Tetrahedron 66 (2010) 4719–4729

Contents lists available at ScienceDirect

Tetrahedron

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

Catalytic C–CN activation and asymmetric cyanoamidation of alkenes: total syntheses of (+)-horsfiline, (−)-coerulescine, and (−)-esermethole

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ARTICLE INFO

Article history:
Received 20 January 2010
Received in revised form
24 February 2010
Accepted 25 February 2010
Available online 6 March 2010

Dedicated to Professor Brian M. Stoltz for his many contributions to organic chemistry and his receipt of the 2010 Tetrahedron Young Investigator Award for Organic Synthesis

Keywords:
C–C bond activation
Asymmetric catalysis
Total synthesis
Alkaloids

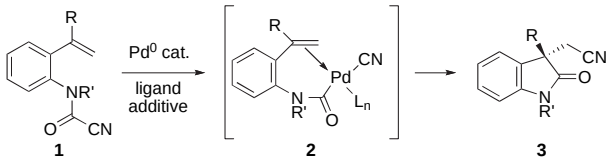
ABSTRACT

The detailed study of Pd-catalyzed asymmetric cyanoamidation is reported. Excellent enantioselectivities are attributed to a chiral phosphosphoramidite ligand synthesized in one step from the commercially available materials. Cyanoamidation substrates are easy to prepare from the corresponding anilines. The 3,3-disubstituted oxindole products bear all-carbon quaternary stereocenters and contain a nitrile and an amide, which are valuable functional handles for the synthesis of many indole-containing natural products. Cyanoamidation tolerates free N–H groups, as demonstrated by the successful use of cyanoamidation in the syntheses of (+)-horsfiline and (−)-coerulescine.

1. Introduction

Increasingly complex pharmaceutical alkaloid targets require the continued development of new strategies and methodologies to synthesize them efficiently. One potential new strategy is the activation of C–C sigma bonds and functionalization of alkenes or alkynes (cyanoamidation),[1] allowing for rapid increase in molecular complexity. Recent work from Nakao and Hiyama[2] and Jacobsen[3] highlights the utility of activating *aryl nitriles*, while Takemoto has reported the activation of *cyanoformamide* C–CN bonds and asymmetric cyanoamidation of alkenes providing 3,3-disubstituted oxindoles with ee's up to 86%.[4]

The reactivity of cyanoformamides toward activation (**1** to **2**, Scheme 1) and cyanoamidation (**2** to **3**), their ease of preparation (discussed in this report), and their synthetic potential in preparing indole-containing natural products (Fig. 1) led us to continue pursuing cyanoamidation conditions giving products with synthetically useful ee's. We now report our comprehensive account of cyanoamidation conditions that give oxindoles bearing all-carbon quaternary stereocenters[5] with ee's up to 99% and our syntheses of (−)-esermethole, (+)-horsfiline, and (−)-coerulescine.[6]



Scheme 1.

2. Results and discussion

2.1. Optimization of asymmetric cyanoamidation

Our laboratory independently observed many of the same features of cyanoamidation as reported in a previous report.[4] Detailed in this section is our quest for synthetically useful enantioselectivities of oxindoles, which we eventually achieved by synthesizing a chiral ligand and using it in cyanoamidation. We also detail our observations in probing the role of additives.

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doi:10.1016/j.tet.2010.02.096

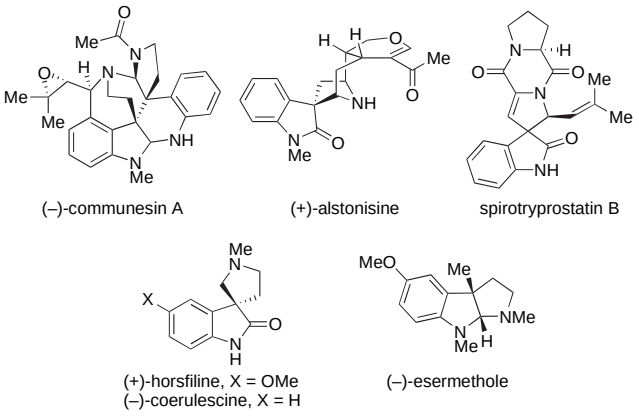
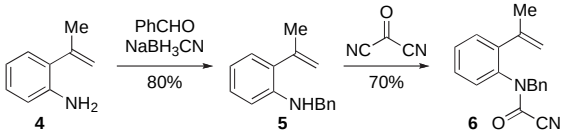


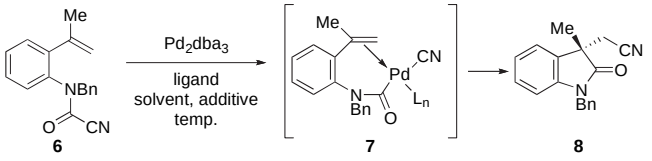
Figure 1.

We initiated our study by synthesizing cyanoformamide **6** via the reductive amination of aniline **4**[7] with benzaldehyde to give the *N*-benzyl aniline **5** (Scheme 2). Subsequent treatment of **5** with carbonyl cyanide[8] provided the cyanoformamide **6** in 70% yield.



Scheme 2.

Table 1
Optimization of asymmetric cyanoamidation.[a]



Entry	Solvent	Ligand	Temp (°C)	Additive	Yield[b] (%)	ee[c] (%)
1	Xylene	None	130	None	28	—
2	Xylene	**L1**	130	None	81	<5
3	Xylene	**L2**	130	None	89	23
4	Xylene	**L3**	130	None	40	<5
5	Xylene	**L4**	130	None	58	33
6	Xylene	**L5**	130	None	42	<5
7	Xylene	**L6**	130	None	51	52
8	Xylene	**L7**	130	None	58	48
9	Xylene	**L8**	130	None	51	62
10	PhMe	**L8**	120	None	50	52
11	DCE	**L8**	100	None	0	—
12	THF	**L8**	100	None	70	68
13	THF	**L8**	100	NMP	69	73
14	THF	**L8**	100	DMPU	80	86
15	Decalin	**L8**	100	NMP	80	91
16	Decalin	**L8**	100	DMPU	81	87
17	THF	**L9**	100	NMP	68	90
18[d]	*THF*	**L9**	100	*DMPU*	*72*	*94*
19	THF	**L9**	100	HMPA	64	91
20	Decalin	**L9**	100	NMP	66	89
21	Decalin	**L9**	100	DMPU	68	95
22[e]	THF	**L9**	100	DMPU	70	86

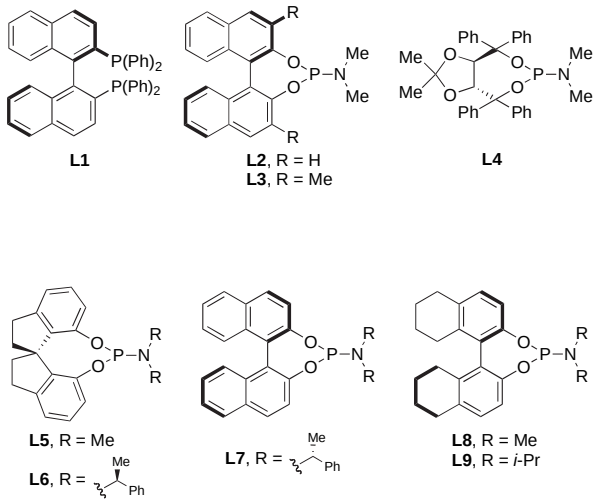
[a] Entries 1–12: 10 mol % Pd_2dba_3, 20 mol % ligand. Entries 13–21: 2 mol % Pd_2dba_3, 16 mol % ligand. THF=tetrahydrofuran, DCE=1,2-dichloroethane, NMP=*N*-methylpyrrolidinone, DMPU=*N*,*N*-dimethylpropylene urea, HMPA=Hexamethylphosphoramide.

[b] Yields after silica gel chromatography.

[c] ee determined by HPLC (Chiralcel OD-H, *n*-hexane/isopropanol (9:1), λ=220 nm).

[d] Conditions in entry 18 were used for the remainder of the study.

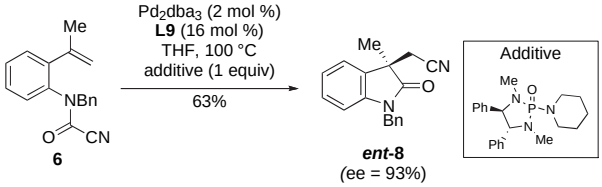
[e] 8 mol % **L9**.



We observed that catalytic Pd_2dba_3, phosphoramidite ligands, Lewis basic additives, and solvents THF or decalin[4] cyclized cyanoformamide **6** to oxindole **8**, presumably via intermediate **7**. We found that absence of ligand gave poor yield of **8** (entry 1, Table 1). Addition of bidentate BINAP **L1** (entry 2) and monodentate MonoPhos **L2** (entry 3) gave yields of **8** exceeding 80%, with MonoPhos also providing some enantioinduction. After screening several commercially available phosphoramidites (**L2**–**L8**, entries 3–9),[9] we identified octahydro-MonoPhos **L8** (entry 9, ee=66%) as a promising lead to optimize. Attempting cyanoamidation with various solvents (xylene, toluene, DCE, THF, entries 9–12) showed that THF was the preferred option. Additives such as *N*-methylpyrrolidinone (NMP), *N*,*N*-dimethylpropylene urea (DMPU), and hexamethylphosphoramide (HMPA) enhanced enantioselectivity (entries 12–14 and 19), particularly with decalin[4] (entries 15–16). We concluded that commercially available ligands would only give our desired oxindole **8** in ee's up to 86–91%, only slightly better than the previous study.[4]

Postulating that increasing ligand nitrogen substituent bulk would improve selectivity, we prepared the *N*,*N*-(*i*-Pr)$_2$ derivative of octahydro-MonoPhos **L9** in one step from the corresponding amine and phosphorochloridite.[10] We were able to achieve ee's up to 94% using **L9** (entries 17–22). Screening various additives showed that usage of DMPU gave the highest enantioselectivity (entry 18). The comparable yields and enantioinduction with THF and decalin as solvents (entries 18–21) prompted us to continue using THF because of its ease of removal during work-up. Reducing the concentration of **L9** to 8 mol % decreased the ee of **8** from 94% to 86% (entry 22). Therefore, we used the conditions shown in entry 18 for the remainder of our study.

We briefly probed the role of the Lewis base additive by using our optimized conditions while substituting DMPU with stoichiometric chiral phosphoramide (Scheme 3).[11] We were able to obtain the opposite enantiomer of **8** in 63% yield (ee=93%). Based on the limited results, we hypothesize that the phosphoramide oxygen may coordinate to the palladium complex and impart stereocontrol during



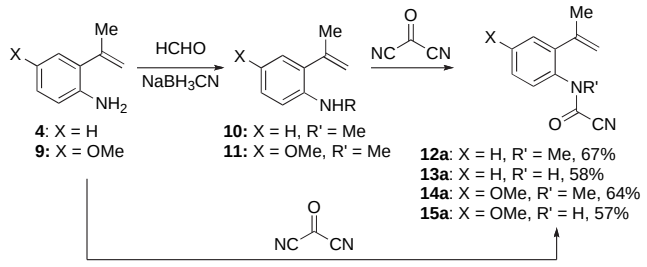
Scheme 3.

the enantioinduction step. Our brief study suggested that chiral 'additives' might be useful upon further optimization. We plan to continue studying the role of these additives in cyanoamidation.

2.2. Substrate synthesis for exploring the scope of asymmetric cyanoamidation

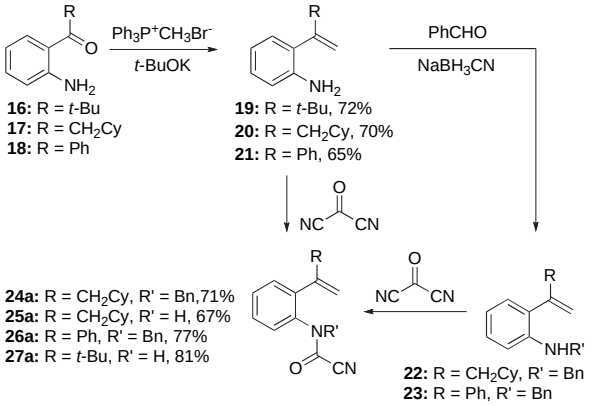
An advantage of cyanoamidation is the ease in preparing the cyanoformamides. Unprotected cyanoformamides are typically available in two to four steps from commercially available compounds, while *N*-protected cyanoformamides require an additional step. When coupled with cyanoamidation, oxindoles bearing all-carbon quaternary stereocenters can be rapidly synthesized. This section details the preparation of our substrates for exploring the scope of cyanoamidation.

Substrates with a methyl alkene substituent (**12a**–**15a**) were synthesized similar to cyanoformamide **6** in two to three steps from commercially available substances (Scheme 4). Beginning with the corresponding methyl anthranilates, anilines **4**/**9** were synthesized in one step according to Spaeth.[7] To generate the *N*-methyl cyanoformamides, anilines **4** and **9** were treated with formaldehyde and $NaBH_3CN$ to form the *N*-methyl anilines **10**–**11**. The cyanoformamides **12a**–**15a** were generated from the appropriate precursor using carbonyl cyanide in 57 to 67% yield.



Scheme 4.

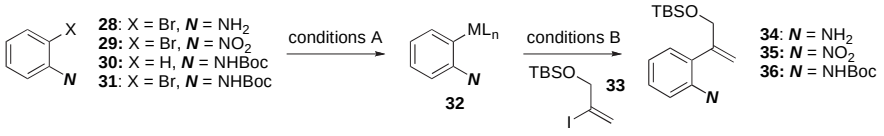
Substrates with alkene substituents R=CH_2Cy, phenyl, and *tert*-butyl (**24a**–**27a**) were synthesized in three to four steps from commercially available substances (Scheme 5). Ketones **16** (R=*t*-Bu)[12] and **17** (R=CH_2Cy)[13] were synthesized in one step from 2-aminobenzonitrile; 2-aminobenzophenone **18** (R=Ph) is commercially available. Wittig reaction installs the styrene to produce **19**–**21** in 65 to 72% yield. Reductive amination with benzaldehyde forms the *N*-benzyl anilines **22** and **23**. Cyanoformamides **24a**–**27a** were generated from the appropriate precursor using carbonyl cyanide in 67 to 81% yield.



Scheme 5.

We opted for a three- to four-step approach via an aryl/vinyl Pd-catalyzed cross-coupling reaction to build substrates with siloxy methyl substituents on the alkene (R=CH_2OTBS). The cross-coupling proved quite difficult, likely due to the presence of the *ortho*-aniline (Table 2). Our initial goal was to avoid protecting group manipulations by using the free aniline **28** to generate organometallic reagents for the cross-coupling. Producing the corresponding metalloaniline was unexpectedly difficult (entries 1 and 2); even when the metalloaniline was formed, the Suzuki cross-coupling[15] with vinyl iodide **33**[14] gave the styrene **34** in 15% yield (entry 2). A Negishi cross-coupling strategy[16] beginning with 1-bromo-2-nitrobenzene **29** fared no better (entry 3). Hypothesizing that the nitro group or free aniline was interfering with successful cross-coupling, we chose to work with *N*-Boc-aniline **30**.[17] Arene deprotonation of **30** with *t*-BuLi followed by a $(n\text{-Bu})_3SnCl$ (entry 4) or $B(OMe)_3$ (entry 5) quench provided the corresponding metalloanilines. Attempted Stille (entry 4)[18] and Suzuki cross-couplings (entry 5) with the metalloanilines and vinyl iodide **33** provided minor amounts of styrene **36**. Qualitatively, it appeared that sluggish arene deprotonation was hampering formation of the metalloaniline. Switching cross-coupling partners was one alternative to circumvent arene deprotonation: we generated vinylborolane **37**[19] from vinyl iodide **33**, followed by cross-coupling with

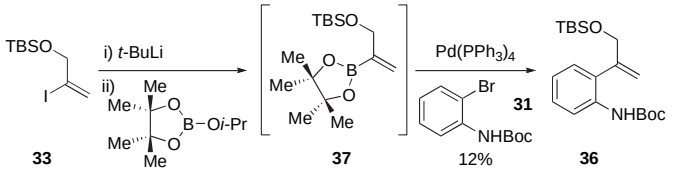
Table 2
Palladium-catalyzed cross-coupling of metalloanilines and a vinyl iodide



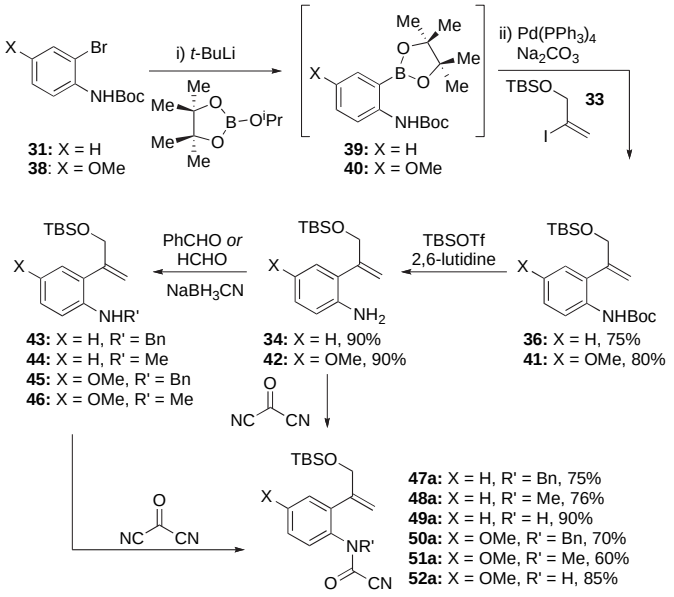
Entry	Aniline	Conditions A[a]	**32**[b]	Conditions B	Product, yield[c]
1	**28**	$Pd(dppf)_2$ (10 mol %), pinB(O*i*-Pr) (1.3 equiv), THF	Not obs	—	—
2	**28**	$Pd(dppf)_2$ (5 mol %), $(pinB)_2$ (1.3 equiv), THF	Obs	$Pd(PPh_3)_4$ (5 mol %), CuBr (5 mol %), LiCl (2.4 equiv), **33** (1.5 equiv), dioxane	**34**, 15%
3	**29**	(i) *t*-BuLi (1.65 equiv), THF (ii) $ZnBr_2$ (1.8 equiv)	—	$Pd(PPh_3)_4$ (5 mol %), **33** (1.5 equiv), THF	**35**, 10%
4	**30**	(i) *t*-BuLi (2.5 equiv), THF (ii) $(n\text{-Bu})_3SnCl$ (1.1 equiv)	—	$Pd(PPh_3)_4$ (10 mol %), **33** (1.5 equiv), dioxane	**36**, 10%
5	**30**	(i) *t*-BuLi (2.5 equiv), THF (ii) $B(OMe)_3$ (1.1 equiv)	Obs	$Pd(PPh_3)_4$ (10 mol %), **33** (1.5 equiv), dioxane	**36**, 15%
6	**31**	(i) *t*-BuLi (2.5 equiv), THF (ii) pinB(O*i*-Pr) (1.5 equiv)	Obs	$Pd(PPh_3)_4$ (10 mol %), CuBr (5 mol %), LiCl (2.4 equiv), **33** (1.5 equiv), dioxane	**36**, 25%
7	**31**	(i) *t*-BuLi (2.5 equiv), THF (ii) pinB(O*i*-Pr) (1.5 equiv)	Obs	$Pd(PPh_3)_4$ (20 mol %), Na_2CO_3 (2 M), **33** (1.5 equiv), MeOH:PhH (1:3)	**36**, 75%

[a] pin=pinacolato.
[b] Obs=observed.
[c] Yields after silica gel chromatography.

bromoaniline **31**[20] to provide a 12% yield of **36** (Scheme 6). The poor yield prompted us to generate lithioanilines via a lithium–halogen exchange of bromoaniline **31** (Table 2, entries 6 and 7). Treatment of the metalloaniline **39** with Stoltz's modified Suzuki cross-coupling conditions[21] provided styrene **36** in good yield (Scheme 7). Applying the same conditions beginning with 4-methoxyaniline **38** gave the styrene **41** in 80% yield.



Scheme 6.



Scheme 7.

The remainder of the synthetic sequence for forming substrates with siloxymethyl substituents on the alkene (R=CH_2OTBS) was straightforward. The Boc groups were removed using TBSOTf in 2,6-lutidine to provide the free anilines **34** and **42**. To provide alkyl-protected cyanoformamides for our comparative study, we protected the anilines using benzaldehyde or formaldehyde in the presence of $NaBH_3CN$ to give the methyl and benzyl anilines **43**–**46**. Finally, cyanoformamides **47a**–**52a** were generated from the appropriate precursors using carbonyl cyanide.

2.3. Scope of asymmetric cyanoamidation

When we subjected our cyanoformamides to our previously optimized conditions (Table 1, entry 18), we observed superb enantioselectivities (ee's up to 99%) with less sterically demanding alkene substituents as detailed in this section.

When the alkene was substituted with methyl (Table 3, entries 1–5), only slight differences in enantioselectivity were observed between *N*-benzyl and *N*-methyl cyanoformamides (entries 1 and 2). Substantial decrease in yield and modest decrease in enantioselectivity was observed when the cyanoformamide was unprotected compared to the protected cyanoformamides (entries 1–3). Addition of a methoxy substituent *para* to the cyanoformamide caused a dramatic increase in yield and enantioselectivity for *N*-methyl cyanoformamides (entries 2 and 4) and unprotected cyanoformamides (entries 3

Table 3
Formation of oxindoles[a]

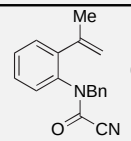
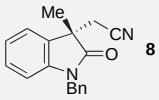
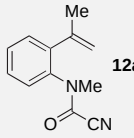
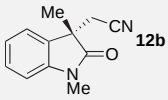
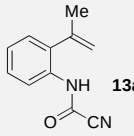
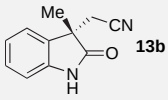
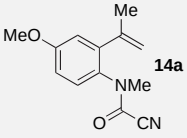
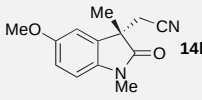
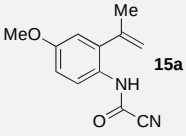
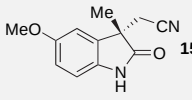
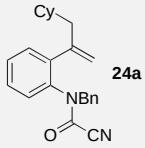
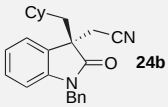
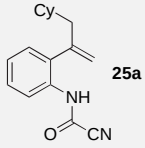
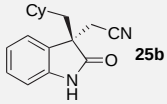
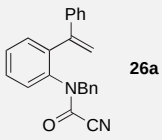
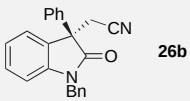
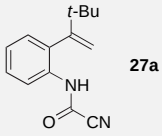
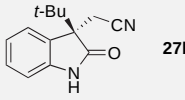
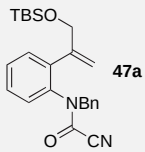
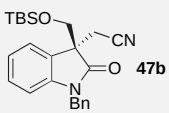
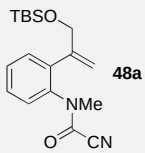
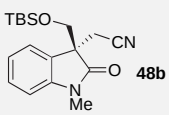
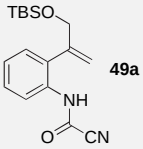
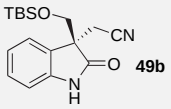
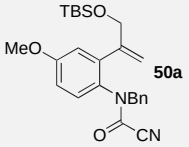
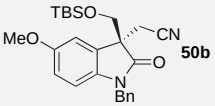
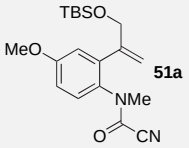
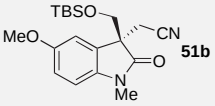
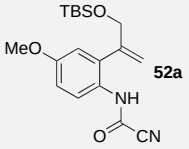
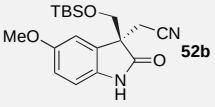
Entry	Substrate	Product	Yield[b] (%)	ee[c] (%)
1	 **6**	 **8**	72	94
2	 **12a**	 **12b**	72	88
3	 **13a**	 **13b**	48	82
4	 **14a**	 **14b**	82	99
5	 **15a**	 **15b**	72	98
6	 **24a**	 **24b**	68	98
7	 **25a**	 **25b**	53	94
8	 **26a**	 **26b**	29	32
9	 **27a**	 **27b**	10	32
10	 **47a**	 **47b**	80	97
11	 **48a**	 **48b**	73	94

Table 3 (*continued*)

Entry	Substrate	Product	Yield[b] (%)	ee[c] (%)
12	 **49a**	 **49b**	56	93
13	 **50a**	 **50b**	88	99
14	 **51a**	 **51b**	78	98
15	 **52a**	 **52b**	72	98

[a] Pd_2dba_3 (2 mol %), **L9** (16 mol %), DMPU (1 equiv), THF (0.25 M), 100 °C. TBS=*tert*-butyl-dimethylsilyl, Cy=cyclohexyl.
[b] Yields after silica gel chromatography.
[c] ee determined by HPLC.

and 5). The yield for unprotected cyanoformamides was still substantially lower than the *N*-methyl compound, even with the additional methoxy substituent (entries 4 and 5). Yields for methyl-substituted alkenes ranged from 48 to 72%, while ee's ranged from 82 to 99%.

Similarly, when the alkene was substituted with CH_2Cy, better yields and ee's were observed with the *N*-benzyl cyanoformamide (entry 6) compared to the unprotected cyanoformamide (entry 7). The unprotected cyanoformamide **25a** with R=CH_2Cy had much better yields and enantioselectivities of the oxindole compared to cyanoformamide **13a** with R=Me (53%, ee=94%, compared to 48%, ee=82%, respectively). As the alkene substituent became more sterically demanding (R=phenyl, entry 8) and (R=*t*-Bu, entry 9), much poorer yields and enantioselectivities were observed compared to their less sterically demanding counterparts.

Substrates with siloxymethyl ether substituents (entries 10–15) consistently gave the highest yields and enantioselectivities of all the substrates we examined. Erosion in yield occurred from *N*-benzyl to *N*-methyl to unprotected cyanoformamides, though ee's for oxindoles remained greater than 90%. When the methoxy substituent *para* to the cyanoformamide was added (entries 13–15), yields for all substrates increased above 70%, while enantioselectivities were exceptional (ee's of 98% and greater).

We conclude that substituents on the alkene R have a large influence on cyanoamidation. Sterically bulky phenyl and *tert*-butyl substituents performed poorly compared to their less sterically demanding counterparts. For yield, the substituents R displayed the following trend: CH_2OTBS=Me>CH_2Cy>Ph>*t*-Bu. Enantioselectivity followed a slightly different pattern: CH_2OTBS=CH_2Cy>Me>Ph=*t*-Bu. One allylic substituent improved enantioselectivity, whereas two or more substituents markedly decreased it.

2.4. Absolute configuration via synthesis of (−)-esermethole

To confirm the absolute configuration of our cyanoamidation products, we synthesized (−)-esermethole.[22,23] (−)-Esermethole is a pyrrolidinoindoline natural product containing an all-carbon quaternary stereocenter at the C-3a position. It is a key intermediate in the synthesis of (−)-physostigmine,[24] a potent reversible inhibitor of acetyl- and butyrylcholinesterase and used clinically to treat to glaucoma.[25] (−)-Esermethole is also a key intermediate in the synthesis of (−)-phenserine (Fig. 2),[24] a congener of physostigmine. (−)-Phenserine displays acetylcholinesterase inhibition,[26] beta-amyloid plaque deposition in the brain,[27] and was in Phase III clinical trials as a treatment for Alzheimer's Disease until the previous year.[28] The potency of the structurally similar pyrrolidinoindolines makes the efficient preparation of the key precursor critically important.

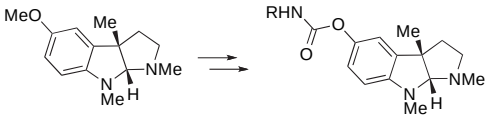
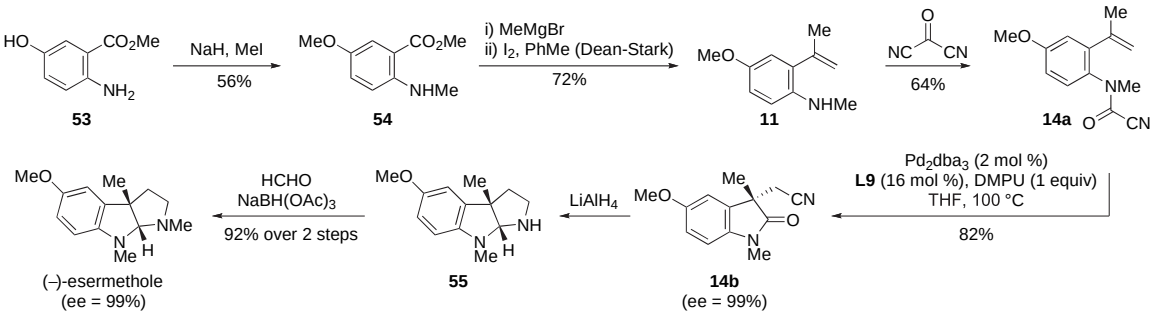


Figure 2.

To begin our synthesis of (−)-esermethole, we made slight changes to our general substrate syntheses to furnish cyanoformamide **14a** (Scheme 8). 5-Hydroxymethylanthranilate **53** was available in one step[29] from commercially available 5-hydroxyanthranilic acid. Treatment of **53** with NaH and MeI provided **54** in 56% yield. The alpha-methyl styrene was installed by treating **54** with excess MeMgBr, followed by dehydration[7] to produce **11** in 72% yield. Installation of the cyanoformamide using carbonyl cyanide provided **14a** in 64% yield. Cyanoamidation of **14a** using our standard conditions gave the 3,3-disubstituted oxindole **14b** in 82% yield (ee=99%).

Following the cyanoamidation, $LiAlH_4$ reduction of oxindole **14b** generated the pyrrolidinoindoline core **55**, and subsequent reductive amination with formaldehyde gave our targeted molecule (−)-esermethole in 92% yield over two steps.[2] Our targeted



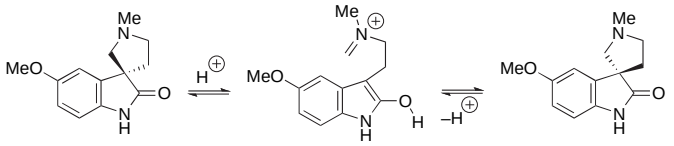
Scheme 8.

compound was produced in seven steps from commercially available materials, in 19.5% overall yield from methylanthralinate **53**, and with high enantiopurity.

Based on the optical rotation of our (−)-esermethole product, were able to assign the absolute stereochemistry of oxindole **14b**. The absolute stereochemistry of many of the remaining oxindoles shown in Table 3 was assigned by analogy to oxindole **14b**.

2.5. Syntheses of (+)-horsfiline and (−)-coerulescine

In addition to synthesizing (−)-esermethole, we also targeted (+)-horsfiline and (−)-coerulescine, which are oxindole natural products with unique spiro stereogenic centers. Their spirocyclic oxindole cores are structurally similar to the spirotryprostatins (Fig. 1), which are cell-cycle inhibitors at micromolar concentrations.[30] The unique structures of horsfiline has inspired synthetic chemists to pursue more efficient strategies toward its construction.[31,32] Notable syntheses include Trost's palladium-catalyzed asymmetric allylic alkylation approach to generate the quaternary stereocenter.[31a] Palmisano utilized a chiral auxiliary-directed 1,3-dipolar cycloaddition of an azomethine ylide to form the quaternary stereocenter.[31b] One well-known synthetic challenge of both (+)-horsfiline and (−)-coerulescine is the acid-promoted retro-Mannich/Mannich, which can racemize the natural product (Scheme 9).



Scheme 9.

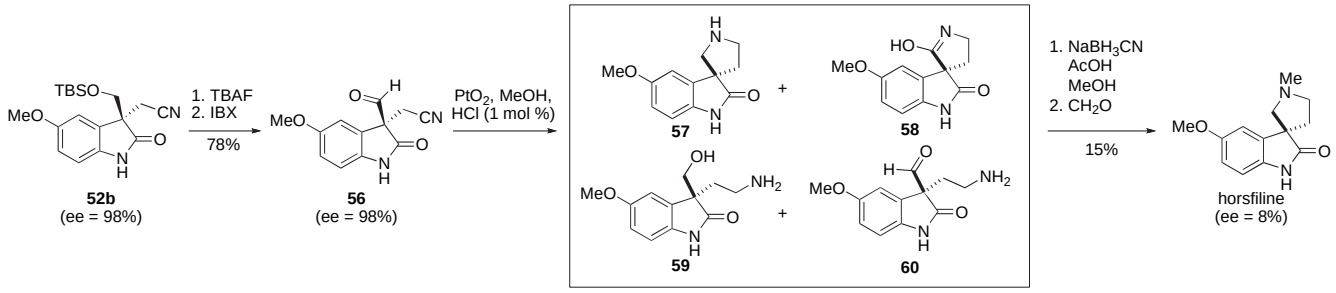
Our oxindoles **49b** (ee=93%) and **52b** (ee=98%) contained ideally situated functional groups to enable rapid syntheses of (−)-coerulescine and (+)-horsfiline, respectively. We originally envisioned constructing the spirocycle via a reductive amination route as shown in Scheme 10. Treatment of oxindole **52b** with TBAF exposed the alcohol, which was subsequently oxidized with IBX to generate the aldehyde **56**. We anticipated that chemoselective reduction of the nitrile in the presence of the aldehyde of **56** would allow efficient reductive amination. Unfortunately, treatment of nitrile **56** with PtO_2/1 M HCl in methanol gave a mixture of compounds **57**–**60**, and subjecting the mixture to reductive amination conditions ($NaBH_3CN$, AcOH, MeOH) caused extensive racemization, presumably via the Mannich/retro-Mannich pathway.

Our alternative route, incorporating an intramolecular S_N2 reaction, was much more successful (Scheme 11). The oxindoles **49b** and **52b** were treated with TBAF, and the resulting crude alcohols exposed to MsCl. Chemoselective reduction of the nitrile was achieved with $NaBH_4/CoCl_2\cdot 6H_2O$,[33] allowing closure of the spirocycle via **61** and **62**. Addition of formaldehyde to the reaction mixture installed the amino methyl groups and completed the syntheses of (−)-coerulescine (54% from **49b**, ee=91%) and (+)-horsfiline (49% from **52b**, ee=98%). Only one purification was performed during the last three steps. The slight decrease in ee during the synthesis of (−)-coerulescine might be attributed to the slightly acidic conditions during workup.

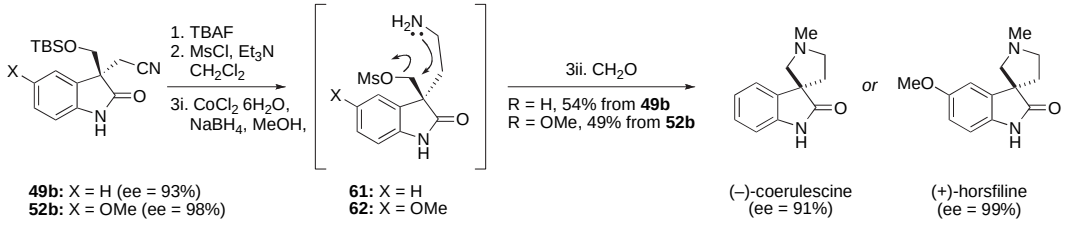
We conclude that cyanoamidation allows (−)-coerulescine to be synthesized in 18% overall yield (ee=91%) in seven steps from aniline **31**, and eight steps from commercially 2-bromoaniline. (+)-Horsfiline was synthesized in 22% overall yield (ee=99%) in seven steps from aniline **38**,[34] and nine steps from commercially available 4-methoxyaniline.

3. Conclusion

We have reported the detailed study of Pd-catalyzed asymmetric cyanoamidation. We attribute our high enantioselectivities to a chiral phosphoramidite ligand synthesized in one step from the commercially available phosphorochloridite and amine. We demonstrated that diverse cyanoformamides are easy to prepare. The 3,3-disubstituted oxindoles resulting from cyanoamidation bear all-carbon quaternary stereocenters, a nitrile, and an amide, which can be valuable functional handles in the synthesis of indole-containing natural products. Cyanoamidation tolerates free N–H groups, as demonstrated by our syntheses of (+)-horsfiline and (−)-coerulescine. Future work on asymmetric cyanoamidation-based strategies for the synthesis of complex alkaloids is ongoing.



Scheme 10.



Scheme 11.

4. Experimental section

4.1. General

All reactions were carried out using flame-dried glassware under a nitrogen or argon atmosphere unless aqueous solutions were employed as reagents or dimethylformamide was used as a solvent. Tetrahydrofuran (THF), dichloromethane (CH_2Cl_2), xylene, diethyl ether and toluene (PhMe) were dried according to published procedures. THF was further degassed by bubbling a stream of argon through the liquid in a Strauss flask and then stored in a nitrogen-filled glove box. Palladium complexes were purchased from Strem and used as received. Phosphoramidite ligands were purchased form Strem or prepared by using the literature procedure and stored in nitrogen-filled glove box. Phosphonium salts for Wittig reactions were purchased from Aldrich and used as received. All types of anilines compounds were purchased from Aldrich and used as received. Tetracyanoethyleneoxide was prepared according to Linn.[35] All cyanoamidation reactions were out in a Vacuum Atmospheres nitrogen-filled glove box in 1 dram vials with PTFE lined caps and heating was applied by aluminum block heaters. Analytical thin layer chromatography (TLC) was carried out using 0.25 mm silica plates from E. Merck. Eluted plates were visualized first with UV light and then by staining with ceric sulfate/molybdic acid or potassium permanganate/potassium carbonate. Flash chromatography was performed using 230–400 mesh (particle size 0.04–0.063 mm) silica gel purchased from Merck unless otherwise indicated. ^{1}H NMR (300 and 500 MHz) and ^{13}C NMR (75 and 125 MHz) spectra were obtained on Varian FT NMR instruments. NMR spectra were reported as δ values in parts per million relative to chloroform or tetramethylsilane. ^{1}H NMR coupling constants are reported in hertz; multiplicity was indicated as follows; s (singlet); d (doublet); t (triplet); q (quartet); quint (quintet); m (multiplet); dd (doublet of doublets); ddd (doublet of doublet of doublets); dddd (doublet of doublet of doublet of doublets); dt (doublet of triplets); dq (doublet of quartets); td (triplet of doublets); ddt (doublet of doublet of triplets); app (apparent); br (broad). Infrared (IR) spectra were obtained as films from CH_2Cl_2 or $CDCl_3$. LRMS and high-resolution mass spectra (HRMS) in electrospray (ESI) experiments were performed on a Bruker BioTOF II. Optical rotation experiments were performed on Rudolph Polarimeter. The ee's were determined by using HPLC with Chiralpak OD-H or AD-H columns by using combination of hexanes and isopropanol as a mobile phase. For oxindoles **14b**, **52b**, and **49b**, the absolute stereochemistry was assigned by chemical correlation to (−)-esermethole, (+)-horsfiline, and (−)-coerulescine, respectively. Other absolute configurations of oxindoles were assigned in analogy.

4.2. Preparation of carbonyl cyanide (~1 M in ether)[8]

To a suspension of tetracyanoethyleneoxide (TCEO) (10.00 g, 69.4 mmol) in ether (40 mL) was added Me_2S (5.19 mL, 68.0 mmol) at 0 °C. After stirring at 0 °C for 1 h, the precipitate was removed by filtration and the filtrate was diluted with ether (30 mL) to give the carbonyl cyanide solution (~1.0 M) in ether, which was used for the following reactions without further purification.

Note: The solution of carbonyl cyanide can be used interchangeably with TCEO/Me_2S. Based on our experience, the solution was stable for a few months in the refrigerator (~5 °C).

4.3. General procedure to generate cyanoformamides

4.3.1. Method A. To a solution of TCEO (0.347 g, 2.4 mmol) in dry Et_2O in a flame-dried round bottom flask was added methyl sulfide (0.25 mL, 3.0 mmol) at 0 °C.[35] The reaction mixture was stirred for one hour at 0 °C, and a solution of benzyl-(2-isopropenyl-phenyl)-amine **5** (0.446 g, 2.0 mmol) in Et_2O was added at 0 °C. The reaction was allowed to stir for 8 h at room temperature. The reaction was filtered through a Celite pad and solvent was evaporated to dryness. The crude product was purified by silica gel chromatography (15:85, EtOAc/Hex) to provide **6** as clear oil (0.375 g, 1.42 mmol, 70%).

4.3.2. Method B. A solution of (2-isopropenyl-phenyl)-methylamine **10** (0.246 g, 1.4 mmol) in Et_2O (2.2 mL) was cooled to 0 °C and carbonyl cyanide[8] (3.0 mL, 3.0 mmol, 1.0 M in Et_2O) was added. The resulting suspension was stirred for 8 h at rt. The reaction mixture was filtered through a pad of Celite and concentrated. The crude product was purified by silica gel chromatography (25:75, EtOAc/Hex) to provide **12a** as a clear oil (0.187 g, 0.93 mmol, 67%).

*4.3.3. N-Benzyl(2-(prop-en-2yl) phenyl)carbamoyl cyanide(**6**). Prepared via Method A* (Section 4.3.1): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44–7.38 (m, 2H), 7.35–7.26 (m, 3H), 7.25–7.16 (m, 3H), 6.80–6.77 (m, 1H), 5.54 (d, J=14.1 Hz, 1H), 5.38 (q, J=3.2 Hz, 1H), 5.12 (s, 1H), 4.13 (d, J=14.1 Hz, 1H), 2.15 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.5, 142.0, 135.0, 134.7, 130.6, 130.4, 130.3, 129.4, 128.8, 128.5, 128.4, 118.3, 110.9, 53.3, 23.7; IR (thin film) 2841, 2023, 1614, 1545, 1504, 1450, 1380, 1016, 912, 660; HRMS (ESI) calcd for $[C_{17}H_{15}N_2O+Na]^+$ 286.1082, found 286.1081. (Mixture of rotamers ~92:8).

*4.3.4. N-Methyl(2-(prop-en-2yl) phenyl)carbamoyl cyanide (**12a**). Prepared via Method B* (Section 4.3.2): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (dd, J=7.7, 1.2 Hz, 1H), 7.40 (dd, J=7.7, 1.6 Hz, 1H), 7.24 (dd, J=7.7, 1.2 Hz, 1H), 5.31 (dq, J=3.2, 1.5 Hz, 1H), 5.03 (d, J=3.2 Hz, 1H), 3.27 (s, 3H), 2.08 (d, J=1.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.4, 142.6, 141.8, 137.1, 130.5, 130.4, 128.9, 118.3, 111.0, 36.8, 23.7; IR (thin film) 2861, 2003, 1604, 1525, 1504, 1470, 1300, 1016, 912, 665; HRMS (ESI) calcd for $[C_{12}H_{12}N_2O+Na]^+$ 223.0847, found 223.0842. (Mixture of rotamers ~93:7).

*4.3.5. (2-(Prop-en-2yl) phenyl)carbamoyl cyanide (**13a**). Prepared via Method B* (Section 4.3.2): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.31 (br s, 1H), 8.10 (d, J=8.2 Hz, 1H), 7.31–7.28 (m, 1H), 7.24–7.22 (m, 2H), 5.49–5.47 (m, 1H), 5.07–4.99 (m, 1H), 2.11 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.6, 140.4, 134.5, 131.4, 128.4, 126.3, 121.8, 121.7, 111.6, 24.3; IR (thin film) 2841, 2023, 1614, 1535, 1504, 1470, 1300, 1016, 912, 665; HRMS (ESI) calcd for $[C_{11}H_{10}N_2O+Na]^+$ 209.0691, found 209.0685. (Mixture of rotamers ~92:8).

*4.3.6. N-Methyl(4-methoxy-2-(prop-1-en-2-yl)phenyl)carbamoyl cyanide (**14a**). Prepared via Method B* (Section 4.3.2): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16 (d, J=8.7 Hz, 1H), 6.90–6.84 (m, 2H), 5.29 (d, J=1.5 Hz, 1H), 5.02 (d, J=1.0 Hz, 1H), 3.84 (s, 3H), 3.23 (s, 3H), 2.07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.7, 156.6, 133.1, 132.9, 116.7, 114.1, 111.1, 110.7, 56.1, 53.3, 46.0, 26.5, 22.5; IR (thin film) 2841, 2023, 1614, 1535, 1504, 1470, 1300, 1280, 1050, 1016, 912, 668; HRMS (ESI) calcd for $[C_{13}H_{14}N_2O_2+Na]^+$ 253.0953, found 253.0952. (Mixture of rotamers ~93:7).

*4.3.7. (4-Methoxy-2-(prop-1-en-2-yl)phenyl)carbamoyl cyanide (**15a**). Prepared via Method A* (Section 4.3.1): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (d, J=9.0 Hz, 1H), 6.85–6.80 (m, 2H), 6.74 (t, J=4.8, 3.0 Hz, 1H), 5.46 (dd, J=3.3, 1.8 Hz, 1H), 5.05 (dd, J=3.3, 1.8 Hz, 1H), 3.80 (s, 3H), 2.07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.3, 142.3, 136.8, 125.2, 123.9, 119.0, 118.7, 114.4, 113.6, 112.4, 56.2, 25.1; IR (thin film) 2841, 2023, 1614, 1535, 1504, 1470, 1300, 1280, 1050, 1016, 912, 668; HRMS (ESI) calcd for $[C_{12}H_{12}N_2O_2+Na]^+$ 239.0796, found 239.0792. (Mixture of rotamers ~95:5).

*4.3.8. N-Benzyl(2-(3-cyclohexylprop-1-en-2-yl)phenyl)carbamoyl cyanide (**24a**). Prepared via Method A* (Section 4.3.1): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44–7.38 (m, 2H), 7.35–7.26 (m, 3H), 7.25–7.16

(m, 3H), 6.80–6.77 (m, 1H), 5.54 (d, *J*=14.1 Hz, 1H), 5.38 (q, *J*=3.2 Hz, 1H), 5.12 (s, 1H), 4.13 (d, *J*=14.1 Hz, 1H), 2.25 (dd, *J*=7.2, 0.9 Hz, 2H), 1.71–1.67 (m, 5H), 1.29–0.87 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.9, 145.3, 134.4, 132.6, 129.1, 128.9, 126.8, 122.0, 119.1, 112.2, 46.8, 35.9, 34.2, 34.0, 27.0, 26.7; IR (thin film) 2841, 2023, 1614, 1535, 1504, 1470, 1300, 1280, 1050, 1016, 912, 668; HRMS (ESI) calcd for $[C_{24}H_{26}N_2O+Na]^+$ 381.1943, found 381.1948. (Mixture of rotamers ~94:6).

*4.3.9. (2-(3-Cyclohexylprop-1-en-2-yl)phenyl)carbamoyl cyanide (**25a**). Prepared via Method A* (Section 4.3.1): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13 (dd, *J*=7.1, 1.5 Hz, 1H), 7.39–7.14 (m, 3H), 5.42 (dd, *J*=1.5, 1.0 Hz, 1H), 5.10 (d, *J*=1.5 Hz, 1H), 2.25 (dd, *J*=7.2, 0.9 Hz, 2H), 1.71–1.67 (m, 5H), 1.29–0.87 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.9, 145.3, 134.4, 132.6, 129.1, 128.9, 126.8, 122.0, 119.1, 112.2, 46.8, 35.9, 34.2, 34.0, 27.0, 26.7; IR (thin film) 2841, 2023, 1614, 1535, 1504, 1470, 1300, 1280, 1050, 1016, 912, 668; HRMS (ESI) calcd for $[C_{17}H_{20}N_2O+Na]^+$ 291.1473, found 291.1480. (Mixture of rotamers ~93:7).

*4.3.10. N-Benzyl(2-(1-phenylvinyl)phenyl)carbamoylcyanide (**26a**). Prepared via Method A* (Section 4.3.1): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60–7.43 (m, 2H), 7.42–7.22 (m, 9H), 7.15–7.06 (m, 2H), 6.80–6.77 (m, 1H), 5.77 (s, 1H), 5.45 (s, 1H), 5.04 (d, *J*=14.1 Hz, 1H), 3.68 (d, *J*=14.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.5, 143.4, 137.3, 135.8, 130.3, 129.8, 129.6, 129.1, 128.5, 127.8, 127.4, 125.9, 124.1, 117.1, 110.8, 53.4, 44.9, 26.9; IR (thin film) 2841, 2003, 1604, 1515, 1513, 1460, 1300, 1006, 902, 655; HRMS (ESI) calcd for $[C_{23}H_{19}N_2O+H]^+$ 339.1497, found 339.1497. (Mixture of rotamers: 98:2).

*4.3.11. (2-(3,3-Dimethylbut-1-en-2-yl)phenyl)carbamoyl cyanide(**27a**). Prepared via Method B* (Section 4.3.2): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13 (d, *J*=8.4 Hz, 1H), 7.93 (br s, 1H), 7.36–7.31 (m, 1H), 7.22–7.12 (m, 2H), 5.57 (d, *J*=0.9 Hz, 1H), 4.99 (d, *J*=0.9 Hz, 1H), 1.14 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.4, 140.4, 133.6, 130.5, 128.7, 126.0, 121.8, 111.6, 112.7, 37.9, 30.7; IR (thin film) 2840, 2013, 1610, 1530, 1504, 1470, 1300, 1016, 912, 665; HRMS (ESI) calcd for $[C_{14}H_{16}N_2O+Na]^+$ 251.1160, found 251.1160. (Mixture of rotamers ~93:7).

*4.3.12. N-Benzyl(2-(3-(tertbutyldimethylsilyloxy)prop-1-en-2-yl)-phenyl)carbamoyl cyanide (**47a**). Prepared via Method B* (Section 4.3.2): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45–7.08 (m, 8H), 6.73 (dd, *J*=7.8, 1.2 Hz, 1H), 5.64 (dd, *J*=3.3, 1.5 Hz, 1H), 5.50 (d, *J*=14.8 Hz, 1H), 5.23 (dd, *J*=3.3, 1.5 Hz, 1H), 4.40 (s, 2H), 4.14 (d, *J*=14.8 Hz, 1H), 0.89 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.1, 146.0, 139.8, 135.3, 131.5, 131.4, 130.8, 130.7, 130.1, 129.7, 129.7, 129.6, 129.5, 129.4, 129.3, 129.0, 116.9, 111.5, 66.4, 53.8, 26.6, 26.5, 19.1, −4.5, −4.6; IR (thin film) 2881, 2033, 1600, 1535, 1504, 1470, 1300, 1280, 1050, 1016, 912, 678; HRMS (ESI) calcd for $[C_{24}H_{30}N_2O_2Si+Na]^+$ 429.1974, found 429.1970. (Mixture of rotamers ~95:5).

*4.3.13. N-Methyl(2-(3-(tert-butyldimethylsilyloxy)prop-1-en-2-yl)-phenyl)carbamoyl cyanide (**48a**). Prepared via Method B* (Section 4.3.2): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49–7.34 (m, 3H), 7.29–7.24 (m, 1H), 5.58 (dd, *J*=3.3, 1.8 Hz, 1H), 5.17 (dd, *J*=3.0, 1.5 Hz, 1H), 4.33 (s, 2H), 3.26 (s, 3H), 0.89 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.8, 145.7, 139.9, 138.2, 131.5, 130.7, 129.9, 129.7, 116.6, 111.4, 66.2, 37.5, 26.5, 19.0, −4.6, −4.7; IR (thin film) 2831, 2033, 1600, 1535, 1504, 1470, 1300, 1280, 1050, 1016, 912, 678; HRMS (ESI) calcd for $[C_{18}H_{26}N_2O_2Si+Na]^+$ 353.1661, found 353.1660. (Mixture of rotamers ~94:6).

*4.3.14. (2-(3-(tert-Butyldimethylsilyloxy)prop-1-en-2-yl)phenyl)carbamoyl cyanide (**49a**). Prepared via Method B* (Section 4.3.2): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49–7.43 (m, 2H), 7.41–7.34 (m, 1H), 7.29–7.24 (m, 1H), 5.58 (dd, *J*=3.3, 1.8 Hz, 1H), 5.17 (dd, *J*=3.0, 1.5 Hz, 1H), 4.33 (s, 2H), 0.89 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.8, 145.7, 139.9, 138.2, 131.5, 130.7, 129.9, 129.7, 116.6, 111.4, 37.5, 26.5, 19.0, −4.6, −4.7; IR (thin film) 2831, 2033, 1600, 1535, 1504, 1470, 1300, 1280, 1050, 1016, 912, 678; HRMS (ESI) calcd for $[C_{17}H_{24}N_2O_2Si+Na]^+$ 339.1505, found 339.1507. (Mixture of rotamers ~95:5).

*4.3.15. N-Benzyl(2-(3-(tert-butyldimethylsilyloxy)prop-1-en-2-yl)-4-methoxyphenyl)carbamoyl cyanide (**50a**). Prepared via Method B* (Section 4.3.2): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38–7.24 (m, 5H), 6.72–6.69 (m, 1H), 6.61–6.52 (m, 2H), 5.60 (d, *J*=1.8 Hz, 1H), 5.18 (d, *J*=1.8 Hz, 1H), 4.72 (d, *J*=7.5 Hz, 2H), 4.28 (s, 2H), 3.73 (s, 3H), 0.91 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.1, 146.0, 138.8, 136.2, 135.3, 131.5, 131.4, 130.8, 129.7, 116.9, 111.5, 66.3, 53.8, 30.5, 26.6, 26.5, 19.1, −4.6; IR (thin film) 3021, 2841, 2023, 1614, 1535, 1504, 1470, 1300, 1280, 1050, 1016, 912, 668; HRMS (ESI) calcd for $[C_{25}H_{32}N_2O_3Si+Na]^+$ 459.1974, found 459.1970. (Mixture of rotamers ~95:5).

*4.3.16. N-Methyl(2-(3-(tert-butyldimethylsilyloxy)prop-1-en-2-yl)-4-methoxyphenyl)carbamoyl cyanide (**51a**). Prepared via Method B* (Section 4.3.2): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09–8.06 (m, 1H), 7.16–7.35 (m, 2H), 5.59 (s, 1H), 5.14 (s, 1H), 4.34 (s, 2H), 3.76 (s, 3H), 3.30 (s, 3H), 0.83 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.9, 147.3, 138.0, 127.8, 117.2, 115.4, 114.6, 114.2, 66.0, 56.4, 31.8, 26.6, 26.3, 19.1, −4.6; IR (thin film) 3021, 2841, 2023, 1614, 1535, 1504, 1470, 1300, 1280, 1050, 1016, 912, 668; HRMS (ESI) calcd for $[C_{19}H_{28}N_2O_3Si+Na]^+$ 383.1767, found 383.1760. (Mixture of rotamers ~94:6).

*4.3.17. (2-(3-(tert-Butyldimethylsilyloxy)prop-1-en-2-yl)-4-methoxy phenyl)carbamoyl cyanide (**52a**). Prepared via Method B* (Section 4.3.2): ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.16 (br s, 1H), 8.09–8.06 (m, 1H), 7.16–7.35 (m, 2H), 5.59 (s, 1H), 5.14 (s, 1H), 4.34 (s, 2H), 3.76 (s, 3H), 0.83 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.9, 147.3, 8.0, 127.8, 117.2, 115.4, 114.6, 114.2, 66.0, 56.4, 26.6, 26.3, 19.1, −4.6; IR (thin film) 3021, 2841, 2023, 1614, 1535, 1504, 1470, 1300, 1280, 1050, 1016, 912, 668; HRMS (ESI) calcd for $[C_{18}H_{26}N_2O_3Si+Na]^+$ 369.1610, found 369.1610. (Mixture of rotamers ~95:5).

4.4. General procedure for cyanoamidation

In a N_2 filled glove box, cyanoformamide (1.0 equiv), Pd_2dba_3 (0.02 equiv), **L9** (0.16 equiv), DMPU (1.0 equiv) were combined in a PTFE-lined screw-cap vial. THF was added (0.25 M in cyanoformamide) and the vial was sealed. The resulting solution was maintained at 100 °C for 24 h, after which the reaction was removed from the glove box. The reaction mixture was diluted with CH_2Cl_2 (2×volume), filtered through Celite and concentrated in vacuo. The resulting crude product was purified by flash chromatography and the resulting product analyzed by HPLC.

*4.4.1. (S) 2-(1-Benzyl-3-methyl-2-oxoindolin-3-yl)acetonitrile (**8**).* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (td, *J*=7.5, 0.9 Hz, 1H), 7.37–7.22 (m, 6H), 7.11 (dt, *J*=7.5, 1.2 Hz, 1H), 6.80 (d, *J*=7.8 Hz, 1H), 4.95 (s, 2H), 2.93 (d, *J*=16.8 Hz, 1H), 2.66 (d, *J*=16.8 Hz, 1H), 1.60 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.8, 141.8, 135.4, 131.0, 129.2, 129.0, 127.9, 127.2, 123.3, 123.3, 123.2, 116.6, 45.0, 44.0, 26.4, 22.6; IR (thin film) 2841, 2023, 1614, 1545, 1504, 1450, 1380, 1016, 912, 660; HRMS (ESI) calcd for $[C_{17}H_{15}N_2O+Na]^+$ 286.1082, found 286.1081; HPLC [Chiralcel OD-H, Hex/IPA=90/10, 1.0 mL/min, λ=220 nm] 95% ee, $[\alpha]_D^{23}$ −32.0 (0.45 in $CHCl_3$).

*4.4.2. (S) 2-(1,3-Dimethyl-2-oxoindolin-3-yl)acetonitrile (**12b**).* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (d, *J*=8.0 Hz, 1H), 7.36 (d, *J*=8.0 Hz, 1H), 7.14 (dd, *J*=8.0 Hz, 1H), 6.90 (d, *J*=7.9 Hz, 1H), 3.25 (s, 3H), 2.85

(d, J=16.8 Hz, 1H), 2.58 (d, J=16.4 Hz, 1H), 1.53 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.5, 142.9, 131.2, 129.3, 123.4, 123.3, 116.8, 108.8, 44.9, 26.6, 26.3, 22.2; IR (thin film) 2861, 2003, 1604, 1525, 1504, 1470, 1300, 1016, 912, 665; HRMS (ESI) calcd for $[C_{12}H_{12}N_2O+Na]^+$ 223.0847, found 223.0844; HPLC [Chiralcel OD-H, Hex/IPA=90/10, 1.0 mL/min, λ=220 nm] 88% ee, $[\alpha]_D^{23}$ +64.1 (0.45 in $CHCl_3$).

*4.4.3. (S) 2-(3-Methyl-2-oxoindolin-3-yl)acetonitrile (**13b**).* ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.15 (br s, 1H), 7.45 (d, J=7.3 Hz, 1H), 7.30 (t, J=7.8 Hz, 1H), 7.12 (t, J=7.6 Hz, 1H), 7.00 (d, J=7.6 Hz, 1H), 2.85 (d, J=16.5 Hz, 1H), 2.64 (d, J=16.8 Hz, 1H), 1.56 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.2, 139.9, 131.4, 123.4, 123.2, 116.5, 110.6, 45.3, 26.1, 22.1; IR (thin film) 3000, 2861, 2003, 1604, 1525, 1504, 1470, 1300, 1016, 912, 665; HRMS (ESI) calcd for $[C_{11}H_{10}N_2O+Na]^+$ 209.0691, found 209.0690; HPLC [Chiralcel OD-H, Hex/IPA=90/10, 1.0 mL/min, λ=220 nm] 82% ee, $[\alpha]_D^{23}$ +52.0 (0.65 in $CHCl_3$).

*4.4.4. (S)-2-(5-Methoxy-1,3-dimethyl-2-oxoindolin-3-yl)acetonitrile (**14b**).* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.07 (d, J=2.4 Hz, 1H), 6.87–6.78 (m, 2H), 3.80 (s, 3H), 3.20 (s, 3H), 2.82 (d, J=16.8 Hz, 1H), 2.58 (d, J=16.5 Hz, 1H), 1.54 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.8, 157.1, 136.7, 132.9, 117.3, 114.1, 111.1, 109.8, 56.5, 45.9, 27.2, 26.9, 22.8; IR (thin film) 3000, 2861, 2003, 1604, 1525, 1504, 1470, 1300, 1280, 1180, 1016, 912, 665; HRMS (ESI) calcd for $[C_{13}H_{14}N_2O_2+Na]^+$ 253.0953, found 253.0951; HPLC [Chiralcel OD-H, Hex/IPA=90/10, 1.0 mL/min, λ=220 nm] 99% ee, $[\alpha]_D^{23}$ +57.0 (1.0 in $CHCl_3$).

*4.4.5. (S)-2-(5-Methoxy-3-methyl-2-oxoindolin-3-yl)acetonitrile (**15b**).* ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25 (br s, 1H), 7.04 (d, J=1.8 Hz, 1H), 6.87–6.78 (m, 2H), 3.80 (s, 1H), 2.82 (d, J=12.4 Hz, 1H), 2.64 (d, J=13.1 Hz, 1H), 1.54 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.7, 156.6, 133.1, 132.9, 116.7, 114.1, 111.1, 110.7, 56.1, 46.0, 26.5, 22.5; IR (thin film) 3000, 2861, 2003, 1604, 1525, 1504, 1470, 1300, 1280, 1180, 1016, 912, 665; HRMS (ESI) calcd for $[C_{12}H_{12}N_2O_2+Na]^+$ 239.0796, found 239.0794; HPLC [Chiralcel OD-H, Hex/IPA=90/10, 1.0 mL/min, λ=220 nm] 98% ee, $[\alpha]_D^{23}$ +48.2 (1.5 in $CHCl_3$).

*4.4.6. (S) 2-(1-Benzyl-3-(cyclohexylmethyl)-2-oxoindolin-3-yl)acetonitrile (**24b**).* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (td, J=7.5, 0.9 Hz, 1H), 7.37–7.22 (m, 6H), 7.11 (dt, J=7.5, 1.2 Hz, 1H), 6.80 (d, J=7.8 Hz, 1H), 4.95 (s, 2H), 2.93 (d, J=16.8 Hz, 1H), 2.66 (d, J=16.8 Hz, 1H), 2.25 (d, J=7.2 Hz, 2H), 1.71–1.67 (m, 5H), 1.29–0.87 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.8, 145.3, 134.4, 132.6, 129.1, 128.9, 126.8, 122.0, 119.1, 112.2, 46.8, 35.9, 34.2, 34.0, 27.0, 26.7; IR (thin film) 2841, 2023, 1614, 1535, 1504, 1470, 1300, 1280, 1050, 1016, 912, 668; HRMS (ESI) calcd for $[C_{17}H_{20}N_2O+Na]^+$ 381.1943, found 381.1943. HPLC [Chiralcel OD-H Hex/IPA=90/10, 1.0 mL/min, λ=220 nm] 98% ee; $[\alpha]_D^{23}$ +40.6 (0.6 in $CHCl_3$).

*4.4.7. (S)-2-(3-(Cyclohexylmethyl)-2-oxoindolin-3-yl)acetonitrile (**25b**).* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (d, J=7.3 Hz, 1H), 7.30 (t, J=7.8 Hz, 1H), 7.12 (t, J=7.6 Hz, 1H), 7.00 (d, J=7.6 Hz, 1H), 2.85 (d, J=16.5 Hz, 1H), 2.64 (d, J=16.8 Hz, 1H), 2.25 (d, J=7.2 Hz, 2H), 1.71–1.67 (m, 5H), 1.29–0.87 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.9, 145.3, 134.4, 132.6, 129.1, 128.9, 126.8, 122.0, 119.1, 112.2, 46.8, 35.9, 34.2, 34.0, 27.0, 26.7; IR (thin film) 2841, 2023, 1614, 1535, 1504, 1470, 1300, 1280, 1050, 1016, 912, 668; HRMS (ESI) calcd for $[C_{17}H_{20}N_2O+Na]^+$ 291.1473, found 291.1480; HPLC [Chiralcel OD-H, Hex/IPA=90/10, 1.0 mL/min, λ=220 nm] 94% ee; $[\alpha]_D^{23}$ −20.6 (1.0 in $CHCl_3$).

*4.4.8. (R)-2-(1-Benzyl-2-oxo-3-phenylindolin-3-yl)acetonitrile (**26b**).* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59–7.49 (dd, J=7.2, 1.0 Hz, 1H), 7.37–7.25 (m, 11H), 7.20–7.15 (dt, J=7.5, 0.9 Hz, 1H), 6.85 (d, J=7.5 Hz, 1H), 4.99 (s, 2H), 2.93 (d, J=16.5 Hz, 1H), 2.66 (d, J=16.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.5, 143.4, 137.3, 135.8, 130.3, 129.8, 129.6, 129.1, 128.5, 127.8, 127.4, 125.9, 124.1, 117.1, 110.8, 53.4, 44.9, 26.9; IR (thin film) 2881, 2123, 1600, 1585, 1504, 1400, 1380, 1016, 912, 665; HRMS (ESI) calcd for $[C_{23}H_{19}N_2O+H]^+$ 339.1497, found 339.1497. HPLC [Chiralcel OD-H, hexane/isopropanol=90/10, 1.0 mL/min, λ=220 nm] 32% ee $[\alpha]_D^{23}$ +83.6 (0.5 in $CHCl_3$).

*4.4.9. (R)-2-(3-tert-Butyl-2-oxoindolin-3-yl)acetonitrile (**27b**).* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (br s, 1H), 7.32–7.26 (m, 2H), 7.24–7.08 (m, 1H), 2.99 (d, J=16.2 Hz, 1H), 2.89 (d, J=16.5 Hz, 1H), 1.03 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.2, 139.9, 131.4, 123.4, 123.2, 116.5, 110.6, 45.3, 26.1, 37.1, 30.1; IR (thin film) 3000, 2861, 2003, 1604, 1525, 1504, 1470, 1300, 1016, 912, 665; HRMS (ESI) calcd for $[C_{14}H_{16}N_2O+Na]^+$ 251.1160, found 251.1160; HPLC [Chiralcel OD-H, Hex/IPA=90/10, 1.0 mL/min, λ=220 nm] 32% ee, $[\alpha]_D^{23}$ +32.0 (0.65 in $CHCl_3$).

*4.4.10. (S)-2-(1-Benzyl-3-((tert-butyldimethylsilyloxy)methyl)-2-oxoindolin-3-yl)acetonitrile (**47b**).* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45–7.02 (m, 7H), 7.15–7.10 (m, 1H), 6.80 (d, J=2.4 Hz, 1H), 4.91 (s, 2H) 3.98 (d, J=9.6 Hz, 1H), 3.79 (d, J=12.0 Hz, 1H), 3.04 (d, J=16.8 Hz, 1H), 2.81 (d, J=16.3 Hz, 1H), 0.82 (s, 9H), 0.01 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.7, 143.1, 136.4, 129.4, 129.0, 127.3, 124.2, 123.1, 116.5, 109.7, 66.7, 51.1, 25.7, 21.7, 18.2, −5.5; IR (thin film) 2881, 2033, 1600, 1535, 1504, 1470, 1300, 1280, 1050, 1016, 912, 678; HRMS (ESI) calcd for $[C_{24}H_{30}N_2O_2Si+Na]^+$ 429.1974, found 429.1972; HPLC [Chiralcel OD-H, Hex/IPA=90/10, 1.0 mL/min, λ=220 nm] 97% ee, $[\alpha]_D^{23}$ −7.6 (0.5 in $CHCl_3$).

*4.4.11. (S)-2-(3-((tert-Butyldimethylsilyloxy)methyl)-1-methyl-2-oxoindolin-3-yl)acetonitrile (**48b**).* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52–7.33 (m, 2H), 7.23–6.87 (m, 2H), 3.93 (d, J=9.6 Hz, 1H), 3.75 (d, J=9.6 Hz, 1H), 3.23 (s, 3H) 3.04 (d, J=16.8 Hz, 1H), 2.81 (d, J=16.3 Hz, 1H), 2.10 (s, 3H), 0.89 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.5, 144.0, 134.8, 129.6, 128.7, 128.2, 124.4, 123.2, 116.7, 108.7, 66.7, 51.2, 31.2, 25.7, 21.7, 18.2, −5.3, −5.4; IR (thin film) 2831, 2033, 1600, 1535, 1504, 1470, 1300, 1280, 1050, 1016, 912, 678; HRMS (ESI) calcd for $[C_{18}H_{26}N_2O_2Si+Na]^+$ 353.1661, found 353.1660; HPLC [Chiralcel OD-H, Hex/IPA=90/10, 1.0 mL/min, λ=220 nm] 94% ee, $[\alpha]_D^{23}$ −21.6 (0.3 in $CHCl_3$).

*4.4.12. (S)-2-(3-((tert-Butyldimethylsilyloxy)methyl)-2-oxoindolin-3-yl)acetonitrile (**49b**).* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52–7.33 (m, 2H), 7.23–6.87 (m, 2H), 3.90 (d, J=9.6 Hz, 1H), 3.77 (d, J=9.6 Hz, 1H), 3.23 (s, 3H) 3.04 (d, J=16.8 Hz, 1H), 2.81 (d, J=16.3 Hz, 1H), 0.89 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.5, 144.0, 134.8, 129.6, 128.7, 128.2, 124.4, 123.2, 116.7, 108.7, 66.7, 51.2, 25.7, 21.7, 18.2, −5.3, −5.4; IR (thin film) 2831, 2033, 1600, 1535, 1504, 1470, 1300, 1280, 1050, 1016, 912, 678; HRMS (ESI) calcd for $[C_{17}H_{24}N_2O_2Si+Na]^+$ 339.1505, found 339.1507; HPLC [Chiralcel OD-H, Hex/IPA=90/10, 1.0 mL/min, λ=220 nm] 93% ee, $[\alpha]_D^{23}$ +21.6 (0.5 in $CHCl_3$).

*4.4.13. (S)-2-(1-Benzyl-3-((tert-butyldimethylsilyloxy)methyl)-5-methoxy-2-oxoindolin-3-yl)acetonitrile (**50b**).* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31–7.25 (m, 5H), 7.08 (d, J=2.7 Hz, 1H), 6.76–6.61 (m, 2H), 4.91 (s, 2H), 3.98 (d, J=9.6 Hz, 1H), 3.83 (s, 3H), 3.79 (d, J=9.6 Hz, 1H), 3.04 (d, J=16.8 Hz, 1H), 2.81 (d, J=16.3 Hz, 1H), 0.83 (s, 9H), 0.01 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.7, 143.1, 136.4, 129.4, 129.0, 127.3, 124.2, 123.1, 116.5, 109.7, 66.7, 56.7, 51.1, 25.7, 21.7, 18.2, −5.5; IR (thin film) 3021, 2841, 2023, 1614, 1535, 1504, 1470, 1300, 1280, 1050, 1016, 912, 668; HRMS (ESI) calcd for $[C_{25}H_{32}N_2O_3Si+Na]^+$ 459.1974, found 459.1970; HPLC [Chiralcel OD-H, Hex/IPA=90/10, 1.0 mL/min, λ=220 nm] 99% ee, $[\alpha]_D^{23}$ +42.6 (0.5 in $CHCl_3$).

*4.4.14. (S)-2-(3-((tert-Butyldimethylsilyloxy)methyl)-5-methoxy-1-methyl-2-oxoindolin-3-yl)acetonitrile (**51b**).* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08 (d, J=2.7 Hz, 1H), 6.76–6.61 (m, 2H), 3.96 (d, J=9.6 Hz,

1H), 3.82 (s, 3H), 3.80 (d, J=9.6 Hz, 1H), 3.04 (d, J=16.8 Hz, 1H), 2.83 (d, J=16.3 Hz, 1H), 2.70 (s, 3H), 0.83 (s, 9H), 0.01 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.5, 144.0, 134.8, 129.6, 128.3, 124.4, 123.2, 116.7, 108.7, 66.7, 56.7, 51.1, 31.2, 26.7, 25.8, 18.3, −5.3, −5.4; IR (thin film) 3021, 2841, 2023, 1614, 1535, 1504, 1470, 1300, 1280, 1050, 1016, 912, 668; HRMS (ESI) calcd for $[C_{19}H_{28}N_2O_3Si+Na]^+$ 383.1767, found 383.1760; HPLC [Chiralcel OD-H, Hex/IPA=90/10, 1.0 mL/min, λ=220 nm] 98% ee, $[\alpha]_D^{23}$ −42.8 (0.1 in $CHCl_3$).

*4.4.15. (S)-2-(3-((tert-Butyldimethylsilyloxy)methyl)-5-methoxy-2-oxoindolin-3-yl)acetonitrile (**52b**).* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08 (d, J=2.7 Hz, 1H), 6.76–6.61 (m, 2H), 4.01 (d, J=9.6 Hz, 1H), 3.82 (d, J=9.6 Hz, 1H), 3.80 (s, 3H), 3.04 (d, J=16.8 Hz, 1H), 2.83 (d, J=16.3 Hz, 1H), 0.83 (s, 9H), 0.01 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.5, 144.0, 134.8, 129.6, 128.3, 124.4, 123.2, 116.7, 108.7, 66.7, 56.7, 51.1, 26.7, 25.8, 18.3, −5.3, −5.4; IR (thin film) 3021, 2841, 2023, 1614, 1535, 1504, 1470, 1300, 1280, 1050, 1016, 912, 668; HRMS (ESI) calcd for $[C_{18}H_{26}N_2O_3Si+Na]^+$ 366.1713, found 366.1710; HPLC [Chiralcel OD-H, Hex/IPA=90/10, 1.0 mL/min, λ=220 nm] 98% ee, $[\alpha]_D^{23}$ −88.1 (0.5 in $CHCl_3$).

4.5. General procedure for Suzuki cross-coupling

A solution of (2-bromo-phenyl)-carbamic acid *tert*-butyl ester **31** (1.65 g, 6.06 mmol) in THF (103 mL) was prepared in a flame-dry 500-mL 3-neck round bottom flask and cooled to −78 °C. A solution of *t*-BuLi (12.5 mL, 21.21 mmol, 1.7 M in pentane) was added drop-wise and the solution was maintained at −78 °C for an additional 15 min. Isopropoxy pinacolborane (2.25 g, 12.12 mmol) was added drop-wise and the solution was maintained for 1 h at −78 °C. After that the reaction was allowed to warm to rt and then quenched with satd aqueous NH_4Cl (20 mL). The resulting two layers were separated and the aqueous portion was extracted with Et_2O (2×50 mL). The combined organic portions were dried over Na_2SO_4 and concentrated under reduced pressure. The crude boronic ester **39** was carried forward directly by dissolving in benzene/MeOH (5:1, 120 mL), and adding *tert*-butyl-(2-iodo-allyloxy)-dimethyl-silane **33** (3.41 g, 11.45 mmol) followed by 10 mL of 2 M aqueous Na_2CO_3 solution. A stream of N_2 was bubbled through the reaction mixture for 5 min and $Pd(PPh_3)_4$ (0.991 g, 0.858 mmol) was added in one portion. The resulting mixture was heated to reflux (∼80 °C) and maintained for 90 min, after which TLC indicated the reaction was complete. The mixture was allowed to cool to RT and Na_2SO_4 (15 g) was added. The mixture allowed to stand for 10 min and then filtered through Celite. The filtrate was concentrated and the resulting crude product was purified by silica gel chromatography (5:95, EtOAc/Hex).

*4.5.1. {2-[1-(tert-Butyl-dimethyl-silanyloxymethyl)-vinyl]-phenyl}-carbamic acid tert-butyl ester (**36**).* ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (d, J=8.4, 1H), 7.27–7.18 (m, 1H), 7.14 (br s, 1H), 7.02–6.98 (m, 2H), 5.61 (dd, J=3.6, 1.5 Hz, 1H), 5.15 (dd, J=3.3, 1.5 Hz, 1H), 4.26 (s, 2H), 1.50 (s, 9H), 0.87 (s, 9H), 0.07 (s, 6H); HRMS (ESI) calcd for $[C_{20}H_{33}NO_3Si+Na]^+$ 386.2127, found 386.2126.

*4.5.2. {2-[1-(tert-Butyl-dimethyl-silanyloxymethyl)-vinyl]-4-methoxy-phenyl}-carbamic acid tert-butyl ester (**41**).* ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (d, J=8.4, 1H), 7.27–7.18 (m, 1H), 7.14 (br s, 1H), 7.02–6.98 (m, 2H), 5.61 (dd, J=3.6, 1.5, 1H), 5.15 (dd, J=3.3, 1.5 Hz, 1H), 4.26 (s, 2H), 1.50 (s, 9H), 0.87 (s, 9H), 0.07 (s, 6H); HRMS (ESI) calcd for $[C_{21}H_{35}NO_4Si+Na]^+$ 416.2233, found 416.2234.

4.6. Synthesis of (−)-coerulescine and (+)-horsfiline

The oxindole (1.0 equiv) was dissolved in dry THF (10 mL) in flame dried RBF and then added TBAF (5.0 equiv) (1.0 M solution in THF) and stirred at rt for 2 h. TLC checked (reaction completed) and then the THF removed under reduced pressure. The crude product was immediately carried on to next step without purification. The free alcohol (1.0 equiv) in methylene chloride was then treated with MsCl (1.1 equiv) and triethylamine (2.5 equiv) at rt and stirred for 15 min then quenched with saturated NH_4Cl solution, separated two layers and extracted the aqueous layer with methylene chloride (2×10 mL) and combined organic portions were dried over anhydrous Na_2SO_4 and evaporated under vacuum. The mesylate was then treated with $CoCl_2\cdot 6H_2O$ (1.5 equiv), $NaBH_4$ (3.0 equiv) in MeOH (10 mL) at rt and stirred for 2 h and then added HCHO (2.0 equiv), and the suspension was stirred for 6 h at room temperature. The reaction was quenched with saturated aqueous NH_4Cl solution, evaporated MeOH, then EtOAc (10 mL) was added and washed with 2 N aqueous EDTA solution and evaporated the solvent after drying with anhydrous Na_2SO_4. The crude compound was purified by silica-gel chromatography using EtOAc/MeOH (95:5 and added 2–3 drops of triethylamine).

4.6.1. (−)-Coerulescine. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.16 (1H, br s, NH), 7.42 (d, J=7.2 Hz, 1H), 7.20 (m, 1H), 7.07 (m, 1H), 6.88 (d, J=8.0 Hz, 1H), 3.11–3.05 (m, 1H), 2.96–2.89 (m, 2H), 2.86–2.80 (m, 1H), 2.50 (s, 3H), 2.45–2.39 (m, 1H), 2.18–2.10 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 183.4, 140.4, 136.1, 128.0, 123.5, 123.1, 109.7, 66.4, 56.7, 55.9, 54.1, 41.8, 38.1; IR (thin film): 3223, 2940, 2835, 1707, 1603, 1484; HRMS (ESI) calcd for $[C_{12}H_{14}N_2O+Na]^+$ 225.1004, found 225.1000; HPLC [Chiralcel OD-H, Hex/IPA=90/10, 1.0 mL/min, λ=220 nm] 91% ee, $[\alpha]_D^{23}$ −0.9 (0.10 in MeOH).

4.6.2. (+)-Horsfiline. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.47 (br s, 1H), 7.04 (d, J=2.0 Hz, 1H), 6.76 (d, J=8.0 Hz, 1H), 6.72 (dd, J=8.0, 2.0 Hz, 1H), 3.80 (s, 3H), 2.98–3.03 (m, 1H), 2.86 (s, 2H), 2.76 (dd, J=9.0,8.0, 9.0 Hz, 1H), 2.45 (s, 3H), 2.40 (ddd, J=12.0, 7.5, 4.5 Hz, 1H), 2.08 (dt, J=13.0, 7.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 182.6, 156.1, 137.7, 133.3, 112.4, 110.3, 109.7, 66.4, 56.7, 55.9, 54.1, 41.8, 38.1; IR (neat): 3223, 2940, 2835, 1707, 1603, 1484 cm^{-1}; HRMS (ESI) calcd for $[C_{13}H_{16}N_2O_2+Na]^+$ 255.1109, found 255.1110; HPLC [Chiralcel OD-H, Hex/IPA=90/10, 1.0 mL/min, λ=220 nm], 99% ee, $[\alpha]_D^{23}$ −5.9 (0.40 in MeOH).

4.7. Synthesis of (−)-esermethole

Procedure: this procedure is adapted from Nakao and Hiyama:[2] a solution of (*S*)-2-(5-methoxy-1,3-dimethyl-2-oxoindolin-3-yl) acetonitrile **14b** (78 mg, 0.34 mmol) and $LiAlH_4$ (52 mg, 1.36 mmol) in THF (12 mL) were stirred under an argon atmosphere at rt for 1 h, and then heated at the reflux temperature for 0.5 h. The reaction was quenched by careful addition of 2 mL of THF–H_2O (10:1) solution at 0 °C, and the resulting mixture was diluted with CH_2Cl_2 and filtered through a fritted-glass filter. The resulting precipitates were washed thoroughly with CH_2Cl_2, and the filtrate was concentrated in vacuo. The residue was dissolved in EtOAc (5 mL) and added 1 M HCl aqueous solution (5 mL). After being stirred for 5 min, the solution was neutralized by adding solid K_2CO_3, and then extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered through a Celite pad, and concentrated in vacuo.

A solution of above crude (47 mg, 0.21 mmol) in MeOH (12 mL) was added HCHO aqueous solution (37 wt %, 79 μl, 1.07 mmol) at 0 °C under an argon atmosphere, and the whole was stirred for 5 min. $NaBH(OAc)_3$ (1.07 mmol, 230 mg) was added to the resulting mixture, and the solution was stirred at rt for 1.5 h. The solution was diluted with EtOAc and concentrated. The residue was treated with a saturated $NaHCO_3$ aqueous solution and extracted with CH_2Cl_2 for three times. Combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, filtered through Celite, and then concentrated in vacuum. The residue was purified

by flash column chromatography on silica gel (MeOH/$CHCl_3$, 5:95 and few drops of triethylamine) to give (−)-esermethole (46 mg, 92% over the two steps) as an amorphous solid: R_f=0.49 ($CHCl_3$/MeOH, 50:1) ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.68–6.62 (m, 2H), 6.36 (d, J=8.4 Hz, 1H), 4.05 (s, 1H), 3.75 (s, 3H), 2.90 (s, 3H), 2.72 (dt, J=8.8, 5.3 Hz, 1H), 2.64 (dt, J=9.0, 7.4 Hz, 1H), 2.54 (s, 3H), 1.95 (dd, J=7.5, 5.5 Hz, 2H), 1.44 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.7, 146.4, 138.1, 112.0, 109.7, 107.3, 98.3, 56.0, 53.2, 52.8, 40.9, 38.3, 38.1, 27.6; HRMS (ESI) calcd for $[C_{14}H_{20}N_2O+Na]^+$ 255.1473, found 255.1470. HPLC [Chiralcel OD-H, Hex/IPA=90/10, 1.0 mL/min, λ=220 nm, 99% ee, $[\alpha]_D^{23}$ −130.0 (1.0 in MeOH).

Acknowledgements

We thank the University of Minnesota (UMN) for start-up funds, Prof. Andrew Harned (UMN) for use of a shared HPLC, and Ms. Rosalind Douglas (UMN) for assistance in manuscript preparation.

Supplementary data

^{1}H and ^{13}C NMR spectra and HPLC chromatograms for chiral compounds not previously reported. Spectra and chromatograms for many compounds were already reported in a recent communication.[5a] Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.02.096.

References and notes

1. (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.
2. Nakao, Y.; Ebata, S.; Yada, A.; Hiyama, T.; Ikawa, M.; Ogoshi, S. *J. Am. Chem. Soc.* **2008**, *13*, 12874.
3. Watson, M. P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2008**, *13*, 12594.
4. (a) Yasui, Y.; Kamisaki, H.; Takemoto, Y. *Org. Lett.* **2008**, *10*, 3303; (b) Yasui, Y.; Kamisaki, H.; Ishida, T.; Takemoto, Y. *Tetrahedron* **2010**, *66*, 1980.
5. Reviews: (a) Trost, B. M.; Jiang, C. *Synthesis* **2006**, 369; (b) *Quaternary Stereocenters*; Christoffers, J., Baro, A., Eds.; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, 2005; (e) Douglas, C. J.; Overman, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5363.
6. (a) Reddy, V. J.; Douglas, C. J. *Org. Lett.* **2010**, *12*, 952; (b) Reddy, V.J.; Douglas, C.J. Abstracts of Papers, 238th National Meeting of the American Chemical Society, Washington, DC, Aug 16–20, 2009; ORGN 669.
7. Jacobs, T. L.; Winstein, S.; Henderson, R. B.; Spaeth, E. C. *J. Am. Chem. Soc.* **1946**, *68*, 1310.
8. Martin, E. L. *Org. Synth.* **1971**, *51*, 268.
9. 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.
10. Zhang, F.-Y.; Chan, A. S. C. *Tetrahedron: Asymmetry* **1998**, *9*, 1179.
11. Denmark, S. E.; Yutaka, X. S.; Nishigaichi, Y.; Coe, D. M.; Wong, D.-T.; Winter, S. B. D.; Choi, J. Y. *J. Org. Chem.* **1999**, *64*, 1958.
12. Ueno, S.; Chatani, N.; Kakiuchi, F. *J. Am. Chem. Soc.* **2007**, *129*, 6098.
13. McDonald, I. M.; Austin, C.; Buck, I. M.; Dunstone, D. J.; Gaffen, J.; Griffin, E.; Harper, E. A.; Hull, R. A. D.; Kalindjian, S. B.; Linney, I. D.; Low, C. M. R.; Patel, D.; Pether, M. J.; Raynor, M.; Roberts, S. P.; Shaxted, M. E.; Spencer, J.; Steel, K. I. M.; Sykes, D. A.; Wright, P. T.; Xun, W. *J. Med. Chem.* **2007**, *50*, 4789.
14. (a) Appukkuttan, P.; Van der Eycken, E.; Dehaen, W. *Synlett* **2003**, 1204; (b) Gómez-Bengoa, E.; Echavarren, A. M. *J. Org. Chem.* **1991**, *56*, 3497.
15. Preparation of **32**: (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.; Qiang, W.; Bernal, F.; Chen, D. Y.-K. *Angew. Chem., Int. Ed.* **2003**, *42*, 3643.
16. Clay, M. D.; Fallis, A. G. *Angew. Chem., Int. Ed.* **2005**, *44*, 4039.
17. Muchowski, J. M.; Venuti, M. C. *J. Org. Chem.* **1980**, *45*, 4798.
18. Myers, A. G.; Tom, N. J.; Fraley, M. E.; Cohen, S. B.; Madar, D. J. *J. Am. Chem. Soc.* **1997**, *119*, 6072.
19. (a) Renaud, J.; Ouellet, S. G. *J. Am. Chem. Soc.* **1998**, *120*, 7995; (b) Takahashi, K.; Ishiyama, T.; Miyaura, N. *J. Organomet. Chem.* **2001**, *625*, 47.
20. Youn, S. W.; Song, J.-H.; Jung, D.-I. *J. Org. Chem.* **2008**, *73*, 5658.
21. Garg, N. K.; Sarpong, R.; Stoltz, B. M. *J. Am. Chem. Soc.* **2002**, *124*, 13179.
22. Selected recent enantioselective syntheses: (a) Bui, T.; Syed, S.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2009**, *131*, 8758; (b) See Ref. 1. (c) Pinto, A.; Jia, Y.; Neuville, L.; Zhu, J. *Chem.—Eur. J.* **2007**, *13*, 961; (d) Trost, B. M.; Quancard, J. *J. Am. Chem. Soc.* **2006**, *128*, 6314; (e) Trost, B. M.; Zhang, Y. *J. Am. Chem. Soc.* **2006**, *128*, 4590; (f) Huang, A.; Kodanko, J. J.; Overman, L. E. *J. Am. Chem. Soc.* **2004**, *126*, 14043.
23. Selected recent syntheses of (±)-esermethole: (a) Kulkarni, M. G.; Dhondge, A. P.; Borhade, A. S.; Gaikwad, D. D.; Chavhan, S. W.; Shaikh, Y. B.; Ningdale, V. B.; Desai, M. P.; Birhade, D. R.; Shinde, M. P. *Tetrahedron Lett.* **2009**, *50*, 2411; (b) Rigby, J. H.; Sidique, S. *Org. Lett.* **2007**, *9*, 1219; (c) See Ref 4b; (d) Nishida, A.; Ushigome, S.; Sugimoto, A.; Arai, S. *Heterocycles* **2005**, *66*, 181; (e) Mukai, C.; Yoshida, T.; Sorimachi, M.; Odani, A. *Org. Lett.* **2006**, *8*, 83.
24. See Ref. 22f.
25. (a) Greig, N. H.; Pei, X.-F.; Soncrant, T. T.; Ingram, D. K.; Brossi, A. *Med. Res. Rev.* **1995**, *15*, 3; (b) Sano, N.; Bell, K.; Marder, K.; Stricks, L.; Stern, Y.; Mayeux, R. *Clin. Neuropharmacol.* **1993**, *16*, 61.
26. Yu, Q.-S.; Holloway, H. W.; Flippen-Anderson, J. L.; Hoffman, B.; Brossi, A.; Greig, N. H. *J. Med. Chem.* **2001**, *44*, 4062.
27. Shaw, K. T. Y.; Utsuki, T.; Rogers, J.; Yu, Q.-S.; Sambamurti, K.; Brossi, A.; Ge, Y.-Y.; Lahiri, D. K.; Greig, N. H. *Proc. Natl. Acad. Sci. U.S.A.* **2001**, *98*, 7605.
28. .http://www.drugdevelopment-technology.com/projects/phenserine/ accessed on 13 January 2010.
29. 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.
30. Cui, C. B.; Kakeya, H.; Osada, H. *J. Antibiot.* **1996**, *49*, 832.
31. Prior enantioselective syntheses: (a) Trost, B. M.; Brennan, M. K. *Org. Lett.* **2006**, *8*, 2027; (b) Cravotto, G.; Giovenzana, G.; 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*, 1979.
32. Syntheses of (±)-horsfiline or (±)-coerulescine: (a) Jaegli, S.; Vors, J.-P.; Neuville, L.; Zhu, J. *Synlett* **2009**, 2997; (b) Murphy, J. A.; Tripoli, R.; Khan, T. A.; Mali, U. W. *Org. Lett.* **2005**, *7*, 3287; (c) Chang, M. Y.; Pai, C.-L.; Kung, Y.-H. *Tetrahedron Lett.* **2005**, *46*, 8463; (d) Lizos, D. E.; Murphy, J. A. *Org. Biomol. Chem.* **2003**, *1*, 117; (e) Selvakumar, N.; Azhagan, A. M.; Srinivas, D.; Krishna, G. G. *Tetrahedron Lett.* **2002**, *43*, 9175; (f) Kumar, U. K.; Syam, I. H.; Junjappa, H. *Org. Lett.* **2001**, *3*, 4193; (g) Fischer, C.; Meyers, C.; Carreira, E. M. *Helv. Chim. Acta* **2000**, *83*, 1175; (h) Bascop, S.; Sapi, J. A.; Laroze, J.; Levy, J. *Heterocycles* **1994**, *38*, 725; (i) Jones, K.; Wilkinson, J. *J. Chem. Soc., Chem. Commun.* **1992**, 1767.
33. (a) Satoh, T.; Suzuki, S.; Suzuki, Y.; Miyaji, Y.; Imai, X. *Tetrahderon Lett.* **1969**, *10*, 4555; (b) Zhu, U.; Quirion, J.-C.; Husson, H.-P. *J. Org. Chem.* **1993**, *58*, 6451.
34. Jensen, T.; Pedersen, H.; Bang-Anderson, B.; Madsen, R.; Jørgensen, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 888.
35. Linn, W. J. *Org. Synth.* **1969**, *49*, 103.