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Palladium Asymmetric Allylic Alkylation of Prochiral Nucleophiles: Horsfiline

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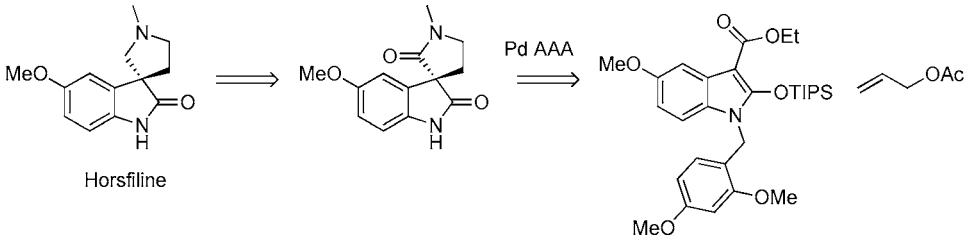
ABSTRACT



The asymmetric synthesis of the oxindole alkaloid horsfiline is described. A palladium-catalyzed asymmetric allylic alkylation (AAA) is used to set the spiro(pyrrolidine-oxindole) stereogenic center.

(−)-Horsfiline was first isolated in 1991 from the leaves of the *Horsfieldia superba* plant by Bodo and co-workers.[1] Biologically active alkaloids such as spirotryptostatin A and B, vincristine, and vinblastine have resulted in increased interest for oxindole natural products such as horsfiline. The unique spiro stereogenic center of horsfiline has challenged synthetic chemists to develop imaginative approaches toward its construction. As a result, there has been much synthetic effort toward horsfiline, resulting in several syntheses, three of which were asymmetric.[2] In 1994, Borschberg confirmed the absolute configuration of horsfiline through the synthesis of both enantiomers via a diastereoselective oxidative rearrangement of an (L)-tryptophan derivative.[2i] In 1999, Fuji et al. used a chiral auxiliary for nitro olefination of a substituted oxindole to set the stereochemistry at the quaternary chiral center.[2h] Palmisano and co-workers used an azomethine ylide cycloaddition reaction to form the pyrrolidine and subsequently formed the oxindole by intramolecular cleavage of the chiral auxiliary.[2f]

We envisioned constructing the stereogenic quaternary carbon via a palladium-catalyzed asymmetric allylic alkylation (AAA) employing oxindole as the nucleophile. The use of 3-aryl oxindoles in palladium AAA has been previously reported;[3] however, oxindole nucleophiles with substituents other than aryl groups have not been employed in this chemistry. In our proposed synthesis of horsfiline, an ester or aldehyde substituent in the 3 position would provide a stabilized, compatible nucleophile for palladium allylic alkylation (Scheme 1). The carbonyl group also provides a handle for further manipulation. Oxidative cleavage of the allyl group followed by reductive amination would introduce the nitrogen of the pyrrolidine. Cyclization via reductive amination or S_N2 substitution would complete the tricyclic system.

Initially, an aldehyde was installed in the 3 position of the oxindole following a known procedure using sodium methoxide and ethyl formate.[4] However, the product from

(1) Jossang, A.; Jossang, P.; Hadi, H.; Sevenet, T.; Bodo, B. *J. Org. Chem.* **1991**, *56*, 6527.

(2) (a) Murphy, J. A.; Tripoli, R.; Khan, T. A.; Mali, U. W. *Org. Lett.* **2005**, *7*, 3287. (b) Marti, C.; Carreira, E. M. *Eur. J. Org. Chem.* **2003**, *12*, 2209. (c) Lizos, D. E; Murphy, J. A. *Org. Biomol. Chem.* **2003**, *1*, 117. (d) Selvakumar, N.; Azhagan, A. M.; Srinivas, D.; Krishna, G. G. *Tetrahedron Lett.* **2002**, *43*, 9175. (e) Kumar, U.K.; Syam; Illa, H.; Junjappa, H. *Org. Lett.* **2001**, *3*, 4193. (f) Cravotto, G.; Giovenzana, G.; Pilati, T.; Sisti, M.; Palmisano, G. *J. Org. Chem.* **2001**, *66*, 8447. (g) Fischer, C.; Meyers, C.; Carreira, E. M. *Helv. Chim. Acta* **2000**, *83*, 1175. (h) Lakshmaiah, G.; Kawabata, T.; Shang, M.; Fuji, K. *J. Org. Chem.* **1999**, *64*, 1699. (i) Pellegrini, C.; Strässler, C.; Weber, M.; Borschberg, H. *Tetrahedron: Asymmetry* **1994**, *5*, 1979. (j) Bascop, S.; Sapi, J.; Laronze, J.; Levy, J. *Heterocycles* **1994**, *38*, 725. (k) Jones, K.; Wilkinson, J. *Chem. Commun.* **1992**, 1767. (l) Chang, M. Y.; Pai, C.-L.; Kung, Y.-H. *Tetrahedron Lett.* **2005**, *46*, 8463.

(3) Trost, B. M.; Fredericksen, M. U. *Angew. Chem., Int. Ed.* **2005**, *44*, 308.

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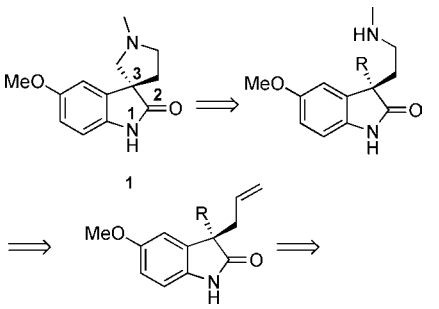
Scheme 1. Retrosynthetic Analysis of Horsfiline Using Pd AAA



the AAA reaction with allyl acetate was unstable to purification (Figure 1), resulting in deformylation.

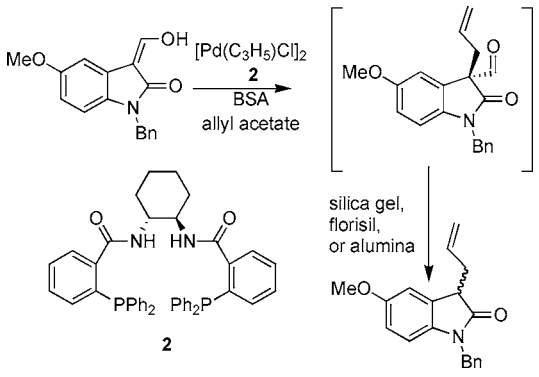
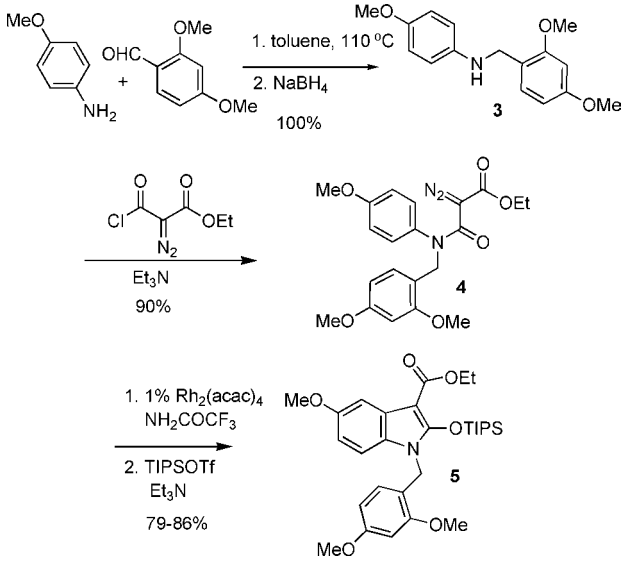


Figure 1. Deformylation of the initial Pd AAA Adduct

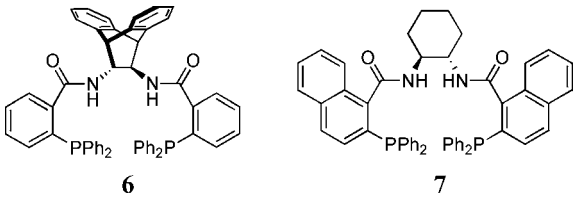
To avoid this decomposition, the aldehyde functionality was changed to an ester. A rhodium-catalyzed C−H insertion method developed by Padwa and co-workers was used to build the desired oxindole.[5] Refluxing *p*-anisidine with 2,4-dimethoxybenzaldehyde in toluene followed by reduction of the imine with sodium borohydride in methanol resulted in quantitative yield of the desired amine **3** (Scheme 2). Acylation with the acid chloride derivative of ethyl diazoacetate in the presence of triethylamine led to formation of amide **4** in 90% yield. Padwa discovered that $Rh_2(acac)_4$ led to β-lactam formation with diazoamides containing benzyl protecting groups, whereas the corresponding $Rh_2(CF_3CONH_2)_4$ catalyst led to oxindole formation. Therefore, Rh C−H insertion of amide **4**, followed by protection of the oxindole with TIPSOTf, resulted in 79−86% yield of **5** over two steps varying with the catalyst load from 1 to 3 mol %. Protection of the oxindole was necessary to avoid hydrolysis.[8]

With the protected oxindole in hand, the next step was the asymmetric allylic alkylation. A fluoride source was

Scheme 2. Synthesis of the Oxindole Core



added to generate the enolate anion nucleophile. Initially, CsF and ligand **2** were investigated with DME as the solvent, resulting in 77% ee. A significant improvement in ee occurred by switching the counterion from cesium to tetra-*n*-butylammonium. Various conditions were then screened for optimization (Table 1). Other Trost family ligands, such as **6** and **7**, resulted in lower enantioselectivity.



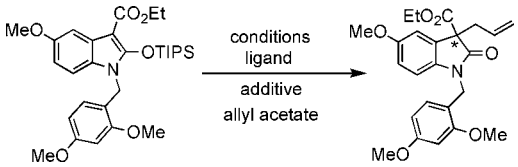
Surprisingly, lowering the temperature resulted in a slightly lower ee (74%). Changing the fluoride source to TBAT and the solvent to toluene increased the ee to 84%. Moreover, the major enantiomer could be purified to 98% ee with 69% yield by recrystallizing out the minor/major enantiomer pair using heptane or cyclohexane. Furthermore, the yield for this reaction was 96−100% even when the catalyst loading was dropped from 1% to 0.25% $[Pd(C_2H_5)Cl]_2$.

Oxidative cleavage of the allyl group was accomplished by catalytic osmium tetraoxide and *N*-methylmorpholine *N*-oxide (NMO) followed by cleavage of the diol with lead tetraacetate in methylene chloride (Scheme 3). Sodium periodate cleavage required somewhat aqueous conditions, which led to the formation of the five-membered lactone as a byproduct. The initial plan to close the pyrrolidine was to reduce the ester and aldehyde to the diol, followed by bis mesylation and S_N2 substitution with methylamine. Another route involved reductive amination of the aldehyde and reduction of the ester to the alcohol followed by intramolecular S_N2 substitution. However, all attempts to reduce the ester resulted in low yields of the alcohol with the major product resulting from loss of CO.

(4) (a) Wenkert, E.; Bose, A. K.; Reid, T. L. *J. Am. Chem. Soc.* **1953**, *75*, 5514. (b) Wenkert, E.; Bhattacharyya, N. K.; Reid, T. L.; Stevens, T. E. *J. Am. Chem. Soc.* **1956**, *78*, 797.

(5) Brown, D. S.; Elliott, M. C.; Moody, C. J.; Mowlem, T. J.; Marino, J. P.; Padwa, A. *J. Org. Chem.* **1994**, *59*, 2447.

Table 1. Pd AAA Reaction with Oxindole



entry	conditions	ligand	additive	ee (%)[a]
1	2.5% $[Pd(C_2H_5)Cl]_2$ DME, rt	7.5% **2**	CsF	77
2	2.5% $[Pd(C_2H_5)Cl]_2$ DME, rt	7.5% **6**	CsF	21
3	2.5% $[Pd(C_2H_5)Cl]_2$ DME, rt	7.5% **7**	CsF	62
4	2.5% $[Pd(C_2H_5)Cl]_2$ DME, 0−4 °C	7.5% **2**	CsF	74
5	2.5% $[Pd(C_2H_5)Cl]_2$ DCM, rt	7.5% **2**	CsF	61
6	2.5% $[Pd(C_2H_5)Cl]_2$ DME, rt	7.5% **2**	CsF	78
7	2.5% $[Pd(C_2H_5)Cl]_2$ toluene, rt	7.5% **2**	15% TBAT	81
8	1% $[Pd(C_2H_5)Cl]_2$ toluene, rt	3% **2**	15% TBAT	84
9	1% $[Pd(C_2H_5)Cl]_2$ toluene, rt	3% **2**	5% TBAT	79
10	0.25% $[Pd(C_2H_5)Cl]_2$ toluene, rt	1% **2**	15% TBAT	84

[a] 3.0 equiv of CsF was added. [b] Enantiomeric excess was determined by HPLC, AD column, 90% heptane/10% ^{i}PrOH.

Reductive amination of the aldehyde using $NaBH_3CN$ and the hydrochloride salt of methylamine resulted in the formation of the five-membered lactam in low yields (25%). Switching to a solution of methylamine in THF and acetic acid with $NaBH_3CN$ led to a number of products, which was dependent on the amount and order in which the acetic acid was added to the reaction mixture. Reductive amination in a two-step procedure, by first forming the imine in dry THF with $MgSO_4$ and then reducing with $NaBH_4$ in EtOH,[6] provided lactam **10** in 65% yield. The byproduct of the reaction was the lactam alcohol **11**, which presumably forms from cyclization of the hemiaminal onto the ester. Once lactam **10** was formed, only deprotection and a chemoselective reduction remained. The removal of the 2,4-dimethoxybenzyl group from the oxindole nitrogen was accomplished in 60% yield using DDQ in refluxing aqueous methylene chloride.

The chemoselective reduction of **12** proved to be a difficult challenge (Table 2). Initially, it was believed that 3 equiv of DIBAL-H would first deprotonate the secondary amide, protecting it from further reduction. However, it appeared that the oxindole was reduced preferentially under these conditions. Even by initially deprotonating with *n*BuLi and then adding DIBAL-H, the desired product was not observed.

Scheme 3. Ring Closure

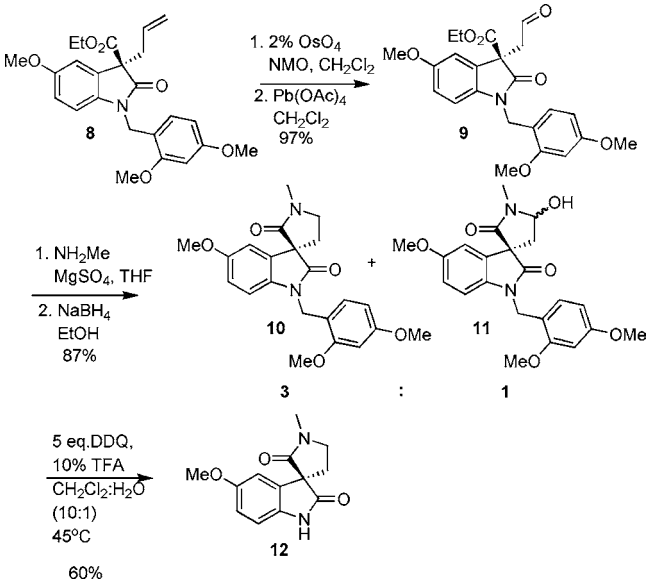
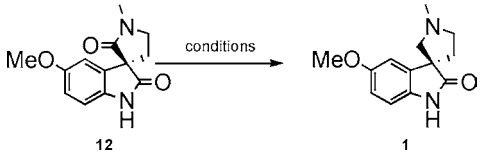


Table 2. Chemoselective Reduction



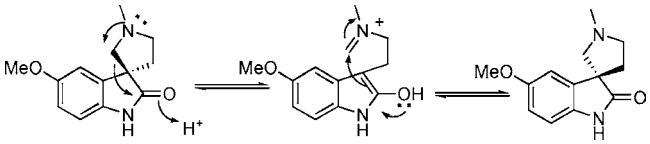
conditions	yield
3 equiv of DIBLAH, −78 °C	no reaction
3 equiv of DIBAL-H, −78 °C	reduced oxindole
1. *n*BuLi (1 equiv) 2. DIBAL (2 equiv), −78 °C→0 °C	no reaction
1. *n*BuLi (1 equiv) 2. DIBAL (2 equiv) 0 °C→rt	no reaction
1. *n*BuLi, −78 °C 2. DIBAL-H/*n*BuLi, 0 °C→rt	no reaction
BH_3 in THF, rt	no reaction
1. *n*BuLi/TIPSOTf 2. DIBAL-H (2 equiv)	only SM and silylated SM
1. *n*BuLi (1 equiv), −78 °C→0 °C 2. LAH soln ($2H^-$ equiv), −78 °C→0 °C	20%
1. NaH (30 min), rt 2. LAH soln ($2H^-$ equiv), −78 °C→0 °C	<5%
1. *n*BuLi, −78 °C for 30 min 2. LAHs soln ($4H^-$ equiv), −78 °C→0 °C	0%
1. *n*BuLi, −78 °C for 30 min 2. LAHs soln ($4H^-$ equiv), −78 °C→0 °C column (NH_3/MeOH/EtOAc)	32%
1. Ph_3CLi in DME 2. LAH soln ($2H^-$ equiv of DME), rt	48%

(6) Trost, B. M.; Godleski, S. A.; Genet, J. P. *J. Am. Chem. Soc.* **1978**, *100*, 3930.

Numerous reducing agents and conditions were applied to both lactams **10** and **12** in an attempt to successfully differentiate the two amides. Finally, it was found that the addition of 1 equiv of *n*BuLi, followed by 2 equiv of LAH in THF (from a freshly prepared and titrated solution), led to the desired product in 25−30% yield. Although the *n*BuLi was titrated before use,[7] low yields could have resulted from incomplete deprotonation, perhaps due to extraneous water. To avoid addition of excess base, a solution of tritylllithium in DME was prepared. This solution was then added to the solution of amide **12** in DME until a slight pink color remained indicating the complete deprotonation of the secondary amide. Upon addition of 2 hydride equiv of the LAH solution at 0 °C, horsfiline was formed in 45% yield.

It is noteworthy that horsfiline, along with other oxindole natural products, are prone to racemization via a retro-Mannich reaction that occurs in the presence of acid[8] (Scheme 4). Because this synthesis avoids revealing the

Scheme 4. Racemization Mechanism

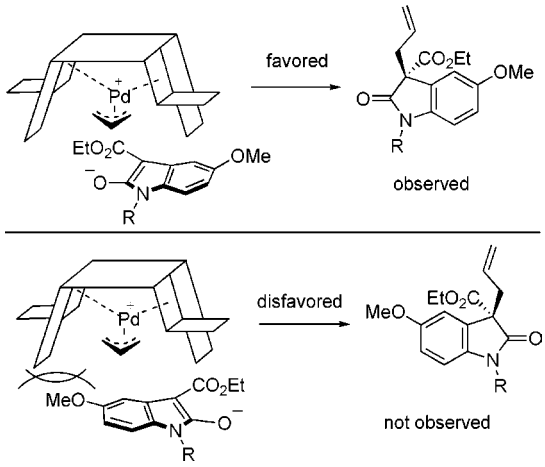


pyrrolidine until the last step, this problem is carefully avoided. Optical rotation verified this and also determined that the (+)-horsfiline enantiomer had been synthesized.

The enantiomer formed in the Pd AAA reaction can be rationalized by using the model previously described[9] (Scheme 5). The nucleophile prefers to approach underneath a flap and in an orientation that minimizes steric interactions with a nearby wall.

In conclusion, a concise total synthesis of horsfiline was achieved in eight steps and 11.1% yield starting from

Scheme 5. Rationalization of Stereochemistry



p-anisidine and 2,4-dimethoxybenzaldehyde using an oxindole nucleophile in the palladium asymmetric allylic alkylation. A new class of prochiral nucleophiles, 3-carbalkoxyoxindoles, prove to be good substrates for asymmetric allylic alkylation. This synthesis circumvents the problems associated with racemization of the natural product by only exposing the pyrrolidine ring to a chemoselective reduction in the final step of the synthesis.

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Supporting Information Available: Full experimental details and tabulated NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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