JOC The Journal of Organic Chemistry

Note

pubs.acs.org/joc

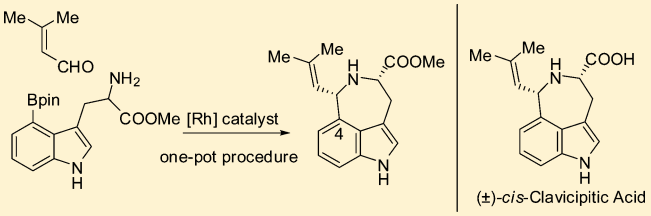
Synthesis of (±)-*cis*-Clavicipitic Acid by a Rh(I)-Catalyzed Intramolecular Imine Reaction

Francesca Bartoccini, Mariangela Casoli, Michele Mari, and Giovanni Piersanti*

Department of Biomolecular Sciences, University of Urbino "Carlo Bo", Piazza del Rinascimento 6, 61029 Urbino (PU), Italy

Supporting Information

ABSTRACT: A new and short synthesis of racemic *cis*-clavicipitic acid was achieved by taking advantage of the double nucleophilic character of indole-4-pinacolboronic ester. Key to the success of the synthesis were an efficient and selective C-3 indole Friedel–Crafts alkylation and the development of an unprecedented intramolecular rhodium-catalyzed 1,2-addition of an aryl pinacolboronic ester to an unactivated imine.



Fungi utilize tryptophan and prenyl moieties to form numerous natural molecules with diverse chemical structures and intriguing biological and pharmacological activities.[1] These compounds are usually derived from L-tryptophan or derivatives thereof as backbones and prenyl moieties as modifications.[2] A subset of this class of molecules containing the unusual azepinoindole tricyclic subunit presents a unique structural challenge that attracted our attention (Figure 1).

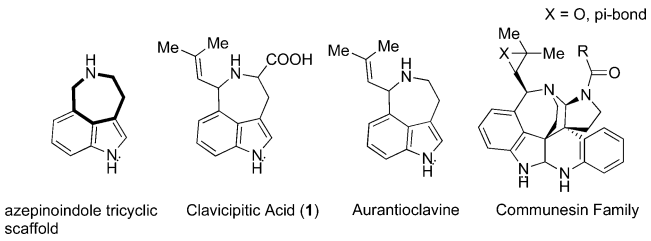


Figure 1. Structures of naturally occurring indole-annulated nitrogen-containing seven-membered rings.

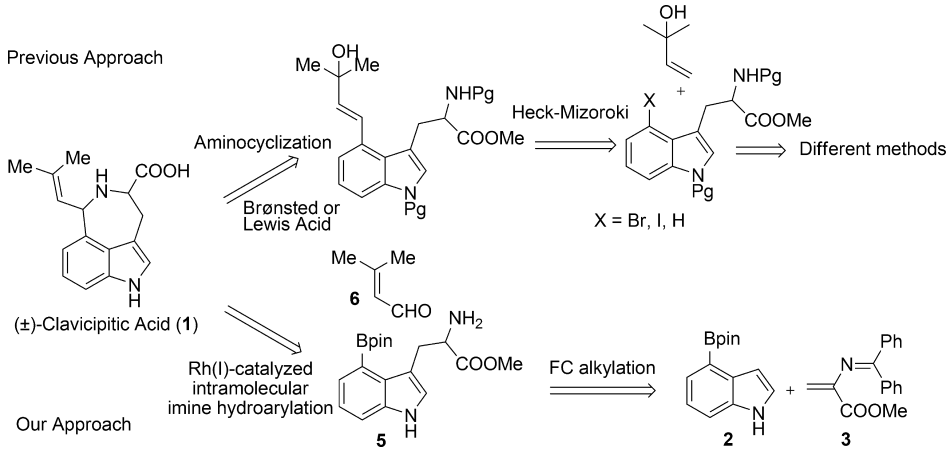
In particular, the ergot alkaloid biosynthesis derailment product clavicipitic acid (**1**) was first isolated from the Claviceps strain SD58 and from *Claviceps fusiformis* as a mixture of *cis* and *trans* diastereoisomers, the proportions of which depend on the specific microorganism from which it is isolated.[3] Together with aurantioclavine,[4] it is a member of the large family of 3,4-ring-fused indole alkaloids characterized by a nitrogen-containing seven-membered ring[5] and has emerged as a target of interest not only for its intriguing molecular architecture but also for its proposed role as an intermediate in the biosynthesis of complex polycyclic alkaloids of the communesin family.[6] Nearly all of the previous synthetic pathways[7] share a common scheme, which involves the construction of the azepinoindole ring system via a palladium(0)-catalyzed Heck–Mizoroki reaction of protected 4-halotryptophan derivatives with 1,1-dimethylallyl alcohol, followed by intramolecular aminocyclization catalyzed by Brønsted and/or Lewis acids (Scheme 1). These reactions afforded the desired product as approximately equal mixtures of *cis* and *trans* isomers and consisted of many classical synthetic procedures. Very recently, Jia et al. reported an elegant approach to clavicipitic acid in which the synthesis of 4-substituted tryptophan was obtained by direct olefination at the C-4 position of protected tryptophan derivatives via C–H activation using 1,1-dimethylallyl alcohol as the terminal olefin.[7i]

We report herein a strategically distinct approach to **1**, which is enabled by an unprecedented Rh(I)-catalyzed intramolecular 1,2-addition of an aryl pinacolboronic ester to an unactivated imino group as the key carbon–carbon forming step.[8] Retrosynthetically, we envisioned that the tricyclic framework of **1** (Scheme 1) could arise from a late-stage intramolecular Rh-catalyzed hydroarylation on the imine, obtained by condensation of unprotected 4-boronated tryptophan methyl ester (**5**) and prenal (**6**) as a suitable five-carbon unit. In view of the stereochemical and structural complexity of **1**, this powerful disconnection of the natural product presented an opportunity to highlight the utility of prenal as a surrogate for 1,1-dimethylallyl alcohol to introduce the dimethylallyl unit into a natural product. The unprotected and racemic 4-boronated tryptophan methyl ester (**5**) could, in turn, easily arise from the Friedel–Crafts alkylation of 4-boronate indole (**2**) and 2-amidoacrylate.[9] Basically, we recognized the double-nucleophilic character of the C-3 and the C-4 carbon equipped with the boryl group of indole **2** and opted to investigate the possibility of chemoselective transformations of nucleophilic C–B bonds. It must be stressed that, even if Pictet–Spengler condensation between L-tryptophan methyl ester and prenal **6** under acidic conditions has been developed,[10] related transformations giving regio- and chemoselective 3,4-fused indoles are, to the best of our knowledge, unprecedented.[11]

Received: January 31, 2014
Published: March 7, 2014

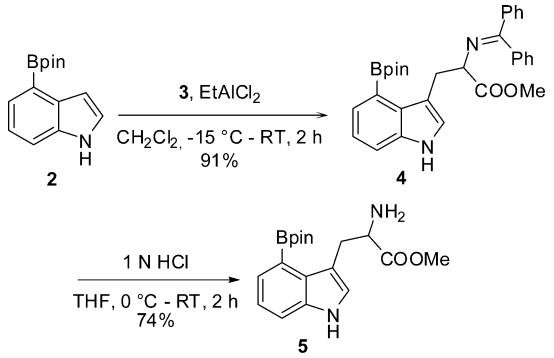
   dx.doi.org/10.1021/jo500245s | J. Org. Chem. 2014, 79, 3255–3259

Scheme 1. Retrosynthetic Analysis of (±)-Clavicipitic Acid (1)



Our approach commenced with the synthesis of 4-boronated tryptophan methyl ester (**4**) by Lewis acid mediated Friedel–Crafts alkylation of the easily accessible and commercially available 4-boronated indole (**2**) and methyl 2-(diphenylmethyleneamino)acrylate (**3**) in excellent yield with high regio- and chemoselectivity (Scheme 2).[12] Acrylate **3** was chosen among other available acrylates based on its reported good reactivity as well as the mild and selective reaction conditions required for the deprotection of the amino group in the final compound. Indeed, the benzophenone imine moiety of **4** was selectively hydrolyzed under acidic conditions. The best conditions found involved the treatment of **4** with 1 M HCl–THF (0 °C to RT, 2 h) to afford **5** in 74% yield. The Friedel–Crafts alkylation/hydrolysis reaction sequence could be performed routinely on a multigram scale.

Scheme 2. Formation of 4-Pinacolboronate Tryptophan Methyl Ester



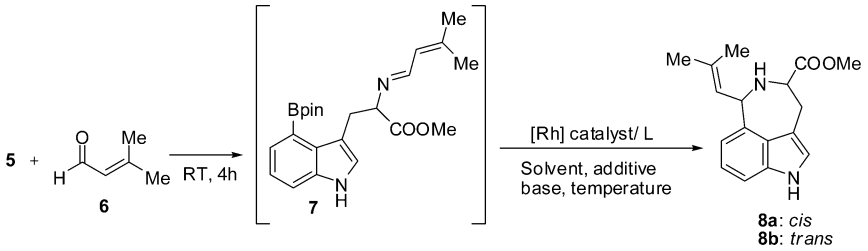
With a robust route to aminoboronate **5** secured, we next explored the condensation of **5** with prenal (**6**) (Table 1). As anticipated, condensation of amine **5** with prenal produced the imine **7** as a stable entity. Initial attempts to cyclize pinacolyl boronate **5** using the Petasis[13] protocol with prenal in 1,1,1,3,3,3-hexafluoro-2-propanol as the solvent[14] only produced the formation of imine **7**.[15] Importantly, no regular Pictet–Spengler product was detected in the course of this reaction, even with different solvents or microwave irradiation. Encouraged by the precedent set by Lu et al., Lam et al., and Sarpong et al.[16] using the intramolecular transition-metal-catalyzed addition of arylboronic acids and aryl pinacolboronic esters to ketones, we began to investigate achieving the desired 1,2-addition using a palladium(II) catalyst. However, conversion of boronic ester **5** to the corresponding boronic acid and subsequent exposure to different kinds of palladium(II) salts and complexes led only to deborylation with very low conversion, probably due to the slow transmetalation step of the arene from boron to the palladium complex.[16a] We then considered the possibility of effecting this transformation using rhodium catalysis, knowing the more nucleophilic nature of arylrhodium species compared with that of arylpalladium species.[16d] We also decided to use pinacolboronic ester, **5**, which would be expected to be more robust and easier to synthesize, handle, and purify than the corresponding acid, but still reactive for subsequent arylation by a rhodium catalyst.[16b,c] The reaction conditions for the intramolecular hydroarylation of **7** are summarized in Table 1.

The combined use of a chlororhodium complex [{RhCl(cod)}$_2$] and bases such as KOH and K_3PO_4, which are often used in the rhodium-catalyzed addition of arylboron reagents, provided very low catalytic activity in the present arylation (entries 1 and 2).

A better yield and a shorter reaction time were obtained using CsF as the base/additive (entry 3), probably accelerating the transmetalation step and enhancing the nucleophilicity of the arylrhodium species. Furthermore, we found that dioxane, which is generally used as the solvent in this reaction,[17] could be replaced by the nontoxic solvent dimethoxyethane (DME). NMR analysis of the crude reaction mixture revealed two major byproducts in addition to the desired tricyclic azepinoindole **8**, the corresponding phenol and protodeboronation and/or protodemetalation products resulting from deborylation of the boronic ester under the reaction conditions, a catalytic dead end for the C–C coupling step. Although detected in the LC-MS of the crude reaction mixture, no intermolecular product or homocoupling product was ever isolated or detected by NMR analysis, thus suggesting that <5% was formed. These results prompted us to use a more efficient dimeric rhodium complex for transmetalation with the arylboronic acid derivative, i.e., [Rh(OH)(cod)]$_2$ (entry 4).[18] Further studies demonstrated that the phosphine ligand (dppp) was unnecessary for the promotion of arylation,[19] whereas CsF was required to maintain the reactivity (entries 5 and 6). No cyclization product was obtained when KHF_2 was added, suggesting that intramolecular hydroarylation proceeds without formation of the aryl trifluoroborate (entry 7). After screening various conditions,[20] we were delighted to find that treatment of **5** with

dx.doi.org/10.1021/jo500245s | J. Org. Chem. 2014, 79, 3255–3259

Table 1. Some Examples for the Optimization of the Reaction Conditions for the Intramolecular Rhodium-Catalyzed Hydroarylation

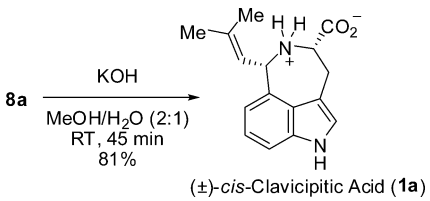


entry[a]	catalyst/base	solvent	T (°C)/t (h)	yield (%)[b]	dr[c] (**8a**/**8b**)
1	$[RhCl(cod)]_2$/dppp/K_3PO_4	dioxane	80/60	9	nd
2	$[RhCl(cod)]_2$/dppp/KOH	dioxane	80/60	18	nd
3	$[RhCl(cod)]_2$/dppp/CsF	DME	85/48	25	nd
4	$[Rh(OH)cod]_2$/dppp/CsF	DME	85/48	41	nd
5	$[Rh(OH)cod]_2$/CsF	DME	85/16	55	100/0
6	$[Rh(OH)cod]_2$	DME	85/16		
7	$[Rh(OH)cod]_2$/KHF_2	DME	85/60		
8[d]	$[Rh(OH)cod]_2$/CsF	DME	85/16	63	100/0

[a]Reaction conditions: **5** (0.1 mmol), solvent (0.8 mL), 4 Å molecular sieves (MS) (100 mg), and **6** (0.11 mmol) at RT for 4 h, followed by rhodium catalyst (10 mol %), additive (3 equiv), and ligand (20 mol %). [b]Yield of isolated product. [c]Diastereoisomeric ratio determined by analysis of the crude ^{1}H NMR with comparison to reported spectra. [d]After imine formation, DME (1.2 mL) was added. nd = not determined; pin = pinacolyl; DME = dimethoxyethane.

prenal (1.1 equiv) in DME and 4 Å molecular sieves at 23 °C for 2 h, followed by the addition of more DME to bring the solution to a final concentration of 0.05 M, CsF (3 equiv), and 10 mol % $[\{Rh(OH)(cod)\}_2]$ efficiently executed the 1,2-addition to form the azepine moiety **8** in 63% yield with complete *cis* diastereoselectivity (entry 8). At the moment, we do not have any evidence or explanations regarding the reasons for this high *cis*-diastereoselectivity. We are currently undergoing studies to clarify the exact mechanism of the reaction.[21] *To the best of our knowledge, this is the first example of the addition of an aryl pinacolboronic ester species to an unactivated imine using Rh(I) catalysis.* The NMR spectra were identical to those reported and revised for the synthetic *cis*-clavicipitic acid methyl ester.[7h] Alkaline hydrolysis of the ester **8a** provided (±)-*cis*-clavicipitic acid (**1a**) in 81% yield, according to the literature procedure (Scheme 3).[7a]

Scheme 3. Final Hydrolysis to the Natural Product



In summary, the concise total synthesis of (±)-*cis*-clavicipitic acid (**1a**), a 3,4-fused-indole alkaloid carrying a prenyl substituent at the C-4 position, was achieved in only four total steps from 4-boronate indole (**2**) with high diastereoselectivity. Key to the completion of the synthesis were a selective Friedel–Crafts alkylation and an unprecedented intramolecular Rh(I)-catalyzed imine hydroarylation reaction via a one-pot procedure. This diastereoselective intramolecular rhodium-catalyzed "normal" prenylation of tryptophan allowed the regioselective introduction of the prenyl side chain at C-4 of tryptophan, forming a C–C bond at the least nucleophilic position (C-4) of the indole core, instead of at the highly nucleophilic positions C-2 and C-3,[22] thanks to the proper choice of easily handled pinacolboronic ester as the latent nucleophilic handle in the 1,2-addition reaction.

EXPERIMENTAL SECTION

General Methods. All reactions were run in air unless otherwise noted. Column chromatography purifications were performed in flash conditions using 230–400 mesh silica gel. Analytical thin layer chromatography (TLC) was carried out on silica gel plates (silica gel 60 F254) that were visualized by exposure to ultraviolet light and an aqueous solution of cerium ammonium molybdate (CAM), *p*-anisaldehyde, or ninhydrin. ^{1}H NMR, ^{13}C NMR, and ^{11}B NMR spectra were recorded at 200/50/64 MHz on a spectrometer, using $CDCl_3$, DMSO-d_6, or CD_3OD as solvent. Chemical shifts (δ scale) are reported in parts per million (ppm) relative to the central peak of the solvent. Coupling constants (J values) are given in hertz (Hz). In ^{13}C NMR, carbon adjacent to boron was not observed.[23] Molecular ions (M + 1) or (M − 1) are given for ESI-MS analysis. Optical absorbances are reported in cm^{-1} for the IR analysis. Melting points were determined using a capillary melting point apparatus and are uncorrected. Elemental analyses were within ±0.4 of the theoretical values (C, H, N). 4-Bromo-1*H*-indole, 4,4,4′,4′,5,5,5′,5′-octamethyl-2,2′-bi(1,3,2-dioxaborolane) (B_2pin_2), serine methyl ester hydrochloride, and 3-methylbut-2-enal (**6**) are commercially available. 4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole[11] (**2**) and methyl 2-(diphenylmethyleneamino)acrylate[24] (**3**) were synthesized according to the literature procedure.

Methyl 2-(Diphenylmethyleneamino)-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indol-3-yl)propanoate (4). To a solution of **2** (3 g, 12.3 mmol) and methyl 2-(diphenylmethyleneamino)acrylate (**3**) (2.7 g, 10.2 mmol) in CH_2Cl_2 anhydrous (50 mL) was added dropwise 1 M $EtAlCl_2$ in hexane (10.2 mL, 10.2 mmol), at −15 °C, under argon. The solution was stirred at −15 °C for 30 min and then at room temperature for 2 h. The mixture was diluted with CH_2Cl_2 (50 mL), and a saturated solution of $NaHCO_3$ (100 mL) was added. The resulting suspension was filtered over Celite and washed with CH_2Cl_2 (3 × 30 mL). The two layers were separated, and the aqueous phase was extracted with further CH_2Cl_2 (2 × 30 mL). The combined organic phases were washed with brine and dried over anhydrous Na_2SO_4, and the solvent

dx.doi.org/10.1021/jo500245s | J. Org. Chem. 2014, 79, 3255–3259

was evaporated under reduced pressure. The residue was purified by flash chromatography on deactivated silica gel (silica gel was deactivated by flushing with 1% TEA in cyclohexane/EtOAc 8:2 and then was washed with cyclohexane/EtOAc 8:2 prior to use) to give 4.7 g (9.3 mmol) of **4** as a pale-yellow solid. Yield 91%. TLC (cyclohexane/EtOAc 8: 2 + 0.1% TEA), R_f = 0.24 (UV, CAM, *p*-anisaldehyde); MS (ESI) 509 $[M + H]^+$; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.20 (s, 6H), 1.23 (s, 6H), 3.31 (dd, J_1 = 14.0, J_2 = 10.5 Hz, 1H), 3.78 (s, 3H), 4.00 (dd, J_1 = 14.0, J_2 = 3.0 Hz, 1H), 4.63 (dd, J_1 = 10.5, J_2 = 3.0 Hz, 1H), 6.25 (br s, 1H), 6.86 (t, J = 7.5 Hz, 2H), 7.06−7.17 (m, 4H), 7.25−7.43 (m, 4H), 7.53−7.57 (m, 3H), 7.99 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 24.3, 24.8, 26.9, 51.9, 65.5, 83.2, 113.4, 114.2, 120.6, 125.6, 127.5, 127.6, 127.7, 127.9, 128.7, 129.3, 130.0, 130.4, 135.8, 136.2, 139.6, 170.8, 173.1 (carbon adjacent to boron was not observed); ^{11}B NMR (200 MHz, $CDCl_3$ $BF_3{\cdot}OEt_2$) δ 32.0; FTIR (film, cm^{-1}) 3370, 1732, 1614; mp: 155−157 °C (acetone/petroleum ether); Anal. Calcd for $C_{31}H_{33}BN_2O_4$ (508.25): C, 73.23; H, 6.54; N, 5.51. Found: C, 73.31; H, 6.49; N, 5.53. The chemical−physical data are according to the literature.[11]

Methyl 2-Amino-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indol-3-yl)propanoate (5). To a solution of **4** (2 g, 3.94 mmol) in THF (freshly distilled) (16 mL) was added 1 N HCl (8 mL) at 0 °C. The mixture was stirred at 0 °C for 30 min and then at room temperature for 2 h. The mixture was diluted with CH_2Cl_2 (30 mL) and poured into a saturated solution of $NaHCO_3$ (25 mL) at 0 °C. The phases were separated, and the aqueous phase was extracted with further CH_2Cl_2 (10 × 20 mL). The combined organic phases were dried over anhydrous Na_2SO_4, and the solvent was evaporated under reduced pressure. The residue obtained was triturated with *n*-hexane (2 × 15 mL), and then ether anhydrous (20 mL) and pinacol (931 mg, 7.88 mmol) were added. The mixture was stirred at room temperature for 12 h. The solvent was evaporated under reduced pressure, and the residue obtained was purified by flash chromatography (gradient from EtOAc to EtOAc/MeOH 97:3) to obtained 1 g (2.91 mmol) of **5** as a white solid. Yield 74%. TLC (EtOAc), R_f = 0.24 (UV, *p*-anisaldehyde); MS (ESI) 345 $[M + 1]^+$; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.40 (s, 12H), 1.80 (br s, 2H), 3.22 (dd, J_1 = 14.0, J_2 = 9.0 Hz, 1H), 3.63 (dd, J_1 = 14.0, J_2 = 5.0 Hz, 1H), 3.71 (s, 3H), 3.89 (dd, J_1 = 9.0, J_2 = 5.0 Hz, 1H), 7.06 (d, J = 2.0 Hz, 1H), 7.18 (d, J = 7.5 Hz, 1H), 7.43 (d, J = 7.5 Hz, 1H), 7.66 (d, J = 7.5 Hz, 1H), 8.47 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 24.8, 24.9, 31.5, 51.7, 55.6, 83.7, 113.2, 114.2, 121.1, 124.5, 128.8, 130.1, 136.3, 175.8 (carbon adjacent to boron was not observed); ^{11}B NMR (64 MHz, $CDCl_3$ $BF_3{\cdot}OEt_2$) δ 32.27; IR (nujol, cm^{-1}) 3524, 1738; mp: 150−153 °C (CH_2Cl_2/*n*-hexane); Anal. Calcd for $C_{18}H_{25}BN_2O_4$ (344.19): C, 62.81; H, 7.32; N, 8.14. Found: C, 62.96; H, 7.28; N, 8.10.

***cis*-Methyl 1-(2-Methylprop-1-enyl)-2,3,4,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indole-3-carboxylate (8a).** To a solution of **5** (344 mg, 1 mmol) in DME (freshly distilled) (8 mL) were added 4 Å molecular sieves (1 g) and 3-methylbut-2-enal (**6**) (105 μL, 1.1 mmol). The mixture was stirred at 30 °C for 4 h. The solution was diluted with further DME (12 mL), and then CsF (456 mg, 3 mmol) and $[Rh(OH)cod]_2$ (46 mg, 0.1 mmol) were added. The mixture was stirred at 85 °C for 16 h. The solvent was evaporated under reduced pressure, and the residue obtained was purified by flash chromatography (cyclohexane/EtOAc 7:3) to give 178 mg (0.63 mmol) of **8a** as yellowish solid. Yield 63%. TLC (cyclohexane/EtOAc, 7:3), R_f = 0.35 (UV, *p*-anisaldehyde); MS (ESI) 285 $[M + 1]^+$; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.85 (d, J = 1.0 Hz, 3H), 1.89 (d, J = 1.0 Hz, 3H), 2.68 (br s, 1H), 3.07 (ddd, J_1 = 15.5, J_2 = 12.0, J_3 = 1.0 Hz, 1H), 3.56 (dd, J_1 = 15.5, J_2 = 2.5 Hz, 1H), 3.83 (s, 3H), 3.84 (dd, J_1 = 12.0, J_2 = 2.5 Hz, 1H), 4.90 (d, J = 9.0 Hz, 1H), 5.52 (d, J = 9.0 Hz, 1H), 6.87 (d, J = 7.5 Hz, 1H), 6.97 (s, 1H), 7.11 (t, J = 7.5 Hz, 1H), 7.21 (d, J = 7.5 Hz, 1H), 8.44 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 18.4, 25.8, 33.7, 52.4, 61. 9, 62.2, 109.4, 113.0, 117.8, 121.51, 121.53, 125.0, 127.4, 134.4, 137.0, 137.4, 174.6; IR (nujol, cm^{-1}) 2923, 2853, 1726; mp: 133−134 °C (*n*-hexane/DCM); Anal. Calcd for $C_{17}H_{20}N_2O_2$ (284.15): C, 71.81; H, 7.09; N, 9.85. Found: C, 72.02; H, 7.16; N, 9.76. The chemical−physical data are according to the literature.[7h]

An analytical sample of the intermediate imine **7** was purified by flash chromatography (EtOAc) for the characterization. MS (ESI) 411 $[M + 1]^+$; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.38 (s, 12H), 1.59 (s, 3H), 1.81 (s, 3H), 3.25(dd, J_1 = 14.0, J_2 = 9.5 Hz, 1H), 3.75 (s, 3H), 3.96 (dd, J_1 = 14.0, J_2 = 4.0 Hz, 1H), 4.13 (dd, J_1 = 9.5, J_2 = 4.0 Hz, 1H), 5.98 (d, J = 9.5 Hz, 1H), 6.98 (d, J = 2.0 Hz, 1H), 7.18 (t, J = 7.5 Hz, 1H), 7.45 (t, J = 7.5 Hz, 1H), 7.56 (d, J = 9.5 Hz, 1H), 7.69 (d, J = 7.5 Hz, 1H), 8.17 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 18.5, 24.6, 24.9, 26.6, 29.7, 51.9, 73.7, 83.7, 112.9, 114.2, 120.9, 125.0, 126.0, 129.0, 136.3, 147.6, 148.1, 162.1, 173.1 (carbon adjacent to boron was not observed); IR (nujol, cm^{-1}) 1735, 1655. The compound is too unstable to obtain a good elemental analysis.

(1*S*,3*S*)-1-(2-Methylprop-1-enyl)-2,3,4,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indol-2-ium-3-carboxylate (1a). A solution of **8a** (35 mg, 0.12 mmol) in 3.8 mL of 4% KOH in MeOH−H_2O (2:1) was stirred for 45 min at room temperature. The solution was concentrated to half volume and purified by flash chromatography (CH_2Cl_2/MeOH/NH_3 90:9:1) to give 26 mg (0.096 mmol) of **1a** as a white solid. Yield 81%. TLC (CH_2Cl_2:MeOH:NH_4OH/75:25:1) R_f = 0.16 (UV, *p*-anisaldehyde, ninhydrin); MS (ESI) 271 $[M + H]^+$; 269 $[M - H]^+$; ^{1}H NMR (200 MHz, CD_3OD) δ 1.96 (s, 3H), 1.99 (s, 3H), 3.21 (ddd, J_1 = 16.5, J_2 = 12.0, J_3 = 1.5 Hz, 1H), 3.85 (dd, J_1 = 16.5, J_2 = 3.5 Hz, 1H), 4.13 (dd, J_1 = 12.0, J_2 = 3.5 Hz, 1H), 5.57 (d, J_2 = 10.0 Hz, 1H), 5.63 (d, J_2 = 10.0 Hz, 1H), 6.85 (d, J = 8.0 Hz,1H),7.12 (t, J = 8.0 Hz,1H), 7.25 (s, 1H), 7.37 (d, J = 8.0 Hz, 1H); ^{13}C NMR (50 MHz, CD_3OD) δ 17.1, 24.6, 27.3, 59.9, 109.5, 111.3, 117.6, 120.8, 120.9, 122.8, 124.0, 127.4, 137.3, 141.6, 174.3. The chemical−physical data are according to the literature.[7h]

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Tables 1−5 and copies of ^{1}H NMR and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: giovanni.piersanti@uniurb.it.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We would like to thank Prof. Gilberto Spadoni, University of Urbino, for useful discussions.

■ REFERENCES

(1) (a) Li, S.; Finefield, J. M.; Sunderhaus, J. D.; McAfoos, T. J.; Williams, R. M.; Sherman, D. H. *J. Am. Chem. Soc.* **2012**, *134*, 788. (b) Lindel, T.; Marsch, N.; Adla, S. K. *Top. Curr. Chem.* **2012**, *309*, 67. (c) Li, S.-M. *Nat. Prod. Rep.* **2010**, *27*, 57.

(2) Williams, R. M.; Stocking, E. M.; Sanz-Cervera, J. F. *Top. Curr. Chem.* **2000**, *209*, 97.

(3) (a) Robbers, J. E.; Floss, H. G. *Tetrahedron Lett.* **1969**, *10*, 1857. (b) King, G. S.; Mantle, P. G.; Szczyrbak, C. A.; Waight, E. S. *Tetrahedron Lett.* **1973**, *14*, 215. (c) King, G. S.; Waight, E. S.; Mantle, P. G.; Szczyrbak, C. A. *J. Chem. Soc., Perkin Trans. 1* **1977**, 2099. (d) Robbers, J. E.; Otsuka, H.; Floss, H. G.; Arnold, E. V.; Clardy, J. *J. Org. Chem.* **1980**, *45*, 1117.

(4) (a) Kozlovskii, A. G.; Soloveva, T. F.; Sakharobskii, V. G.; Adanin, V. M. *Dokl. Akad. Nauk SSSR* **1981**, *260*, 230. For its synthesis: (b) Yamada, F.; Makita, Y.; Suzuki, T.; Somei, M. *Chem. Pharm. Bull.* **1985**, *33*, 2162. (c) Hegedus, L. S.; Toro, J. L.; Miles, W. H.; Harrington, P. J. *J. Org. Chem.* **1987**, *52*, 3319. (d) Yamada, K.; Namerikawa, Y.; Haruyama, T.; Miwa, Y.; Yanada, R.; Ishikura, M. *Eur. J. Org. Chem.* **2009**, 5752. (e) Brak, K.; Ellman, J. A. *Org. Lett.* **2010**, *12*, 2004.

(5) For a nice discussion of indole-based natural products that contain tricyclic benzo[*cd*]indole cores, see: Greshock, T. J.; Funk, R. L. *J. Am. Chem. Soc.* **2006**, *128*, 4946.
(6) (a) May, J. A.; Stoltz, B. M. *Tetrahedron* **2006**, *62*, 5262. (b) May, J. A.; Zeidan, R. K.; Stoltz, B. M. *Tetrahedron Lett.* **2003**, *44*, 1203. (c) Krishnan, S.; Bagdanoff, J. T.; Ebner, D. C.; Ramtohul, Y. K.; Tambar, U. K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2008**, *130*, 13745.
(7) (a) Yokoyama, Y.; Matsumoto, T.; Murakami, Y. *J. Org. Chem.* **1995**, *60*, 1486. (b) Yokoyama, Y.; Hikawa, H.; Mitsuhashi, M.; Uyama, A.; Murakami, Y. *Tetrahedron Lett.* **1999**, *40*, 7803. (c) Yokoyama, Y.; Hikawa, H.; Mitsuhashi, M.; Uyama, A.; Hiroki, Y.; Murakami, Y. *Eur. J. Org. Chem.* **2004**, 1244. (d) Shinohara, H.; Fukuda, T.; Iwao, M. *Tetrahedron* **1999**, *55*, 10989. (e) Ku, J.-M.; Jeong, B.-S.; Jew, S.-s.; Park, H.-g. *J. Org. Chem.* **2007**, *72*, 8115. (f) Xu, Z.; Li, Q.; Zhang, L.; Jia, Y. *J. Org. Chem.* **2009**, *74*, 6859. (g) Xu, Z.; Li, Q.; Zhang, L.; Jia, Y. *J. Org. Chem.* **2010**, *75*, 6316. (h) Xu, Z.; Hu, W.; Liu, Q.; Zhang, L.; Jia, Y. *J. Org. Chem.* **2010**, *75*, 7626. (i) Liu, Q.; Li, Q.; Ma, Y.; Jia, Y. *Org. Lett.* **2013**, *15*, 4528. (j) Harrington, P. J.; Hegedus, L. S.; McDaniel, K. F. *J. Am. Chem. Soc.* **1987**, *109*, 4335.
(8) For general reviews, see: (a) Tian, P.; Dong, H.-Q.; Lin, G.-Q. *ACS Catal.* **2012**, *2*, 95. (b) Marques, C. S.; Burke, A. J. *ChemCatChem* **2011**, *3*, 635. (c) Partyka, D. V. *Chem. Rev.* **2011**, *111*, 1529. For recent selected examples to activated aldimines, see: (d) Tokunaga, N.; Otomaru, Y.; Okamoto, K.; Ueyama, K.; Shintani, R.; Hayashi, T. *J. Am. Chem. Soc.* **2004**, *126*, 13584. (e) Weix, D. J.; Shi, Y.; Ellman, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 1092. (f) Jagt, R. B. C.; Toullec, P. Y.; Geerdink, D.; de Vries, J. G.; Feringa, B. L.; Minnaard, A. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 2789. (g) Wang, Z.-Q.; Feng, C.-G.; Xu, M.-H.; Lin, G.-Q. *J. Am. Chem. Soc.* **2007**, *129*, 5336. (h) Trincado, M.; Ellman, J. A. *Angew. Chem., Int. Ed.* **2008**, *47*, 5623. (i) Cui, Z.; Yu, H.-J.; Yang, R.-F.; Gao, W.-Y.; Feng, C.-G.; Lin, G.-Q *J. Am. Chem. Soc.* **2011**, *133*, 12394. For an example of Rh(I)-catalyzed 1,2-addition of sodium tetraphenylborate to unactivated imines, see: (j) Ueura, K.; Miyamura, S.; Satoh, T.; Miura, M. *J. Organomet. Chem.* **2006**, *691*, 2821.
(9) For selected recent work on the reaction of 2-amidoacrylates with simple indoles, see: (a) Angelini, E.; Balsamini, C.; Bartoccini, F.; Lucarini, S.; Piersanti, G. *J. Org. Chem.* **2008**, *73*, 5654. (b) Repka, L. M.; Ni, J.; Reisman, S. E. *J. Am. Chem. Soc.* **2010**, *132*, 14418. (c) Lucarini, S.; Bartoccini, F.; Battistoni, F.; Diamantini, G.; Piersanti, G.; Righi, M.; Spadoni, G. *Org. Lett.* **2010**, *12*, 3844. (d) Righi, M.; Bartoccini, F.; Lucarini, S.; Piersanti, G. *Tetrahedron* **2011**, *67*, 7923. (e) Kieffer, M. E.; Repka, L. M.; Reisman, S. E. *J. Am. Chem. Soc.* **2012**, *134*, 5131. (f) Lucarini, S.; Mari, M.; Piersanti, G.; Spadoni, G. *RSC Adv.* **2013**, *3*, 19135. (g) Ni, J.; Wang, H.; Reisman, S. E. *Tetrahedron* **2013**, *69*, 5622.
(10) (a) Wang, H.; Ganesan, A. *Tetrahedron Lett.* **1997**, *38*, 4327. (b) Bailey, P. D.; Cochrane, P. J.; Lorenz, K.; Collier, I. D.; Pearson, D. P. J.; Rosair, G. M. *Tetrahedron Lett.* **2001**, *42*, 113. (c) Wang, H.; Usui, T.; Osada, H.; Ganesan, A. *J. Med. Chem.* **2000**, *43*, 1577.
(11) Recent methods delivering other types of 3,4-fused tricyclic indole frameworks: (a) Shan, D.; Gao, Y.; Jia, Y. *Angew. Chem., Int. Ed.* **2013**, *52*, 4902. (b) Park, I.-K.; Park, J.; Cho, C.-G. *Angew. Chem., Int. Ed.* **2012**, *51*, 2496. (c) Cheng, D.-J.; Wu, H.-B.; Tian, S.-K. *Org. Lett.* **2011**, *13*, 5636. (d) Schönherr, H.; Leighton, J. L. *Org. Lett.* **2012**, *14*, 2610. (e) Xu, Q.-L.; Dai, L.-X.; You, S.-L. *Chem. Sci.* **2013**, *4*, 97. (f) Mari, M.; Bartoccini, F.; Piersanti, G. *J. Org. Chem.* **2013**, *78*, 7727. (g) Caruana, L.; Fochi, M.; Franchini, M. C.; Ranieri, S.; Mazzanti, A.; Bernardi, L. *Chem. Commun.* **2014**, *50*, 445.
(12) Bartolucci, S.; Bartoccini, F.; Righi, M.; Piersanti, G. *Org. Lett.* **2012**, *14*, 600.
(13) (a) Petasis, N. A.; Akritopoulou, I. *Tetrahedron Lett.* **1993**, *34*, 583. (b) Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc.* **1997**, *119*, 445. (c) Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc.* **1998**, *120*, 11798.
(14) The Petasis reaction has been reported to be strongly dependent on the solvent. For the best reaction conditions for aryl pinacolboronic esters, see: Jourdan, H.; Gouhier, G.; Van Hijfte, L.; Angibaud, P.; Piettre, S. R. *Tetrahedron Lett.* **2005**, *46*, 8027.
(15) However, the classical Petasis reaction is restricted to activated aldehydes (e.g., glyoxalates) or aldehydes bearing a suitable boron-activating group, typically a free hydroxyl group (e.g., α-hydroxyaldehydes or salicylaldehyde). For a recent comprehensive review, see: Candeias, N. R.; Montalbano, F.; Cal, P. M. S. D.; Gois, P. M. P. *Chem. Rev.* **2010**, *110*, 6169 and references therein.
(16) (a) Liu, G. X.; Lu, X. Y. *J. Am. Chem. Soc.* **2006**, *128*, 16504. (b) Sarpong, R.; Gallego, G. L *Chem. Sci.* **2012**, *3*, 1338. (c) Low, D. W.; Pattison, G.; Wieczysty, M. D.; Churchill, G. H.; Lam, H. *Org. Lett.* **2012**, *14*, 2548. (d) For a nice discussion on the reactivity of arylpalladium(II) species, see: Miura, M.; Nomura, M. *Top. Curr. Chem.* **2002**, *219*, 211.
(17) (a) Tokunaga, N.; Otomaru, Y.; Okamoto, K.; Ueyama, K.; Shintani, R.; Hayashi, T. *J. Am. Chem. Soc.* **2004**, *126*, 13584. (b) Otomaru, Y.; Tokunaga, N.; Shintani, R.; Hayashi, T. *Org. Lett.* **2005**, *7*, 307.
(18) (a) Itooka, R.; Iguchi, Y.; Miyaura, N. *Chem. Lett.* **2001**, *30*, 722. (b) Hayashi, T.; Takahashi, M.; Takaya, Y.; Ogasawara, M. *J. Am. Chem. Soc.* **2002**, *124*, 5052.
(19) Diene complexes exhibit higher catalytic activity than chiral Rh phosphine complexes; see: (a) Sakuma, S.; Miyaura, N. *J. Org. Chem.* **2001**, *66*, 8944. (b) Itooka, R.; Iguchi, Y.; Miyaura, N. *J. Org. Chem.* **2003**, *68*, 6000.
(20) For more information concerning the initial reaction optimization, see the Supporting Information.
(21) However, we think that the *cis* diastereoisomer is more stable than the *trans* compound, because the various nonbonded (trans-annular) interactions associated with placing substituents around a fairly constrained seven-membered ring are apparently minimized.
(22) For appropriate discussion about regioselective prenyl transfer reactions, see: (a) Westermaier, M.; Mayr, H. *Org. Lett.* **2006**, *8*, 4791. (b) Luk, L. Y. P.; Qian, Q.; Tanner, M. E. *J. Am. Chem. Soc.* **2011**, *133*, 12342. (c) Schwarzer, D. D.; Gritsch, P. J.; Gaich, T. *Angew. Chem., Int. Ed.* **2012**, *51*, 11514. (d) Rudolf, J. D.; Wang, H.; Poulter, C. D. *J. Am. Chem. Soc.* **2013**, *135*, 1895. (e) Liebhold, M.; Li, S.-M. *Org. Lett.* **2013**, *15*, 5834−5837.
(23) (a) Darses, S.; Michaud, G.; Genêt, J.-P. *Eur. J. Org. Chem.* **1999**, 1875. (b) Körner, C.; Starkov, P.; Sheppard, T. D. *J. Am. Chem. Soc.* **2010**, *132*, 5968. (c) Adamczyk-Woźniak, A.; Madura, I.; Velders, A. H.; Sporzyński, A. *Tetrahedron Lett.* **2010**, *51*, 6181.
(24) Tarzia, G.; Balsamini, C.; Spadoni, G.; Duranti, E. *Synthesis* **1988**, *7*, 514.