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Pd(0)-Catalyzed Tandem Deprotection/Cyclization of Tetrahydro-β-carbolines on Allenes: Application to the Synthesis of Indolo[2,3-*a*]quinolizidines

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Supporting Information

ABSTRACT: The pallado-catalyzed tandem deprotection/cyclization reaction of enantioenriched *N*-allyl tetrahydro-β-carbolines on allenes is described. The first step generates in situ a deprotected tetrahydro-β-carboline, which then undergoes a cyclization on the allene function via an intermediate π-allyl Pd(II) derivative. This reaction results in the synthesis of various chiral indolic tetracycles (mainly indolo[2,3*a*]-quinolizidine derivatives) presenting a vinyl function.

The indole ring is the most abundant nitrogen heterocycle found in nature and is considered a privileged scaffold for the discovery of novel bioactive compounds.[1] It is involved in thousands of natural products, presenting a wide panel of biological activities.[2] It is thus not surprising that the synthesis of such compounds has been the object of deep attention from chemists and has led to the development of a rich chemistry.[1,3] Indolo[2,3*a*]quinolizidines are attractive targets found in many natural products[4] for which in most cases a diastereoselective Pictet−Spengler reaction[5] is often the key reaction of the synthesis. Enantioselective organocatalyzed Pictet−Spengler reactions have been developed using chiral thioureas[6] or chiral phosphoric acids.[7] However, such reactions are often limited to *N*-acylative reactions, to *gem*-diester tryptamines,[7b] or to *N*-protected tryptamines.[7c−e] Smart use of this *N*-protecting group led to elegant total syntheses,[1,6b,8] while in the vast majority of the other cases it has to be removed for further functionalization of the nitrogen and synthetically useful applications. We assumed that the *N*-allyl protecting group would be suitable for (1) the enantioselective formation of tetrahydro-β-carbolines bearing a pendant allene function and (2) a concomitant Pd-catalyzed deprotection/addition of the amine on the allene affording indolo[2,3*a*]quinolizidines functionalized by a vinyl function, suitable for further transformations. Herein, we report our efforts directed to the synthesis of chiral indolo[2,3-*a*]quinolizidines from tetrahydro-β-carbolines via this tandem procedure.

An initial experiment was performed by reaction of known allenal **2a** (obtained from the corresponding alcohol **1a**)[9] with *N*-allyltryptamine **3a** catalyzed by diphenyl phosphate, yielding the tetrahydro-β-carboline **5a** (Table 1, eq i). The tandem pallado-catalyzed deprotection/cyclization was then investigated (Table 1, eq ii). *N*,*N*-Dimethylbarbituric acid **6** (DMBA) was chosen as the allyl scavenger[10] to trigger the *N*-allyl deprotection. The resulting intermediate free amine is then expected to add to the allene moiety via a transient π-allyl Pd(II) intermediate.[11] Reaction of racemic tetrahydro-β-carboline **5a** with DMBA **6** in CH_2Cl_2 and in the presence of 1 mol % of $Pd(PPh_3)_4$ afforded the indolo[2,3-*a*]quinolizidine **7a** in 52% yield with moderate diastereoselectivity (Table 1, entry 1). Addition of benzoic acid did not favor the reaction as expected[11i] (Table 1, entry 2), whereas more diluted conditions afforded at 40 °C the product in 88% yield with a good 84/16 diastereoselectivity (Table 1, entry 3) in favor of the *syn* product,[12] although it was necessary to increase the catalyst loading to ensure cyclization (Table 1, entry 4). The palladium source and the phosphine ligand influence were studied with no improvement (Table 2, entries 5−8). Finally, the replacement of the CH_2Cl_2 by either THF, toluene, DMF, or DMSO lowered both the diastereoselectivity and yield (Table 1, entries 9−12). These experiments validate the global strategy and show that a good diastereocontrol is possible. The next step was consequently to transpose this strategy to asymmetric compounds, the key point being the applicability of the *N*-allyl protecting group and the 1,*n*-allenals to Brønsted acid-catalyzed Pictet−Spengler reaction.

The catalytic enantioselective Pictet−Spengler reaction between *N*-allyltryptamine **3a** and 1,5-allenal **2a** was next studied using 5 mol % of both Binol-[7d] and Spinol-derived[7e] phosphoric acids **4a−e** (Table 2). In all cases, the reaction provided **5a** in high yields.[13] Among the catalysts used in the Binol series (Table 2, entries 1−3), **4c** furnished the best result (ee = 84%) (Table 2, entry 3). Catalyst **4d** provided compound **5a** in a disappointing 73% ee (Table 2, entry 4), whereas **4e** led to an excellent 91% ee (Table 2, entry 5). Decreasing the catalyst loading and the temperature (Table 2, entries 6 and 7) afforded the product in 91% ee and 94% ee, respectively.

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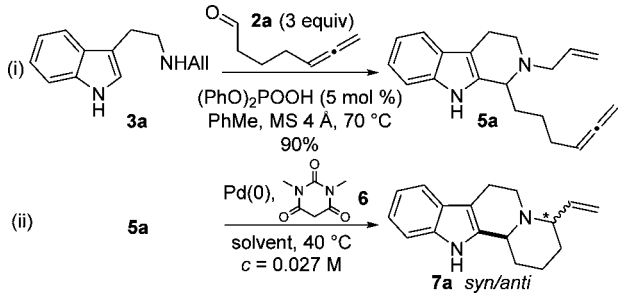
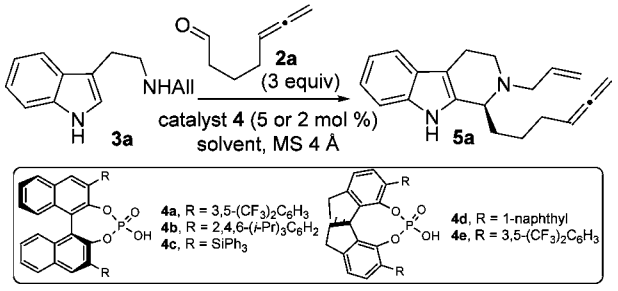
Table 1. Initial Attempts for the Pictet–Spengler Tandem Deprotection/Cyclization Sequence



entry	[Pd] (mol %)/additive (mol %)	solvent	dr[a] (*syn*/*anti*)	**7a**, yield[b] (%)
1	$Pd(PPh_3)_4$ (1)/no additive	CH_2Cl_2	71/29	52[c]
2	$Pd(PPh_3)_4$ (1)/PhCOOH (10)	CH_2Cl_2	66/34	39[c]
3	**$Pd(PPh_3)_4$ (5)**/no additive	**CH_2Cl_2**	**84/16**	**88**
4	$Pd(PPh_3)_4$ (1)/no additive	CH_2Cl_2	–	–[d]
5	$Pd_2(dba)_3$ (2.5)/PPh_3 (10)	CH_2Cl_2	60/40	15
6	$(allyl)_2Pd_2Cl_2$(2.5)/dppf (5.5)	CH_2Cl_2	86/24	74
7	Pd_2dba_3 (2.5)/(−)-DACH (5.5)	THF	–	–
8	Pd_2dba_3 (2.5)/(+)-DACH (5.5)	THF	–	–
9	$Pd(PPh_3)_4$ (5)/no additive	THF	65/35	71
10	$Pd(PPh_3)_4$ (5)/no additive	PhMe	61/39	68
11	$Pd(PPh_3)_4$ (5)/no additive	DMF	80/20	65
12	$Pd(PPh_3)_4$ (5)/no additive	DMSO	75/25	44

[a]Measured by ^{1}H NMR. [b]Isolated yields. [c]The reactions were performed at c = 0.27 M at 50 °C in Schlenk tubes. [d]The corresponding deprotected amine was obtained in 56% yield.

Table 2. Asymmetric Pictet–Spengler Reaction Optimization

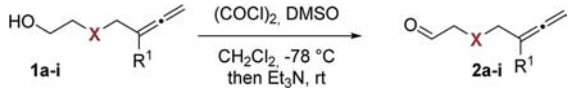


entry	**4** (mol %)	solvent	temp (°C)	ee[b] (%)	**5a**, yield[a] (%)
1	**4a** (5)	PhMe	70	74	97
2	**4b** (5)	PhMe	70	70	86
3	**4c** (5)	PhMe	70	84	quant
4	**4d** (5)	PhMe	70	73	69
5	**4e** (5)	PhMe	70	91	94
6	**4e** (2)	PhMe	70	91	86
7	**4e (2)**	**PhMe**	**30**	**94**	**88**
8	**4e** (2)	C_6H_6	30	94	87
9	**4e** (2)	THF	30	83	41
10	**4e** (2)	CH_2Cl_2	30	75	73

[a]Isolated yields. [b]Determined by chiral HPLC analysis.

Finally, benzene gave comparable results (Table 2, entry 8), whereas THF and dichloromethane dropped the ee to 83% and 75%, respectively (Table 2, entries 9 and 10). The catalyst **4e** was consequently chosen, and the scope of the reaction was further studied. Accordingly, various 1,*n*-allenols **1** were prepared by known methods[14] and readily oxidized to allenyl aldehydes **2**, obtained in essentially good yields, in some cases lowered by the high volatility of the compounds (Scheme 1). The chain length, the presence of a heteroatom, and the degree of substitution of the allene moiety were modulated, resulting in a small library of aldehydes **2** presenting good molecular diversity.

Scheme 1. Synthesis of 1,*n*-Allenals 2 from Alcohols 1



Asymmetric catalytic Pictet–Spengler reactions were performed by reaction of *N*-allyltryptamines **3a–c** with aldehydes **2a–i** in the presence of 2 mol % of the Spinol-derived catalyst **4e** (Table 3, entries 1–13). The corresponding tetrahydro-*β*-carbolines **5** were obtained in essentially good yields and excellent enantioselectivities (93–97% ee), demonstrating the low influence of the length, and/or functionalization of the side chain. Compound **5i** was obtained in low ee (Table 3, entry 9), likely explained by the bulk of the NBoc group. In sharp contrast, the aldehyde bearing an ether function furnished **5h** in an excellent 97% ee (Table 3, entry 8). Neither the substituent R^1 present on the tryptamine moiety nor the R^2 group of the allene did affect significantly the enantioselectivity or the yield of those reactions (Table 3, entries 10–13).

We then turned our attention to the pallado-catalyzed one-pot deprotection/cyclization process. The tetrahydro-*β*-carbolines **5a–m** were submitted to the optimized deprotection/cyclization conditions developed above. As expected, compounds **5a–c** underwent six-membered ring cyclization pathway that resulted in compounds **7a–c** in good yields and with diastereoselectivities in favor of the *syn* product (Table 3, entries 1–3).[15] In sharp contrast, indolo[2,3-*a*]pyrrolizidines **7d–f** resulting from five-membered ring cyclization were obtained mainly as *anti* compounds (Table 3, entries 4–6), though with lower diastereoselectivities. In those six last cases,

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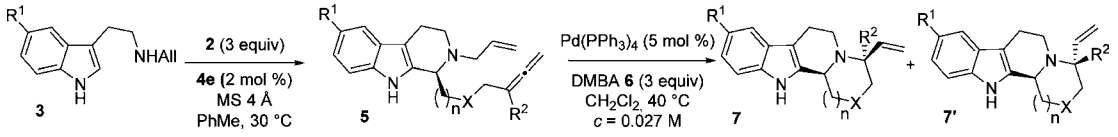
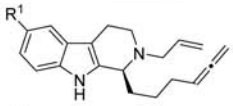
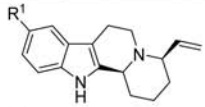
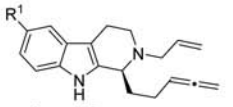
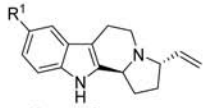
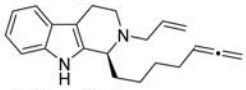
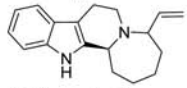
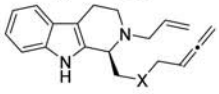
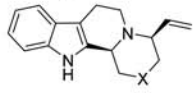
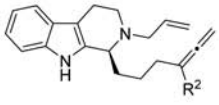
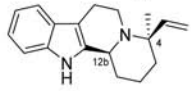
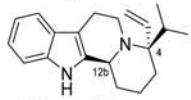
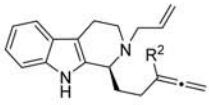
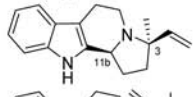
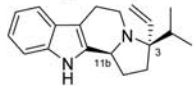
Table 3. Scope of the Asymmetric Pictet–Spengler Reactions and Pallado-Catalyzed Tandem Deprotection/Cyclization Reactions



entry	aldehyde, **2**	**5**	yield in **5**[a] (ee %)[b]	cyclized product, **7**[c]	yield in **7**[a]	**7**/**7'** (dr)
1	**2a**		**5a**, R^1 = H, 88% (94)		**7a-a'**, 79%	**7a**/**7a'**, R^1 = H (85/15)
2	**2a**		**5b**, R^1 = OMe, 88% (94)		**7b-b'**, 77%	**7b**/**7b'**, R^1 = OMe (85/15)
3	**2a**		**5c**, R^1 = F, 63% (93)		**7c-c'**, 70%	**7c**/**7c'**, R^1 = F (80/20)
4	**2b**		**5d**, R^1 = H, 92% (93)		**7d-d'**, 42%[d]	**7d**/**7d'**, R^1 = H (23/77)
5	**2b**		**5e**, R^1 = OMe, 90% (94)		**7e-e'**, 67%[d]	**7e**/**7e**, R^1 = OMe (21/79)
6	**2b**		**5f**, R^1 = F, 68% (93)		**7f-f'**, 79%[d]	**7f**/**7f'**, R^1 = F (27/73)
7	**2c**		**5g**, 87% (93)		**7g-g'**, 0%	**N/A**
8	**2d**		**5h**, X = O, 67% (97)		**7h-h'**, 37%[e]	**7h**/**7h'**, X= O (70/30)
9	**2e**		**5i**, X = NBoc, 65% (54)		**7i-i'**, 78%[f]	**7i**/**7i'**, X= NBoc (72/28)
10	**2f**		**5j**, R^2 = Me, 75% (94)		**7j-j'**, 82%	**7j**/**7j'**, R^2= Me (79 /21)
11	**2g**		**5k**, R^2 = *i*-Pr, 91% (95)		**7k-k'**, 70%	**7k**/**7k'**, R^2= *i*-Pr (7/93)
12	**2h**		**5l**, R^2 = Me, 83% (94)		**7l-l'**, 67%[d]	**7l**/**7l'**, R^2= Me (55/45)
13	**2i**		**5m**, R^2 = *i*-Pr, 88% (95)		**7m-m'**, 64%	**7m**/**7m'**, R^2= *i*-Pr (9 /91)

[a]Isolated yields. Each reaction was performed at least twice. [b]Enantiomeric excess was determined by chiral HPLC analysis. [c]The major diastereoisomer is represented in all cases. [d]The reaction was performed at c = 0.01 M. [e]The reaction was performed over 72 h. The yield is given for the pure *syn* diastereoisomer. [f]The reaction was performed on racemic **5i**.

the indole substituent R^1 did not show any strong influence. A 7-membered ring cyclization pathway did not occur from 1,7-aminoallene **5g** (Table 3, entry 3).

Cyclization from **5h** (X = O) furnished **7h** in a moderate 37% yield after 72 h of reaction (Table 3, entry 8).[16] It is likely that coordination of palladium to the ether function lowered the conversion and prolonged the reaction time. Compounds **7i–i'** featuring a piperazine moiety were obtained from **5i** (X = NBoc) as a 72/28 mixture of *syn*/*anti* diastereomers (Table 3, entry 9). Disubstituted allenes were next screened, leading to compounds **7j–j'** and **7k–k'** in excellent yields from **5j** (R^2 = Me) and **5k** (R^2 = *i*-Pr), respectively (Table 3, entries 10 and 11). In **7j**, diagnostic correlations in NOESY showed that the major diastereoisomer presents a *syn* relationship between H_{12b} and the methyl group. Interestingly, the stereodemanding isopropyl group induces a higher diastereoselectivity than the methyl group and **7k–k'** were obtained in an excellent 7/93 diastereoisomeric ratio. The same phenomenon was observed with the formation of compounds **7l–l'** and **7m–m'** (Table 3, entries 12 and 13). While the methyl substituted tetrahydro-*β*-carboline **5l** (R^2 = Me) led to **7l–l'** in very poor diastereoselectivity, **7m–m'** were obtained from **5m** (R^2 = *i*-Pr) in an excellent 9/91 diastereoselectivity in favor of the diastereoisomer presenting an *anti*-relationship between H_{11b} and the *i*-Pr group. In all cases, a better diastereocontrol is consequently reached by increasing the bulk of the R^2 group. It is worth noting that this set of reactions was successfully performed on deprotected indoles, for both atom economy considerations and with the aim of avoiding any potentially challenging deprotection, demonstrating the chemoselectivity of this process.

The mechanism of the one-pot deprotection/cyclization sequence is postulated to combine two catalytic cycles in which the Pd(0) and DMBA **6** play key roles (Scheme 2). Starting material **5a** enters in the first catalytic cycle and reacts with Pd(0) to generate a *π*-allyl species (i), which in turn is trapped by DMBA, liberating the free intermediate tetrahydro-*β*-carboline **8a** and the monoallyl DMBA.[17] The reaction of Pd(0) with the proton donor DMBA generates a Pd(II)-H (iii)[11e] that adds to the allene via hydropalladation, resulting in the formation of a *π*-allyl complex (iv). Subsequent intramolecular allylic substitution by the nucleophilic amine, then creates the second stereogenic center and ensures regeneration of the DMBA **6** and the formation of compound **7a**.

In conclusion, we have shown the applicability of the Brønsted acid-catalyzed Pictet–Spengler reaction to 1,*n*-allenals **2** and have obtained various tetrahydro-*β*-carbolines **5** bearing pendent allene function in good yield and ee's. The pallado-catalyzed tandem *N*-allyl deprotection/cyclization afforded numerous tetracyclic indolic compounds **7**, possessing various

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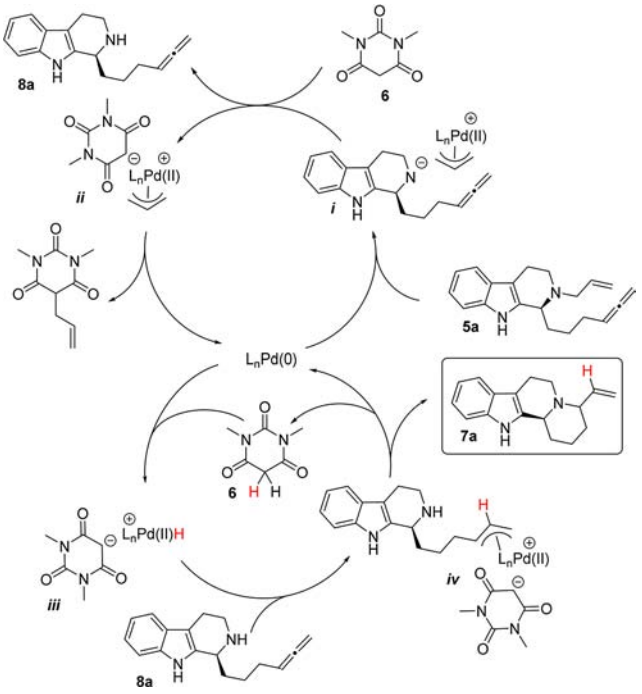
Scheme 2. Postulated Mechanism



patterns via a "self-relay catalysis"[18] type mechanism. This tandem process saves both a deprotection step, and the loss of a leaving group for the π-allyl formation (usually generated from an allyl acetate for instance rather than from an allene function) can be considered as a step- and atom-economical process for the synthesis of complex polycyclic indolic compounds. Efforts directed toward the synthesis of more functionalized products are in progress.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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