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Stereogenic Lock in 1-Naphthylethanamine Complexes for Catalyst and Auxiliary Design: Structural and Reactivity Analysis for Cycloiridated Pseudotetrahedral Complexes

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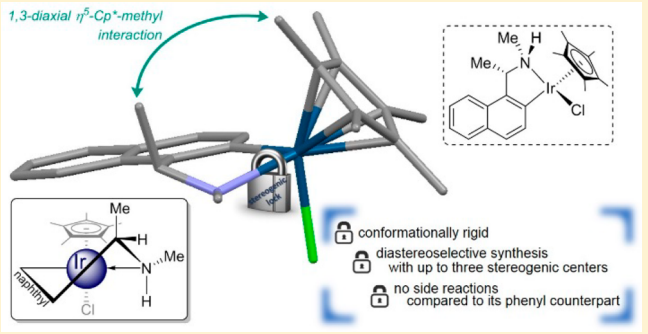
Supporting Information

ABSTRACT: A series of optically active pseudo-tetrahedral five-membered cyclometalated 1-naphthylethanamine iridium(III) complexes were prepared and characterized to analyze the efficacy of the stereogenic conformational lock in both solid and solution phases. The synthesis of the iridacycles was diastereoselective, and the compounds were found to be conformationally rigid. In comparison to its phenyl derivative, the structural lock prevented oxidation of the amine moiety within the five-membered organometallic ring during its synthesis. With up to three stereogenic centers in one of the naphthalene complexes, the stereochemistry of the metallacycle remained stable to both thermal and chemical changes. In terms of catalytic performance, the complexes displayed excellent activity for the asymmetric hydrogen transfer reaction, albeit with modest enantioselectivities.



INTRODUCTION

Steric interactions play a significant role in the design of chiral catalysts and auxiliaries for asymmetric catalysis and syntheses.[1] To control enantioselectivity in reactions, rational modifications to the molecular framework are usually incorporated during its design phase. Specifically, the introduction of a steric bulk near the active site is a standard approach.[2]

For multidentate complexes with some form of chiral helicity on its backbone, a structural lock within the cyclic system could dramatically amplify their stereoinduction effects. This critical aspect can be exemplified by the cyclopalladated complexes of 1-phenylethylamine and 1-naphthylethylamine (Figure 1).[3]

It is well-established that the chiral square planar *N,N*-dimethyl-1-naphthylethylamine cyclopalladated complex can impart conformational rigidity within the five-membered organometallic ring due to intramolecular steric repulsion between the methyl substituent at the stereogenic carbon center and the neighboring naphthalene proton. The phenyl derivative, on the other hand, has its ortho proton too far away to interact sterically with any neighboring groups, resulting in the puckered-ring system undergoing a continuous C_2/C_s-interchanging conformational ring flip (Figure 2).

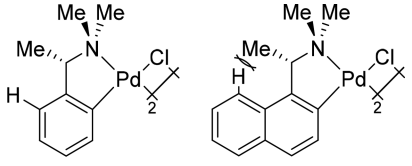


Figure 1. Chiral (*S*)-*N,N*-dimethyl-1-phenylethylamine and (*S*)-*N,N*-dimethyl-1-naphthylethylamine palladacycles.

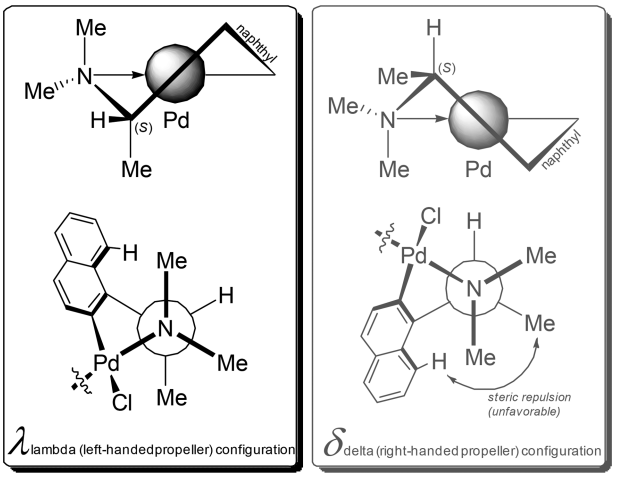


Figure 2. Possible conformations of cyclopalladated complex (*S*)-*N,N*-dimethyl-1-naphthylethylamine.

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This retention of configuration in the naphthalene system was, therefore, found to be superior since the lack of interchangeability permits the stereogenic information to be transferred more efficiently to the substrates from the cyclopalladated framework via the metal center. The effect of this critical feature in the design of these palladacyclic analogues has indeed been evident in numerous asymmetric applications performed by our group (Figure 3).[4]

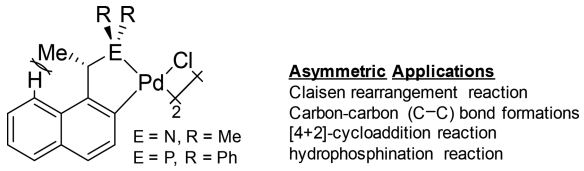


Figure 3. Chiral (*S*)-1-naphthylethylamine cyclopalladated complex and its applications.

In addition, structural studies through variation of substituents within this system were also examined to determine the boundaries of stereogenic lock.[5] With significant knowledge on the effect of the ligand framework in cyclopalladation chemistry and consequently asymmetric applications in place, we now seek to understand and, possibly, extend the concept of stereogenic lock to metallacycles of other transition-metal elements. Furthermore, we believe the concept of structural lock could be applied to other multidentate ligands and five-membered cyclic organocatalysts with analogous frameworks.

The piano-stool d^6-iridium(III)-based cyclometalated compounds have been popular in recent decades.[6] These complexes, although they are of the type ML_3X_3, exhibit a pseudo-tetrahedral structure and are active as catalysts for various reactions.[7] Furthermore, the ease of synthesis and stability of these compounds to air and moisture make such metallacyclic complexes an obvious choice for investigation with focus on the aforementioned perspective.

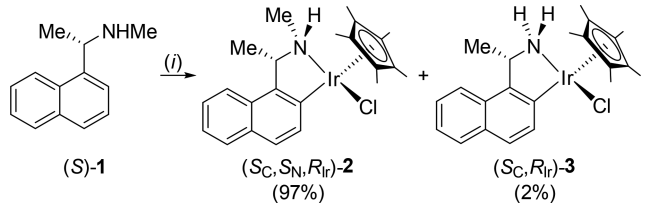
We herein report the synthesis of several cyclometalated 1-naphthylalkylamine iridium(III) complexes. A comparative study involving the structural aspects and their effectiveness in catalytic asymmetric hydrogen transfer reactions will also be discussed.

RESULTS AND DISCUSSION

Synthesis, Characterization, and Stereogenic Lock. It is widely established that cyclometalation is driven by both electronic and steric factors at the donor moiety.[8] As such, our initial attempts at cycloiridation involved the tertiary amine (*S*)-*N*,*N*-dimethyl-1-naphthylethylamine as the ligand, identical with that used in our model palladacycle. Disappointingly, the amine failed to cyclometalate and the reaction afforded numerous side products.[9]

It is worth mentioning that a primary amine derived iridacycle has been prepared by Ikariya and co-workers previously for their study on asymmetric hydrogen transfer reactions.[10] As such, we believe that the cyclometalation protocol could be sensitive to steric factors, although it can also be a driving force via the Thorpe−Ingold effect.[11] To understand how steric hindrance affects cycloiridation of such a framework, we turned to its secondary amine derivative (*S*)-**1**. Gratifyingly, the procedure proceeded efficiently, affording the two cyclic organometallic complexes (S_C,S_N,R_{Ir})-**2** and (S_C,R_{Ir})-**3**, with the former being the major product (Scheme 1).

Scheme 1. Cycloiridation of Optically Active Secondary Amine (*S*)-1[a]



[a]Reaction conditions: (i) $[IrCp^*Cl_2]_2$, NaOAc, CH_2Cl_2, room temperature.

The reaction presented two notable findings: (a) the existence of only one stereoisomer for each of the primary and secondary amino complexes and (b) the formation of *N*-demethylated complex (S_C,R_{Ir})-**3** where a C−N bond was cleaved during the transformation. Arguably, the formation of (S_C,R_{Ir})-**3** as a minor product is questionable, since it could have originated from the ortho-metalation of the residual primary amine present in (*S*)-**1** during its synthesis. To eliminate this possibility, its racemic variant, prepared via a protocol that did not involve the primary amine derivative, was used for cycloiridation (see the Supporting Information for details). As expected, the reaction once again yielded both complexes. It is worth mentioning that a similar cleavage of the C−N bond was observed in one of the byproducts during the attempted cycloiridation of the tertiary amine (*S*)-*N*,*N*-dimethyl-1-naphthylamine.[9] Such N-demethylation processes are also prevalent if bulky ligands are utilized for cyclometalation.[12]

Iridacycle (S_C,S_N,R_{Ir})-**2** was isolated as an orange powder and, expectedly, is stable in air and moisture. Spectroscopically, the ^{1}H NMR spectrum displayed one Cp* singlet at 1.67 ppm at room temperature, indicating the presence of only one isomer despite the complex consisting of three stereocenters. Stereochemical inversion at the nitrogen and iridium central chirality was also found to be nonexistent at other temperatures (discussed in greater detail below). As mentioned earlier, this was surprising since numerous Cp*-based cycloiridated complexes were found to provide diastereomers upon cyclometalation.[6d,13]

To characterize and determine the existence of the stereogenic lock in the complex, crystals of iridacycle **2**, in the form of orthorhombic orange blocks, were obtained through recrystallization from a mixture of hexane and dichloromethane (Figure 4).

The complex conforms to a pseudotetrahedral structure at the iridium center, with stereochemistry at carbon, nitrogen, and iridium determined to be *S*, *S*, and *R*, respectively, according to Cahn−Ingold−Prelog sequence rules.[14] Along the plane of the naphthylene ring, the complex resembles an expected octahedral geometry, typical of pseudotetrahedral complexes, with its bulky Cp* moiety occupying much of the coordination sphere, as evident from the bond angles between the carbon, nitrogen, chlorine, and iridium entities. In addition, the structure features a five-membered organometallic ring adopting a static λ conformation with the stereogenic methyl substituent locked in place at the axial position (Figure 5).

The determination of the stereogenic lock in the solution phase was performed by means of 2D ^{1}H−^{1}H NOESY NMR spectroscopy (Figure 6). Cross peaks relating to H^a−H^c interactions revealed that the five-membered puckered ring

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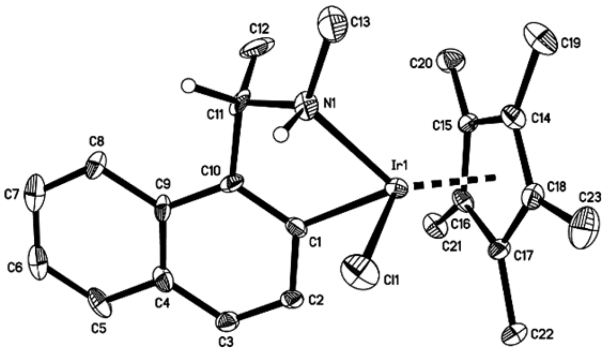

Figure 4. Molecular structure of cycloiridated complex (S_C,S_N,R_{Ir})-**2** with thermal ellipsoids shown at 50% probability. Hydrogen atoms except H(C11) and H(N1) are omitted for clarity. Selected bond lengths and angles: N−Ir (2.151 Å), C−Ir (2.040 Å), Cl−Ir (2.425 Å), N−Ir−C (76.7°), N−Ir−Cl (82.5°), C−Ir−Cl (86.6°).

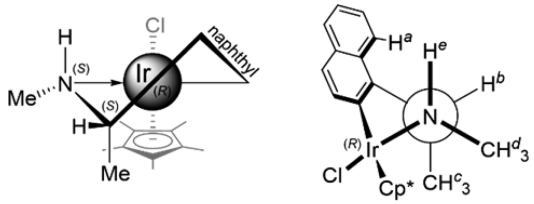

Figure 5. Preferred λ conformation of cycloiridated complex (S_C,S_N,R_{Ir})-**2**.

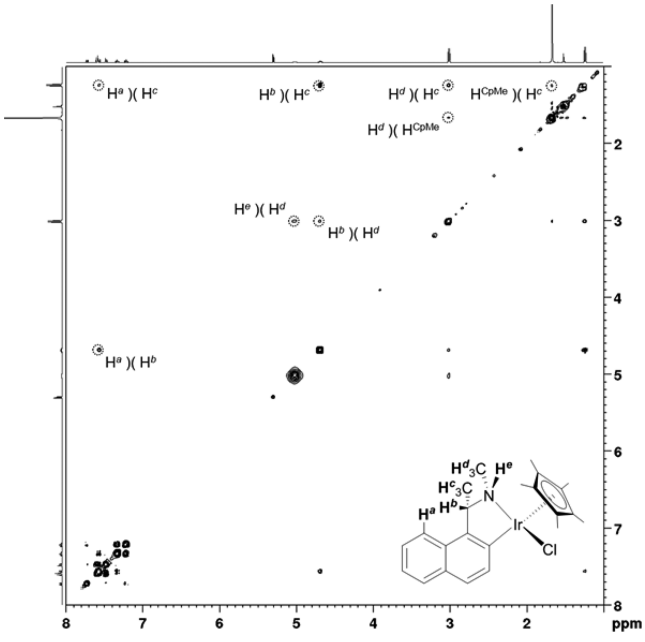

Figure 6. 2D ^{1}H−^{1}H NOESY NMR spectrum of cycloiridated complex (S_C,S_N,R_{Ir})-**2**.

has adopted a single configuration, affirming that a structural lock exists between the methyl substituent at the carbon stereogenic center and its neighboring naphthalene proton. In addition, the spectrum exhibited spatial interactions between the C-chiral methyl substituent, as well as the N-chiral methyl group, with the large cyclopentadienyl methyl moiety, as shown by cross peaks H^c−H^{CpMe} and H^d−H^{CpMe} respectively. Furthermore, the lack of NOE interactions of H^b and H^e with the bulky Cp* ring system detailed the absence of interchanging conformational ring flip within the molecule. Overall, this information provided evidence to support the static λ configuration, as observed in the puckered-ring system (Figure 5).

The orange primary amine-based ortho-iridated complex **3** could be isolated as a byproduct from the reaction, although the fraction was only evident to us on chromatography at a 1 mmol scale. Despite its low yield (2%) in the reaction, it should be noted that the iridacycle could be generated in higher yields (90%) through direct cyclometalation of the primary amine under similar experimental conditions.

Like the secondary amine analogue, iridacycle **3** was found to afford only one diastereomer based on the Cp* singlet (1.74 ppm) within the ^{1}H NMR spectrum. The spectrum also revealed a set of broad nonequivalent NH_2 signals at 3.70 and 4.78 ppm, typical of chelating complexes. Single-crystal X-ray crystallographic studies determined that the recrystallized ortho-metalated complex conforms to a pseudotetrahedral structure with chirality at carbon and iridium to be *S* and *R*, respectively (Figure 7). The molecule also presented a static λ conformation about the organometallic ring in its solid state.

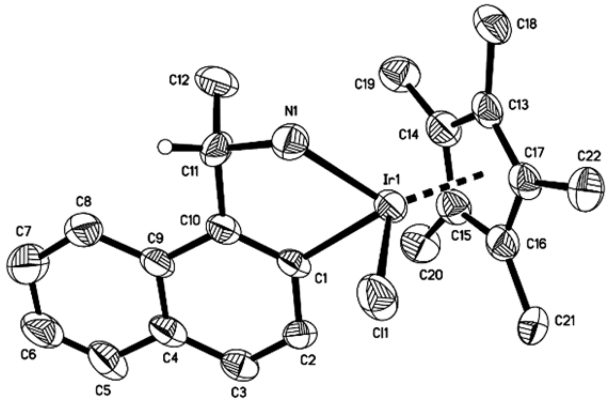

Figure 7. Molecular structure of cycloiridated complex (S_C,R_{Ir})-**3** with thermal ellipsoids shown at 50% probability. Hydrogen atoms except H(C11) are omitted for clarity. Selected bond lengths and angles: N−Ir (2.122 Å), C−Ir (2.060 Å), Cl−Ir (2.431 Å), N−Ir−C (76.7°), N−Ir−Cl (82.5°), C−Ir−Cl (86.8°).

In the solution phase, (S_C,R_{Ir})-**3** presented similar key interactions, although fewer cross peaks were seen due to the increased spatial capacity, in comparison to (S_C,S_N,R_{Ir})-**2** (see the 2D ^{1}H-^{1}H NOESY NMR spectrum of (S_C,R_{Ir})-**3** in the Supporting Information). In particular, the continual presence of the C-chiral methyl group adjacent aromatic proton interaction fixes the organometallic ring system to a single conformation.

While the apparent progression to the investigation was to include the phenyl derivatives in the study, the desired primary amine and secondary amine analogues were unattainable under similar conditions or at elevated temperatures. The primary amine (*R*)-1-phenylethanamine gave only coordination product (*R*)-**4** and unidentifiable compounds at room temperature and 60 °C, respectively (Scheme 2). In the case of the secondary amine (*R*)-*N*-methyl-1-phenylethan-1-amine ((*R*)-**5**), the racemic imino-iridacycle **6** can be obtained as the major product. It should also be mentioned that an additional optically active orange oil-like substance, in significant amounts, could also be obtained. However, further purification and characterization of the fraction proved to be challenging.

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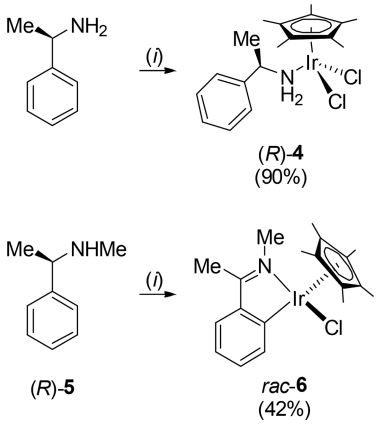
Scheme 2. Attempted Direct Cycloiridation of Optically Active 1-Phenylethylamine Derivatives[a]



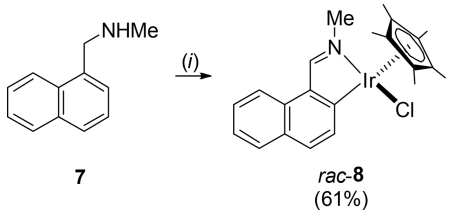
[a]Reaction conditions: (i) $[IrCp^*Cl_2]_2$, NaOAc, CH_2Cl_2, room temperature.

Oxidation of the amine moiety during the process of cyclometalation is not unheard of and has been observed by Pfeffer and co-workers during their cycloiridation procedure.[15] The stepwise oxidation−cyclometalation process presents one of the methods for obtaining these imino-metallacycles. Stirling has reported the racemization of enantiopure amines by an iridium(III) Cp* dihalogen complex through an imino intermediate, although it tends to proceed much more slowly in chloro complexes than in its bromo counterparts.[16] The resultant imine could then undergo ortho-metalation to afford the cycloiridated imine species. Alternatively, a cyclometalation−oxidation protocol could take place. Feringa and de Vries have documented the self-oxidation of a cationic (κ^2-*C*,*N*)-*N*-methylbenzylamine cycloiridated system to its imino variant in solution.[13b]

It is important to note that Ikariya and Kayaki have recently synthesized various chiral cycloiridated benzylic amino complexes.[6b] As such, we questioned the difference in reactivities between the amines of Ikariya and Kayaki with those of ours. It is known that the cyclopalladated equivalents of the former amines were conformationally rigid through stereogenic lock in both solid and solution phases.[5b,17] Noting that our structurally locked iridacycles (S_C,S_N,R_{Ir})-**2** and (S_C,R_{Ir})-**3** can be isolated in their optically active forms, we believed that the locking mechanism must have hindered the oxidative process. To provide the cycloiridated imine complex, the coordinated or cycloiridated amine would need to adopt a planar intermediary structure. However, due to the immense steric crowding about the metal center, the C-chiral methyl substituent-adjacent naphthalene proton interaction may have prevented the oxidation of the amine. We proceeded to verify the concept utilizing *N*-methyl-1-naphthalenemethylamine (**7**), a naphthyl-CH_2-amine for which its cyclopalladated species is not known to be conformationally rigid, for cycloiridation (Scheme 3). Consistent with our hypothesis, the reaction afforded the aldimino complex *rac*-**8** in good yield.

Structural Analysis of the Pseudotetrahedral Iridium(III) Complexes. To gain a further understanding of the steric and electronic properties of the synthesized iridium(III) complexes, we prepared the analogous imine iridacycle for comparison in the solid state. It is important to reiterate that the imino complex has to be synthesized from the direct

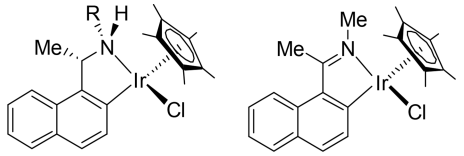
Scheme 3. Cycloiridation of *N*-Methyl-1-naphthalenemethylamine (7)[a]



[a]Reaction conditions: (i) $[IrCp^*Cl_2]_2$, NaOAc, 1,2-dichloroethane, 60 °C.

cycloiridation of the imine derivative, since the oxidation of the naphthalene-based amine moiety was not observed during the process.

Table 1. Selected Bond Lengths (Å) and Bond Angles (deg) of Structurally Analogous Cycloiridated Complexes



R = Me (S_C,S_N,R_{Ir})-**2**
R = H (S_C,R_{Ir})-**3**
rac-**9**

	bond length (Å)		
	N−Ir	C_{Ar}−Ir	Cl−Ir
(S_C,S_N,R_{Ir})-**2**	2.151	2.040	2.425
(S_C,R_{Ir})-**3**	2.122	2.060	2.431
rac-**9**	2.137	2.032	2.418
	bond angle (deg)		
	N−Ir−C_{Ar}	N−Ir−Cl	C_{Ar}−Ir−Cl
(S_C,S_N,R_{Ir})-**2**	76.7	82.5	86.6
(S_C,R_{Ir})-**3**	76.7	82.5	86.8
rac-**9**	76.4	83.5	88.5

Assessment of the optically active secondary amine iridacycle (S_C,S_N,R_{Ir})-**2** showed a slightly longer N−Ir bond in comparison to the primary amino analogue (S_C,R_{Ir})-**3**. Despite the difference in electronic densities, it seems that steric crowding within the complex limits the σ donation of the lone electron pair from the electronically richer secondary amine ligand to the electron-deficient iridium. The data also revealed a significantly larger dihedral angle between $C_{stereogenic\ center}$−N and the aromatic ring axes for (S_C,S_N,R_{Ir})-**2** in comparison to the primary amine counterpart (28.43° vs 19.15°). This was despite smaller deviation to the N−Ir and C_{Ar}−Ir bond lengths, and N−Ir−C_{Ar} and C_{Ar}−Ir−Cl bond angles.

With reference to the cycloiridated imine complex *rac*-**9**, the N−Ir bond length was found to lie between the corresponding bond distances in (S_C,S_N,R_{Ir})-**2** and (S_C,R_{Ir})-**3**. This further instills the idea of steric crowding within (S_C,S_N,R_{Ir})-**2**, since the imino moiety is known to be less basic than the amine functionality. Spatially, it is obvious that the imine ligand framework presents the least steric crowding within the complex. This was supported by the small dihedral angle of 13.92° and the larger bond angles about the iridium center.

Finally, on comparison of the cycloiridated primary amine complex (S_C,R_{Ir})-**3** with its structurally analogous ruthenium

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counterparts,[18] the iridacycle is consistent in terms of conformation. The structurally-locked ruthenacycles also exhibited a static λ conformation with the stereogenic carbon center at the axial position in both the solid and solution phase. Unsurprisingly, when the naphthalene moiety was traded for a phenyl substituent, the 1,3-diaxial η^6-aromatic−methyl interaction within the ruthenacycle pushed for a more stable δ conformation in the solid phase.[19] Consequently, a rapid interchanging conformational ring flip could occur within the puckered ring system on solvation.

The analysis, thus, presents plausible explanations to the diastereospecificity of the ortho-iridated complex (S_C,S_N,R_{Ir})-**2**. With the orientation of its C-chiral methyl group already defined by the amine, the ligand framework would have to conform itself to its most sterically favorable configuration within the three-legged piano-stool Cp*-iridium(III) complex upon cyclometalation. Such diastereoselectivity has also been observed in similar sterically demanding complexes with planar chirality within its framework.[6c,20]

Stability of Stereochemistry within Cycloiridated Complex (S_C,S_N,R_{Ir})-2. With three stereogenic centers that can be generated diastereoselectively, the ortho-iridated complex (S_C,S_N,R_{Ir})-**2** could present a variety of potential applications ranging from asymmetric catalysis and syntheses to therapeutic biological agents.[7,21]

As such, it is imperative to investigate the stability of the stereogenic centers upon chemical transformation.[1a]

As with various pseudotetrahedral cycloiridated complexes, epimerization of the cycloiridated compound is not uncommon,[13] albeit less likely due to the fixed C-chiral center in complex (S_C,S_N,R_{Ir})-**2**. Nonetheless, we proceeded with NMR studies to analyze the possible epimerization of the iridacycle in solution.

At room temperature, the stereochemistry of the complex is stable, as indicated by its ^{1}H NMR spectrum. However, it is not known if the compound could isomerize when it is subjected to heat. The complex was dissolved in 1,2-dichloroethane (bp 83 °C) and placed under reflux conditions over a period of 5 days. The resulting red-brown solution was subsequently evaporated to dryness prior to analysis via ^{1}H NMR spectroscopy. When the methyl substituents on the Cp* ligand were used as a spectroscopic handle for the determination of isomeric ratio, the resultant solution revealed only one Cp* resonance signal at 1.67 ppm, offering no indication of isomerization. To further investigate possible stereochemical inversion within the molecule during the heating process, variable-temperature (VT) NMR studies were performed in *d*-chloroform (bp 61 °C; mp −64 °C) at high and low temperatures (Figure 8).

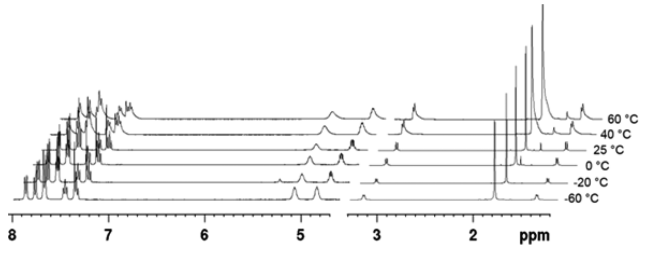
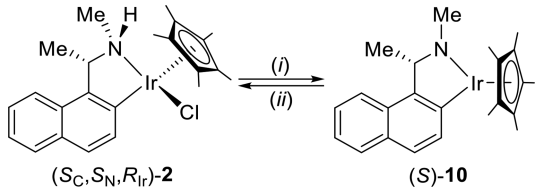


Figure 8. Variable temperature (VT) ^{1}H NMR studies on cycloiridated complex (S_C,S_N,R_{Ir})-**2** from −60 to 60 °C. The chemical shift range from 4.7 to 8.0 ppm has been magnified for clarity.

The VT NMR studies revealed no visible epimerization at both low and elevated temperatures. The spectroscopic handle remained as a singlet during both cooling and heating processes. Furthermore, the multiplities of the other resonance signals generally remained unchanged with only slight deviation in chemical shifts.

Unlike the fixed stereogenic center at carbon, isomerization at the nitrogen center is probable within the complex due to nitrogen inversion upon decoordination. Furthermore, due to the acidic nature of the proton on the amine moiety, it could isomerize if a sufficiently strong base is present. As such, we aimed to determine if isomerization would take place at the nitrogen atom when a deprotonation−protonation protocol was effected. Iridacycle (S_C,S_N,R_{Ir})-**2** was subjected to deprotonation with potassium *tert*-butoxide in d_2-dichloromethane at room temperature under an inert atmosphere (Scheme 4). Upon complete conversion to the amido

Scheme 4. Experiment on the Stability of Stereochemistry at the Nitrogen Center[a]

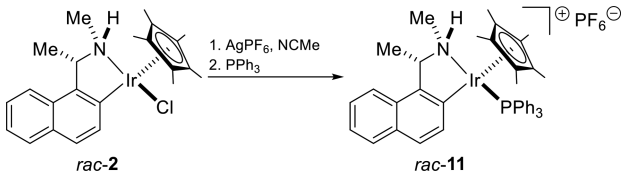


[a]Reaction conditions: (i) KO^{t}Bu, CD_2Cl_2; (ii) HCl(aq), room temperature.

intermediate (*S*)-**10**, the dark red mixture was hydrolyzed with aqueous hydrochloric acid to return iridacycle (S_C,S_N,R_{Ir})-**2**. Spectroscopic analysis revealed no isomerization of the hydrolyzed complex, offering a spectrum similar to that of pure (S_C,S_N,R_{Ir})-**2**. Analysis of the compound's optical activity also returned a similar specific optical rotation ($[\alpha]_D$(21 °C, *c* 0.1) = +106.8°), indicating that the complex remained structurally unaltered.

In another experiment, the stability of the chiral center at iridium was explored. It is postulated that an exchange of ligand at the metal center must undergo a dissociative mechanism, since the 18-electron species is coordinatively saturated. The replacement of a chloride ligand with a phosphine moiety would also provide a spectroscopic handle for the determination of epimerization by ^{31}P{^{1}H} NMR. The ligated chloride in cycloiridated complex *rac*-**2** was first abstracted with silver hexafluorophosphate in acetonitrile at room temperature (Scheme 5). Triphenylphosphine was subsequently added to the pale yellow mixture, with its crude ^{31}P{^{1}H} NMR spectrum revealing a singlet at 16.0 ppm, indicative of only one coordinated triphenylphosphine complex, and a PF_6^- septet resonance signal at −144.3 ppm. The phosphino complex *rac*-

Scheme 5. Experiment on the Stability of Stereochemistry at the Iridium Center during Ligand Exchange



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11 was subsequently recrystallized, and its molecular structure and relative stereochemistry were confirmed by single-crystal X-ray crystallography (see the molecular structure of *rac*-**11** in the Supporting Information).

Effects of Structure on Catalysis: Application in Asymmetric Hydrogen Transfer Reaction. With the knowledge that the stereogenic lock within the naphthalene-based cycloiridated complexes are active under a broad range of temperatures and reaction conditions, we proceeded to examine its effectiveness in the transmission of stereogenic information to the substrate in asymmetric applications. Considering that many pseudotetrahedral metallacycle catalyzed reactions involved asymmetric hydrogen transfer reactions,[22] a model catalytic reduction was employed for the study.

The transfer hydrogenation protocol was carried out with acetophenone as the substrate and 2-propanol as the reducing agent. The optically active cycloiridated precursors comprised of complexes (S_C,S_N,R_{Ir})-**2** and (S_C,R_{Ir})-**3**, which then can be readily deprotonated with potassium *tert*-butoxide to provide the active amido species. The initial run of the catalytic reaction was performed at −15 °C, and its activity profile is shown in Figure 9.

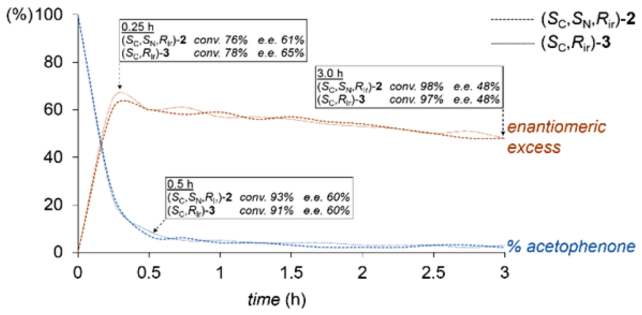
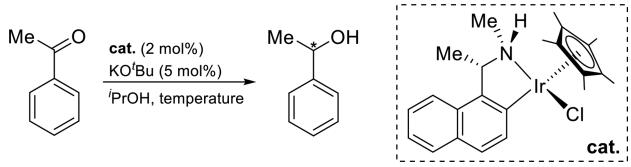


Figure 9. Conversion (blue) and enantiomeric excess (orange) profiles of the asymmetric hydrogen transfer reaction of acetophenone by chiral cycloiridated complexes at −15 °C.

In terms of activity, both complexes performed outstandingly with the hydrogen transfer protocol approaching near completion (ca. 90% conversion) after 30 min, although the reactivities decrease exponentially with time after the initial burst at the beginning. Both compounds displayed similar reactivity with their conversion of acetophenone within 4% of each other at any point of time. With regard to its enantioselectivity, the catalysts only gave modest enantiomeric excess (ee) at best, with the primary amino-iridacycle achieving the highest measured ee after 15 min at 65%, although the reaction was only moderately complete (78%). Expectedly, the enantioselectivity declined with time due to the continuous oxidation−reduction processes within the reaction vessel, reaching complete racemization overnight for both complexes.

We proceeded to vary the reaction conditions with complex (S_C,S_N,R_{Ir})-**2** as the catalyst. At room temperature, the transfer hydrogenation protocol progressed extremely efficiently, with the reaction approaching complete conversion within 15 min, albeit with a slight reduction in enantioselectivity. In the absence of base, the reaction was found to proceed, although its reactivity was greatly hindered, being incomplete even after 4 days of reaction time at room temperature. Nonetheless, the entry gave an ee similar (Table 2, 58%; entry 2) to that of the amido complex mediated reaction at the same temperature

Table 2. Asymmetric Hydrogen Transfer Reaction of Acetophenone by Chiral Cycloiridated Complexes[a]



entry	temp (°C)	time (h)	conversn[b] (%)	ee[b,c] (%)
1	20	0.25	99	+52
2[d]	20	96[e]	75	+58
3	−15	1	96	+59
4	−30	1.5	97	+69

[a]Reactions were carried out with acetophenone (0.5 mmol), 1,4-dimethoxybenzene (0.5 mmol), (S_C,S_N,R_{Ir})-**2** (0.01 mmol), and KO*t*Bu (0.05 mmol) in *i*PrOH at the desired temperature for the stated duration. [b]Conversion and ee were determined by HPLC (Diacel Chiralpak IF column). [c]± notation was determined by optical activity studies. [d]Reaction was conducted without KO*t*Bu. [e]Reactions were halted after 96 h reaction time.

(52%; entry 1). Finally, at lower temperature (−30 °C), the reaction remained efficient with a slight increase in enantioselectivity to 69%, in comparison to its counterpart at −15 °C (59%).

CONCLUSION

A series of pseudotetrahedral cycloiridated 1-naphthylethylamine complexes were synthesized, characterized, and studied for their structure and stereoselectivity in the catalytic asymmetric hydrogen transfer reaction. The investigation revealed the relevance of a stereogenic lock—defined by the fixation of configuration within a small ring system through steric interaction within the molecular framework—in both structural aspects, in terms of diastereoselectivity and stereostability, and enantioselectivity in asymmetric catalysis. Furthermore, we reviewed the practicality for structural lock to avoid side reactions within the complex which may render the enantiopure compound less beneficial for asymmetric applications.

Through this work, we aimed to establish the concepts of stereogenic lock which could be applied to the rational design of chiral catalysts and templates for asymmetric applications. We have also demonstrated the relevance of conformational rigidity in the outcome of asymmetric applications.

EXPERIMENTAL SECTION

General Considerations. Reactions involving air- or moisture-sensitive compounds were carried out by means of conventional Schlenk techniques under a positive pressure of nitrogen gas. Unless stated otherwise, chemicals and solvents were used as received from commercial vendors without further purification. When necessary, anhydrous solvents were freshly distilled and dried according to standard procedures prior to use. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance III 400 (BBFO 400) spectrometer at 400 MHz for ^{1}H NMR, 100 MHz for ^{13}C NMR, and 161 MHz for ^{31}P{^{1}H} NMR. Chemical shifts (δ) are quoted in ppm and referenced to chemical shifts of residual solvent peaks. High-resolution mass spectrometry via electrospray ionization (ESI) was performed on the Waters Q-Tof Premier spectrometer. Elemental analysis was performed on the EuroVector Euro EA elemental analyzer at Nanyang Technological University Division of Chemistry and Biological Chemistry Central Facilities Laboratory. Optical rotation studies were measured on the Jasco P-1030 polarimeter in a 0.1 dm

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polarimetry cell at the specified temperature using the D line of sodium (589 nm) as the source of light.

General Procedure for the Cycloiridation of 1-Arylalkylamines. $[Cp^*IrCl_2]_2$ (40 mg, 0.05 mmol) and NaOAc (10 mg, 0.12 mmol) were added to a stirred solution of 1-arylalkylamine (0.10 mmol) in dichloromethane (3 mL). The reaction mixture was stirred at room temperature until full conversion or over 3 days, whichever was shorter. The crude reaction mixture was then evaporated to dryness and purified by column chromatography on silica gel with hexane/ethyl acetate as the eluent.

*(S_C,S_N,R_{Ir})-(1,2,3,4,5-Pentamethylcyclopentadienyl){(κ²-C,N)-1-[1-(N-methylamino)ethyl]naphthyl}iridium(III) chloride ((S_C,S_N,R_{Ir})-**2**):* yield, 53 mg (97%); $[\alpha]_D$(22 °C, *c* 0.5) = +102.1°; ^{1}H NMR (400 MHz, CD_2Cl_2) δ 1.24 (d, $^3J_{HH}$ = 6.5 Hz, 3H, ArCH(CH_3)), 1.67 (s, 15H, Cp(CH_3)), 3.02 (d, $^3J_{HH}$ = 6.4 Hz, 3H, NH(CH_3)), 4.69 (dq, $^3J_{HH}$ = 4.2 and 6.4 Hz, 1H, ArC*H*(CH$_3$)), 5.02 (br s, 1H, N*H*(CH$_3$)), 7.20−7.74 (m, 6H, Ar*H*); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 9.36, 17.39, 39.57, 66.89, 87.35, 122.66, 123.41, 125.41, 126.05, 127.92, 128.38, 131.07, 136.07, 144.65, 153.10; HRMS (ESI) *m*/*z* [negative mode] calcd for $C_{23}H_{29}ClIrN$ 547.1618, found 547.1619. Anal. Calcd for $C_{23}H_{29}ClIrN$: C, 50.49; H, 5.34; N, 2.56. Found: C, 50.02; H, 5.56; N, 2.31.

*(S_C,R_{Ir})-(1,2,3,4,5-Pentamethylcyclopentadienyl){(κ²-C,N)-1-[1-aminoethyl]naphthyl}iridium(III) chloride ((S_C,R_{Ir})-**3**):* yield, 11 mg (2%) (from N-demethylation of secondary amine at 1 mmol scale), 48 mg (90%) (from direct cycloiridation of primary amine); $[\alpha]_D$(22 °C, *c* 0.5) = +110.3°; ^{1}H NMR (400 MHz, CD_2Cl_2) 1.32 (d, $^3J_{HH}$ = 6.6 Hz, 3H, ArCH(CH_3)), 1.74 (s, 15H, Cp(CH_3)), 3.70 (br s, 1H, N*H*), 4.78 (br s, 1H, N*H*), 5.06 (m, 1H, ArC*H*(CH$_3$)), 7.21−7.74 (m, 6H, Ar*H*); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 10.77, 23.95, 60.92, 88.44, 124.08, 124.93, 126.82, 127.39, 129.61, 129.82, 132.59, 137.72, 147.15, 155.07; HRMS (ESI) *m*/*z* [negative mode] calcd for $C_{22}H_{27}ClIrN$ 533.1461, found 533.1456. Anal. Calcd for $C_{22}H_{27}ClIrN$: C, 49.56; H, 5.10; N, 2.63. Found: C, 49.46; H, 5.29; N, 2.79.

*(1,2,3,4,5-Pentamethylcyclopentadienyl){(κ²-C,N)-1-[1-(N-methylimino)ethyl]phenyl}iridium(III) chloride (rac-**6**):* yield, 21 mg (42%); ^{1}H NMR (400 MHz, CD_2Cl_2) δ 1.67 (s, 15H, Cp(CH_3)), 2.50 (s, 3H, ArC(CH_3)), 3.84 (s, 3H, N(CH_3)), 6.95−7.76 (m, 4H, Ar*H*); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 8.99, 14.65, 45.09, 88.67, 121.07, 127.34, 130.77, 135.10, 148.18, 167.89, 180.04; HRMS (ESI) *m*/*z* [negative mode] calcd for $C_{19}H_{25}ClIrN$ 495.1305, found 495.1292. Anal. Calcd for $C_{19}H_{25}ClIrN$: C, 46.10; H, 5.09; N, 2.83. Found: C, 45.62; H, 5.38; N, 2.83.

*(1,2,3,4,5-Pentamethylcyclopentadienyl){(κ²-C,N)-1-[(N-methylimino)methyl]naphthyl}iridium(III) chloride (rac-**8**):* yield, 32 mg (61%) (heating to 60 °C in 1,2-dichloroethane required); ^{1}H NMR (400 MHz, CD_2Cl_2) δ 1.76 (s, 15H, Cp(CH_3)), 3.99 (s, 3H, N(CH_3)), 7.32−8.10 (m, 6H, Ar*H*), 9.07 (s, 1H, *H*C(=N)); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 9.05, 49.71, 89.57, 121.79, 123.35, 126.87, 128.82, 129.95, 130.55, 132.81, 134.33, 139.61, 171.64, 174.53; HRMS (ESI) *m*/*z* [negative mode] calcd for $C_{22}H_{25}ClIrN$ 531.1305, found 531.1297. Anal. Calcd for $C_{22}H_{25}ClIrN$: C, 49.75; H, 4.74; N, 2.64. Found: C, 49.59; H, 5.21; N, 2.91.

*(1,2,3,4,5-Pentamethylcyclopentadienyl){(κ²-C,N)-1-[1-(N-methylimino)ethyl]naphthyl}iridium(III) chloride (rac-**9**):* yield, 22 mg (41%) (cis/trans mixture of *N*-methyl-1-(naphthalen-1-yl)ethan-1-imine was used); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.73 (s, 15H, Cp(CH_3)), 2.98 (s, 3H, C(=NMe) (CH_3)Ar)), 3.98 (s, 3H, NCH_3), 7.32−8.22 (m, 6H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.16, 20.65, 45.68, 89.34, 122.11, 122.46, 125.92, 129.57, 130.95, 131.17, 132.80, 134.49, 140.83, 174.92, 180.39; HRMS (ESI) *m*/*z* [negative mode] calcd for $C_{23}H_{27}ClIrN$ 545.1461, found 545.1451. Anal. Calcd for $C_{23}H_{27}ClIrN$: C, 50.68; H, 4.99; N, 2.57. Found: C, 50.50; H, 5.07; N, 2.73.

Procedure for the Determination of Stereostability at Nitrogen. KO^{t}Bu (3.4 mg, 0.03 mmol) was added to a stirred mixture of complex (S_C,S_N,R_{Ir})-**2** (11 mg, 0.02 mmol) in d_2-dichloromethane (1.5 mL). The reaction mixture was stirred at room temperature for 24 h. The crude reaction mixture was then filtered and characterized by ^{1}H NMR spectroscopy. Dilute aqueous HCl (1 M, 1.5 mL) was added to the dark red solution, and this mixture was stirred for 1 h. The organic phase of the biphasic solution was collected, and the aqueous partition was further extracted with dichloromethane. The organic extracts were then combined, dried over anhydrous $MgSO_4$,and evaporated to dryness, affording an orange powder.

*(S_C)-(1,2,3,4,5-Pentamethylcyclopentadienyl){(κ²-C,N)-1-[1-(N-methylamido)ethyl]naphthyl}iridium(III) complex ((S_C)-**10**):* ^{1}H NMR (400 MHz, CD_2Cl_2) δ 1.45 (d, $^3J_{HH}$ = 6.4 Hz, ArCH(CH_3), 1.94 (s, 15H, Cp(CH_3)), 2.80 (q, $^3J_{HH}$ = 6.4 Hz, ArC*H*(CH$_3$)), 3.48 (d, $^4J_{HH}$ = 0.6 Hz, 3H, N(CH_3)), 7.19−8.19 (m, 6H, Ar*H*); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 10.00, 19.96, 54.57, 82.01, 87.57, 122.65, 124.12, 124.78, 124.89, 127.46, 128.25, 130.89, 135.10, 155.37, 160.26.

Procedure for the Determination of Stereostability at Iridium. $AgPF_6$ (7.6 mg, 0.03 mmol) was added to a stirred acetonitrile solution (3 mL) of complex (S_C,S_N,R_{Ir})-**2** (11 mg, 0.02 mmol) in the dark. The reaction mixture was stirred at room temperature for 1 h. PPh_3 (5.2 mg, 0.02 mmol) was subsequently added to the reaction mixture, and this mixture was stirred for another 2 h. The crude mixture was filtered over Celite, evaporated to dryness, and recrystallized from a solvent mixture of hexane and ethyl acetate.

*rac-(1,2,3,4,5-pentamethylcyclopentadienyl){(κ²-C,N)-1-[1-(N-methylamino)ethyl]naphthyl}(triphenylphosphine)iridium(III) Hexafluorophosphate (rac-**11**):* yield, 9.7 mg (53%) (recrystallized); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14 (d, $^3J_{HH}$ = 6.6 Hz, 3H, ArCH(CH_3)), 1.65 (d, 15H, Cp(CH_3)), 2.94 (d, $^3J_{HH}$ = 6.3 Hz, 3H, NH(CH_3)), 3.92 (m, 1H, ArC*H*(CH$_3$)), 4.38 (br s, 1H, N*H*(CH$_3$)), 7.11−7.74 (m, 21H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.48, 16.83, 41.15, 68.86, 96.15 (d, Cp(CH$_3$)), 123.47, 123.99, 126.32, 126.54, 128.27, 128.49, 128.92 (d, $^1J_{CP}$ = 10.2 Hz), 131.20, 132.01, 133.93 (br s), 134.44 (d, $^4J_{CP}$ = 2.4 Hz), 136.79, 136.91, 146.69; ^{31}P{^{1}H} NMR (161 MHz, $CDCl_3$) δ −144.32 (sep, *P*F_6^-), 16.03 (s, *P*Ph_3); HRMS (ESI) *m*/*z* [negative mode] calcd for $C_{41}H_{44}F_6IrNP_2$ 919.2483, found 919.2482. Anal. Calcd for $C_{41}H_{44}F_6IrNP_2$: C, 53.59; H, 4.83; N, 1.52. Found: C, 53.39; H, 4.78; N, 1.29.

General Procedure for Catalytic Asymmetric Hydrogen Transfer Reactions. Acetophenone (58.3 μL, 60 mg, 0.5 mmol), 1,4-dimethoxybenzene (69 mg, 0.5 mmol), and KO^{t}Bu (2.8 mg, 0.025 mmol) were added sequentially to a stirred solution of cycloiridated complex (0.01 mmol) in dry 2-propanol (10 mL) at the desired temperature. The reaction mixture was stirred at the temperature for the indicated time. The pale brown mixture was then diluted with water (10 mL), extracted with ethyl acetate (10 mL × 3), washed with brine (20 mL), dried over anhydrous $MgSO_4$, filtered, and evaporated to dryness. The crude mixture was then purified by column chromatography on silica gel with hexane/ethyl acetate as the eluent to afford a colorless oil.

1-Phenylethanol: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.49 (d, $^3J_{HH}$ = 6.4 Hz, 3H, PhCH(CH_3)), 1.88 (d, $^3J_{HH}$ = 3.4 Hz, 1H, O*H*), 4.89 (dq, $^3J_{HH}$ = 3.3 Hz, $^3J_{HH}$ = 6.4 Hz, 1H, PhC*H*(CH$_3$)), 7.25−7.38 (m, 5H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.12, 70.39, 125.35, 127.45, 128.48, 145.78; HRMS (ESI) *m*/*z* [negative mode] calcd for $C_8H_{10}O$ 112.0732, found 122.0726. Anal. Calcd for $C_8H_{10}O$: C, 78.65; H, 8.25. Found: C, 78.69; H, 8.44.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.organomet.7b00760.

Preparative methods for the ligands, spectral data of synthesized compounds, and X-ray crystallographic data of compounds (S_C,S_N,R_{Ir})-**2**, (S_C,R_{Ir})-**3**, *rac*-**9**, and *rac*-**11** (PDF)

Accession Codes

CCDC 1577410−1577411, 1578300, and 1578840 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/

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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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