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Enantioselective Fujiwara–Moritani Indole and Pyrrole Annulations Catalyzed by Chiral Palladium(II)–NicOx Complexes

Julia A. Schiffner,[a] Thorsten H. Wöste,[a] and Martin Oestreich*[a]

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The catalytic asymmetric Fujiwara–Moritani ring closures of several indole- and pyrrole-based cyclization precursors are reported. These unprecedented oxidative palladium(II)-catalyzed annulations allow for the formation of a stereogenic quaternary carbon atom, and decent levels of enantiocontrol are seen in 5-*exo*-*trig* cyclizations (54 % *ee* for an indole and 76 % *ee* for a pyrrole) while 6-*exo*-*trig* ring closures afford essentially racemic material. Novel oxazoline ligands with a nicotine platform (NicOx) are pivotal for good catalytic turnover as conventional PyOx ligands failed to produce acceptable chemical yields. The preparation of these NicOx ligands as well as the syntheses of the cyclization precursors are described in detail.

Introduction

C–H Bond activation moved the oxidative palladium(II)-catalyzed arylation of alkenes back into focus of current transition metal catalysis.[1] The basic principles of this fundamental C–C bond-forming reaction were established in a series of seminal papers nearly half a century ago[2,3] but the initial momentum dwindled to merely a handful contributions to the area over the decades.[4,5] Parallel to the recent progress in direct C–H bond activation, pivotal issues of the original Fujiwara–Moritani protocol were addressed.[6–12] Apart from substantial improvement of the oxidant system,[6–10] the regioselectivity of C–H bond activation is now controlled by a directing group attached to an electron-rich or -neutral arene,[8] by a protecting group at the nitrogen atom of a hetarene,[11] or by the solvent system.[12] Ongoing mechanistic investigations[13] are directed towards the understanding of the C–H bond activation and the palladium(0)→palladium(II) reoxidation steps.[14] A related palladium(II)-catalyzed C–C bond formation, that is the oxidative Heck reaction,[15] had a fate similar to that of the Fujiwara–Moritani reaction, and it was also greatly advanced in recent years, again through optimization of the reoxidation process.[16] Unlike the Fujiwara–Moritani catalysis, the catalytic cycle of the oxidative Heck reaction commences with the transmetalation of a boronic acid and a palladium(II) complex, a situation that unambiguously sets the regiochemistry.

These oxidative palladium(II)-catalyzed C–C couplings are both closely connected to the prevalent Mizoroki–Heck reaction, and these catalyses share several mechanistic features.[1] A number of facets of the Mizoroki–Heck reaction account for the tremendous impact it had on organic synthesis, in particular the enantioselective construction of all-carbon quaternary carbon atoms.[17] Conversely, asymmetric C–C bond formation under oxidative palladium(II) catalysis is largely underdeveloped, and examples of that are infrequent. Its inherent attractiveness was realized by the Mikami group,[18,19] and catalytic asymmetric inter-[18] and intramolecular[19] oxidative Heck reactions were developed using bidentate phosphane ligands and oxazoline-based (PyOx and Box) ligands. While the former were superior in that work,[18–20] Jung demonstrated shortly thereafter that PyOx ligands are also promising ligand motifs.[21] A major step forward was then reported by Jung, where a newly designed, chiral carbene–palladium(II) complex was shown to induce excellent enantioselectivity in an intermolecular oxidative Heck reaction.[22] Compared to those developments, asymmetric Fujiwara–Moritani chemistry still tends to be sidelined, and there is only a single report on an intermolecular reaction[23] and none on an intramolecular reaction.

We became attracted to Fujiwara–Moritani chemistry through a paper by Stoltz,[10a,24] in which oxidative indole annulations accompanied by formation of an all-carbon quaternary carbon atom were elaborated. To us, an asymmetric variant of these cyclizations was the obvious next step but it had not been realized yet. Since pyridine–palladium(II) combinations had been identified as productive in palladium(II)-catalyzed alcohol oxidation,[25] we decided to approach the challenge of an enantioselective Fujiwara–Moritani cyclization by testing PyOx[26] ligand **L2a** (R^2 = *i*Pr) in a model indole annulation (**1**→**2**, Scheme 1).[27]

[a] Organisch-Chemisches Institut,
Westfälische Wilhelms-Universität Münster,
Corrensstrasse 40, 48149 Münster, Germany
Fax: +49-251-83-36501
E-mail: martin.oestreich@uni-muenster.de
http://www.uni-muenster.de/Chemie.oc/oestreich

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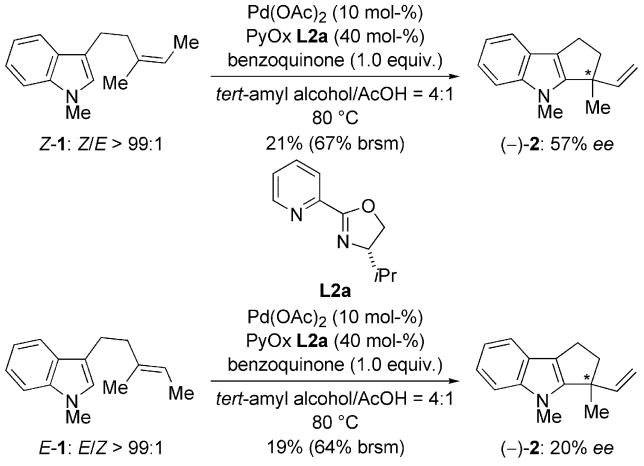
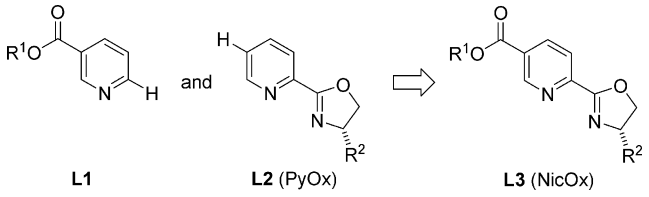
Aware of any influence of the double bond configuration in **1** on the stereochemical outcome in **2**, we separated diastereomers *Z*-**1** and *E*-**1** by conventional flash column chromatography on silver(I)-impregnated silica gel and subjected both precursors to our enantioselective Fujiwara–Moritani protocol using benzoquinone as oxidant.[27] As expected, annulations *Z*-**1**→(–)-**2** (57% *ee*) and *E*-**1**→(–)-**2** (20% *ee*) differed significantly in the level of enantioinduction while producing the same absolute configuration;[28] the alkene geometry in unreacted **1** remained unchanged, and *Z*-**1** and *E*-**1** cyclized at approximately identical reaction rates. The low chemical yields downgraded the promising enantioselectivity though.



Scheme 1. Enantioselective Fujiwara–Moritani cyclization (brsm = based on recovered starting material).

The poor performance of our catalytic system was not entirely unprecedented. Stoltz had found that pyridine itself is unsuited for these indole annulations, which suggests that PyOx ligands **L2** (Scheme 2) might also form palladium(II) complexes of similar reactivity. A central finding in the aforementioned work of Stoltz[24] emerged from a screening of electronically altered pyridines: an electron-withdrawing carboxyl group at C-3 makes pyridines excellent ligands in these oxidative C–C bond formations. For example, isolated yields in the racemic ring closure **1**→*rac*-**2** (Scheme 1) were 23% with unsubstituted but 82% with a 3-carboxylated pyridine, namely ethyl nicotinate. We reasoned that merging the structural motifs of nicotine-based **L1** and pyridine-based **L2** (PyOx) will result in novel NicOx ligands **L3** (Scheme 2), which might then form catalytically active palladium(II) complexes.[27,29]



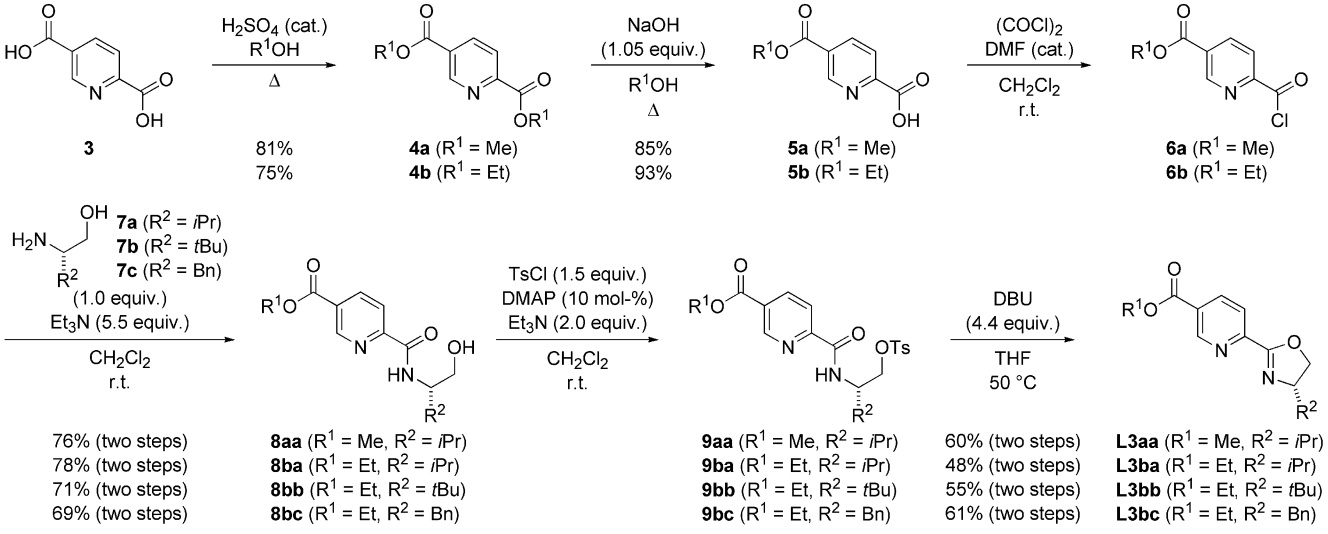
Scheme 2. Ligand design: from PyOx to NicOx ligands.

In this full account, we report detailed procedures for the preparation of these NicOx ligands[29] (**L3**, Scheme 2), potentially useful for enantioselective oxidative palladium(II) catalysis. The syntheses of several indole and pyrrole cyclization precursors are also described. A systematic screening of six NicOx ligands in an indole annulation (Scheme 1) is then followed by application of the most effective palladium(II)–**L3** combination discovered thus far to the asymmetric intramolecular Fujiwara–Moritani reaction of six additional indole and pyrrole substrates.

Results and Discussion

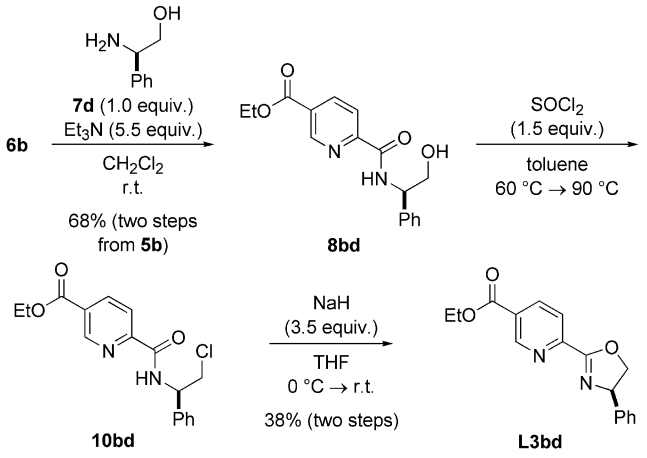
Preparation of NicOx Ligands

In NicOx ligands, the carbon atoms at C-2 and C-5 are at the same oxidation state. We therefore decided to prepare these ligands from pyridine 2,5-dicarboxylic acid (**3**), which however requires differentiation of the two carboxyl groups. This was achieved by acid-catalyzed esterification[30] in the



Scheme 3. Preparation of NicOx ligands **L3** (part I).

requisite alcohol (**3**→**4a**–**b**, Scheme 3) followed by regioselective saponification[31] in the proximity of the pyridine nitrogen atom (**4a**–**b**→**5a**–**b**, Scheme 3). Installation of the chiral oxazoline unit commenced with generation of an acid chloride (**5a**–**b**→**6a**–**b**, Scheme 3) and direct amide coupling with 1,2-amino alcohols **7a**–**d** (**6a**–**b**→**8aa**–**bd**, Schemes 3 and 4). Oxazoline formation was then accomplished by tosylation (**8aa**–**bc**→**9aa**–**bc**, Scheme 3) and DBU-mediated[29] cyclization (**9**→**L3**, Scheme 3).



Scheme 4. Preparation of NicOx ligands **L3** (part II).

The chemical yields of this reaction sequence were almost independent of the R^1 and R^2 groups (Scheme 3) except for a phenyl group attached to the oxazoline. With this substituent, base-mediated β-elimination of the tosylate competed with the desired ring formation (**9**→**L3**). As outlined in Scheme 4, this problem was overcome by transformation of the amide into the corresponding chloride (**8bd**→**10bd**), which underwent oxazoline formation in the presence of excess sodium hydride (**10bd**→**L3bd**).

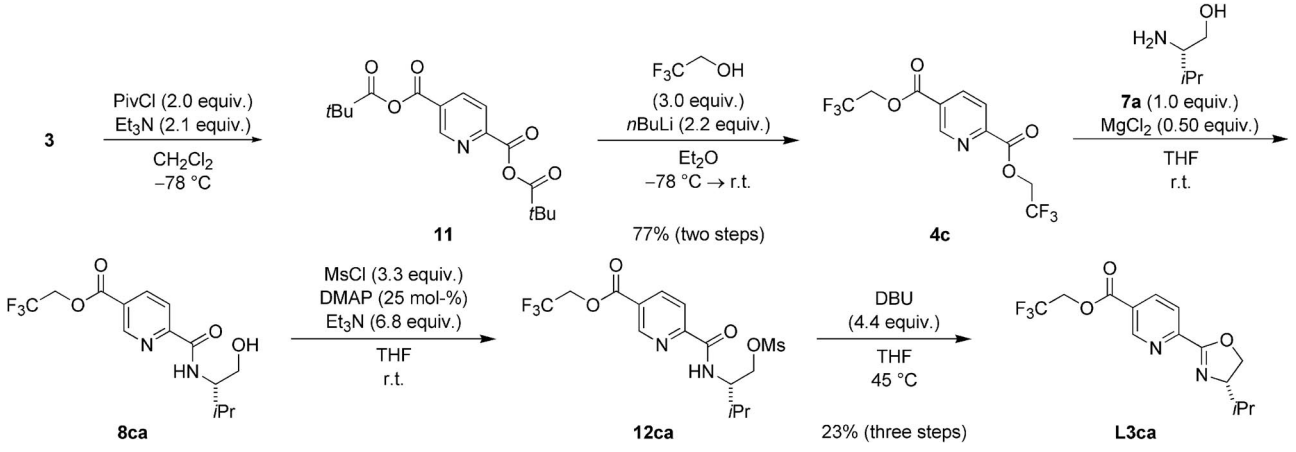
Pyridine 2,5-dicarboxylic acid (**3**) was esterified using the alcohol as solvent (**3**→**4a**–**b**, Scheme 3). For more valuable alcohols such as 2,2,2-trifluoroethanol, a different route might be practicable (Scheme 5); **3** was transformed into the mixed anhydride **11** followed by treatment with a slight excess (1.5 equiv. per anhydride) of the deprotonated alcohol (**3**→**11**→**4c**). The thus-formed **4c** contains two active ester groups both prone to facile hydrolysis. We were pleased to see that amide formation with 1,2-amino alcohol **7a** in the presence of magnesium chloride[32] was regioselective (**4c**→**8ca**). Without purification, sensitive **8ca** was processed to the oxazoline ligand in one pot (**8ca**→**12ca**→**L3ca**).

Preparation of Cyclization Precursors

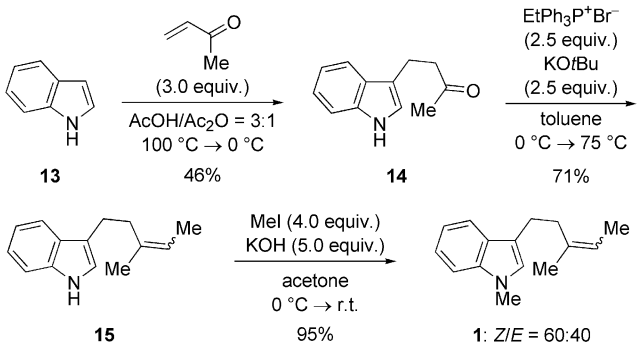
We had previously chosen indole **1** to be our model cyclization precursor (Scheme 1).[27] It was accessed by a straightforward three-step sequence (**13**→**14**→**15**→**1**, Scheme 6).[10a] Unfortunately, the Wittig reaction yielded the trisubstituted alkene as an isomeric mixture (**14**→**15**); nOe measurements showed the *Z* diastereomer to be major. The intricate synthesis of isomerically pure cyclization precursors is a general challenge in this chemistry because of the demonstrated influence of the alkene geometry on the stereochemical outcome of the Fujiwara–Moritani reaction (cf. Scheme 1). As in this case, we attempted to separate the diastereomers by conventional flash column chromatography on silver(I)-impregnated silica gel (vide supra). While it was successful for obtaining isomerically pure *Z*-**1** and *E*-**1**, it failed for most other substrates. – To test for the role of the protective group at the nitrogen atom, we also prepared the corresponding tosylated indole (see Supporting Information for details).

The synthesis of the homologated indole precursor **21**, which would form a six-membered ring in the Fujiwara–Moritani annulation, was again straightforward. Indole (**13**) was transformed into **19** in four routine steps (**13**→**16**→**17**→**18**→**19**, Scheme 7).[10a] The alkene unit was then installed by Li_2CuCl_4-catalyzed $C(sp^3)$–$C(sp^2)$ cross-coupling[33] of *O*-tosylate **19** and vinyl Grignard reagent **20** (**19**→**21**, Scheme 7).

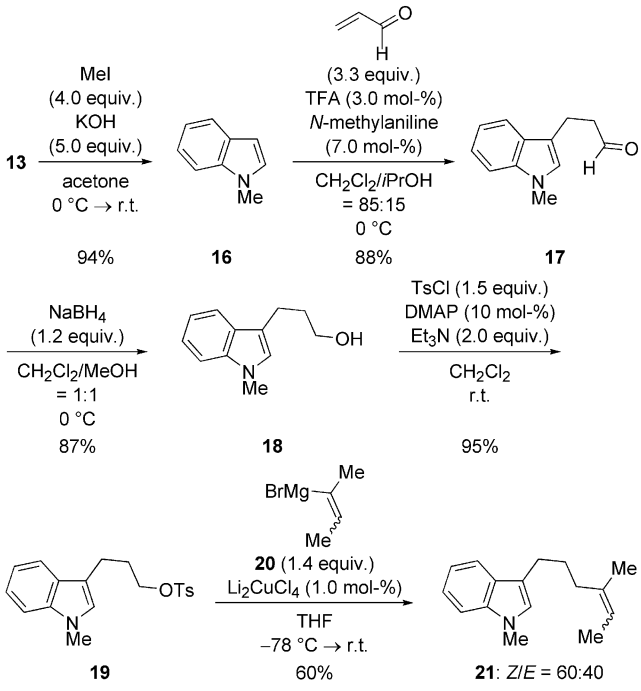
For all *N*-substituted indole and pyrrole cyclization precursors **34**–**38**, we were able to employ the unified three-step protocol outlined in Scheme 8. It allowed for variation



Scheme 5. Preparation of NicOx ligands **L3** (part III).

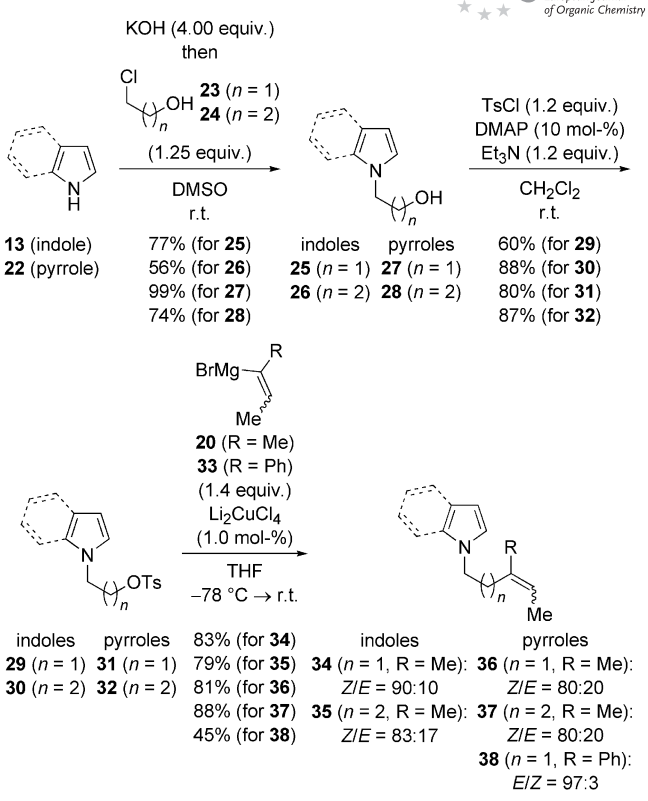


Scheme 6. Preparation of 3-substituted indole cyclization precursors (part I).



Scheme 7. Preparation of 3-substituted indole cyclization precursors (part II).

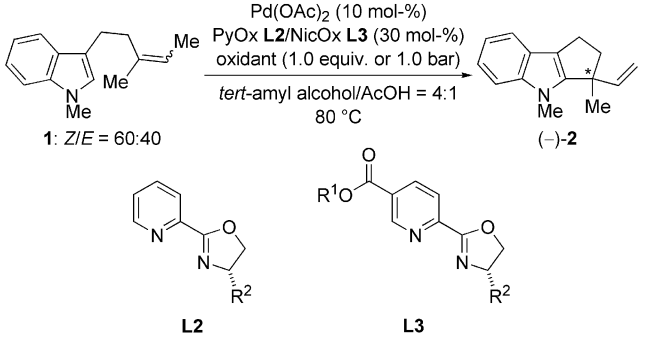
of the tether (n = 1 or 2) and the vinyl substituent (R = Me or Ph). According to a reported procedure,[34] both indole (**13**) and pyrrole (**22**) were β-hydroxy- and γ-hydroxyalkylated, respectively in good chemical yields (**13**→**25** and **26** as well as **22**→**27** and **28**, Scheme 8); 1,2-ethylene and 1,3-propylene glycol oligomers were formed as by-products. Again, Li_2CuCl_4-catalyzed cross-coupling[33] of tosylated **29**–**32** allowed for the introduction of the trisubstituted alkenes (**29**–**32**→**34**–**38**, Scheme 8). For this, we used either methyl- or phenyl-substituted vinyl Grignard reagents **20** and **33**; nOe measurements verified the predominant *Z* (for **34**–**37**) or *E* (for **38**) configuration of the double bond in all cases.



Scheme 8. Preparation of *N*-substituted indole and pyrrole cyclization precursors.

Enantioselective Fujiwara–Moritani Annulations

For the NicOx ligand screening, we chose 5-*exo*-*trig* ring closure **1**→**2** (cf. Scheme 1) and we decided to use three established oxidants[1] (*tert*-butyl peroxybenzoate, molecular dioxygen, and 1,4-benzoquinone) with each ligand (Scheme 9 and Table 1); less common oxidants such as oxone or $PhI(OAc)_2$ had led to decomposition in control experiments. *N*-Protection with a methyl group was also crucial because, for example, the related tosylated indole was prone to serious oxidative degradation (see Supporting Information for details).



Scheme 9. Ligand and oxidant identification in indole annulation **1**→(–)-**2** (see Table 1 for details).

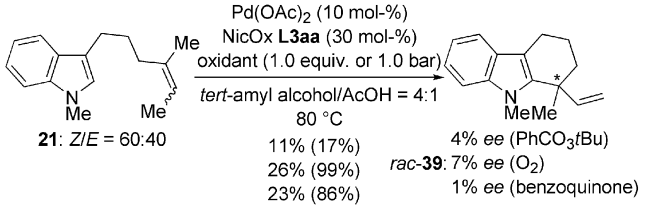
The data obtained in that NicOx ligand and oxidant screening is summarized in Table 1[28] and might be interpreted relating to the results seen for PyOx ligand **L2a** (en-

Table 1. Ligand and oxidant identification in indole annulation **1**→(–)-**2**.

Entry	Ligand	R^1	R^2	Oxidant $PhCO_3tBu$ Yield [%][a]	*ee* [%][b]	O_2 Yield [%][a]	*ee* [%][b]	Benzoquinone Yield [%][a]	*ee* [%][b]
1	**L2a**	–	*i*Pr	28 (74)	51	49 (93)	37	39 (86)	43
2	**L3aa**	Me	*i*Pr	49 (70)	32	65 (81)	39	73 (92)	44[c]
3	**L3ba**	Et	*i*Pr	49 (91)	28	55 (97)	33	59 (84)	32
4	**L3bb**	Et	*t*Bu	26 (85)	24	35 (94)	16	47 (93)	21
5	**L3bc**	Et	Bn	16 (75)	3	37 (74)	21	27 (85)	22
6[d]	**L3bd**	Et	Ph	11 (78)	4	35 (98)	1	38 (76)	3
7	**L3ca**	CH_2CF_3	*i*Pr	–	–	–	–	64 (93)	40

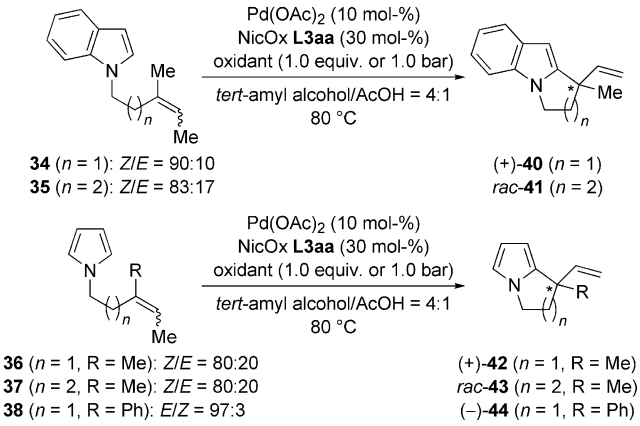
[a] Yield of analytically pure product isolated by flash chromatography on silica gel; yield in parentheses based on recovered starting material. [b] Determined by HPLC analysis using Daicel Chiralcel or Chiralpak columns providing baseline separation of enantiomers. [c] Isomerically pure *Z*-**1** (*Z*/*E* > 99:1) cyclized in 71% (91% brsm) chemical yield and with 54% *ee*. [d] Absolute configuration opposite to general structure **L3**, producing (+)-**2**.

try 1, Table 1);[27] the level of enantioselection was promising with **L2a** (R^2 = *i*Pr) with all oxidants (37–51% *ee*) but chemical yields were poor (vide supra). Chemical yields improved substantially with a carboxyl group attached to the pyridine and leaving the chiral auxiliary unchanged (entries 2 and 3, Table 1). Ligand **L3aa** (R^1 = Me and R^2 = *i*Pr) induced enantioselectivities comparable to those found with **L2a** (R^2 = *i*Pr). Essentially no improvement was achieved by alteration of the substituent at the stereogenic carbon atom in **L3** (entries 4–6, Table 1); in fact, chemical yields decreased, and several ligand–oxidant combinations afforded almost racemic products. We were unable to notice a general trend in this set of data except for the observation that 1,4-benzoquinone as oxidant is superior. Finally, difficult-to-make electron-deficient **L3ca** performed equally well as **L3aa** (entries 2 and 7, Table 1). It seemed reasonable to also investigate the related 6-*exo*-*trig* cyclization under the same reaction conditions (**21**→*rac*-**39**, Scheme 10). To our surprise, the annulation was not only sluggish but also completely unselective. As shown later, the $Pd(OAc)_2$–**L3** system in *tert*-amyl alcohol–acetic acid is generally not applicable to the enantioselective formation of six-membered rings (vide infra).



Scheme 10. Low-yielding and unselective 6-*exo*-*trig* ring closure.

We next turned our attention to Fujiwara–Moritani annulations of precursors **34**–**38** (Scheme 11), in which the alkene is tethered to the indole or pyrrole nitrogen atom. These ring closures were performed using the $Pd(OAc)_2$–NicOx catalyst previously identified (entry 2, Table 1), and three oxidants were again included in this survey (Table 2).[28] As indicated by the isolated yields based on recovered starting material, 2- and 3-unsubstituted indoles and pyrroles were generally prone to oxidation, and oxidative degradation was competing with the palladium(II)-catalyzed cyclization. For example, **1** showed nearly no decomposition whereas regioisomeric **34** was readily decomposed (entry 2, Table 1 vs. entry 1, Table 2); the level of enantioselection for **34**→(+)-**40** was however in the expected range with 51% *ee* for dioxygen as oxidant. In sharp contrast, cyclization **35**→*rac*-**41** afforded the six-membered ring in poor yield and without any stereoinduction (entry 2, Table 2). Similar observations were made for the same pair in the pyrrole series, **36**→(+)-**42** and **37**→*rac*-**43** (entries 3 and 4, Table 2). While the five-membered ring formed in decent yields (42–47%) and (in this chemistry) good enantiomeric excesses (59–70% *ee*), the formation of the six-membered ring would not even occur. Likewise, **38**→(–)-**44** cyclized in 76% *ee* with dioxygen as oxidant, which has been the highest enantioselectivity achieved so far. At the moment, it is not obvious why the 5- and 6-*exo*-*trig* cyclization do behave so differently. We might only speculate that these ring closures might follow different mechanisms,[35] the former through C–H bond activation (electrophilic palladation pathway) and the latter through alkene activation (Friedel–Crafts pathway).[36]



Scheme 11. Indole and pyrrole annulations from *N*-substituted precursors (see Table 2 for details).

Table 2. Indole and pyrrole annulations from *N*-substituted precursors.

Entry	Precursor			Product	Oxidant $PhCO_3tBu$		O_2		Benzoquinone	
		R	*n*		Yield [%][a]	*ee* [%][b]	Yield [%][a]	*ee* [%][b]	Yield [%][a]	*ee* [%][b]
1	**34**	–	1	(+)-**40**	36 (58)	47	38 (76)	51	36 (57)	39
2	**35**	–	2	*rac*-**41**	17 (27)	3	19 (67)	0	18 (31)	0
3	**36**	Me	1	(+)-**42**	44 (44)	70	47 (47)	59	42 (58)[c]	70[d]
4	**37**	Me	2	*rac*-**43**	no conv.	–	no conv.	–	no conv.	–
5	**38**	Ph	1	(–)-**44**	25 (33)	60	15 (45)	76	16 (33)	68

[a] Yield of analytically pure product isolated by flash chromatography on silica gel; yield in parentheses based on recovered starting material. [b] Determined by HPLC analysis using Daicel Chiralcel or Chiralpak columns providing baseline separation of enantiomers. [c] Isomerically pure *Z*-**36** (*Z*/*E* > 99:1) cyclized in 55% (68%) chemical yield and with 72% *ee*. [d] Determined by GLC analysis providing baseline separation of enentiomers.

Conclusions

The development of enantioselective Fujiwara–Moritani reactions is among the current challenges of asymmetric oxidative palladium(II) catalysis.[37] Prior to this investigation, merely one intermolecular[23] and one intramolecular[27] example were known. We were able to introduce chiral NicOx rather than PyOx ligands to this oxidative palladium(II)-catalyzed C–C bond formation allowing for several enantioselective indole and pyrrole annulations. Ligands with a nicotine instead of a pyridine platform display enhanced reactivity in these catalyses. The chemical yields and the enantioselectivities (≈ 50% *ee* for indoles and ≈ 70% *ee* for pyrroles) obtained in these ring closures are not yet where one would like them to be. While the numbers still leave room for improvement, all of these cyclizations were previously unprecedented. From a mechanistic standpoint, the pronounced effect of the ring size in the cyclization on the turnover and enantioinduction is a particularly remarkable finding, which will be addressed in a separate study. Elucidation of the absolute configuration of the annulated heterocycles[28] might help to delineate a model of the origin of asymmetric induction (yet these ligands are not C_2 symmetric). Nevertheless, the targeted identification of novel ligand motifs and solvent systems is currently being investigated in our laboratory.

Experimental Section

Methyl (*S*)-6-(4-Isopropyl-4,5-dihydrooxazol-2-yl)nicotinate [(*S*)-L3aa]: Yield 120 mg, 60% (over two steps); white solid, m.p. 148–149 °C (cyclohexane). R_f = 0.48 (cyclohexane/ethyl acetate = 1:2). $[a]_D^{20}$ = –72.0 (*c* = 1.00, $CHCl_3$, 99% *ee*). IR (ATR): $\tilde{\nu}$ = 2923 (s, C–H), 1716 (s, C=O), 1639 (s, C=N), 1280 (s, C–O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.93 [d, $^3J_{H,H}$ = 6.8 Hz, 3 H, $CH(CH_3)_2$], 1.04 [d, $^3J_{H,H}$ = 6.8 Hz, 3 H, $CH(CH_3)_2$], 1.89 [m, 1 H, $CH(CH_3)_2$], 3.95 (s, 3 H, OCH_3), 4.12–4.25 (m, 2 H, 4-H, 5-H), 4.52 (m, 1 H, 5-H), 8.12 (d, $^3J_{H,H}$ = 8.2 Hz, 1 H, 5-H_{Ar}), 8.35 (dd, $^3J_{H,H}$ = 8.2, $^4J_{H,H}$ = 1.5 Hz, 1 H, 4-H_{Ar}), 9.25 (dd, $^4J_{H,H}$ = 1.6, $^5J_{H,H}$ = 0.8 Hz, 1 H, 2-H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.2, 19.0, 32.7, 52.6, 70.9, 73.1, 123.4, 127.2, 137.7, 150.0, 150.7, 161.9, 165.1 ppm. HRMS (ESI): calcd. for $C_{13}H_{16}N_2O_3H$ $[M + H]^+$: 249.1234; found 249.1220. $C_{13}H_{16}N_2O_3$ (248.28): calcd. C 62.89, H 6.50, N 11.28; found C 62.84, H 6.58, N 10.94.

General Procedure for Asymmetric Fujiwara–Moritani Cyclizations: Under argon atmosphere, a flame-dried Schlenk tube is charged with $Pd(OAc)_2$ (10 mol-%) and the respective ligand **L3aa**–**L3ca** (30 mol-%). If O_2 is used as oxidant, the tube is subsequently evacuated and backfilled with O_2 (three cycles). Otherwise, a solution of the appropriate cyclization precursor (1.0 equiv.) in *tert*-amyl alcohol (0.125 M) and acetic acid (0.25 mL per mL of *tert*-amyl alcohol) are consecutively added and the reaction mixture is maintained under vigorous stirring at room temperature until a homogeneous tawny solution formed. Then, the oxidant (1.0 equiv.), $PhCO_3tBu$ or 1,4-benzoquinone, is added, and the resulting mixture is heated at 80 °C for the indicated time (under O_2 atmosphere, if O_2 is used as oxidant). In the case of indole-derived substrates, the reaction mixture is recooled to room temperature, diluted with *tert*-butyl methyl ether and washed with H_2O (1×) and saturated aqueous $NaHCO_3$ (1×). The aqueous layers are extracted with *tert*-butyl methyl ether (3×) and the combined organic phases are dried with Na_2SO_4. After evaporation of the solvents under reduced pressure, purification of the residue by flash column chromatography on silica gel (cyclohexane/*tert*-butyl methyl ether or cyclohexane/CH_2Cl_2 solvent mixtures as eluent) affords the annulated product. If pyrrole-derived cyclization precursors are used, the reaction mixture is recooled to room temperature, and the residue is directly purified by flash column chromatography on silica gel (cyclohexane/*tert*-butyl methyl ether mixtures as eluent) to afford the cyclization product.

(–)-3,4-Dimethyl-3-vinyl-1,2,3,4-tetrahydrocyclopenta[*b*]indole [(–)-2]:[10a] According to the general procedure (15 h); yield 30.2 mg, 73% (92%), colourless liquid. R_f = 0.72 (cyclohexane/*tert*-butyl methyl ether = 9:1). $[a]_D^{20}$ = –17.7 (*c* = 0.565, $CHCl_3$, 44% *ee*). IR (ATR): $\tilde{\nu}$ = 3052 (m, Ar–H/=C–H), 2926 (s, C–H), 2854 (s, C–H), 1465 (s, C=C) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.50 (s, 3 H, 3-CH_3), 2.36 (ddd, $^2J_{H,H}$ = 13.0, $^3J_{H,H}$ = 7.1, $^3J_{H,H}$ = 6.1 Hz, 1 H, 2-H), 2.47–2.58 (m, 1 H, 2-H), 2.83 (m, 2 H, 1-H), 3.64 (s, 3 H, 4-CH_3), 4.98 (dd, $^3J_{H,H}$ = 17.4, $^2J_{H,H}$ = 1.3 Hz, 1 H, =CH_{2E}), 5.06 (dd, $^3J_{H,H}$ = 10.5, $^2J_{H,H}$ = 1.2 Hz, 1 H, =CH_{2Z}), 6.09 (dd, $^3J_{H,H}$ = 17.4, $^3J_{H,H}$ = 10.5 Hz, 1 H, =C*H*), 7.09 (ddd, $^3J_{H,H}$ = 7.5, $^3J_{H,H}$ = 7.1, $^4J_{H,H}$ = 1.3 Hz, 1 H, 7-H), 7.16 (ddd, $^3J_{H,H}$ = 8.2, $^3J_{H,H}$ = 7.0, $^4J_{H,H}$ = 1.4 Hz, 1 H, 6-H), 7.26 (ddd, $^3J_{H,H}$ = 8.1, $^4J_{H,H}$ = 0.9, $^5J_{H,H}$ = 0.8 Hz, 1 H, 5-H), 7.47 (ddd, $^3J_{H,H}$ = 7.6, $^4J_{H,H}$ = 1.3, $^5J_{H,H}$ = 0.7 Hz, 1 H. 8-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.5, 23.7, 30.0, 46.0, 46.3, 109.3, 111.8, 117.3, 118.8, 119.0, 120.2, 123.9, 141.6, 145.1, 148.7 ppm. HRMS (ESI): calcd. for $C_{15}H_{17}NNa$ $[M + Na]^+$: 234.1253; found 234.1249. The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chiralcel IB column, column temperature 15 °C, solvent *n*-heptane/2-propanol = 100:0, flow rate 0.8 mL/min, λ = 230 nm): 13.9 min (minor enantiomer), 16.1 min (major enantiomer).

***rac*-1,9-Dimethyl-1-vinyl-2,3,4,9-tetrahydrocarbazole (*rac*-39):** According to the general procedure (63 h); yield 8.0 mg, 26% (99%),

colourless liquid. R_f = 0.45 (cyclohexane/*tert*-butyl methyl ether = 99:1). IR (ATR): $\tilde{\nu}$ = 3053 (w, Ar–H/=C–H), 2928 (s, C–H), 2840 (m, C–H), 1471 (s, C=C) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.53 (s, 3 H, 1-CH_3), 1.68–1.90 (m, 4 H, 2-H, 3-H), 2.73–2.79 (m, 2 H, 4-H), 3.69 (s, 3 H, 9-CH_3), 4.90 (dd, $^3J_{H,H}$ = 17.4, $^2J_{H,H}$ = 1.3 Hz, 1 H, =CH_{2E}), 5.15 (dd, $^3J_{H,H}$ = 10.5, $^2J_{H,H}$ = 1.3 Hz, 1 H, =CH_{2Z}), 6.01 (dd, $^3J_{H,H}$ = 17.4, $^3J_{H,H}$ = 10.5 Hz, 1 H, =CH), 7.11 (ddd, $^3J_{H,H}$ = 7.9, $^3J_{H,H}$ = 6.9, $^4J_{H,H}$ = 1.3 Hz, 1 H, 6-H), 7.20 (ddd, $^3J_{H,H}$ = 8.1, $^3J_{H,H}$ = 6.2, $^4J_{H,H}$ = 1.2 Hz, 1 H, 7-H), 7.27 (ddd, $^3J_{H,H}$ = 8.1, $^4J_{H,H}$ = $^5J_{H,H}$ = 1.0 Hz, 1 H, 8-H), 7.53 (ddd, $^3J_{H,H}$ = 7.0, $^4J_{H,H}$ = 1.1, $^5J_{H,H}$ = 0.8 Hz, 1 H, 5-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.8, 21.8, 25.2, 31.5, 39.1, 40.9, 108.5, 110.3, 113.3, 118.1, 118.6, 121.0, 126.7, 137.4, 139.1, 145.9 ppm. HRMS (ESI): calcd. for $C_{16}H_{19}NNa$ $[M + Na]^+$: 248.1410; found 248.1411. The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chiralcel ODH column, column temperature 20 °C, solvent *n*-heptane/2-propanol = 100:0, flow rate 0.8 mL/min, λ = 230 nm): t_R = 18.6 min (major enantiomer), t_R = 22.4 min (minor enantiomer).

(+)-1-Methyl-1-vinyl-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole [(+)-40]: According to the general procedure (18 h); yield 10.5 mg, 38% (76%), colourless liquid. R_f = 0.56 (cyclohexane/*tert*-butyl methyl ether = 49:1). $[\alpha]_D^{20}$ = +3.6 (*c* = 0.585, $CHCl_3$, 47% *ee*, contaminated with cyclization precursor). IR (ATR): $\tilde{\nu}$ = 3052 (w, Ar–H/=C–H), 2965, 2928 (s, C–H), 2871 (m, C–H), 1457 (s, C=C) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.51 (s, 3 H, 1-CH_3), 2.40–2.50 (m, 1 H, 2-H), 2.54–2.64 (m, 1 H, 2-H), 4.02–4.15 (m, 2 H, 3-H), 5.01 (dd, $^3J_{H,H}$ = 17.1, $^2J_{H,H}$ = 1.2 Hz, 1 H, =CH_{2E}), 5.05 (dd, $^3J_{H,H}$ = 10.5, $^2J_{H,H}$ = 1.1 Hz, 1 H, =CH_{2Z}), 6.06 (dd, $^3J_{H,H}$ = 17.2, $^3J_{H,H}$ = 10.5 Hz, 1 H, =CH), 6.17 (d, $^4J_{H,H}$ = 0.8 Hz, 1 H, 9-H), 7.08 (ddd, $^3J_{H,H}$ = 7.8, $^3J_{H,H}$ = 7.2, $^4J_{H,H}$ = 1.4 Hz, 1 H, 7-H), 7.15 (ddd, $^3J_{H,H}$ = 8.3, $^3J_{H,H}$ = 7.1, $^4J_{H,H}$ = 1.3 Hz, 1 H, 6-H), 7.26 (ddd, $^3J_{H,H}$ = 8.0, $^4J_{H,H}$ = 2.0, $^5J_{H,H}$ = 0.9 Hz, 1 H, 5-H), 7.58 (ddd, $^3J_{H,H}$ = 7.6, $^4J_{H,H}$ = 1.4, $^5J_{H,H}$ = 0.8 Hz, 1 H, 8-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.4, 42.2, 42.9, 44.6, 92.0, 109.3, 112.5, 119.1, 120.4, 120.6, 132.5, 132.7, 143.4, 149.7 ppm. HRMS (ESI): calcd. for $C_{14}H_{15}NH$ $[M + H]^+$: 198.1277; found 198.1275. The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chiralcel ODH column, column temperature 12 °C, solvent *n*-heptane/2-propanol = 100:0, flow rate 0.8 mL/min, λ = 230 nm): t_R = 25.7 min (minor enantiomer), t_R = 27.6 min (major enantiomer).

***rac*-9-Methyl-9-vinyl-6,7,8,9-tetrahydropyrido[1,2-*a*]indole (*rac*-41):** According to the general procedure (26 h); yield 5.0 mg, 17% (27%), colourless viscous oil. R_f = 0.50 (cyclohexane/*tert*-butyl methyl ether = 9:1). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.50 (s, 3 H, 9-CH_3), 1.72–1.80 (m, 1 H, 8-H), 1.88–1.93 (m, 1 H, 8-H), 2.00–2.20 (m, 2 H, 7-H), 3.86–3.94 (m, 1 H, 6-H), 4.14–4.19 (m, 1 H, 6-H), 4.81 (dd, $^3J_{H,H}$ = 17.2, $^2J_{H,H}$ = 1.3 Hz, 1 H, =CH_{2E}), 5.04 (dd, $^3J_{H,H}$ = 10.4, $^2J_{H,H}$ = 1.3 Hz, 1 H, =CH_{2Z}), 5.94 (dd, $^3J_{H,H}$ = 17.2, $^3J_{H,H}$ = 10.4 Hz, 1 H, =CH), 6.31 (s, 1 H, 10-H), 7.10–7.13 (m, 1 H, 2-H), 7.16 (ddd, $^3J_{H,H}$ = 8.3, $^3J_{H,H}$ = 7.1, $^4J_{H,H}$ = 1.3 Hz, 1 H, 3-H), 7.28 (ddd, $^3J_{H,H}$ = 8.2, $^4J_{H,H}$ = 1.5, $^5J_{H,H}$ = 0.9 Hz, 1 H, 4-H), 7.58 (ddd, $^3J_{H,H}$ = 7.7, $^4J_{H,H}$ = 1.0, $^5J_{H,H}$ = 0.7 Hz, 1 H, 1-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.5, 28.5, 34.6, 39.3, 42.2, 98.1, 108.9, 113.3, 119.6, 119.9, 120.4, 128.0, 136.2, 142.6, 146.3 ppm. HRMS (ESI): calcd. for $C_{15}H_{17}NNa$ $[M + Na]^+$: 234.1253; found 234.1249. The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chiralcel OJ-RH column, column temperature 20 °C, solvent MeCN/H_2O = 70:30, flow rate 0.5 mL/min, λ = 230 nm): t_R = 19.9 min (major enantiomer), t_R = 25.3 min (minor enantiomer).

(+)-1-Methyl-1-vinyl-2,3-dihydro-1*H*-pyrrolizine [(+)-42]: According to the general procedure (15 h); yield 12.6 mg, 42% (58%), yellow oil. R_f = 0.33 (cyclohexane/*tert*-butyl methyl ether = 30:1). $[\alpha]_D^{20}$ = +6.7 (*c* = 1.025, $CHCl_3$, 70% *ee*, contaminated with cyclization precursor). ^1H NMR (500 MHz, C_6D_6): δ = 1.24 (s, 3 H, 1-CH_3), 1.80 (ddd, $^2J_{H,H}$ = 12.2, $^3J_{H,H}$ = 7.0, $^3J_{H,H}$ = 7.7 Hz, 1 H, 2-H), 1.96 (ddd, $^2J_{H,H}$ = 12.2, $^3J_{H,H}$ = 7.2, $^3J_{H,H}$ = 4.9 Hz, 1 H, 2-H), 3.31 (ddd, $^2J_{H,H}$ = 10.3, $^3J_{H,H}$ = 7.7, $^3J_{H,H}$ = 4.9 Hz, 1 H, 3-H), 3.36 (ddd, $^2J_{H,H}$ = 10.3, $^3J_{H,H}$ = 7.2, $^3J_{H,H}$ = 7.0 Hz, 1 H, 3-H), 4.91 (dd, $^3J_{H,H}$ = 10.3, $^2J_{H,H}$ = 1.5 Hz, 1 H, =CH_{2Z}), 4.96 (dd, $^3J_{H,H}$ = 17.2, $^2J_{H,H}$ = 1.5 Hz, 1 H, =CH_{2E}), 5.83 (dd, $^3J_{H,H}$ = 17.2, $^3J_{H,H}$ = 10.3 Hz, 1 H, =CH), 6.02 (dd, $^3J_{H,H}$ = 3.4, $^4J_{H,H}$ = 1.3 Hz, 1 H, 7-H), 6.43 (dd, $^3J_{H,H}$ = 2.6, $^4J_{H,H}$ = 1.3 Hz, 1 H, 5-H), 6.46 (dd, $^3J_{H,H}$ = $^3J_{H,H}$ = 2.6 Hz, 1 H, 6-H) ppm. ^{13}C NMR (125 MHz, C_6D_6): δ = 25.7, 43.2, 44.4, 44.7, 99.3, 111.9, 112.7, 113.4, 122.1, 144.7 ppm. HRMS (ESI): calcd. for $C_{10}H_{13}NNa$ $[M + Na]^+$: 170.0946; found 170.0940. The enantiomeric excess was determined by chiral gas liquid chromatography analysis (FS-Cyclodex β-I/P, column temperature 105 °C isotherm, flow rate 0.6 mL/min): t_R = 29.5 min (minor enantiomer), t_R = 30.0 min (major enantiomer).

***rac*-8-Methyl-8-vinyl-5,6,7,8-tetrahydroindolizine (*rac*-43):** According to the general procedure (15 h); yield 6.3 mg, 20% [obtained with **L1** (R^1 = Me)], yellow oil. R_f = 0.37 (cyclohexane/*tert*-butyl methyl ether = 30:1). ^1H NMR (400 MHz, C_6D_6): δ = 1.32 (s, 3 H, 8-CH_3), 1.45–1.77 (m, 6 H, 5-H, 6-H, 7-H), 4.88 (dd, $^3J_{H,H}$ = 17.1, $^2J_{H,H}$ = 1.7 Hz, 1 H, =CH_{2E}), 4.97 (dd, $^3J_{H,H}$ = 10.3, $^2J_{H,H}$ = 1.7 Hz, 1 H, =CH_{2Z}), 5.77 (dd, $^3J_{H,H}$ = 17.1, $^3J_{H,H}$ = 10.3 Hz, 1 H, =CH), 6.15 (dd, $^3J_{H,H}$ = 3.4, $^4J_{H,H}$ = 1.9 Hz, 1 H, 1-H), 6.37 (dd, $^3J_{H,H}$ = 3.2, $^4J_{H,H}$ = 1.9 Hz, 1 H, 3-H), 6.39 (dd, $^3J_{H,H}$ = $^3J_{H,H}$ = 3.2 Hz, 1 H, 2-H) ppm. ^{13}C NMR (100 MHz, C_6D_6): δ = 23.3, 28.9, 29.7, 35.3, 39.1, 105.5, 108.3, 108.7, 112.8, 118.9, 147.7 ppm. HRMS (ESI): calcd. for $C_{11}H_{15}NNa$ $[M + Na]^+$: 184.1102; found 184.1097.

(–)-1-Phenyl-1-vinyl-2,3-dihydro-1*H*-pyrrolizine [(–)-44]: According to the general procedure (15 h); yield 6.8 mg, 16% (33%), yellow oil. R_f = 0.57 (cyclohexane/*tert*-butyl methyl ether = 10:1). $[\alpha]_D^{20}$ = –11.1 (*c* = 0.425, $CHCl_3$, 68% *ee*, contaminated with cyclization precursor). ^1H NMR (500 MHz, C_6D_6): δ = 2.32 (dd, $^3J_{H,H}$ = 6.6, $^3J_{H,H}$ = 6.5 Hz, 2 H, 2-H), 3.25 (ddd, $^2J_{H,H}$ = 10.1, $^3J_{H,H}$ = 6.5, $^3J_{H,H}$ = 5.0 Hz, 1 H, 3-H), 3.33 (ddd, $^2J_{H,H}$ = 10.1, $^3J_{H,H}$ = 6.7, $^3J_{H,H}$ = 6.4 Hz, 1 H, 3-H), 4.95 (dd, $^3J_{H,H}$ = 17.1, $^2J_{H,H}$ = 1.3 Hz, 1 H, =CH_{2E}), 4.99 (dd, $^3J_{H,H}$ = 10.4, $^2J_{H,H}$ = 1.3 Hz, 1 H, =CH_{2Z}), 6.09 (dd, $^3J_{H,H}$ = 17.1, $^3J_{H,H}$ = 10.4 Hz, 1 H, =CH), 6.14 (dd, $^3J_{H,H}$ = 3.5, $^4J_{H,H}$ = 1.5 Hz, 1 H, 7-H), 6.46 (dd, $^3J_{H,H}$ = 2.7, $^4J_{H,H}$ = 1.4 Hz, 1 H, 5-H), 6.48 (dd, $^3J_{H,H}$ = 3.3, $^3J_{H,H}$ = 2.8 Hz, 1 H, 6-H), 7.00–7.21 (m, 5 H, C_6H_5) ppm. ^{13}C NMR (75 MHz, C_6D_6): δ = 43.3, 44.4, 44.7, 102.0, 110.8, 112.8, 113.1, 121.9, 126.7, 127.1, 128.7, 137.4, 142.8 ppm. HRMS (ESI): calcd. for $C_{15}H_{15}NNa$ $[M + Na]^+$: 232.1102; found 232.1097. The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chiralcel OD-RH column, column temperature 20 °C, solvent MeCN/H_2O = 60:40, flow rate 0.6 mL/min, λ = 230 nm): t_R = 15.4 min (minor enantiomer), t_R = 16.5 min (major enantiomer).

Supporting Information (see also the footnote on the first page of this article): Analytical data of all new compounds.

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