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Enantioselective Synthesis of 3-Allylindolizines via Sequential Rh-Catalyzed Asymmetric Allylation and Tschitschibabin Reaction

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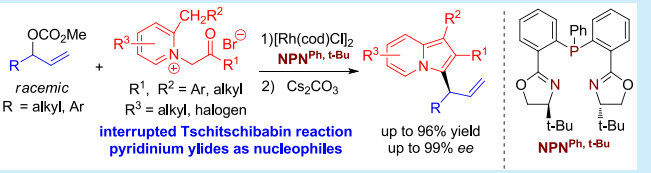
ABSTRACT: The first highly regio- and enantioselective synthesis of 3-allylindolizines has been developed by the sequential Rh-catalyzed asymmetric allylation and Tschitschibabin reaction. Above the 20:1 branch/linear ratio, up to a 96% yield and 99% *ee* could be obtained with the help of *tert*-butyl-substituted chiral bisoxazolinephosphine ligand. In situ generated highly nucleophilic 2-alkylpyridinium ylides are utilized to undergo the asymmetric alkylation reaction before cyclization.

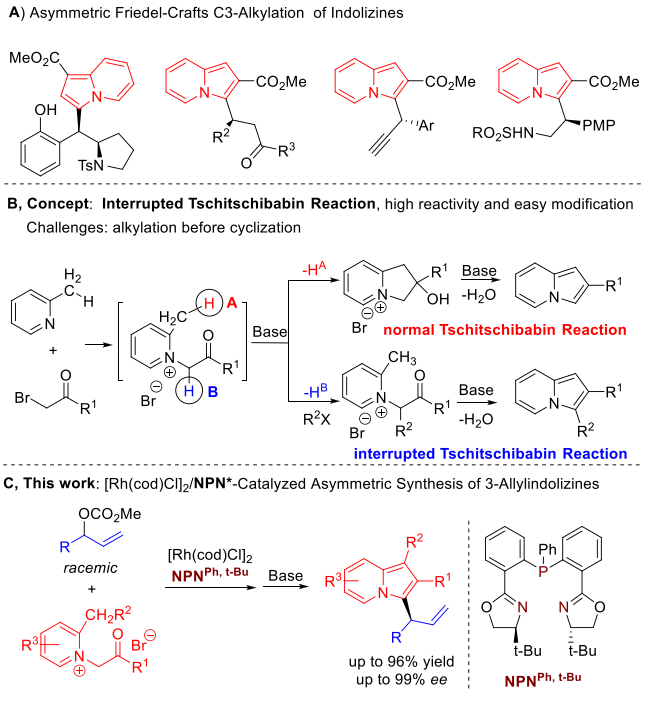


As one of the privileged nitrogen-containing heterocycles, the indolizine skeleton can be found in many biologically active molecules[1] and fluorescent sensors.[2] In addition, its saturated counterpart, the indolizidine, is the core structure of various alkaloids, such as (−) 205B and 261C.[3] Although the late stage functionalization of the C3 position of existing indolizine molecules provides a straightforward synthetic method to many new indolizine derivatives, the asymmetric versions remained very rare. Indolizines usually react as electron-rich heterocycles in Friedel−Crafts type transformations, such as Michael addition with quinone methides and acid-activated α,β-unsaturated ketones, Cu-catalyzed asymmetric propargylation, and ring-opening of aziridines, in which highly reactive electrophiles are usually generated (Scheme 1A).[4] Due to the lack of activation mode on the indolizine skeleton, a new strategy for the asymmetric synthesis of chiral indolizines derivatives is highly desired.

Tschitschibabin reaction is a frequently utilized synthetic approach to indolizines, involving the base-promoted intramolecular condensation of 1-(2-oxoalkyl)-2-methylpyridinium salts by removing proton H^A (Scheme 1B).[5] We envisioned that an alkylation of the α-carbon of the ketone before the cyclization would lead to an interrupted Tschitschibabin process, in which a 3-substituted indolizine could be generated. The strong nucleophilicity of the pyridinium ylides is expected to extend the scope of electrophiles.[6] The challenge is to guarantee the alkylation of pyridinium ylide occurs before the Tschitschibabin cyclization when less reactive electrophiles are utilized.

Transition-metal-catalyzed regio- and enantioselective allylic substitutions provide powerful methods to construct new carbon−carbon and carbon−heteroatom bonds.[7] Our group recently developed a new catalyst based on Rh[8] and chiral bisoxazolinephosphine ligands (NPN*) to realize the highly branch-selective allylic alkylation of a variety of weakly acidic nitrogen, oxygen, carbon, and sulfur pronucleophiles.[9] The

Scheme 1. Synthesis Chiral 3-Allylindolizines by Interrupted Tschitschibabin Reaction



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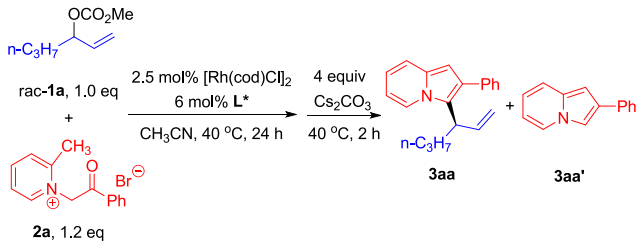
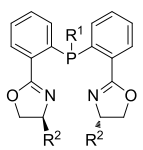
carbonate or the alkoxide anion generated during the formation of the π-allyl rhodium intermediate could be used as the mild base to activate the neutral pronucleophiles. This small amount of gradually released base is expected to selectively remove the H^B in the pyridinium salts to achieve the interrupted Tschitschibabin reaction. Herein, we report a Rh/NPN*-catalyzed highly regio- and enantioselective allylic alkylation of pyridinium salts and base-promoted cyclization sequence to prepare 3-substituted indolizines (Scheme 1C). Chiral 3-allylindolizines bearing aliphatic groups could be synthesized from 2-alkylpyridines and α-bromoketones. Above the 20:1 branch/linear ratio, up to a 96% yield and 99% *ee* could be obtained with the help of the chiral bisoxazoline-phosphine ligand with *tert*-butyl groups on the oxazoline rings.

We started the study with racemic allylic carbonate **1a** and 2-methyl-1-(2-oxo-2-phenylethyl)pyridin-1-ium bromide **2a** as the model substrates (Table 1). The reactions were conducted

Table 1. Optimization of the Reaction Conditions[a]





L1, R^1 = Ph, R^2 = Me
L2, R^1 = Ph, R^2 = Bn
L3, R^1 = Ph, R^2 = Ph
L4, R^1 = Ph, R^2 = i-Pr
L5, R^1 = Ph, R^2 = t-Bu
L6, R^1 = 3,5-t-Bu$_2$-4-MeOC$_6$H$_2$, R^2 = t-Bu
L7, R^1 = 4-CF$_3$C$_6$H$_4$, R^2 = t-Bu
L8, R^1 = 4-OMeC$_6$H$_4$, R^2 = i-Pr

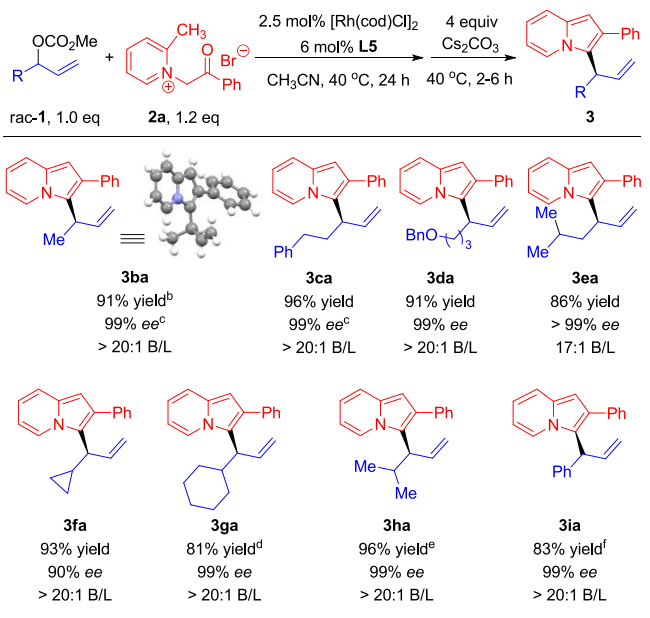
entry	L*	3aa/3aa′[b]	yield (%)[c]	*ee* (%)[d]	B/L[e]
1	**L1**	0.25:1	23	33	3:1
2	**L2**	0.24:1	21	23	2:1
3	**L3**	1.38:1	65	98	>20:1
4	**L4**	1.05:1	61	98	>20:1
5	**L5**	3.85:1	95	99	>20:1
6	**L6**	2.99:1	88	>99	13:1
7	**L7**	2.64:1	85	99	>20:1
8	**L8**	0.88:1	51	98	12:1
9[f]	**L5**	2.15:1	82	99	>20:1
10[g]	**L5**	1.75:1	76	99	>20:1

[a]All reactions were run with 2.5 mol % catalyst precursor and 6 mol % ligand on a 0.3 mmol scale at 40 °C for 24 h unless otherwise noted, and the reactions with 4 equiv Cs_2CO_3 were conducted in the presence of air. [b]The ratios were determined by ^{1}H NMR. [c]Yield of isolated product. [d]The enantiomeric excess values were determined by HPLC analysis with a chiral column. [e]The ratios of branch products to linear products were determined by ^{1}H NMR. [f]The reaction was carried out at room temperature. [g]The reaction was carried out at 60 °C.

with 2.5 mol % $[Rh(cod)Cl]_2$ and 6 mol % chiral NPN ligand in acetonitrile (0.15 M) at 40 °C for 24 h. A 4 equiv amount of Cs_2CO_3 was then added into the reaction tube to promote the cyclization. The substituent R^2 on the oxazoline rings in the NPN ligands has a significant influence on the reactivity and selectivity of the reaction. Reactions in the presence of **L1** and **L2** with methyl and benzyl respectively gave the desired product **3aa** in low yield, branch/linear ratio, and enantioselectivity (entries 1 and 2). A large amount of side product **3aa′** was obtained.[10] However, **L3** and **L4** with bulkier isopropyl and phenyl groups lead to moderate yields, above the 20:1 branch/linear ratio and 98% *ee* for **3aa** (entries 3 and 4). To our delight, full conversion of the allylic carbonate **1a** was observed when **L5** with a *tert*-butyl group was applied (entry 5), which might be caused by the noncovalent dispersion interaction between the ligand and the substrate.[11] Compound **3aa** was isolated in 95% yield, >20:1 b/l ratio, and 99% *ee*. The effect of the R^1 group on the phosphine atom was further investigated. For highly effective ligands with a *tert*-butyl group, the electron-donating or electron-withdrawing groups at the R^1 position have little effect on the outcome of the reactions (entries 6 and 7). Nevertheless, an inferior effect of the 4-OMe group in **L8** was observed by comparison to **L4** with the isopropyl group at R^2 (entry 8). The reaction at room temperature was less efficient (entry 9). Higher temperature (60 °C) caused the faster consumption of **2a** to form more cyclization byproduct **3aa′** (entry 10). CH_3CN was proven to be superior compared to other solvents examined.

With the optimized reaction conditions in hand (entry 5, Table 1), we then investigated the scope of allylic carbonates (Scheme 2). The reactions of allylic carbonates with simple methyl, phenylethyl, and benzylether protected alkyl groups afford the desired chiral 3-allylindolizines in high yields and 99% *ee* (**3ba**, **3ca**, and **3da**). The formation of **3ba** could be conducted in 5 mmol scale without erosion of reactivity and

Scheme 2. Reaction Scope of Allylic Carbonates[a]



[a]All reactions were run with 2.5 mol % catalyst precursor and 6 mol % ligand on a 0.3 mmol scale at 40 °C for 24 h unless otherwise noted, and the reactions with 4 equiv of Cs_2CO_3 were conducted in the presence of air. [b]Reaction at 5 mmol scale. [c]The *ee* value was determined after the hydroboration/oxidation sequence. [d]1.5 equiv of allyl carbonate, 1.0 equiv of **2a**, and 3 equiv of BSA were used and the reaction was run for 72 h. [e]1.5 equiv of allyl carbonate, 1.0 equiv of **2a**, and 3 equiv of BSA were used and the reaction was run for 48 h. [f]2.0 equiv of allyl carbonate, 1.0 equiv of **2a**, and 3 equiv of BSA were used and the reaction was run for 72 h.

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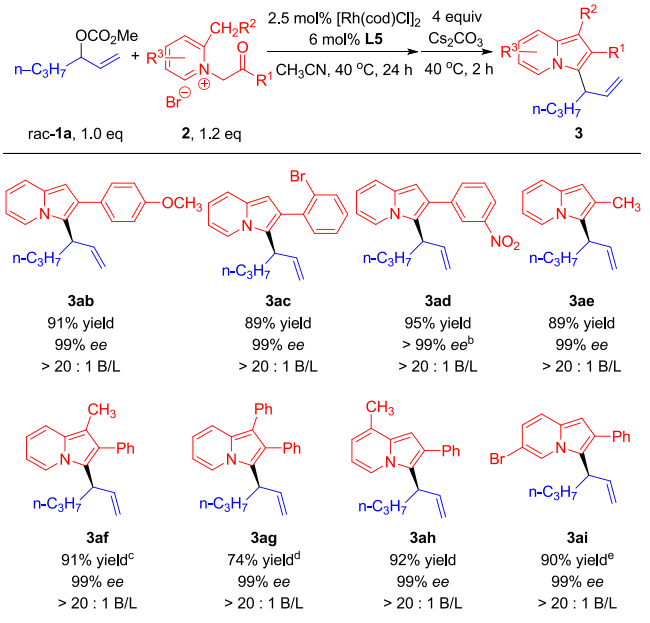
selectivities. The absolute configuration of **3ba** was assigned to be *R* by the single crystal X-ray diffraction analysis. In addition, allyl carbonates with *β*-branched isobutyl (**3ea**) and *α*-branched cyclopropyl groups react smoothly to give the allylation products in high yields and *ee* (**3ea** and **3fa**). Sterically more hindered cyclohexyl, isopropyl, and phenyl groups in the allylic carbonates cause the reactions to become sluggish. To our delight, high conversions could be obtained by changing the reaction conditions appropriately. More allylic carbonates, extra base N,O-bis(trimethylsilyl)acetamide (BSA), and a longer reaction time were necessary to obtain high yields for **3ga**, **3ha**, and **3ia**.

To further explore the substrate scope, various 2-alkylpyridinium salts were synthesized and evaluated (Scheme 3). Several *α*-bromoacetophenones could be used in this

Scheme 3. Reaction Scope of 2-Substituted Pyridinium Salts[a]

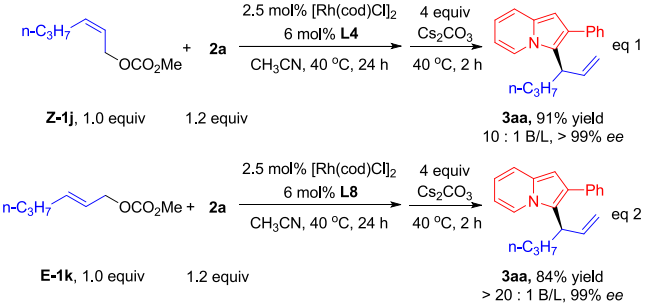


[a]All reactions were run with 2.5 mol % catalyst precursor and 6 mol % ligand on a 0.3 mmol scale at 40 °C for 24 h unless otherwise noted, and the reactions with 4 equiv of Cs_2CO_3 were conducted in the presence of air. [b]The *ee* value was determined after the hydroboration/oxidation sequence. [c]The reaction was carried out with 1.5 equiv of pyridinium salt **2f** with 2 equiv of BSA (N,O-Bis(trimethylsilyl)acetamide) and **L7** ligand for 48 h. [d]The reaction was carried out with 2 equiv of BSA and **L7** ligand. [e]The reaction was carried out with 1.2 equiv of allyl carbonate **rac-1a** and 1.0 equiv of **2i** for 48 h.

transformation. Electron-donating and -withdrawing groups as well as bromide at para-, meta-, and ortho- positions on the phenyl ring of the ketone have neglectable effect on the yields and *ee* (**3ab**, **3ac**, and **3ad**). Moreover, the phenyl ring could be replaced by a simple methyl group when *α*-bromoacetone was used to prepare the pyridinium salts (**3ae**). Besides the ketone side, the 2-methylpyridine part could also be modified. Application of 2-ethyl and 2-benzylpyridines in the pyridinium salts preparation led to the formatin of 1-methyl and 1-phenyl 3-allylindolizines in high yields and *ee* when electron-withdrawing **L7** was used as ligand (**3af** and **3ag**). In addition, the pyridinium salts from 2,3-dimethylpyridine and 5-bromo-2-methylpyridine could be converted to the 3-allylindolizines with a 5- and 7-substituent successfully (**3ah** and **3ai**).

To demonstrate the broad scope of this Rh-catalyzed allyl substitution reaction, linear allylic methyl carbonates with both *Z* and *E* geometries were tested. When **L4** was used as the ligand instead of **L5**, *Z*-**1j** could be transformed smoothly to the branched product **3aa** with a 10:1 branch/linear ratio, 91% yield, and >99% *ee* (Scheme 4, eq 1). For *E*-**1k**, ligand **L8**

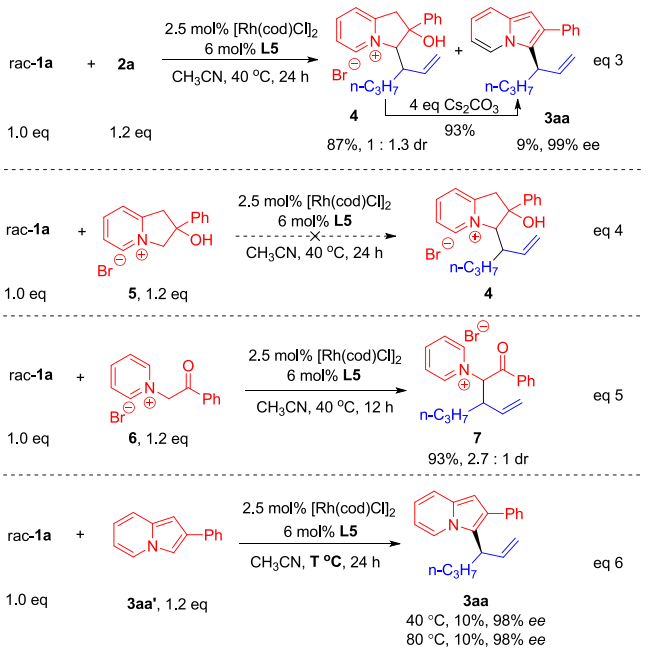
Scheme 4. Reactions of Linear Allylic Carbonates



could lead to a higher yield and selectivity (eq 2). Both branched and linear allylic carbonates react to give the same branched 3-allylindolizine **3aa**.

Some control experiments were conducted to understand the reaction mechanism (Scheme 5). First, without Cs_2CO_3

Scheme 5. Control Experiments



addition, the allylated bicyclic pyridinium salts intermediate **4** was isolated as 1:1.3 diastereomer mixture in 87% yield, along with 9% of **3aa** (eq 3). Compound **4** reacts with Cs_2CO_3 in CH_3CN to give **3aa** in 93% yield and 99% *ee*. However, the corresponding allylation product **4** cannot be obtained from the bicyclic pyridinium salt **5**[10] under otherwise identical conditions (eq 4). The in situ generated methoxide base is prone to remove the H^B first (Scheme 1B). The allylic alkylation of the *α*-carbon of ketone in **2a** may occur before the cyclization. This was further confirmed by the fact that pyridinium salt **6** without the 2-methyl group could react under the identical conditions to give **7** in 93% yield with a

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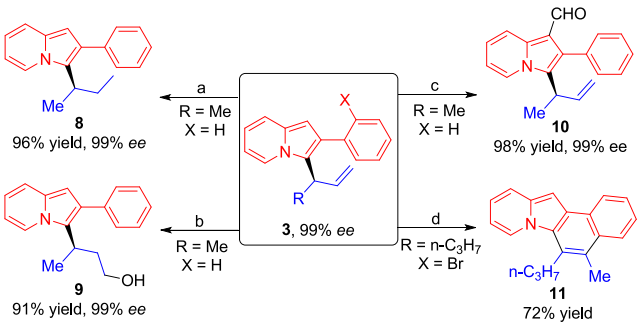
2.7:1 dr (eq 5). Finally, when **3aa′** was subjected to the same conditions, only 10% of **3aa** was isolated. No higher yields could be obtained with other conditions. The nucleophilicity of pyridinium ylides is higher than that of the electron-rich heterocycles, which is the key for a successful reaction with a less electrophilic π-allylrhodium intermediate.[12]

The chiral 3-allylindolizines could be converted to other indolizines derivatives by further functional group manipulations (Scheme 6). Pd/C-catalyzed hydrogenation and

Scheme 6. Synthetic Transformation of the Chiral 3-Allyl Indolizines[a]



[a]Reaction conditions: (a) Pd/C (5 wt %), H_2 balloon, CH_3OH, rt, 12 h. (b) 9-borabicyclo[3.3.1]nonane (9-BBN) (2.5 equiv), 0 °C−rt, 12 h, then EtOH, NaOH, H_2O_2 (30 wt % in water), rt, 3 h. (c) $POCl_3$ (1.2 equiv), DMF, 40 °C, 45 min. (d) $Pd(OAc)_2$ (10 mol %), PPh_3 (40 mol %), Et_3N (1 equiv) in DMF at 130 °C for 12 h.

hydroboration/oxidation at the double bond gave products **8** and **9** respectively in high yields without any erosion of the enantioselectivity. Treatment of **3ba** with Vilsmeier's reagent affords the formylated indolizine **10** in 98% yield. The tetracyclic N-heterocycle **11** could be prepared from **3ac** by Pd-catalyzed intramolecular Heck reaction/isomerization.

In summary, we have developed the first highly regio- and enantioselective synthesis of 3-allylindolizines via the Rh/bisoxazolinephosphine-catalyzed asymmetric allylic substitution/Tschitschibabin reaction sequence. Chiral 3-allyl indolizines could be prepared with an above 20:1 branch/linear ratio, up to 96% yield, and normally 99% *ee* from 2-alkylpyridines, α-bromomethylketones, and three different types of allylic carbonates. The moderate nucleophilicity of the indolizine molecule could be overcome by applying highly nucleophilic 2-alkylpyridinium ylides. The utilization of a *tert*-butyl-based NPN ligand is the key to enabling the allylation to occur before the Tschitschibabin cyclization process.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03383.

Detailed experimental procedures, characterization data, copies of ^1H, ^{13}C NMR spectra, HPLC spectra, and X-ray crystal structure of **3ba** (PDF)

Accession Codes

CCDC 2015160 (**3ba**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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(11) *tert*-Butyl-substituted NPN ligand normally leads to low conversion in the Rh- or Co-catalyzed asymmetric allylic alkylation reactions; see ref 9b to 9e. The accelerating effect of the *tert*-butyl groups in the NPN ligand might be caused by the noncovalent dispersion interaction between the ligand and the substrate. For selected examples, see: (a) Gridnev, I. D. Attraction versus Repulsion in Rhodium-Catalyzed Asymmetric Hydrogenation. *ChemCatChem* **2016**, *8*, 3463−3465. (b) Lu, G.; Liu, R. Y.; Yang, Y.; Fang, C.; Lambrecht, D. S.; Buchwald, S. L.; Liu, P. Ligand−Substrate

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(12) The electrophilicity of the π-allylRh/NPN* intermediate is believed to be lower than that of the iridium or rhodium π-allylcomplex with π-acidic phosphite or phosphoramidite ligands.

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