Asymmetric Synthesis of Indolines Bearing a Benzylic Quaternary Stereocenter through Intramolecular Arylcyanation of Alkenes

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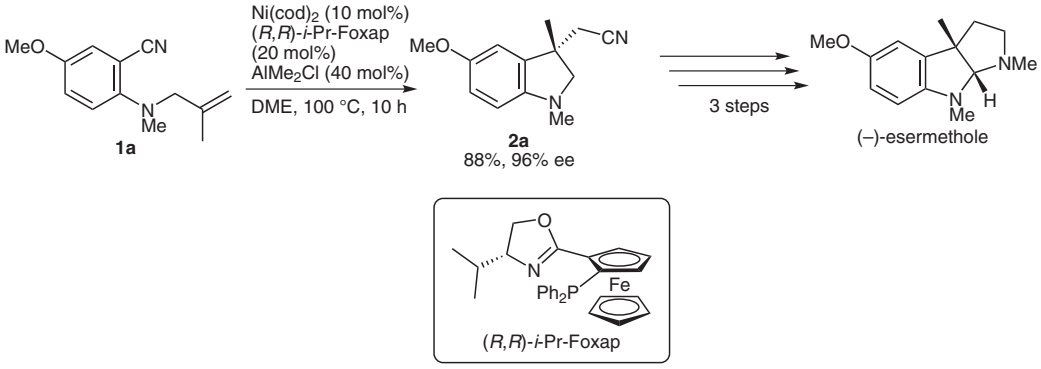
Abstract: Enantioselective intramolecular arylcyanation of olefins is achieved by a Ni(cod)$_2$/chiral phosphinoxazoline/AlMe$_2$Cl catalyst to give chiral, substituted indoline derivatives bearing a benzylic quaternary stereocenter in high yields with good to excellent enantioselectivities.

Key words: asymmetric synthesis, carbocyanation, C–C bond activation, nickel, indoline

An indoline substructure bearing substituents at its 3-position is frequently found in alkaloids having significant biological activities.[1] To access this structural motif, intramolecular addition of arylpalladium species across olefins tethered by an *ortho*-amino group has often been a choice of strategy for synthetic organic chemists. This elemental step is followed either by β-hydride elimination[2,3] (the Mizoroki–Heck reaction) or reactions with nucleophiles[4,5] to achieve catalytic synthesis of 3,3-disubstituted indolines starting from relatively simple aromatic compounds. These strategies have also been successfully extended to catalytic asymmetric transformations.[6,7] In the former case, however, preinstallation of functional groups into an olefinic substituent is necessary to further elaborate complex indoline derivatives, and a stoichiometric amount of a waste is generated from the halogen and nucleophile during the transformations. On the other hand, we[8] and others[9] have recently disclosed that catalytic intramolecular insertion of olefins into C–CN bonds of nitriles is an atom-economical alternative that can facilitate access to 3,3-disubstituted indolines and oxindoles from readily available nitriles. Our preliminary result for the enantioselective cyclization of **1a** was successfully applied to the total synthesis of (–)-esermethole, which is a pyrroloindoline that serves as a synthetic precursor of potent acetylcholinesterase inhibitors such as (–)-physostigmine and (–)-phenserine (Scheme 1).[8] This scheme prompted us to examine the generality of the transformation and thus gain access to a variety of enantiomerically enriched 3,3-disubstituted indoline derivatives. The results are reported herein.

The conditions previously optimized for the enantioselective cyclization of **1a** using commercially available (*S*,*S*)-*i*-Pr-Foxap[10] were, this time, simply applied to the reactions of a range of 2-aminobenzonitriles bearing an olefinic moiety tethered by an amino group (Equation 1 and Table 1).[11] When halides were present on the benzene ring, the yield and enantioselectivities were slightly lower than those achieved with **1a** (entries 1–3). Thus, the benzonitrile derivative with a chloro group *meta* to the cyano group **1b** underwent the asymmetric arylcyanation with only 39% ee (entry 1). The use of (*S*)-*i*-Pr-Phox,[12] on the other hand, increased the ee of **2b** to 88% with a slightly lowered chemical yield. The absolute configuration of **2b** was assigned as *R* by comparing its data (including HPLC analyses and optical rotations) with that obtained for **2a**.[13] Nitrile **1c**, having a chloro group *para* to the cyano group, underwent the reaction under the original conditions to give **2c** in 93% ee and 56% yield (entry 2). Fluorine-substituted indoline **2d** (90% ee) was also obtained in 72% yield (entry 3). These results showed that the electron den-



Scheme 1 Asymmetric total synthesis of (–)-esermethole through enantioselective intramolecular arylcyanation of alkenes

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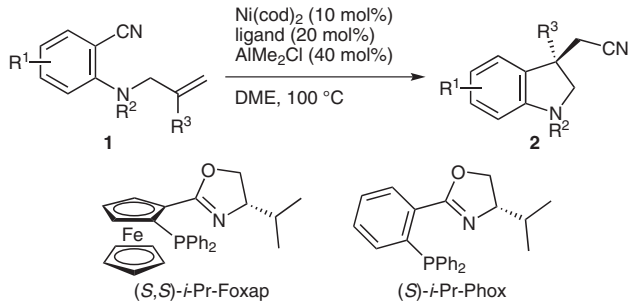
sity on the benzene ring slightly affected the enantioselectivity, possibly through altering the ability of the nitrogen and/or olefin to coordinate to nickel. It is worth noting that aryl–halogen bonds, which are normally labile to nickel(0) species, were tolerated, and that the C–CN bonds were activated exclusively by the nickel/$AlMe_2Cl$ cooperative catalyst.[14] Nevertheless, the observed decrease in the reaction rate and yield could be ascribed to some competitive side reactions occurring through activation of the aryl–halogen bonds. The size of the N-substituents affected both chemical yield and enantioselectivity significantly (entries 4–7). Bulkier substituents might retard oxidative addition of the Ar–CN bond as well as coordination of the double bond to nickel. A range of alkyl substituents, on the other hand, could be introduced to the olefin moiety to give the corresponding 3,3-disubstituted indolines with good to excellent enantioselectivities (entries 8–12). An internal double bond and a protected hydroxy group were tolerated (entries 11 and 12), although the latter affected the enantioselectivity to some extent. Prenylated indoline **2l** may be transformed into natural products such as pseudophrynamine A,[15] deoxypseudophrynaminol,[16] and debromoflustramine B.[17] Nitriles having phenyl and 4-chlorophenyl groups on the double bond afforded 3-arylindolines **2n** and **2o** with high enantioselectivities (entries 13 and 14).



Equation 1

Table 1 Nickel/$AlMe_2Cl$-Catalyzed Asymmetric Intramolecular Arylcyanation of Alkenes[a]

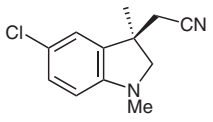
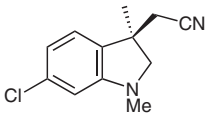
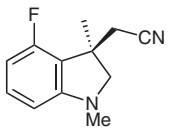
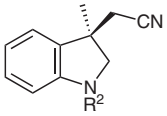
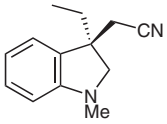
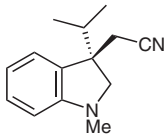
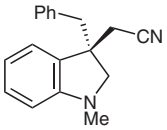
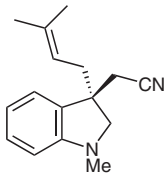
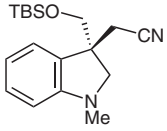
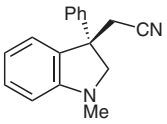
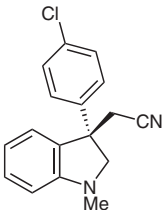
Entry	Products	Time (h)	Yield (%)[b]	ee (%)[c]
1	 **2b**	180	82 (67)[d]	39 (88)[d]
2	 **2c**	140	56	93
3	 **2d**	80	72	90

Table 1 Nickel/$AlMe_2Cl$-Catalyzed Asymmetric Intramolecular Arylcyanation of Alkenes[a] (continued)

Entry	Products	Time (h)	Yield (%)[b]	ee (%)[c]
				
4	**2e** (R^2 = Me)	40	87	93
5	**2f** (R^2 = Et)	40	54	81
6	**2g** (R^2 = Pr)	40	41	69
7	**2h** (R^2 = Bn)	120	20[d]	61[d]
8	 **2i**	40	87	93
9	 **2j**	40	93	96
10	 **2k**	160	88	95
11	 **2l**	120	46	93
12	 **2m**	80	91[d]	73[d]
13	 **2n**	40	55	97
14	 **2o**	160	56[d]	92[d]

[a] Reactions were carried out on a 0.50 mmol scale.
[b] Isolated yield.
[c] Determined by HPLC analysis.
[d] Run with (*S*)-*i*-Pr-Phox.

In summary, we have demonstrated an enantioselective intramolecular arylcyanation that provides a variety of 3,3-disubstituted indolines bearing a benzylic quaternary carbon. The approach uses chiral nickel/Lewis acid cooperative catalysis with phosphinoxazoline ligands. This reaction may be used to access biologically active natural products and pharmaceuticals containing the indoline structural core. Current efforts are directed towards the enantioselective construction of oxindoles by this methodology.[18]

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(11) **General Experimental Procedure:** An aryl cyanide (0.50 mmol) and a solution of $AlMe_2Cl$ (1.04 M in hexane, 0.20 mL, 0.20 mmol) were added sequentially to a solution of $Ni(cod)_2$ (13.8 mg, 50 μmol) and a ligand (50 μmol) in 1,2-dimethoxyethane (0.50 mL) prepared in a 3 mL vial under an argon atmosphere in a dry-box. The vial was sealed with a screw-cap, taken outside the dry-box and heated at 100 °C for the time specified Table 1. The resulting mixture was filtered through a silica gel pad, concentrated in vacuo, and purified by flash column chromatography on silica gel to give the corresponding arylcyanation products in the yields listed in Table 1

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