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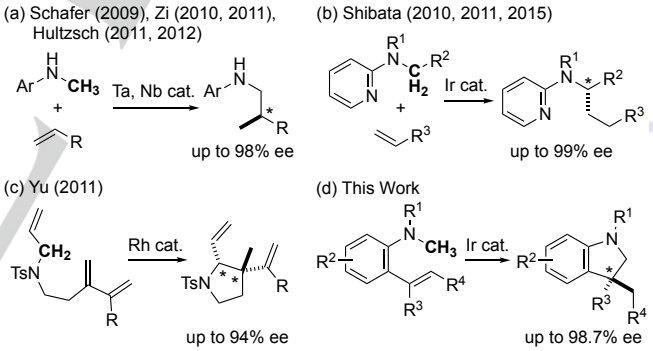
Asymmetric Cycloisomerization of *o*-Alkenyl-*N*-methylanilines to Indolines through Iridium-Catalyzed C(sp^3)–H Addition to Carbon–Carbon Double Bonds

Takeru Torigoe,[a] Toshimichi Ohmura,*[a] and Michinori Suginome*[a]

Abstract: Highly enantioselective cycloisomerization of *N*-methylanilines bearing *o*-alkenyl groups to indolines is established. An iridium catalyst bearing a bidentate chiral diphosphine effectively promotes the intramolecular addition of the C(sp^3)–H bond across a carbon–carbon double bond with highly enantioselective fashion. The reaction gives indolines bearing quaternary stereogenic carbon centers at the 3-positions. The reaction mechanism involves rate-determining oxidative addition of the *N*-methyl C–H bond, followed by intramolecular carboiridation and subsequent reductive elimination.

Asymmetric catalysis based on transition-metal-catalyzed C–H functionalization can provide the most atom- and step-economical synthetic accesses to chiral organic molecules.[1] Particular attention has focused on the asymmetric C–C bond forming reactions via addition of the C–H bond across C–C multiple bonds, since such a process allows 100% atom-economical transformations with use of unelaborated starting materials.[2] Therefore, high demand is seen for the exploration of such C–H addition reactions in order to realize sustainable chemical processes for the production of enantioenriched chiral organic materials.

Chiral nitrogen-containing molecules are recognized as a highly important class of organic compounds in the exploration of drugs and agrochemicals. Transition-metal-catalyzed asymmetric addition of the C(sp^3)–H bond of a *N*-alkyl group across C=C bonds via a C–M intermediate is expected to be a highly efficient strategy for the synthesis of chiral amines. Indeed, the asymmetric addition of the α-C(sp^3)–H bond of *N*-alkyl groups of secondary amines has been reported, using tantalum and niobium catalysts bearing chiral ligands [Scheme 1(a)].[3] The catalysis proceeds through the initial formation of metal amides followed by β-hydrogen elimination, which affords an active organometallic intermediate that reacts with an alkene.[4] Although up to 98% ee was attained in one example,[3e] enantioselectivities were generally moderate. Activation of the C(sp^3)–H bond α to the nitrogen atom was also promoted by use of a 2-pyridyl directing group.[5] This type of activation enables the iridium-catalyzed intermolecular asymmetric addition of 2-(alkylamino)pyridines to terminal alkenes, in which one of the two enantiotopic hydrogen atoms of the nitrogen-bound methylene group takes part in the reaction selectively [Scheme 1(b)].[6] At around the same time, rhodium-catalyzed enantioselective cycloisomerization of conjugated dienes tethered to an allylamino group has successfully shown the potential of catalytic addition of the *N*-alkyl C(sp^3)–H bond across C=C bonds in organic synthesis [Scheme 1(c)].[7] It should be noted that, in all of those examples, activation of the α-C(sp^3)–H bonds of *N*-alkyl groups required additional structural setups, such as a N–H bond, a pyridyl directing group, and an allyl group, to facilitate the C(sp^3)–H activation process. To expand the substrate scope and to make this strategy more applicable, it is truly important to establish a corresponding process devoid of such additional structural requirements. We herein describe the iridium-catalyzed asymmetric cycloisomerization of 2-alkenyl-*N*-methylanilines to 3-substituted indolines, where the *N*-methyl C(sp^3)–H bond undergoes direct activation and addition to an intramolecular C=C bond in a highly enantioselective fashion [Scheme 1(d)]. We show wide reaction scope and propose a reaction mechanism in which activation of the methyl C(sp^3)–H bond α to the nitrogen atom is involved as the rate-determining step, based on labeling experiments.



Scheme 1. Transition-Metal-Catalyzed Asymmetric Addition of C(sp^3)–H Bond of *N*-Alkyl Group across C=C Bond.

The new cycloisomerization was designed on the basis of our recent study on the cycloisomerization of *o*-alkynylanisoles to benzofurans, which proceeds through activation of the methoxy C(sp^3)–H bond.[8] *N*,*N*-Dimethylaniline **1a** bearing a 1-phenylvinyl group at the *ortho* position was reacted in toluene at 110 °C in the presence of $[IrCl(C_2H_4)_2]_2$ (3 mol %, 6 mol % Ir) as a catalyst precursor and (*S*)-SEGPHOS (**L1**, 6 mol %) as a ligand (entry 1, Table 1). Intramolecular addition of the C(sp^3)–H bond of the methyl group on nitrogen took place to give 1,3-dimethyl-3-phenylindoline (**2a**) in 11% yield after 24 h. Enantiomeric excess (ee) of the product was appreciably high (85% ee), indicating that enantioface discrimination of the double bond was accomplished efficiently by **L1**. The ee of **2a** improved to 91% (38% yield) when (*S*)-DM-SEGPHOS (**L2**) was used as a ligand (entry 2). The reactions with **L1** and **L2** gave hydrogenated **3** as a side product in 5-14% yield (entries 1 and

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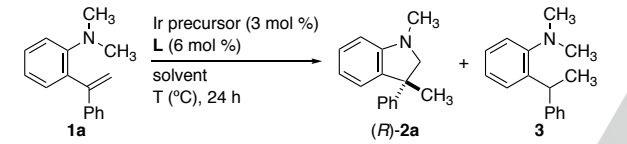
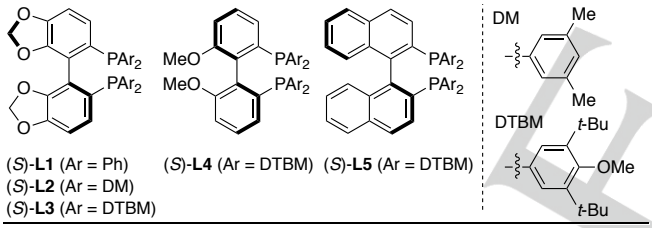
2). We found that an iridium catalyst bearing (*S*)-DTBM-SEGPHOS (**L3**), bearing the bulky and electron donating 3,5-di-*tert*-butyl-4-methoxyphenyl group (DTBM) on the phosphorus atoms promoted the reaction more efficiently to give **2a** in 85% yield with 97% ee, in which the formation of **3** was completely suppressed (entry 3). The absolute configuration of the major enantiomer of **2a** was determined to be *R* by single crystal X-ray diffraction of the corresponding ammonium salt prepared from **2a** with iodomethane (see Supporting Information). DTBM-substituted ligands (*S*)-DTBM-MeOBIPHEP (**L4**) and (*S*)-DTBM-BINAP (**L5**) both afforded high yields, although **L5** afforded slightly lower ee than **L4** (entries 4 and 5). The Ir-**L3**-catalyzed reaction proceeded even at 80 ºC, leading to the highest ee of **2a** (98.7% ee) (entry 6). Commercially available $[IrCl(cod)]_2$ was also an effective catalyst precursor, although the yield of **2a** was slightly low due to the formation of **3** (entry 7). Toluene was the solvent of choice, while the reaction in THF resulted in preferential formation of **3** through hydrogen transfer from THF (entry 8).[8,9]

Table 1. Iridium-catalyzed asymmetric cycloisomerization of *o*-(1-phenylvinyl)-*N*,*N*-dimethylaniline (**1a**) in the presence of chiral phosphorus ligands **L1**-**L5**[a]

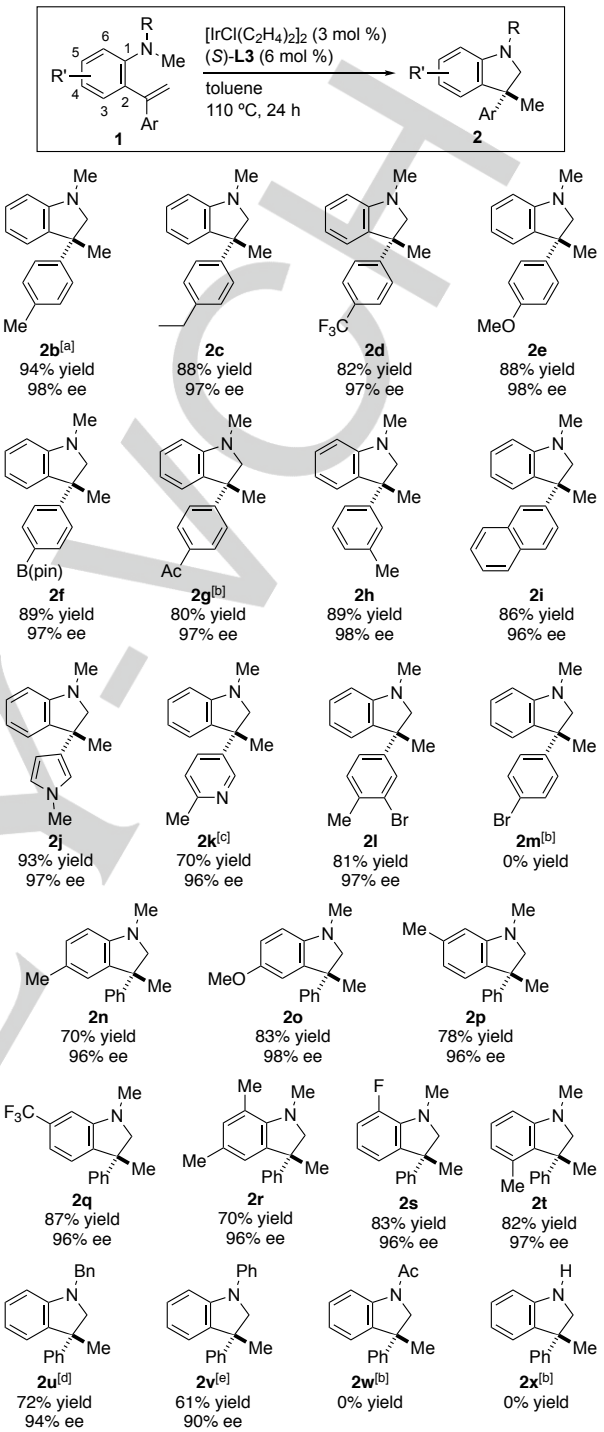




(*S*)-**L1** (Ar = Ph) (*S*)-**L2** (Ar = DM) (*S*)-**L3** (Ar = DTBM) (*S*)-**L4** (Ar = DTBM) (*S*)-**L5** (Ar = DTBM)

entry	Ir precursor	L	solvent	T (°C)	**2a**[b]	**3**[c]
1	$[IrCl(C_2H_4)_2]_2$	(*S*)-**L1**	toluene	110	11[c], 85	5
2	$[IrCl(C_2H_4)_2]_2$	(*S*)-**L2**	toluene	110	38, 91	14
3	$[IrCl(C_2H_4)_2]_2$	(*S*)-**L3**	toluene	110	85, 97	0
4	$[IrCl(C_2H_4)_2]_2$	(*S*)-**L4**	toluene	110	88, 96	1
5	$[IrCl(C_2H_4)_2]_2$	(*S*)-**L5**	toluene	110	81, 91	2
6	$[IrCl(C_2H_4)_2]_2$	(*S*)-**L3**	toluene	80	45, 98.7	2
7	$[IrCl(cod)]_2$	(*S*)-**L3**	toluene	110	76, 97	10
8	$[IrCl(C_2H_4)_2]_2$	(*S*)-**L3**	THF	110	6[c], nd	80

[a] **1a** (0.20 mmol), an Ir precursor (0.0060 mmol), and **L** (0.012 mmol) were stirred in solvent (0.2 mL) at 80-110 °C for 24 h. [b] Isolated yield (%) and ee (%) determined by SFC with chiral stationary phase column. [c] ^{1}H NMR yield (%).



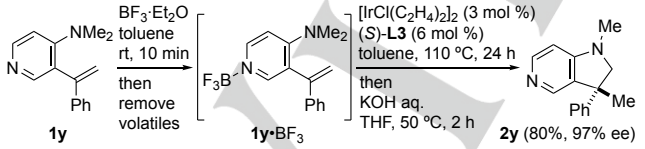
Scheme 2. Iridium-catalyzed asymmetric cycloisomerization of **1**. Reaction conditions: **1** (0.20 mmol), $[IrCl(C_2H_4)_2]_2$ (0.0060 mmol), and (*S*)-**L3** (0.012 mmol) were stirred in toluene (0.2 mL) at 110 °C for 24 h unless otherwise noted. Isolated yields are given. Enantiomeric excesses (ees) were determined by SFC with chiral stationary phase column. [a] 5.0 mmol (1.2 g) scale. [b] In *p*-xylene at 135 °C. [c] In *p*-xylene at 135 °C for 36 h with 8 mol % of Ir. [d] 0.60 mmol scale. [e] In *p*-xylene at 135 °C with 8 mol % of Ir.

A range of *N*-methylaniline derivatives **1** were subjected to the iridium-catalyzed enantioselective cycloisomerization

(Scheme 2). The reaction of *N*,*N*-dimethylanilines **1b**-**f** bearing *para*-substituted aryl groups on the double bonds took place efficiently in toluene at 110 ºC in the presence of Ir-(*S*)-**L3** (6 mol %) to give indolines **2b**-**f** in 82-94% yields with 97-98% ees. Under these reaction conditions, **2b** was obtained on a gram scale (1.1 g, 94% yield, 98% ee). No significant influence of either Me, Et, CF_3, OMe, or B(pin) groups on the reactivity and enantioselectivity was observed (**2b**-**f**). By contrast, the reaction of **1g** bearing an acetyl group was sluggish at 110 ºC; it required elevation of the reaction temperature to 135 ºC to give **2g** in good yield without a significant decrease in ee. 3-Methylphenyl- and 2-naphthyl-substituted **1h** and **1i** also afforded **2h** and **2i** in high yields with 96-98% ees. Pyrrolyl- and pyridyl-substituted **1j** and **1k** affored the corresponding products with high ees, although the latter substrate required forced reaction conditions (8 mol % Ir, 135 °C, 36 h). It is interesting to note that 4-bromophenyl-substituted **1m** resulted in no reaction (**2m**), while 3-bromo-4-methylphenyl-substituted **1l** gave **2l** in high yield with 97% ee, probably because of steric shielding of the Br–C bond.

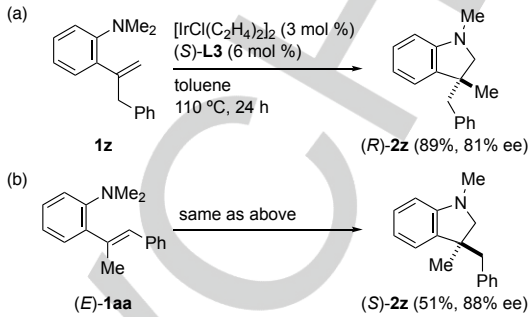
Compounds **1n**-**q**, which bear the 4-Me, 4-OMe, 5-Me, and 5-CF_3 groups on the aniline ring, respectively, gave the corresponding products **2n**–**q** in good yields with 96-98% ees (Scheme 2). A substituent *ortho* to either the dimethylamino or the alkenyl group did not affect the reaction; **2r**-**t** were obtained in good yields with 96-97% ees. In the reaction of *N*-benzyl-*N*-methylaniline **1u**, selective conversion of the *N*-methyl C–H took place to give **2u** with slightly low ee (94% ee), where the methylene C–H of the *N*-benzyl group left untouched.[10] The reaction of *N*-methyl-*N*-phenylaniline **1v** proceeded slowly, giving **2v** in 61% yield with 90% ee when using 8 mol % catalyst at 135 °C. On the other hand, no reaction took place with *N*-methylanilines **1w** and **1x** bearing an acetyl and hydrogen on the nitrogen atoms (**2w** and **2x**).

Cycloisomerization of the 4-(*N*,*N*-dimethylamino)pyridine derivative **1y** was not observed under the standard conditions (Scheme 3). It is presumed that coordination of the sp^2 nitrogen atom to the iridium center shut down the catalyst activity. This problem was overcome by pretreatment of **1y** with BF_3•OEt_2 to form **1y**•BF_3, which was found to undergo cycloisomerization under the standard conditions. The cyclized product was then treated with aqueous KOH in THF at 50 °C, giving **2y** in 80% yield with 97% ee.



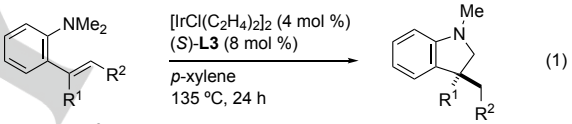
Scheme 3. Asymmetric Cycloisomerization of 4-(*N*,*N*-Dimethylamino)pyridine Derivative **1y**

We then compared the cycloisomerization of two isomeric substrates, terminal alkene **1z** and trisubstututed internal alkene (*E*)-**1aa**, which are potentially interconvertible via double bond migration (Scheme 4). It should be noted that they afforded enantiomeric products (*R*)- and (*S*)-**2z** enantioselectively. These results indicate that even isomerizable C=C bonds including trisubstituted C=C bonds undergo cycloisomerization with no prior double bond migration.



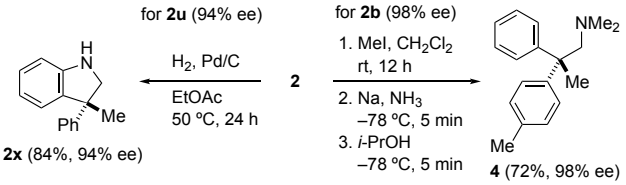
Scheme 4. Asymmetric Cycloisomerization of Potentially Interconvertible Alkenes **1z** and (*E*)-**1aa**

Reaction of **1ab** and **1ac** bearing tri-substituted alkenes proceeded at 135 °C to afford the corresponding indolines **2ab** and **2ac** with 95 and 96% ees, respectively, with moderate yields [Eq.(1)].



1ab (R^1 = *n*-C_4H_9, R^2 = Ph) **2ab** (50% from **1ab**, 95% ee)
1ac (R^1 = *n*-C_5H_{11}, R^2 = CO_2Me) **2ac** (45% from **1ac**, 96% ee)

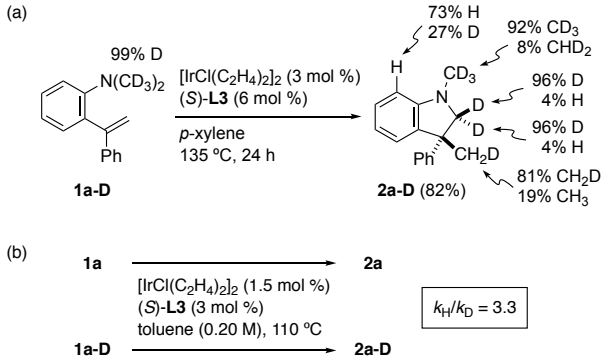
The asymmetric cycloisomerization of **1** enables efficient access to enantioenriched unprotected indoline **2x** and acyclic amine **4** both containing a quaternary carbon center (Scheme 5). Although **2x** could not be synthesized by the cycloisomerization of **1x** directly (Scheme 2), debenzylation of **2u** by hydrogenolysis led to **2x** in high yield (Scheme 5, left). According to the procedure reported by MacMillan et al., **2b** was reacted with iodomethane in CH_2Cl_2 and the resulting ammonium salt was treated with Na/NH_3 (Scheme 5, right).[11] Cleavage of the C(sp^2)–N bond took place smoothly at –78 °C, giving **4** in good total yield and with retention of enantiopurity.



Scheme 5. Synthetic Conversion of Enantioenriched Indolines **2**

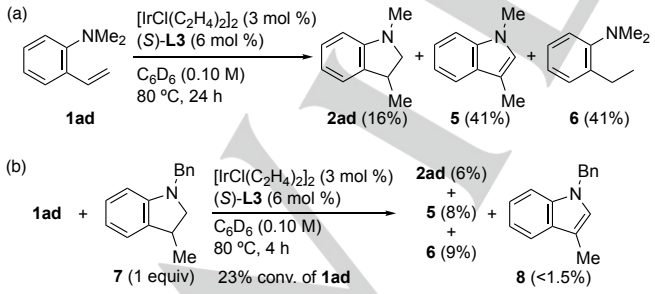
To gain insight into the reaction mechanism, deuterium-labeling experiments were carried out (Scheme 6). Deuterium-labeled **1a-D** gave indoline **2a-D** at 135 °C in 82% yield [Scheme 6(a)]. While almost perfect deuterium incorporation

was observed at the *N*-methyl and the methylene group of the product, lower deuterium incorporation at the 3-methyl group (81%) with its delivery to the *ortho*-position (27%) was noticed. A large kinetic isotope effect (k_H/k_D = 3.3) was observed in the independent reactions of **1a** and **1a-D** [Scheme 6(b)], suggesting that oxidative addition of the C–H bond of the *N*-methyl group to iridium is the rate-determining step.



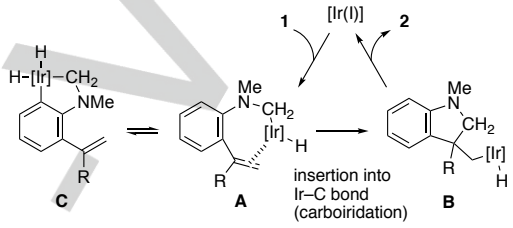
Scheme 6. Deuterium-Labeling Experiments

We also carried out the reaction of vinyl-substituted *N*,*N*-dimethylaniline **1ad** [Scheme 7(a)]. We obtained indole **5** and ethyl-substituted aniline **6** both in 41% yield along with the cycloisomerization product **2ad** in low yield. The formation of **5** may be explained either by dehydrogenation from the cycloisomerization product **2ad** or by β-H-elimination of an iridium intermediate in the catalytic cycle. We could exclude the former possibility by the reaction of **1ad** in the presence of an equimolar amount of *N*-benzylindoline **7** as a mimic of product **2ad** [Scheme 7(b)].[12] At 23% conversion, the reaction afforded **5** (8%) and **6** (9%) along with the cycloisomerization product **2ad** in 6% yield with formation of only a small amount of indole **8** (<1.5%), which was derived from **7**. This result clearly excludes the possibility of a dehydrogenation process after the formation of **2ad**, but suggests a β-elimination process in the catalytic cycle.



Scheme 7. Mechanistic Study Based on the Reaction of **1ad**

Based on these results, we propose the following mechanism for the present cycloisomerization (Scheme 8). The rate-determining oxidative addition of the *N*-methyl C(sp^3)–H bond to iridium is followed by insertion of a C=C bond into the Ir–C bond, i.e., carboiridation, in a 5-exo fashion, to form the Ir–H species **B**. Intermediate **B** undergoes reductive elimination of the C–H bond to form the cycloisomerization product **2**. The observed formation of indole **5** can only be explained by β-elimination from **B** (R = H) by this mechanism, but not by an alternative mechanism involving insertion of a C=C bond into the Ir–H bond (hydroiridation) of intermediate **A**. In the (*S*)-**L3**/Ir-catalyzed reaction of **1a** (R = Ph), the carboiridation proceeds selectively on the *Re*-face of the C=C bond to afford *R* enantiomer through a configuration that avoids steric repulsion between the substituent R and the DTBM groups on the phosphorus atoms.[13] Partial H/D exchange at C7 shown in Scheme 6(a) is likely to indicate existence of a non-productive iridacycle **C** formed from **A**.



Scheme 8. A Possible Mechanism

In conclusion, we established an efficient Ir-(*S*)-**L3** catalyst system, for cycloisomerization of *N*-methylanilines **1** into indolines **2** with the construction of quaternary stereogenic centers in a highly enantioselective fashion. Mechanistic investigations revealed that oxidative addition of a C–H bond to Ir(I) is the rate-determining step, and the following insertion of a C=C bond takes place via carboiridation rather than hydroiridation.

Acknowledgements

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Keywords: Asymmetric synthesis • C–H activation • Heterocycles • Quaternary stereogenic center • Synthetic methods

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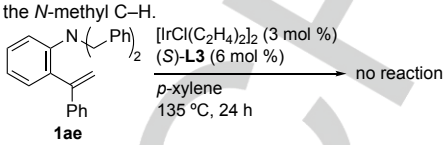
[10] *N*,*N*-dibenzylaniline **1ae** did not undergo cycloisomerization even at 135 °C, indicating that the methylene C–H is much less reactive than the *N*-methyl C–H.



1ae

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[12] A competitive dehydrogenation of **2ad** (0.5 equiv) and **7** (0.5 equiv) in a single pot using styrene (1 equiv) as a hydrogen acceptor indicates that the two substrates show comparable reactivates under the conditions shown in Scheme 7 [conversions in C_6D_6 at 80 °C for 4 h with 6 mol % of Ir/(*S*)-**L3**: **2ad** (5.2%) and **7** (3.6%)].

[13] Hartwig et al. have reported X-ray crystallographic analysis of [(*S*)-**L3**]IrCl(1-octene), which indicates that the first and third quadrants are blocked by DTBM groups. C. S. Sevov, J. F. Hartwig, *J. Am. Chem. Soc.* **2013**, *135*, 2116–2119.

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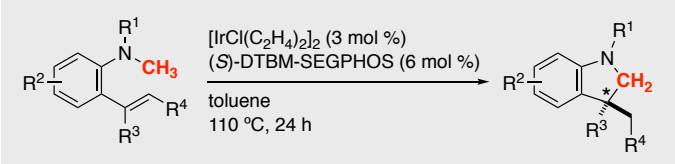

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Asymmetric Cycloisomerization of *o*-Alkenyl-*N*-methylanilines to Indolines through Iridium-Catalyzed C(sp^3)–H Addition to Carbon–Carbon Double Bonds

Build a bridge: Highly enantioselective cycloisomerization of *N*-methylanilines bearing *o*-alkenyl groups to indolines is established. An iridium catalyst bearing a bidentate chiral diphosphine effectively promotes the intramolecular addition of the C(sp^3)–H bond across a carbon–carbon double bond with highly enantioselective fashion. The reaction gives indolines bearing quaternary stereogenic carbon centers at the 3-positions. Twenty two indolines were synthesized over 95% ees.