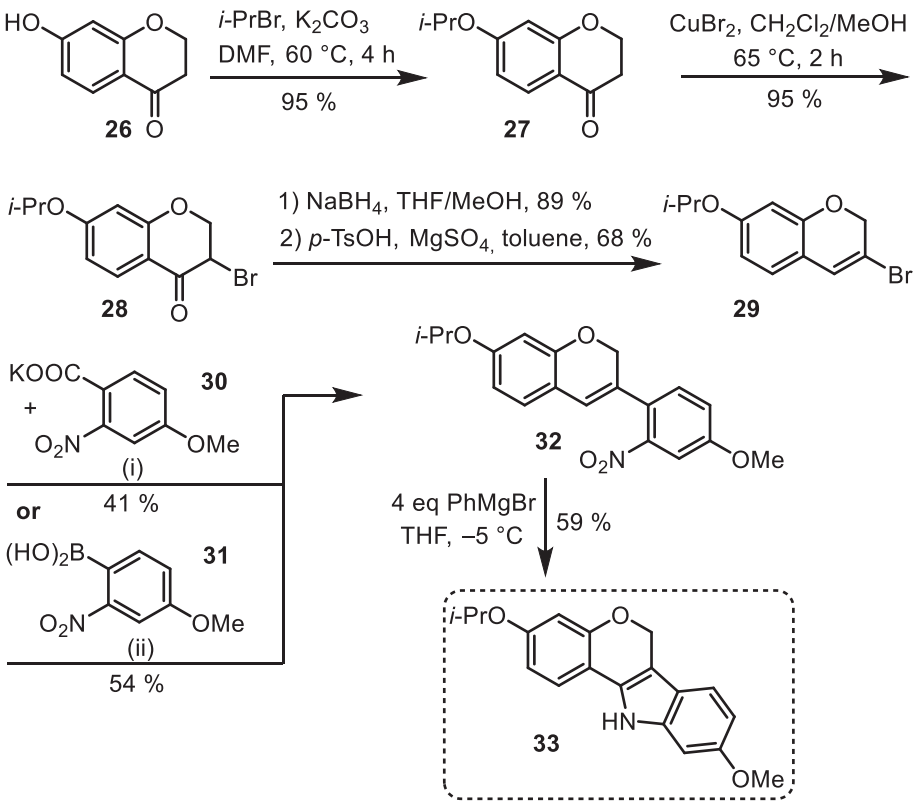


Scheme 5. Synthesis of the aza-carba-pterocarpens **7**

pterocarpens as well (compared to Schemes 3 and 4). To achieve the substitution pattern of the representative **2**, for example, we prepared the 3-bromo-2*H*-chromene **29** in a four-step sequence from the known 7-hydroxychroman-4-one (**26**) [48]. Decarboxylative coupling with the o-nitrobenzoic acid K-salt **30** yielded 3-(*o*-nitrophenyl)-2*H*-chromene **32**, which could then be cyclized to the aza-pterocarpen **33** (Scheme 6). Note that the precursor **32** for the electrophilic amination alternatively could be obtained by Suzuki coupling of **29** with the boronic acid **31** [49].

Conclusion

The Grignard-induced electrophilic amination of arene C−H bonds, starting with o-nitro-aryl compounds, was used for the first time to



Scheme 6. Alternative synthesis of the aza-pterocarpen **33**

efficiently synthesize representative aza- and aza-carba-pterocarpens [50]. Both chromene- and naphthalene-based routes were employed with respect to both subtypes. Our work expands the scope of transition-metal-free amination strategies to include pterocarpen-derived tetracyclic scaffolds, which are of considerable interest due to their diverse biological activities.

CRediT authorship contribution statement

Jannik Eckert: Investigation, Data curation. **Lisa Marx:** Investigation, Data curation. **Tobias Sauter:** Investigation, Data curation. **Rafael Valentin:** Investigation, Data curation. **Andreas Speicher:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2025.155919.

Data availability

Data will be made available on request.

References and notes

[1] A. Goel, A. Kumar, A. Raghuvanshi, Chem. Rev. 113 (2013) 1614–1640, https://doi.org/10.1021/cr300219y.
[2] R.A. Dixon, L.W. Sumner, Plant Physiol. 131 (2003) 878–885, https://doi.org/10.1104/pp.102.017319.
[3] M.A. Gordon, E.W. Lapa, M.S. Fitter, M. Lindsay, Antimicrob. Agents Chemother. 17 (1980) 120–123, https://doi.org/10.1128/AAC.17.2.120.
[4] B.M.R. Bandara, N.S. Kumar, K.M.S. Samaranayake, J. Ethnopharmacol. 25 (1989) 73–75, https://doi.org/10.1016/0378-8741(89)90046-9.
[5] G. Belofsky, D. Percivill, K. Lewis, G.P. Tegos, J. Ekart, J. Nat. Prod. 67 (2004) 481–484, https://doi.org/10.1021/np030409c.
[6] Z.-L. Liu, S. Tanaka, H. Horigome, T. Hirano, K. Oka, Biol. Pharm. Bull. 25 (2002) 37–41, https://doi.org/10.1248/bpb.25.37.
[7] L. Dejon, H. Mohammed, P. Du, C. Jacob, A. Speicher, Med. Chem. Comm. 4 (2013) 1580–1583, https://doi.org/10.1039/c3md00213f.
[8] E. Von Angerer, J. Prekajac, J. Med. Chem. 29 (1986) 380–386, https://doi.org/10.1021/jm00153a013.
[9] J.A. Mendes, E.J. Salustiano, C.S. de Pires, T. Oliveira, J.C.F. Barcellos, J.M. C. Cifuentes, P.R.R. Costa, M.N. Rennó, C.D. Buarque, Bioorg. Chem. 80 (2018) 585–590, https://doi.org/10.1016/j.bioorg.2018.07.004.
[10] C. Buarque, J. Domingos, C. Netto, P. Costa, Curr. Org. Synth. 12 (2015) 772–794, https://doi.org/10.2174/1570179412061508281125O2.
[11] H. Chen, S. Zhao, S. Cheng, X. Dai, X. Xu, W. Yuan, X. Zhang, J. Heterocyclic Chem. 56 (2019) 1672–1683, https://doi.org/10.1002/jhet.3543.
[12] N.P. Buu-Hoi, A. Martani, A. Croisy, P. Jacquignon, F. Périn, J. Chem. Soc. (C) (1966) 1787–1789, https://doi.org/10.1039/J39660001787.
[13] T. Eicher, S. Hauptmann, A. Speicher, The Chemistry of Heterocycles, 3rd ed., Wiley-VCH, Weinheim, 2012.
[14] C.A. James, A.L. Coelho, M. Gevaert, P. Forgione, V. Snieckus, J. Org. Chem. 74 (2009) 4094–4103, https://doi.org/10.1021/jo900146d.
[15] M.C. Willis, G.N. Brace, I.P. Holmes, Angew. Chem. Int. Ed. 44 (2005) 403–406, https://doi.org/10.1002/anie.200461598.
[16] M. Nazaré, C. Schneider, A. Lindenschmidt, D.W. Will, Angew. Chem. Int. Ed. 43 (2004) 4526–4528, https://doi.org/10.1002/anie.200460122.
[17] S. Kakuda, M. Ninomiya, K. Tanaka, M. Koketsu, ChemistrySelect 1 (2016) 4203–4208, https://doi.org/10.1002/slct.201600834.
[18] L.-L. Fan, Z.-P. Che, R. Zhang, X. Yu, X.-Y. Zhi, H. Xu, Mol. Divers. 16 (2012) 415–421, https://doi.org/10.1007/s11030-012-9370-5.

[19] G.L. Trammel, R. Kuniyil, P.F. Crook, P. Liu, M.K. Brown, J. Am. Chem. Soc. 143 (2021) 16502–16511, https://doi.org/10.1021/jacs.1c05902.
[20] D. Bansal, P. Sivaganesan, G. Nataraj, C. Elanchezhian, C.; M. K. Das, S. Chaudhuri, Tetrahedron Lett. 2025, 165-166, 155660. doi:https://doi.org/10.1016/j.tetlet.2025.155660.
[21] H. Gao, Q.-L. Xu, M. Yousufuddin, D.H. Ess, L. Kürti, Angew. Chem. Int. Ed. 53 (2014) 2701–2705, https://doi.org/10.1002/anie.201309973.
[22] L.G. O'Neil, J.F. Bower, Angew. Chem. Int. Ed. 60 (2021) 25640–25666, https://doi.org/10.1002/anie.202102864.
[23] Z. Zhou, L. Kürti, Synlett 30 (2019) 1525–1535, https://doi.org/10.1055/s-0037-1611861.
[24] X. Dong, Q. Liu, Y. Dong, H. Liu, Chem. A Eur. J. 23 (2017) 2481–2511, https://doi.org/10.1002/chem.201601607.
[25] P.V. Kattamuri, J. Yin, S. Siriwongsup, D.-H. Kwon, D.H. Ess, Q. Li, G. Li, M. Yousufuddin, P.F. Richardson, S.C. Sutton, L. Kürti, J. Am. Chem. Soc. 139 (2017) 11184–11196, https://doi.org/10.1021/jacs.7b05279.
[26] K. Hirano, M. Miura, J. Am. Chem. Soc. 144 (2022) 648–661, https://doi.org/10.1021/jacs.1c12663.
[27] B.S. Zhang, W.-Y. Jia, X.-Y. Gou, Y.-H. Yang, F. Wang, Y.-M. Wang, X.-C. Wang, Z.-J. Quan, Org. Lett. 24 (2022) 2104–2109, https://doi.org/10.1021/acs.orglett.2c00318 [.
[28] T.K. Das, A. Ghosh, Z. Grimm, U. Aguinaga, M. Yousufuddin, L. Kürti, Chem. A Eur. J. 31 (2025) e202403524, https://doi.org/10.1002/chem.202403524.
[29] M. Bairwa, R.K. Verma, K.C. Bharadwaj, J. Org. Chem. 89 (2024) 14811–14817, https://doi.org/10.1021/acs.joc.4c01542.
[30] H. Gao, D.H. Ess, M. Yousufuddin, L. Kürti, J. Am. Chem. Soc. 135 (2013) 7086–7089, https://doi.org/10.1021/ja400897u.
[31] G. Bartoli, G. Palmieri, Tetrahedron Lett. 30 (1989) 2129–2132, https://doi.org/10.1016/S0040-4039(01)93730-X.
[32] W. Dohle, A. Staubitz, P. Knochel, Chem. A Eur. J. 9 (2003) 5323–5331, https://doi.org/10.1002/chem.200305090.
[33] B. Begasse, M. Le Corre, Tetrahedron 36 (1980) 3409–3412, https://doi.org/10.1016/0040-4020(80)80192-X.
[34] J. Cornella, I. Larrosa, Synthesis 44 (2012) 653–676, https://doi.org/10.1055/s-0031-1289686.
[35] Z. Fu, Z. Li, Y. Song, R. Yang, Y. Liu, H. Cai, J. Org. Chem. 81 (2016) 2794–2803, https://doi.org/10.1021/acs.joc.5b02873.
[36] Y. Wei, P. Hu, M. Zhang, W. Su, Chem. Rev. 117 (2017) 8864–8907, https://doi.org/10.1021/acs.chemrev.6b00516.
[37] D. He, J. Yao, B. Ma, J. Wei, G. Hao, X. Tuo, S. Guo, Z. Fu, H. Cai, Green Chem. 22 (2020) 1559–1564, https://doi.org/10.1039/C9GC03797G.
[38] B. Song, T. Knauber, L.J. Gooßen, Angew. Chem. Int. Ed. 52 (2013) 2954–2958, https://doi.org/10.1002/anie.201208025.
[39] R.M. Boden, Synthesis 12 (1975) 784, https://doi.org/10.1055/s-1975-23924.
[40] T. Yamakawa, E. Ideue, Y. Iwaki, A. Sato, H. Tokuyama, J. Shimokawa, T. Fukuyama, Tetrahedron 67 (2011) 6547–6560, https://doi.org/10.1016/j.tet.2011.05.112.
[41] M. Jacubert, O. Provot, J.-F. Peyrat, A. Hamze, J.-D. Brion, M. Alami, Tetrahedron 66 (2010) 3775–3787, https://doi.org/10.1016/j.tet.2010.03.055.
[42] B. Mohan Reddy, V. Venkata Ramana Kumar, N. Chinna Gangi Reddy, S. Mahender Rao, Chin. Chem. Lett. 25 (2014) 179–182, https://doi.org/10.1016/j.cclet.2013.09.014.
[43] G.D. McAllister, R.C. Hartley, M.J. Dawson, A.R. Knaggs, J. Chem. Soc. Perkin Trans. 1 (1998) 3453–3458, https://doi.org/10.1039/a805026k.
[44] C. Salomé, N. Ribeiro, T. Chavagnan, F. Thuaud, M. Serova, A. de Gramont, S. Faivre, E. Raymond, L. Désaubry, Eur. J. Med. Chem. 81 (2014) 181–191, https://doi.org/10.1016/j.ejmech.2014.05.014.
[45] M. Voets, I. Antes, C. Scherer, U. Müller-Vieira, K. Biemel, S. Marchais-Oberwinkler, R.W. Hartmann, J. Med. Chem. 49 (2006) 2222–2231, https://doi.org/10.1021/jm060055x.
[46] J. Tang, L.J. Gooßen, Org. Lett. 16 (2014) 2664–2667, https://doi.org/10.1021/ol500876x.
[47] A.M. Jeffrey, D.M. Jerina, J. Am. Chem. Soc. 94 (11) (1972) 4048–4049, https://doi.org/10.1021/ja00766a084.
[48] J.Y. Koo, S. Oh, S.-R. Cho, M. Koh, W.-K. Oh, H.-S. Choi, S.B. Park, Org. Biomol. Chem. 11 (2013) 5782–5786, https://doi.org/10.1039/c3ob41264d.
[49] S.E. Collibee, J. Yu, Tetrahedron Lett. 46 (2005) 4453–4455, https://doi.org/10.1016/j.tetlet.2005.04.129.
[50] **General procedure for the electrophilic amination**: In a pre-dried reaction flask, the nitroarene (1.0 equiv.) was dissolved in anhydrous THF (10 mL/mmol) under an argon atmosphere. Phenylmagnesium bromide (4.0 equiv., 1 M in THF) was slowly added at –10 to –5 °C. After 1 h, the reaction was carefully quenched by adding a saturated NH_4Cl solution (5 mL/mmol). The aqueous layer was extracted with EtOAc (3 × 10 mL/mmol), and the combined organic layers were washed with saturated NaCl solution, dried ($MgSO_4$) and concentrated. The crude product was purified by flash chromatography and/or preparative HPLC (*n*-hexane/EtOAc). **6,11-Dihydrochromeno[4,3-*b*]indole (15)**: ^{1}H NMR ($CDCl_3$): δ (ppm) = 8.24 (broad s, 1 H), 7.44 (d, *J* = 7.7 Hz, 1 H), 7.41 (d, *J* = 8.1 Hz, 1 H), 7.29 (d, *J* = 7.5 Hz, 1 H), 7.21 (td, *J* = 7.1 Hz, 1.0 Hz, 1 H), 7.17–7.12 (m, 2 H), 6.96 (d, J = 7.7 Hz, 2 H), 5.64 (s, 2 H). ^{13}C NMR ($CDCl_3$): δ (ppm) = 153.8, 137.2, 129.0, 128.8, 125.0, 122.6, 121.3, 120.5, 120.1, 118.3, 117.4, 116.8, 111.3, 106.4, 65.49. HR MS (ESI, $[M+H]^+$): calcd for $C_{15}H_{11}NO$ (221.0841): 222.0919, found 222.0913. **6,11-Dihydro-5*H*-benzo[*a*]carbazole (7a)** ^{1}H NMR (500 MHz, DMSO-d_6): δ (ppm) = 11.43 (s, 1 H, NH), 7.63 (dd, *J* = 8.0, 1.3 Hz, 1 H), 7.48 (d, *J* = 7.7 Hz, 1 H), 7.37 (d, *J* = 8.2 Hz, 1 H), 7.31–7.24 (m, 2 H), 7.15 (td, *J* = 7.4, 1.4 Hz, 1 H), 7.09 (ddd, *J* = 8.2, 7.1, 1.3 Hz, 1 H), 6.99 (ddd, *J* = 7.9, 7.0, 1.0 Hz, 1 H), 2.99 (dd, *J* = 8.7, 6.5 Hz, 2 H), 2.94–2.85 (m, 2 H). ^{13}C NMR (125 MHz, DMSO-d_6): δ (ppm) = 137.1, 135.9, 133.1, 129.1, 128.3, 126.7, 126.6, 121.7, 120.9, 119.0, 118.4, 111.4, 110.8, 29.03, 19.30. HR MS (ESI, $[M+H]^+$): calcd for $C_{16}H_{13}N$ (219.1048): 220.1126, found 220.1123