Natural Products

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Enantioselective Total Synthesis of (−)-Lansai B and (+)-Nocardioazines A and B**

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Abstract: *The concise total syntheses of the bis(pyrroloindolines) (−)-lansai B and (+)- nocardioazines A and B are reported. The key pyrroloindoline building blocks are rapidly prepared by enantioselective formal [3+2] cycloaddition reactions. The macrocycle of (+)-nocardioazine A is constructed by an unusual intramolecular diketopiperazine formation.*

Pyrroloindoline natural products are a growing family of alkaloids which exhibit promising biological properties, including antibacterial and anticancer activities.[1] Within this family, a number of bis(pyrroloindolines) that are joined through a central diketopiperazine (DKP) ring have been identified.[2] These structures include (−)-lansai B (**1**), (+)-nocardioazine A (**2**), and (+)-nocardioazine B (**3**; see Figure 1). (+)-Nocardioazine A (**2**) is of particular interest because of its activity as an inhibitor of P-glycoprotein, a transmembrane protein overexpressed in many multidrug-resistant tumors.[2b] Although these natural products appear quite similar structurally, close analysis reveals subtle differences in the relative stereochemistry of the pyrroloindoline units. Whereas **1** is composed of two *exo* pyrroloindolines, **2** and **3** each possess one *endo* and one *exo* pyrroloindoline. Moreover, the *endo* and *exo* pyrroloindolines are in the opposite enantiomeric series, which is necessary to geometrically accommodate the macrocycle of **2**. This interesting stereochemical relationship makes **2** and **3** appealing synthetic targets for asymmetric catalysis, where selection of the appropriate enantiomer of the catalyst dictates the absolute stereochemistry of the pyrroloindoline building block. The first diastereoselective total synthesis of **3** was reported in 2012 by the group of Ye and required 10 steps starting from L- and D-tryptophan.[3] No total syntheses of **1** or **2** have been published to date.

Recently, we reported a new method to prepare enantioenriched pyrroloindolines from C3-substituted indoles and 2-amidoacrylates using $SnCl_4$ and catalytic (*R*)-3,3′-dichloro-BINOL (Figure 1).[4] Based on the retrosynthetic analysis shown in Figure 1, we anticipated that this formal (3+2) cycloaddition reaction could be used to rapidly and enantioselectively prepare natural products **1**, **2**, and **3**. Herein, we report the successful execution of this plan and demonstrate the utility of this catalytic asymmetric method for the synthesis of diketopiperazine-containing bis(pyrroloindolines).

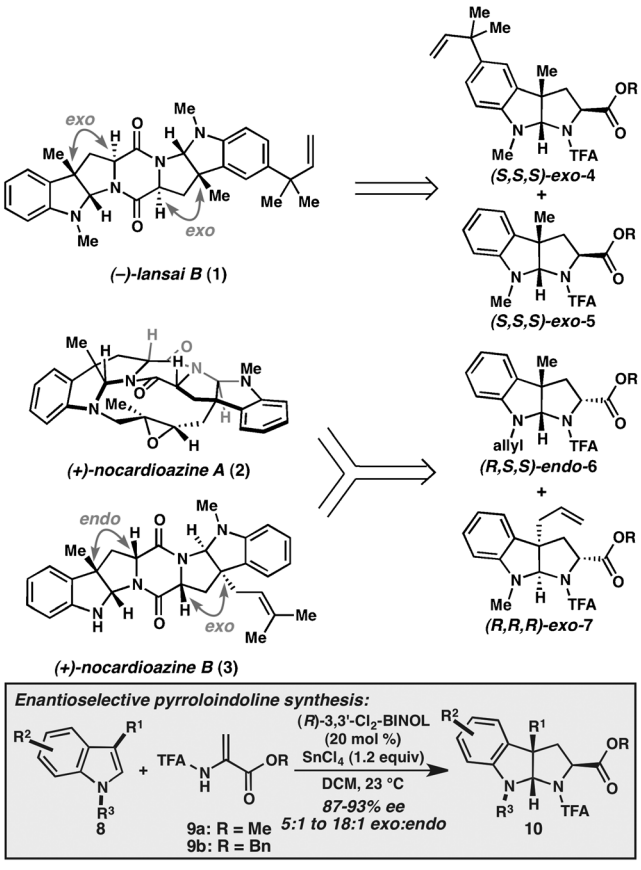

Figure 1. Retrosynthetic analysis of (−)-lansai B (**1**), (+)-nocardioazine A (**2**), and (+)-nocardioazine B (**3**). BINOL = 1,1′-binaphthalene-2,2′-diol, TFA = trifluoroacetamido.

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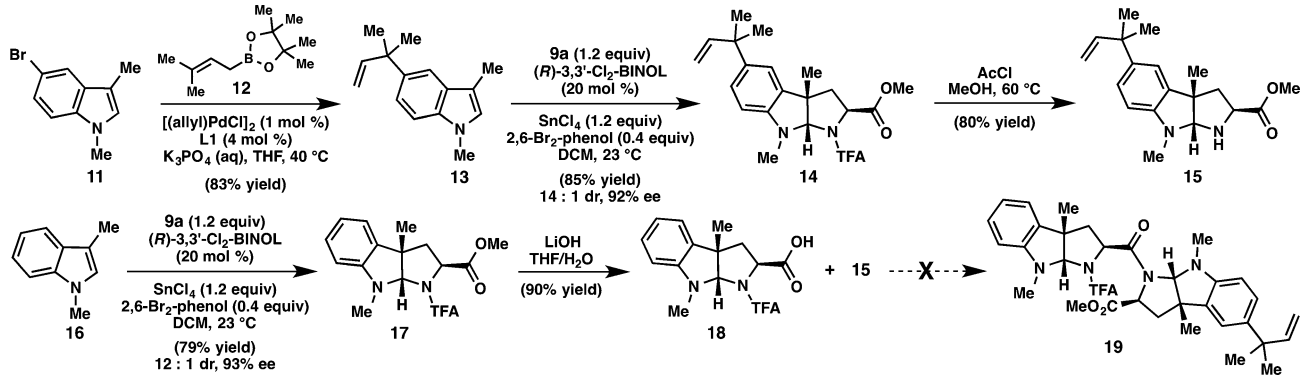
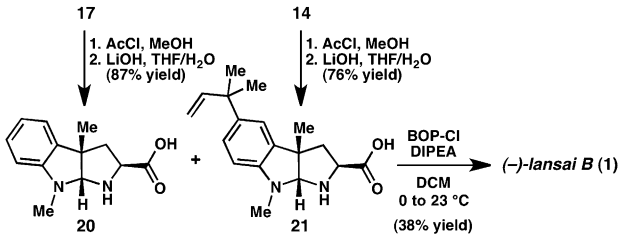


Scheme 1. Synthesis of the pyrroloindoline fragments of (−)-lansai B (**1**). AcCl = acetyl chloride, THF = tetrahydrofuran.

We first targeted (−)-lansai B (**1**, Figure 1). Retrosynthetically, it was envisioned that the DKP core could be prepared from the union of the pyrroloindolines (*S*,*S*,*S*)-*exo*-**4** and (*S*,*S*,*S*)-*exo*-**5** by sequential peptide bond formation. The required pyrroloindolines could in turn be synthesized by formal (3+2) cycloaddition reactions of the corresponding indoles **13** and **16** (Scheme 1).

Our efforts commenced with Suzuki–Miyaura coupling of the bromoindole **11**[4a] and prenylboronate **12** to furnish the reverse-prenylated indole **13** in good yield (Scheme 1).[5] Subjection of **13** and methyl 2-trifluoroacetamidoacrylate (**9a**) to our formal (3+2) cycloaddition conditions on a 0.2 mmol scale provided the pyrroloindoline **14** in 84% yield and 92% *ee*. However, lower yields of **14** were obtained when the reaction was conducted on preparatively useful scales (> 1.0 mmol). It was hypothesized that on small scale trace water might help to turn over the chiral catalyst. A survey of several protic additives revealed that addition of 0.4 equivalents 2,6-dibromophenol to the reaction mixture improves the scalability of the reaction, thus providing **14** in 85% yield, 14:1 d.r., and 92% *ee* (major diastereomer).[4b] Presumably 2,6-dibromophenol facilitates turnover of the chiral catalyst, but is not reactive enough to protonate the transient enolate directly in a nonselective fashion. Cleavage of the TFA group with anhydrous HCl provided the amine **15**.[6] Likewise, the pyrroloindoline **17** could be prepared from 1,3-dimethyl indole **16** and acrylate **9a** in 79% yield, 12:1 d.r., and 93% *ee* (major diastereomer). Treatment with LiOH chemoselectively hydrolyzed the methyl ester to give the carboxylic acid **18**.

With the orthogonally protected pyrroloindolines **15** and **18** in hand, completion of the synthesis required DKP formation. Unfortunately, the amide **19** was not formed under a wide variety of peptide-coupling conditions (Scheme 1).[7] Instead, decomposition of **18** was observed. We note that Danishefsky and co-workers successfully coupled two orthogonally protected *exo* pyrroloindolines in their synthesis of amauromine, however, in contrast to **18**, the carboxylic acid partner in the Danishefsky system contained electron-withdrawing *tert*-butylcarbamate protecting groups on both nitrogen atoms.[8] Taken together, these findings reveal that the N substitution of the *exo* pyrroloindoline significantly influences the stability of the activated ester under peptide coupling conditions. After considerable experimentation, it was determined that the pyrroloindolines **17** and **14** could be converted into amino the acids **20** and **21**, respectively, by TFA deprotection and saponification (Scheme 2). Although we recognized that use of the amino



Scheme 2. Synthesis of (−)-lansai B (**1**). BOP-Cl = bis(2-oxo-3-oxazolidinyl) phosphinic chloride, DIPEA = *N*,*N*-diisopropylethylamine.

acids in the coupling reaction could give rise to a mixture of three possible diketopiperazines (the desired heterodimer and two homodimers), we reasoned that the overall process could still be more efficient than proceeding through a series of protecting-group manipulations. Thus, treatment of an equimolar mixture of **20** and **21** with BOPCl delivered (−)-lansai B (**1**) in 38% yield. Each of the two homodimers was also isolated in 20% yield.[9] Despite the modest yield on the final coupling step, the natural product is accessible in only six steps (longest linear sequence) and 20% overall yield from commercially available materials.

Having completed the synthesis of **1**, we turned our attention to the synthesis of (+)-nocardioazines A (**2**) and B (**3**). Retrosynthetically, it was envisioned that both **2** and **3** could be accessed from the DKP generated by coupling the pyrroloindolines (*R*,*S*,*S*)-*endo*-**6** and (*R*,*R*,*R*)-*exo*-**7** (Figure 1). In the forward sense, treatment of a solution of *N*-methyl-3-allyl indole (**22**) and **9a** with (*S*)-binol (20 mol%) and $SnCl_4$ (1.6 equiv) delivered the *exo*-pyrroloindoline **23** in 52% yield and 90% *ee* (Scheme 3). These reaction conditions were highly diastereoselective for *exo*-**23** (19:1), however, the yield is modest because of allyl migration from C3 to C2 of the indole under the reaction conditions.[9] Neither addition of 2,6-dibromophenol nor use of other catalysts improved the yield of *exo*-**23**. Removal of the TFA group using TfOH in

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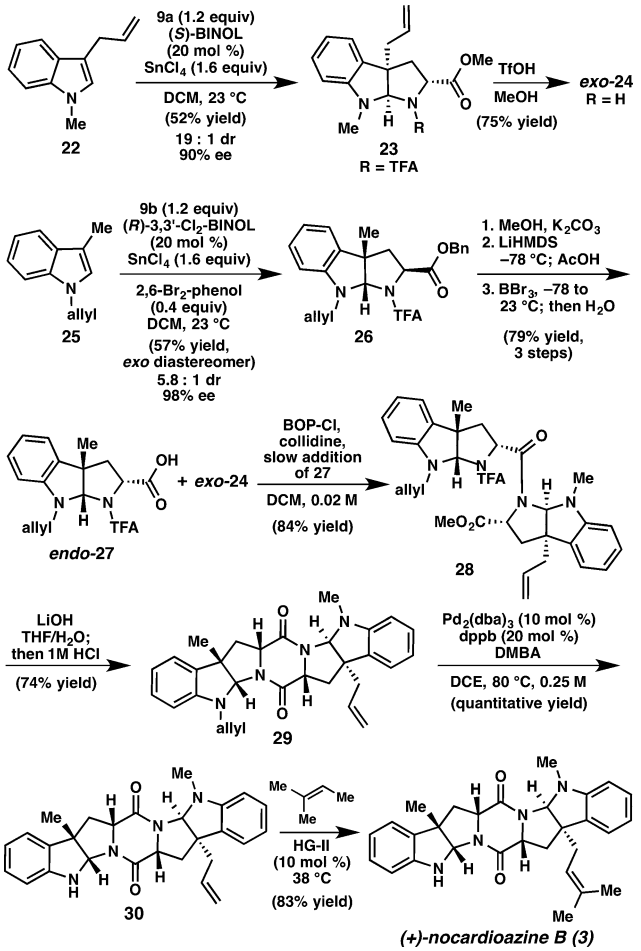


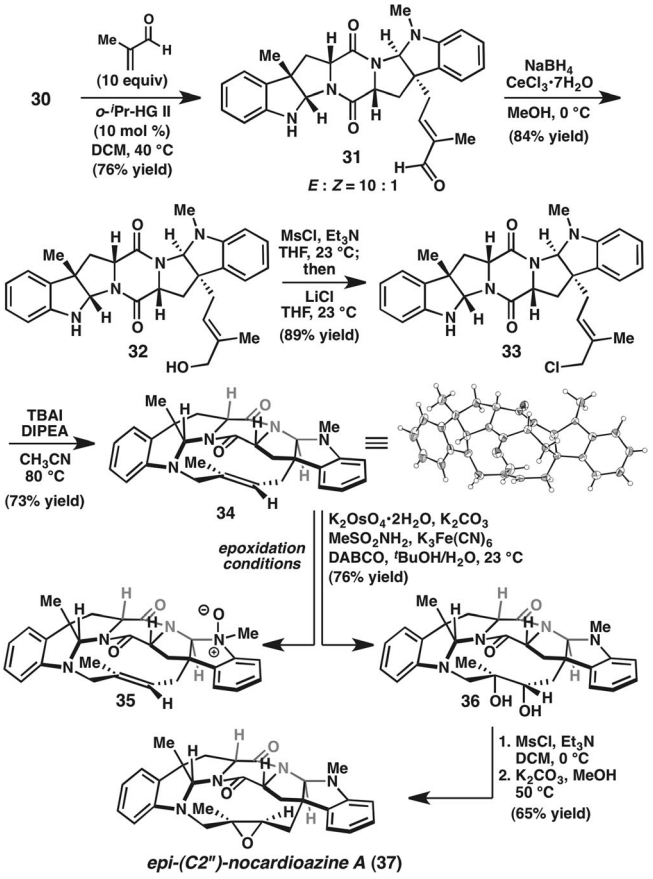
Scheme 3. Synthesis of (+)-nocardioazine B (**3**). dba = dibenzylideneacetone, DCE = dichloroethane, DMBA = 1,3-dimethylbarbituric acid, dppb = 1,4-bis(diphenylphosphino)butane, LiHMDS = lithium hexamethyldisilazide, TfOH = trifluoromethane sulfonic acid.

anhydrous methanol provided, upon basic workup, the *exo*-amine **24**.

In contrast, treatment of the *N*-allylindole **25** and benzyl trifluoroacetamidoacrylate (**9b**) with (*R*)-3,3′-dichloro-BINOL (20 mol%), $SnCl_4$ (1.6 equiv), and 2,6-dibromophenol (0.4 equiv) furnished *exo*-pyrroloindoline **26** in 57% yield and 98% *ee* (Scheme 3). The modest yield of *exo* **26** results from the moderate diastereoselectivity (5.8:1) of the transformation. Following transesterification, epimerization using LiHMDS and subsequent cleavage of the methyl ester with BBr_3 delivered the *endo*-pyrroloindoline **27**.

With access to *endo*-**27** and *exo*-**24**, we were poised to prepare the key DKP **29** (Scheme 3). In contrast to our unsuccessful efforts to couple the *exo*-pyrroloindolines **15** and **18**, it was determined that slow addition of *endo*-**27** to 2.0 equivalents of amine *exo*-**24** and BOP-Cl provides **28** in 84% yield.[10] Importantly, the unreacted *exo*-**24** was recovered by silica gel chromatography. When compared to the challenges encountered in the coupling of *exo*-pyrroloindolines **15** and **18**, the ability to couple *exo*-**24** and *endo*-**27** reveals that, in addition to the identity of the N substituents, the relative stereochemistry of the pyrroloindoline coupling partners is determinate of the ease of peptide formation. Saponification of **28** with LiOH followed by acidification with 1M HCl delivered **29**. Subsequent palladium-catalyzed deallylation of **29** gave the amine **30**,[11] which upon cross-metathesis with 2-methyl-2-butene[12] provided (+)-nocardioazine B (**3**). Thus, the enantioselective total synthesis of **3** was completed in nine linear steps and 21% overall yield from 3-methylindole.

At this stage, our focus shifted to advancing **30** to (+)-nocardioazine A (**2**). Cross-metathesis of **30** with excess methacrolein delivered the enal **31** in 76% yield as a 10:1 *E*/*Z* mixture (Scheme 4). Luche reduction followed by Finkelstein



Scheme 4. Synthesis of the nocardioazine A macrocycle. Atomic displacement parameters shown at 50% probability.[15] DABCO = 1,4-diazabicyclo[2.2.2]-octane, MsCl = methanesulfonyl chloride, TBAI = tetrabutylammonium iodide.

chlorination provided the allyl chloride **33**. Gratifyingly, treatment of **33** with TBAI and base in acetonitrile at 80°C promoted intramolecular N alkylation, thus furnishing the macrocycle **34**. Unfortunately, exposure of **34** to a wide variety of epoxidation conditions, including dimethyldioxirane, *m*-chloroperbenzoic acid, and Jacobsen epoxidation catalysts, failed to produce the natural product. Instead, the major product was the unstable *N*-oxide **35**. Use of excess oxidant or efforts to isolate **35** and resubject it to epoxidation conditions were also unfruitful, thus indicating that the trisubstituted alkenes of **34** and **35** are remarkably inert

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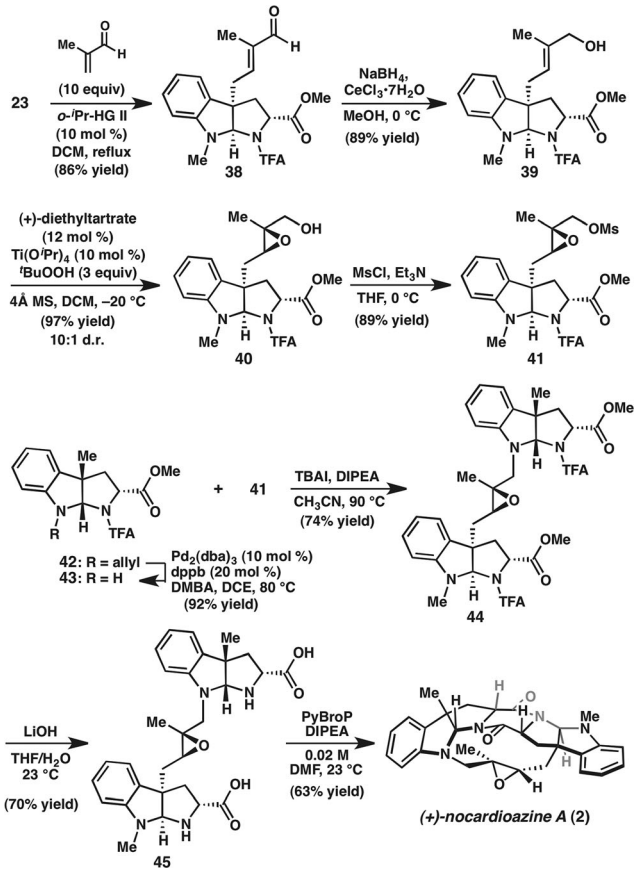
toward epoxidation. Inspection of the crystal structure of alkene **34** suggests that the poor reactivity does not simply result from steric shielding of the double bond. Instead, the electron-withdrawing allylic nitrogen atom might inductively deactivate the alkene toward electrophiles.

Alternatively, it was possible to diastereoselectively dihydroxylate **34** using potassium osmate.[13] Selective mesylation at the secondary alcohol and exposure to potassium carbonate in methanol delivered *epi*-(C2″)-nocardioazine A (**37**). Unfortunately, attempts to correct the stereochemistry by double inversion strategies or oxidation/reduction sequences were unsuccessful.

Given the challenges encountered in attempting to epoxidize **34**, a revised strategy utilizing an early-stage epoxidation and diketopiperazine-forming macrocyclization was pursued (Scheme 5). Thus, the 3a-allyl pyrroloindoline **23**



Scheme 5. Synthesis of (+)-nocardioazine A (**2**). DMF = *N*,*N*-dimethylformamide, MS = molecular sieves, PyBroP = bromotripyrrolidinophosphonium hexafluorophosphate.

was converted into the allylic alcohol **39** in two steps. Sharpless asymmetric epoxidation delivered the epoxy alcohol **40** in 10:1 d.r.,[14] and was converted into the mesylate **41**. Concomitantly, the amine **43** was prepared from the *endo*-pyrroloindoline **42** by palladium-catalyzed deallylation. After extensive optimization of the reaction parameters, it was found that treatment of **43** and **41** with catalytic TBAI and Hünig's base in acetonitrile at 90 °C delivers the bis(pyrroloindoline) **44** in 74 % yield. Exposure of **44** to excess LiOH resulted in saponification of the methyl esters and hydrolysis of the trifluoroacetamides to give the bis(amino acid) **45**. We were pleased to find that subjection of **45** to PyBroP in DMF promoted intramolecular DKP formation to afford (+)-nocardioazine A (**2**). The optical rotation of synthetic **2** was determined to be the same sign and similar magnitude as that reported by Capon and co-workers in the original isolation paper.[2b] As a result, we have revised Capon's assignment of the absolute stereochemistry of **2** to that shown throughout this manuscript, which is consistent with Ye and co-workers's reassignment of **3**.[3] The synthesis of **2** requires nine linear steps and proceeds in 11 % overall yield from 3-allylindole. In addition, these findings establish the viability of macrocyclization by intramolecular DKP formation.

In summary, the enantioselective total syntheses of the DKP-containing pyrroloindoline natural products (−)-lansai B (**1**), (+)-nocardioazine A (**2**), and (+)-nocardioazine B (**3**) were accomplished. These studies demonstrate the utility of enantioselective formal (3+2) cycloaddition reactions to prepare highly functionalized pyrroloindolines for applications in total synthesis. In addition, subtle changes in the relative stereochemistry and nitrogen substitution patterns of pyrroloindolines were shown to significantly influence the ability to prepare bis(pyrroloindolines) by DKP formation. Further investigations of **3** as an inhibitor of P-glycoprotein are ongoing in our laboratory.

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[1] a) K. T. Y. Shaw, T. Utsuki, J. Rogers, Q.-S. Yu, K. Sambamurti, A. Brossi, Y.-W. Ge, D. K. Lahiri, N. H. Greig, *Proc. Natl. Acad. Sci. USA* **2001**, *98*, 7605 – 7610; b) C. R. Isham, J. D. Tibodeau, W. Jin, R. Xu, M. M. Timm, K. C. Bible, *Blood* **2007**, *109*, 2579 – 2588.

[2] a) P. Tuntiwachwuttikul, T. Taechowisan, A. Wanbanjob, S. Thadaniti, W. C. Taylor, *Tetrahedron* **2008**, *64*, 7583 – 7586; b) R. Raju, A. M. Piggott, X. Huang, R. J. Capon, *Org. Lett.* **2011**, *13*, 2770 – 2773.

[3] M. Wang, X. Feng, L. Cai, Z. Xu, T. Ye, *Chem. Commun.* **2012**, *48*, 4344 – 4346; This communication resulted in the reassignment of the absolute stereochemistry of nocardioazine B.

[4] a) L. M. Repka, J. Ni, S. E. Reisman, *J. Am. Chem. Soc.* **2010**, *132*, 14418 – 14420; b) J. Ni, H. Wang, S. E. Reisman, *Tetrahedron* **2013**, *69*, 5622 – 5633; For a review of catalytic, asymmetric methods to prepare pyrroloindolines, see: c) L. M. Repka, S. E. Reisman, *J. Org. Chem.* **2013**, *78*, 12314.

[5] Y. Yang, S. L. Buchwald, *J. Am. Chem. Soc.* **2013**, *135*, 10642 – 10645; **L1** = dicyclohexyl(2-(2-methoxynaphthalen-1-yl)phenyl)phosphine. See the Supporting Information for structure.

[6] S. B. King, B. Ganem, *J. Am. Chem. Soc.* **1994**, *116*, 562 – 570.

[7] E. Valeur, M. Bradley, *Chem. Soc. Rev.* **2009**, *38*, 606.

[8] K. M. Depew, S. P. Marsden, D. Zatorska, A. Zatorski, W. G. Bornmann, S. J. Danishefsky, *J. Am. Chem. Soc.* **1999**, *121*, 11953 – 11963.

[9] See the Supporting Information.

[10] See the Supporting Information for optimization experiments.

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[11] F. Garro-Helion, A. Merzouk, F. Guibe, *J. Org. Chem.* **1993**, *58*, 6109 – 6113.
[12] A. K. Chatterjee, D. P. Sanders, R. H. Grubbs, *Org. Lett.* **2002**, *4*, 1939 – 1942.
[13] J. Eames, H. J. Mitchell, A. Nelson, P. O'Brien, S. Warren, P. Wyatt, *J. Chem. Soc. Perkin Trans. 1* **1999**, 1095 – 1104.
[14] Y. Gao, J. M. Klunder, R. M. Hanson, H. Masamune, S. Y. Ko, K. B. Sharpless, *J. Am. Chem. Soc.* **1987**, *109*, 5765 – 5780.
[15] CCDC 997790 contains the supplementary crystallographic data for compound **34** in this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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