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Highly Enantioselective Intramolecular Cyanoamidation: (+)-Horsfiline, (−)-Coerulescine, and (−)-Esermethole

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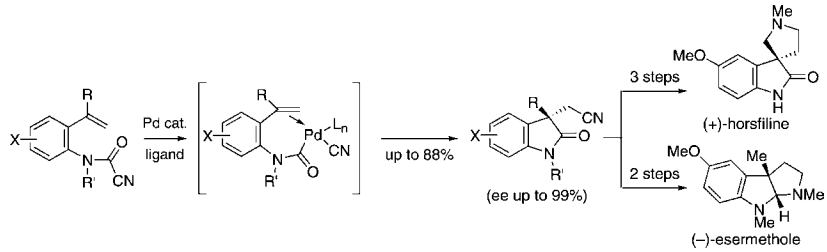
ABSTRACT



The first asymmetric cyanoamidation with synthetically useful enantioselectivity (ee up to 99%) to produce 3,3-disubstituted oxindoles is reported. Palladium catalysts with chiral phosphoramidite ligands activate the cyanoformamide C−CN bond, which is subsequently functionalized with a tethered alkene to give all-carbon quaternary stereocenters. The use of the *N,N*-(*i*-Pr)$_2$ derivative of octahydro-MonoPhos allowed the production of oxindoles with high enantioselectivities. Cyanoformamides bearing free N−H groups are now tolerated, potentially allowing protecting-group-free synthesis. Oxindole products of cyanoamidation are rapidly transformed into (+)-horsfiline, (−)-coerulescine, and (−)-esermethole.

Carbon−carbon σ bond (C−C) activation and functionalization of unstrained bonds is a burgeoning strategy for organic synthesis.[1] Much of the recent work in this area has focused on *aryl* nitriles, and independent reports of activation of organonitriles (C−CN) and asymmetric alkene cyanoarylation highlights this new strategy's potential in organic synthesis.[2] Less well developed is the catalytic activation of *cyanoformamide* C−CN bonds. These easy-to-prepare functional groups readily undergo C−C activation and allow the addition of amide and nitrile functional groups across alkenes or alkynes (cyanoamidation).[3] While our study was underway,[4] Takemoto reported a similar asymmetric cyanoamidation obtaining a maximum ee of 86% for oxindoles.[5]

The synthetic potential of cyanoamidation for preparing indole alkaloids bearing all-carbon quaternary stereocenters[6] (Figure 1) led us to continue pursuing conditions with synthetically useful enantioselectivities. We now report that cyanoamidation reactions can achieve enantioselectivities in *up to 99%* in the construction of all-carbon quaternary stereocenters, and

(1) Reviews: (a) Nájara, C.; Sansano, J. M. *Angew. Chem., Int. Ed.* **2009**, *48*, 2452. (b) Park, Y. J.; Park, J.-W.; Jun, C.-H. *Acc. Chem. Res.* **2008**, *41*, 222. (c) Neças, D.; Kotora, M. *Curr. Org. Chem.* **2007**, *11*, 1566. (d) Murakami, M.; Eto, Y. In *Activation of Unreactive Bonds and Organic Synthesis*; Murai, S., Ed.; Springer-Verlag: New York, 1999; p 97.

(2) Arylnitriles: (a) Watson, M. P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2008**, *130*, 12594. (b) Nakao, Y.; Ebata, S.; Yada, A.; Hiyama, T.; Ikawa, M.; Ogoshi, S. *J. Am. Chem. Soc.* **2008**, *130*, 12874.

(3) (a) Kobayashi, Y.; Kamisaki, H.; Takeda, H.; Yasui, Y.; Yanada, R.; Takemoto, Y. *Tetrahedron* **2007**, *63*, 2978. (b) Kobayashi, Y.; Kamisaki, H.; Yanada, R.; Takemoto, Y. *Org. Lett.* **2006**, *8*, 2711.

(4) Our work was initiated in the Fall of 2007 and a portion of this study was previously disclosed: Reddy, V. J.; Douglas, C. J. *Abstracts of Papers*, 238th National Meeting of the American Chemical Society, Aug 16−20, 2009; American Chemical Society: Washington, DC, 2009; ORGN 669.

(5) Yasui, Y.; Kamisaki, H.; Takemoto, Y. *Org. Lett.* **2008**, *10*, 3303.

(6) Reviews: (a) Trost, B. M.; Jiang, C. *Synthesis* **2006**, 369. (b) Christoffers, J.; Baro, A., Eds. *Quaternary Stereocenters*; Wiley-VCH Verlag GmbH & Co. KGaA : Weinheim, Germany, 2005. (c) Douglas, C. J.; Overman, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5363.

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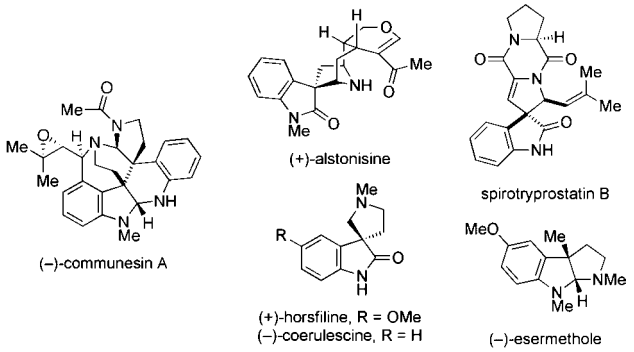
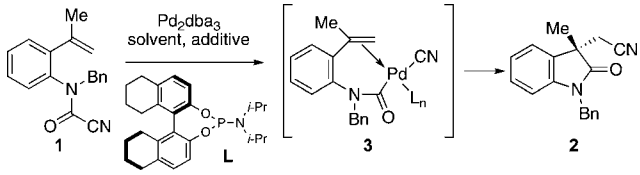


Figure 1. Quaternary carbon-bearing indole alkaloids.

we report demonstrative syntheses of (+)-horsfiline, (−)-coerulescine, and (−)-esermethole with high enantioselectivity.

Our laboratory independently observed that catalytic Pd_2dba_3, phosphoroamidite ligands, Lewis basic additives (HMPA, NMP, DMPU),[7] and solvents THF or decalin cyclized cyanoformamide **1** to oxindole **2**, presumably via intermediate **3** (Table 1).

Table 1. Optimization of Asymmetric Cyanoamidation[a]



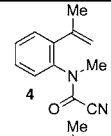
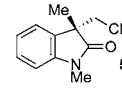
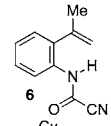
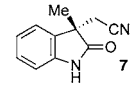
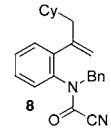
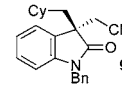
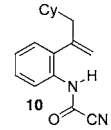
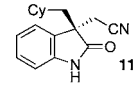
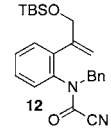
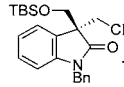
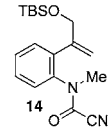
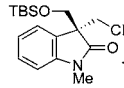
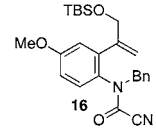
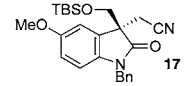
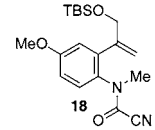
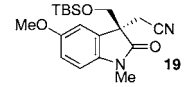
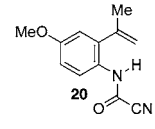
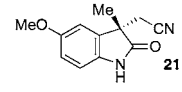
entry	solvent	additive	yield	ee[b]
1	THF	NMP	68%	90%
2[c]	THF	DMPU	72%	94%
3	THF	HMPA	64%	91%
4	decalin	NMP	66%	89%
5	decalin	DMPU	68%	95%
6[d]	THF	DMPU	70%	86%

[a] Pd_2dba_3 (2 mol %), **L** (16 mol %), 100 °C. [b] Determined by HPLC (Chiralcel OD-H, *n*-hexane:IPA (9:1), $\lambda = 220$ nm) after column chromatography on silica gel. [c] Conditions in entry 2 were used for the remainder of the study. [d] **L** (8 mol %).

After examining the effects of the bidentate ligand BINAP and several commercially available monodentate phosphoramidites,[8] we concluded that commercially available ligands would only give oxindole **2** with enantiomeric excesses in up to 86−91%, only slightly better than the previous study.[5] Postulating that increasing ligand nitrogen substituent bulk and hydrogenating the BINOL backbone would improve selectivity, we prepared the *N*,*N*-(*i*-Pr)$_2$ derivative of octahydro-MonoPhos **L** in one step using the corresponding phosphorochloridite and amine.[9] To our delight, we were able to achieve enantiomeric excesses up to 94% using **L** with DMPU as an additive (entry 2). There was no longer a clear advantage in using decalin as solvent with **L**,[5] so we adopted THF as a more convenient solvent for the remainder of our study. Reducing the amount of ligand **L** to 8 mol % decreased enantioinduction from 94% to 86% (entry 6).

Using our optimized conditions (Table 1, entry 2), we explored the formation of other oxindoles (Table 2). Cyanoformamides were readily prepared from the corresponding amines, using either tetracyanoethylene oxide

Table 2. Enantioselective Preparation of Oxindoles[a]

entry	substrate	product	yield[b]	ee[c]
1			72%	88%
2			48%	82%
3			68%	98%
4			53%	94%
5			80%	97%
6			73%	94%
7			88%	99%
8			78%	98%
9			72%	98%

[a] Conditions: Pd_2dba_3 (2 mol %), **L** (16 mol %), DMPU (1 equiv), THF (0.25 M in cyanoformamide), 100 °C. [b] Yields of product determined after silica gel chromatography. [c] Determined by HPLC, absolute configuration assigned in analogy to **25** (Scheme 1).

(7) We do not yet understand the role of these additives in asymmetric cyanoamidation.

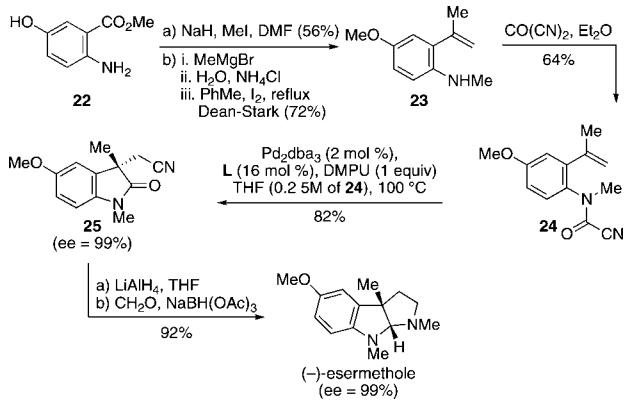
(8) Review on chiral monodentate phosphoramidites in asymmetric catalysis: van den Berg, M.; Minnaard, A. J.; Haak, R. M.; Leeman, M.; Schudde, E. P.; Meetsma, A.; Feringa, B. L.; de Vries, A. H. M.; Maljaars, C. E. P.; Willans, C. E.; Hyett, D.; Boogers, J. A. F.; Hubertus, H. J. W.; de Vries, J. G. *Adv. Synth. Catal.* **2003**, *345*, 308.

(9) Preparation of **L**: Zhang, F.-Y.; Chan, A. S. C. *Tetrahedron: Asymmetry* **1998**, *9*, 1179.

(TCEO) and dimethyl sulfide[10] or carbonyl cyanide.[11] Free N−H containing compounds gave comparable enantioselection to their protected congeners with only a moderate decrease in yield (entries 1−4). Additional protection/deprotection steps might offset decreases in yield associated with utilizing free N−H compounds in multistep synthesis. Alkyl and silyloxymethyl ether substituents on the alkene gave good yields and enantioselectivity (entries 3−9). Adding a methoxy group *para* to the cyanoformamide (entries 7−9) increased yield and enantioselectivity compared to their hydrogen counterparts (entries 2, 5, and 7). Notably, our use of chiral ligand **L** during the cyanoamidation of **4** and **12** (entries 1 and 5) gave us much higher enantiomeric excesses compared to previous work, which used a commercially available ligand[5] (88% vs 75%, and 97% vs 68%, respectively).

We assigned absolute stereochemistry of a cyanoamidation product via chemical correlation with (−)-esermethole (Scheme 1).[2b] Beginning with ester **22**,[12] two methyl groups

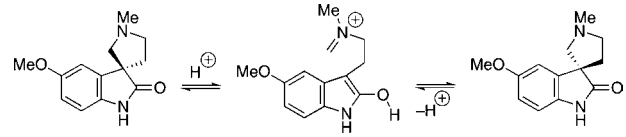
Scheme 1. Assignment of Absolute Configuration via Chemical Correlation with (−)-Esermethole



were installed via alkylation with MeI. The resulting product was subsequently converted to the alkene via attack with excess MeMgBr followed by dehydration to form **23**. After installation of the cyanoformamide with carbonyl cyanide,[11] cyanoamidation provided the corresponding oxindole **25** (82%, ee 99%). $LiAlH_4$ reduction to the pyrrolidinylindoline system and reductive amination installing the *N*-methyl group (92%, 2 steps) completed the correlation with (−)-esermethole. The stereochemistry of the remaining cyanoamidation products was assigned in analogy to oxindole **25**.

We highlighted the synthetic utility of cyanoamidation in the total syntheses of (+)-horsfiline and (−)-coerulescine.[13,14] A synthetic challenge of these alkaloids is the well-known, acid-promoted, racemization of the quaternary stereocenter via retro-Mannich/Mannich reactions (Scheme 2). Therefore,

Scheme 2. Acid-Promoted Retro-Mannich/Mannich Racemization of Horsfiline

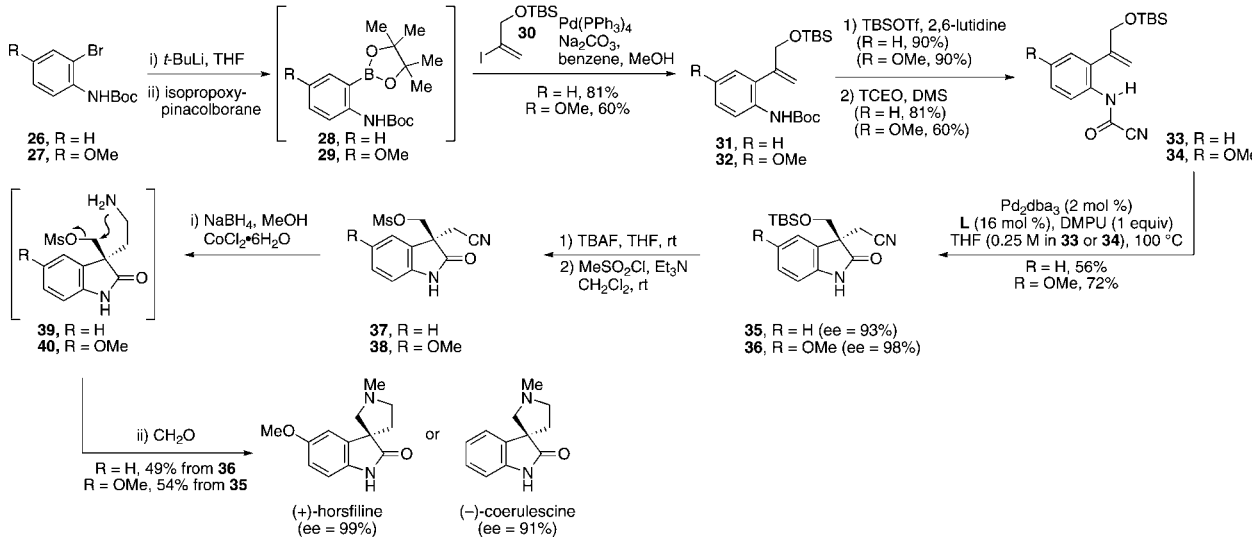


enantioselective routes require endgame strategies avoiding the use of acid. In our approach, we envisioned that mesylates, such as **37**/**38** (Scheme 3), could be converted to the desired alkaloids in a one-pot chemoselective nitrile reduction, which would cascade with cyclization and reductive amination via **39**/**40**.

To realize the above approach, we began our syntheses with the *N*-Boc-protected 2-bromoanilines **26**/**27**. Boc-protected bromoaniline **26** was produced in one step from the commercially available 2-bromoaniline, while **27** was available in two steps from commercially available 4-methoxyaniline.[15] Preparation of alkenes **31**/**32** proceeded with use of a Pd-catalyzed Suzuki coupling[16] of aryl boranes **28**/**29** and iodoalkene **30**.[17] Boc-deprotection with TBSOTf in 2,6-lutidine generated the free anilines in 90% yield for both substrates. We then prepared the corresponding cyanoformamides using TCEO and dimethyl sulfide[10] to give **33**/**34**. C−CN activation of cyanoformamides **35**/**36** provided the corresponding oxindoles bearing a C3 silyloxymethyl group with excellent enantioinduction. The silyl ethers (**35**/**36**) were deprotected with TBAF, and the resulting alcohols were converted to the corresponding mesylates (**37**/**38**). One-pot reductive cyclization to form the spirocyclic skeleton was readily accomplished by reaction of the nitriles with $NaBH_4$/$CoCl_2{\cdot}6H_2O$,[18,19] followed by reductive amination upon addition of CH_2O. We obtained (−)-coerulescine (ee 91%) and (+)-horsfiline (ee 99%) in 54% and 49% yield from silyl

(10) Linn, W. J. *Org. Synth.* **1969**, *49*, 103.
(11) Martin, E. L. *Org. Synth.* **1971**, *51*, 268.
(12) Prepared via Fischer esterification of the 5-hydroxyanthranillic acid according to: Lippa, B.; Kauffman, G. S.; Arcari, J.; Kwan, T.; Chen, J.; Hunderford, W.; Bhattacharya, S.; Zhao, X.; Williams, C.; Xiao, J.; Pustilnik, L.; Su, C.; Moyer, J. D.; Ma, L.; Campbell, M.; Steyn, S. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3081.
(13) Prior enantioselective syntheses: (a) Trost, B. M.; Brennan, M. K. *Org. Lett.* **2006**, *8*, 2027. (b) Cravotto, G.; Giovenzana, C.; Pilati, T.; Sisti, M.; Palmisano, G. *J. Org. Chem.* **2001**, *66*, 8447. (c) Lakshmaiah, G.; Kawabata, T.; Shang, M.; Fuji, K. *J. Org. Chem.* **1999**, *64*, 1699. (d) Pellegrini, C.; Strässler, C.; Weber, M.; Borschberg, H. *Tetrahedron: Asymmetry* **1994**, *5*, 1975.
(14) Syntheses of (±)-horsfiline or (±)-coerulescine: (a) Murphy, J. A.; Tripoli, R.; Khan, T. A.; Mali, U. W. *Org. Lett.* **2005**, *7*, 3287. (b) Chang, M. Y.; Pai, C.-L.; Kung, Y.-H. *Tetrahedron Lett.* **2005**, *46*, 8463. (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. S.; Ila, H.; Junjappa, H. *Org. Lett.* **2001**, *3*, 4193. (f) Fischer, C.; Meyers, C.; Carreira, E. M. *Helv. Chim. Acta* **2000**, *83*, 1175. (g) Bascop, S.; Sapi, J. A.; Laroze, J.; Levy, J. *Heterocycles* **1994**, *38*, 725. (h) Jones, K.; Wilkinson, J. *Chem. Commun.* **1992**, 1767.
(15) Jensen, T.; Pedersen, H.; Bang-Anderson, B.; Madsen, R.; Jørgensen, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 888–890.
(16) Conditions adapted from the following: Garg, N. K.; Sarpong, R.; Stoltz, B. M. *J. Am. Chem. Soc.* **2002**, *124*, 13179.
(17) Preparation of **30**: (a) Kamiya, N.; Chikami, Y.; Ishii, Y. *Synlett* **1990**, 675. (b) Nicolaou, K. C.; Li, Y.; Uesaka, N.; Koftis, T. V.; Vyskocil, S.; Ling, T.; Govindasamy, M.; Qian, W.; Bernal, F.; Chen, D. Y.-K. *Angew. Chem., Int. Ed.* **2003**, *42*, 3643.
(18) Satoh, T.; Suzuki, S.; Suzuki, Y.; Miyaji, Y.; Imai, Z. *Tetrahedron Lett.* **1969**, *10*, 4555.
(19) Zhu, J.; Quirion, J.-C.; Husson, H.-P. *J. Org. Chem.* **1993**, *58*, 6451.

Scheme 3. Total Synthesis of (+)-Horsfiline and (−)-Coerulescine



ethers **35**/**36**, respectively, with only one purification during the last three steps. The slight decrease in enantioselectivity from oxindole **35** to (−)-coerulescine is attributed to slight racemization, possibly during workup. Using our route, (−)-coerulescine is available in eight steps from commercially available materials, while (+)-horsfiline is available in nine.

We have reported a catalytic asymmetric cyanoamidation of alkenes with excellent enantioselectivities. Free N−H groups are tolerated, allowing for future protecting-group-free synthesis of alkaloids. The utility of cyanoamidation is exemplified by the syntheses of (−)-esermethole and spirocyclic alkaloids (+)-horsfiline and (−)-coerulescine. Our synthesis of (+)-horsfiline is similar in length to Trost's[13a] and Palmisano's[13b] recent routes to (−)-horsfiline, while circumventing some of the chemoselectivity and diastereoselectivity issues they encountered. Future work on additional asymmetric cyanoamidation-based strategies for the synthesis of alkaloids is ongoing.

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Supporting Information Available: Experimental procedures, ^{1}H and ^{13}C NMR spectra for new compounds, and HPLC chromatograms for chiral compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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