Intramolecular hydroamination of unactivated alkenes with secondary alkylamines catalyzed by iridium phosphino–phenolate complexes

Kevin D. Hesp, Robert McDonald, and Mark Stradiotto

Abstract: The phosphino–phenolate complex (κ^2-{2-*i*-$Pr_2PC_6H_4$}*O*)Ir(COD) (COD = η^4-1,5-cyclooctadiene; **1**) is shown to be an effective precatalyst for the intramolecular hydroamination of unactivated alkenes with pendant secondary alkylamines, providing either pyrrolidine or piperidine heterocycles in high isolated yields. While monitoring the progress of a selected test reaction of this type, a significant induction period (~3 h) was observed; variable-temperature ^{1}H and ^{31}P NMR studies (25–100 °C) under catalytically relevant conditions revealed no new metal-containing species. In an effort to develop an enantiopure variant of **1**, a synthetic route to the chiral (κ^2-*P*,*O*)Ir(COD) complex (**7**), which features a 1-aryl-2,5-dialkylphospholane structure derived from (2*S*,5*S*)-2,5-hexanediol cyclic sulfate, was developed. The structure of **7** was confirmed by use of single-crystal X-ray diffraction techniques. While **7** failed to provide enantioselectivity in the intramolecular hydroamination of unactivated alkenes with pendant secondary alkylamines, the activity of **7** was found to be comparable to that of **1**.

Key words: catalysis, hydroamination, iridium, ligand design.

Résumé : On montre que le complexe phosphino–phénolate, (κ^2-{2-*i*$Pr_2PC_6H_4$}*O*)Ir(COD) (**1**), est un précatalyseur efficace pour l'hydroamination intramoléculaire d'alcènes non activés portant des chaînes latérales avec des alkylamines secondaires qui conduit à la formation d'hétérocycles pyrrolidine ou pipéridine avec des rendements élevés en produits isolés. En observant le progrès d'une réaction de ce type choisie comme représentative, on a observé une période d'induction significative (environ 3 heures); des études de RMN du ^{1}H et du ^{31}P à température variable (25 à 100 °C), dans des conditions catalytiquement appropriées ont révélé qu'il n'y a pas de nouvelles espèces contenant un métal. Dans un effort pour développer une variété énantiomériquement pure du composé **1**, on a mis au point une voie de synthèse du complexe chiral (κ^2-*P*,*O*)Ir(COD), **7**, qui inclut une structure 1-aryl-2,5-dialkylphospholane obtenue à partir du sulfate cyclique du (2*S*,5*S*)-hexane-2,5-diol. La structure du composé **7** a été confirmée par des techniques de diffraction des rayons X par un cristal unique. Même si le composé **7** n'a pas permis d'obtenir d'énantiosélectivité dans l'hydroamination intramoléculaire d'alcènes non activés portant des chaînes latérales avec des alkylamines secondaires, l'activité de ce produit est comparable à celle du produit **1**.

Mots-clés : Catalyse, hydroamination, iridium, développement d'un ligand.

Introduction

The prevalence of nitrogen-containing moieties in both naturally occurring and biologically active molecules has prompted the development of efficient methods for the formation of C–N bonds, including the use of transition-metal catalysis.[1] Notwithstanding the tremendous success of Buchwald–Hartwig amination and related cross-coupling chemistry,[1b,1c] the inherent lack of atom economy associated with such procedures has prompted the development of hydroamination protocols that enable C–N bond formation via the direct addition of N–H bonds to unsaturated substrates.[1d] In particular, intramolecular hydroamination involving N–H bond addition to an unactivated alkene offers an attractive route to nitrogen-containing heterocycles. However, while catalyst systems employing Brønsted acids,[2] rare earth elements and actinides,[3] alkali and alkaline earth metals,[4] group 4 metals,[5] and groups 8–11 metals[6,7] have all proven capable of mediating the intramolecular hydroamination of such unactivated aminoalkenes, general methods for promoting the cyclization of these challenging substrates under mild conditions and with broad substrate scope remain elusive.

We recently reported on the use of $[Ir(COD)Cl]_2$ (COD = η^4-1,5-cyclooctadiene) as a precatalyst for the intramolecular addition of a variety of secondary alkyl- or aryl-amines to unactivated alkenes, without the requirement of added ligands or cocatalysts[7a]; notably, this represents one of only a

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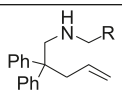
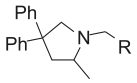
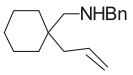
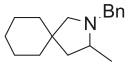
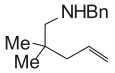
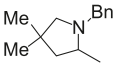
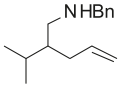
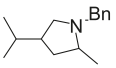
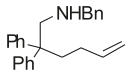
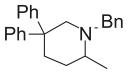
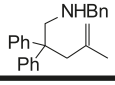
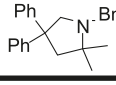
This article is part of a Special Issue dedicated to Professor R. J. Boyd. We dedicate this article to Professor Russ Boyd in recognition of his widespread contributions to the Department of Chemistry at Dalhousie University as well as to the Canadian chemical community.

K.D. Hesp and M. Stradiotto.[1] Department of Chemistry, Dalhousie University, Halifax, NS B3H 4J3, Canada.
R. McDonald. X-Ray Crystallography Laboratory, Department of Chemistry, University of Alberta, Edmonton, AB T6G 2G2, Canada.

[1]Corresponding author (e-mail: mark.stradiotto@dal.ca).

Table 1. Intramolecular hydroamination of unactivated alkenes by secondary alkylamines employing **1** as a precatalyst.

Entry	Aminoalkene	Product	mol% **1** (time, h)	Yield[a]
				
1	R = Ph		1.0 (16)	92
2	R = 4 - C_6H_4Cl		1.0 (16)	86
3	R = 4 - $C_6H_4CO_2Me$		1.0 (16)	85
4	R = 4 - C_6H_4OMe		1.0 (16)	87
5	R = Cy		2.5 (24)	89
6			1.0 (16)	85
7			5.0 (24)	86
8			2.5 (24)	87[b] (1.3:1)[c]
9			1.0 (16)	85
10			1.0 (16)	92

Note: Reaction conditions: 0.25 mmol aminoalkene in 0.50 mL of 1,4-dioxane at 110 °C.

[a] Isolated yield unless otherwise stated.

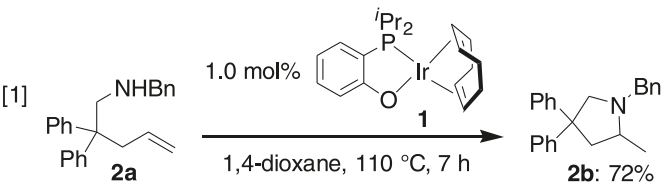
[b] ^{1}H NMR yield.

[c] Diastereomeric ratio (dr, ^{1}H NMR).

small number of examples in which late metal catalysts have been shown to promote the cyclization of such substrates.[7] As such, we became interested in identifying alternative neutral Ir complexes that function as catalysts for the intramolecular hydroamination of unactivated aminoalkenes,[8] especially those for which chiral variants could be developed. Encouraged by our previous observation that the phosphino–phenolate complex (κ^2-{2-*i*-$Pr_2PC_6H_4$}*O*)Ir(COD) (**1**) is a highly active catalyst for the hydrogenation of substituted alkenes under mild conditions,[9] we viewed **1** as being an attractive candidate for use in hydroamination chemistry. We report herein that **1** is a competent catalyst at relatively low catalyst loadings for the intramolecular hydroamination of a variety of unactivated alkenes that feature pendant alkylamines. Furthermore, we report on the synthesis and crystallographic characterization of a first-generation chiral variant of **1**, and our efforts to apply this new chiral (κ^2-*P*,*O*)Ir(COD) complex in intramolecular hydroamination catalysis.[10]

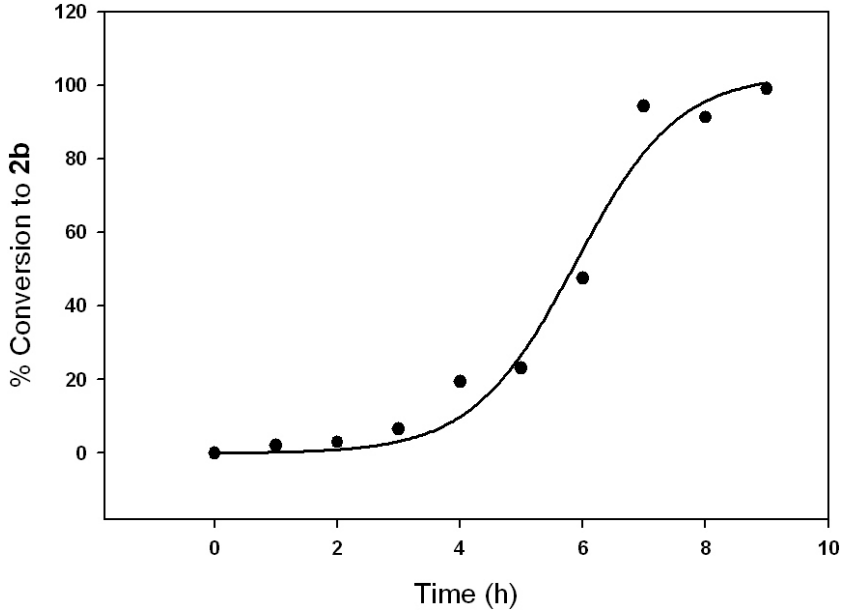
Results and discussion

In a preliminary test experiment, the cyclization of the aminoalkene **2a** to the pyrrolidine **2b** proceeded in a 72% yield (^{1}H NMR) in the presence of 1.0 mol% **1** in 1,4-dioxane at 110 °C over the course of 7 h, with the balance corresponding to unreacted **2a** (eq. [1]). Under similar experimental conditions employing catalyst mixtures comprised of 0.5 mol% $[Ir(COD)Cl]_2$ and 1.0 mol% of a simple phosphine ligand including triphenylphosphine, tricyclohexylphosphine or 1,4-bis(diphenylphosphino)butane, negligible conversion to the desired cyclization product **2b** was achieved. While the use of the Rh variant of **1** under similar experimental conditions resulted in the consumption of **2a**, multiple products were formed in this reaction with the major product corresponding to alkene isomerization within the starting substrate.

[1] 

The utility of **1** as a precatalyst in the hydroamination of a range of *N*-alkyl aminoalkenes was surveyed (Table 1). The cyclization of the parent *N*-benzyl substrate **2a** (Table 1,

Fig. 1. A plot of the conversion of **2a** to **2b** vs time employing 2.5 mol% **1** (1,4-dioxane, 110 °C).

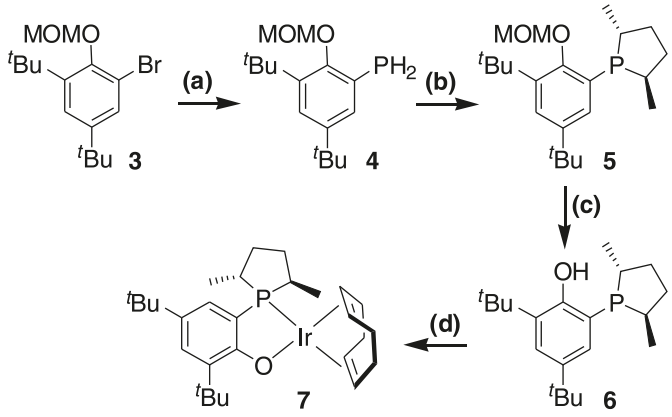


entry 1) as well as para-substituted derivatives featuring chloride (Table 1, entry 2), methyl ester (Table 1, entry 3), or methoxy (Table 1, entry 4) substituents, was in each case achieved in high isolated yield (85%–92%) despite the use of relatively low catalyst loading (1.0 mol% **1**). The sterically hindered *N*-methylcyclohexyl aminoalkene was also cyclized (Table 1, entry 5), as were substrates that feature alternative formulations of mono- and di-substitution on the linker chain of the aminoalkene substrate (Table 1, entries 6–8). Notably, the results featured in Table 1, entries 6–8, clearly underscore the importance of the Thorpe–Ingold effect in promoting these transformations, whereby increased steric elaboration at the β-carbon enables more facile cyclohydroamination at lower catalyst loadings. The hydroamination of the hexenylamine substrate featured in Table 1, entry 9, was also achieved in the presence of **1** to afford the corresponding piperidine. In surveying more challenging substrates, we turned our attention to the intramolecular hydroamination of unactivated disubstituted alkenes. Whereas the efficient cyclization of a 1,1-disubstituted substrate was achieved by use of **1** (Table 1, entry 10), under our standard catalytic conditions, this catalyst proved unreactive toward aminoalkenes featuring unstrained 1,2-substituted olefins or those lacking substituents on the tethering chain that facilitate the cyclization process, as well as primary amine substrates. In comparison to the catalytic performance of $[Ir(COD)Cl]_2$,[7a] longer reaction times were needed when using **1** to achieve similar levels of conversion for the substrates featured in Table 1, entries 1–6; for **2a**, as well as the *N*-methylcyclohexyl aminoalkene substrate (Table 1, entry 5), significantly higher Ir loadings were also required when using **1**. Otherwise, the catalytic performance of **1** in the cyclization of *N*-alkyl aminoalkenes was found to be competitive with that of $[Ir(COD)Cl]_2$, and in the case of the more challenging substrates featured in Table 1, entries 8–10, **1** proved to be superior to $[Ir(COD)Cl]_2$ on the basis of Ir loading, reaction time, and isolated yield.

Having observed that longer reaction times and higher catalyst loadings were needed for **1** relative to $[Ir(COD)Cl]_2$ to achieve similarly high levels of conversion in the cyclization of **2a** to **2b**, we examined the conversion versus time profile for this transformation employing **1** (2.5 mol% Ir, 1,4-dioxane, 110 °C; Fig. 1). Notably, a pronounced induction period (~3 h) was observed under these conditions; by comparison, high conversion to **2b** was achieved after 3 h by using only 0.5 mol% $[Ir(COD)Cl]_2$ under similar conditions in the absence of an induction period.[7a] Variable-temperature ^1H and ^{31}P NMR studies (25–100 °C) of an equimolar mixture of **1** and **2a**, either without preconditioning or following preconditioning for 3 h at 110 °C, revealed the presence of only **1** and **2a**, as well as small quantities of **2b** at elevated temperatures. While we are presently unable to comment definitively regarding the mechanism of hydroamination mediated by **1**, these spectroscopic observations appear to preclude a mechanism in which dissociation of the P,O ligand from Ir is responsible for the observed induction period. Mechanistic investigations regarding the cyclization of **2a** and related substrates by each of **1** and $[Ir(COD)Cl]_2$ are ongoing in our laboratory.

The late metal catalyzed enantioselective intramolecular hydroamination of unactivated alkenes featuring pendant alkylamines has yet to be reported in the literature.[10] Given the desirable catalytic performance of **1**, and encouraged by reports documenting the Ir-mediated enantioselective intermolecular hydroamination of activated alkenes,[11] we sought to construct a chiral variant of **1**. In consideration of the diisopropylphosphino present in **1**, we elected to employ a structurally similar κ^2-*P*,*O* phenylene ligand featuring the 1-aryl-2,5-dialkylphospholane scaffold.[12] Preparation of the target ligand precursor **6** was carried out by adapting previously published methods.[12a,13] As outlined in Scheme 1, the installation of the chiral phospholane fragment required initial treatment of the methoxymethyl (MOM) protected phenol **3** with *n*-BuLi and $P(NMe_2)_2Cl$, followed by in situ methanolysis and reduction with $LiAlH_4$ to afford the primary phosphine **4**. Using the procedure established by Burk

Scheme 1. Synthesis of the new chiral (κ^2-*P*,*O*)Ir(COD) complex **7**. Reagents and conditions: (*a*) *n*-BuLi, Et_2O, –78 °C → 25 °C, 16 h; $P(NMe_2)_2Cl$, Et_2O, –78 °C → 25 °C, 3 h; MeOH, 50 °C, 3 h; $LiAlH_4$, Et_2O, 25 °C, 48 h (36% from **3**). (*b*) *n*-BuLi, THF, 25 °C, 1.5 h; (2*S*,5*S*)-2,5-hexanediol cyclic sulfate, THF, 25 °C, 2 h; *n*-BuLi, THF, 25 °C, 2 h, (68% from **4**). (*c*) 5 mol/L HCl (aq.), THF, 50 °C, 16 h; 7 mol/L NH_4OH (aq.), Et_2O, 25 °C, 5 h, (73% from **5**). (*d*) $[Ir(COD)Cl]_2$, NEt_3, THF, 25 °C, 2 h, 68%.



et al.[12b] for the construction of phospholane moieties, successive treatment of **4** with 1 equiv. *n*-BuLi, followed by 1 equiv. (2*S*,5*S*)-2,5-hexanediol cyclic sulfate, and then an additional 1 equiv. of *n*-BuLi provided the protected intermediate **5**, which was converted to the phosphinoenolate **6** upon exposure to aqueous HCl followed by workup with aqueous NH_4OH. Treatment of **6** with 0.5 equiv. $[Ir(COD)Cl]_2$ and NEt_3 afforded **7** as an analytically pure, isolable orange solid (68% from **6**; 12% from **3**). The connectivity in **7** was established by use of NMR spectroscopic and X-ray crystallographic techniques (Fig. 2, Table 2). The structural features in **7** compare well with those found in **1**,[9] including the observed Ir–P and Ir–O distances (2.2797(7) and 2.0163(18) Å, respectively; cf. 2.289(1) and 2.028(3) Å in **1**, respectively), as well as the observation that in **7** the Ir–alkene distances trans to P (2.167(3) and 2.193(3) Å) are statistically longer than the Ir–alkene distances trans to O (2.114(3) and 2.131(3) Å), which is in keeping with the greater trans influence anticipated for a phosphine fragment relative to an alkoxy donor on Ir. Unfortunately, despite maintaining a catalytic activity profile similar to **1** in the hydroamination of **2a** and related substrates, the chiral complex **7** was incapable of inducing any enantioselectivity in the resulting cyclization product (e.g., **2b**) over a range of reaction conditions (1–5 mol% **7**, 80–110 °C).

Summary and conclusion

In summary, (κ^2-{2-*i*-$Pr_2PC_6H_4$}*O*)Ir(COD) (**1**) is an effective precatalyst for the intramolecular hydroamination of unactivated alkenes with pendant secondary alkylamines, providing either pyrrolidine or piperidine heterocycles in the absence of competing alkene isomerization. We have also succeeded in establishing a synthetic pathway to **7**: a chiral relative of **1** that features a 1-aryl-2,5-dialkylphospholane structure derived from (2*S*,5*S*)-2,5-hexanediol cyclic sulfate. While **7** failed to provide enantioselectivity in this hydroamination chemistry, the activity of **7** was found to be comparable to that of **1**. Future studies will focus both on preparing alternative chiral variants of **1**, as well as on exploring the mechanism of hydroamination processes mediated by (κ^2-*P*,*O*)Ir(COD) species to guide the design of increasingly effective catalysts.

Fig. 2. ORTEP diagram for **7** is shown with 50% displacement ellipsoids; selected hydrogen atoms have been removed for clarity. Selected interatomic distances (Å): Ir—P 2.2797(7), Ir—O 2.0163(18), Ir—C21 2.114(3), Ir—C22 2.131(3), Ir—C25 2.167(3), Ir—C26 2.193(3), P—C2 1.824(3), O—C1 1.343(3).

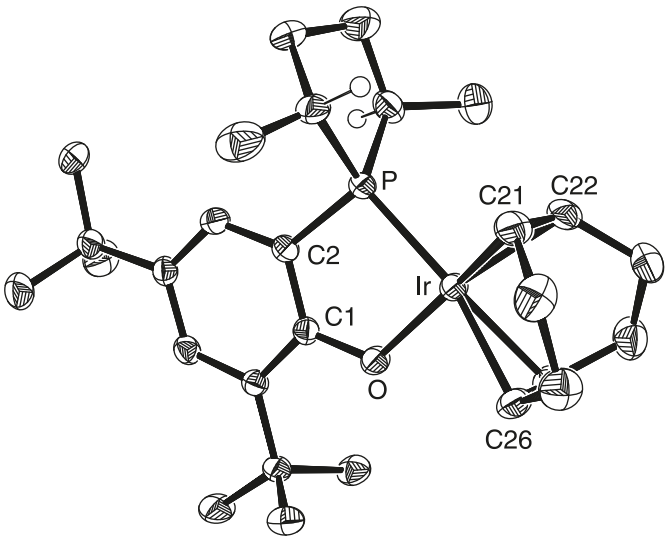


Table 2. Crystallographic data for **7**.

Empirical formula	$C_{28}H_{44}IrOP$
Formula weight	619.80
Crystal dimensions (mm^3)	0.42 × 0.29 × 0.24
Color, habit	Orange, prism
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
a (Å)	10.5353 (10)
b (Å)	12.8694 (12)
c (Å)	19.3425 (18)
V ($Å^3$)	2622.5 (4)
Z	4
Range of transmission	0.3701–0.2201
2θ limit (°)	54.96
Collection ranges	$-13 \le h \le 13$
	$-16 \le k \le 16$
	$-24 \le l \le 25$
Total data collected	22846
Independent reflections	5986
R_{int}	0.0240
Observed reflections	5652
Data / restraints / parameters	5986 / 0 / 280
Absolute structure parameter	0.000 (5)
Goodness-of-fit	1.063
R_1 [$F_o^2 \ge 2\sigma(F_o^2)$]	0.0190
wR_2 [$F_o^2 \ge -3\sigma(F_o^2)$]	0.0453
Largest peak, hole (e $Å^{-3}$)	1.534, –0.262

Experimental

General considerations

All manipulations were conducted in the absence of oxygen and water under an atmosphere of dinitrogen, either by use of standard Schlenk methods or within an MBraun glovebox apparatus, utilizing glassware that was oven-dried (130 °C) and evacuated while hot prior to use. The nondeuterated solvents, tetrahydrofuran, diethyl ether, dichloromethane, benzene, hexanes, and pentane, were deoxygenated and dried by sparging with dinitrogen gas, followed by passage through a double-column solvent purification system purchased from MBraun Inc. Tetrahydrofuran, diethyl ether, and dichloromethane were purified over two alumina-packed columns, while benzene, hexanes, and pentane were purified over one alumina-packed column and one column packed with copper-Q5 reactant. 1,4-Dioxane (Sigma-Aldrich) was dried over Na/benzophenone followed by distillation under an atmosphere of dinitrogen; anhydrous 1,4-dioxane used as received from Sigma-Aldrich provided inferior results. Chloroform-d_1 (Cambridge Isotopes) was used as received. C_6D_6 (Cambridge Isotopes Laboratories) was degassed by using three freeze-pump-thaw cycles and then dried over 3 Å molecular sieves. All solvents used within the glovebox were stored over activated 4 Å molecular sieves. Purification of NEt_3 was achieved by stirring over KOH for 7 d, followed by distillation; the distilled NEt_3 was then refluxed over CaH_2 for 3 d under dinitrogen, followed by distillation. Complex **1**,[9] $P(NMe_2)_2Cl$,[14] (2*S*,5*S*)-2,5-hexanediol cyclic sulfate,[12b] *N*-benzyl-2,2-diphenylpent-4-en-1-amine,[7f] *N*-(4-chlorobenzyl)-2,2-diphenylpent-4-en-1-amine,[2a] methyl 4-[(2,2-diphenylpent-4-enylamino)methyl]benzoate,[7f] *N*-(4-methoxybenzyl)-2,2-diphenylpent-4-en-1-amine,[2a] *N*-(cyclohexylmethyl)-2,2-diphenylpent-4-en-1-amine,[7d] (1-allylcyclohexyl)-*N*-benzylmethanamine,[7f] *N*-benzyl-2,2-dimethylpent-4-en-1-amine,[7f] *N*-benzyl-2-isopropylpent-4-en-1-amine,[7f] *N*-benzyl-2,2-diphenylhex-5-en-1-amine,[7d] and *N*-benzyl-4-methyl-2,2-diphenylpent-4-en-1-amine[15] were synthesized according to literature procedures. The synthetic route to **6** starting from **3** was carried out in accordance with previously published methods.[13] $[Ir(COD)Cl]_2$ (Strem) was dried in vacuo for ~24 h prior to use. All other reagents were used as received. ^1H, ^{13}C, and ^{31}P NMR characterization data were collected at 300 K on a Bruker AV-500 spectrometer operating at 500.1, 125.8, and 202.5 MHz (respectively) with chemical shifts reported in parts per million downfield of $SiMe_4$. Elemental analyses were performed by Canadian Microanalytical Service Ltd., Delta, BC, Canada.

Preparation of 4

To a magnetically stirred solution of **3** (3.96 g, 12.0 mmol) in diethyl ether (10 mL) at –78 °C was added 4.1 mL of a 2.9 mol/L solution of *n*-BuLi in hexanes, which effected the precipitation of a white solid. The resulting mixture was magnetically stirred for 16 h followed by cooling to –78 °C and the dropwise addition of $ClP(NMe_2)_2$ (1.9 mL, 12.0 mmol). The reaction mixture was warmed to ambient temperature and was magnetically stirred for 3 h. The resulting white solid was removed by filtration through a filter stick and from the remaining solution the diethyl ether was removed, which afforded a colorless oil that was dissolved in anhydrous methanol and was heated in an oil bath at 50 °C for 3 h. Subsequent removal of the solvent afforded a colorless oil that was dissolved in diethyl ether (10 mL). The ethereal solution was added dropwise to a Schlenk tube containing $LiAlH_4$ (0.60 g, 15.6 mmol) in diethyl ether (7 mL). The resulting green solution was magnetically stirred at ambient temperature for 48 h. The reaction mixture was quenched with degassed distilled H_2O followed by filtration through a filter stick to remove the solids. The diethyl ether layer was dried over Na_2SO_4. Subsequent filtration and removal of the solvent afforded **4** as a light brown oil, which when purified by vacuum distillation at 80–90 °C (10^{-3} Torr) was obtained as a colorless oil that was used without further purification (1.21 g, 4.28 mmol, 36%). ^1H NMR (C_6D_6) δ: 7.46 (d, $^4J_{HH}$ = 2.5 Hz, 1H, Ar-H), 7.41 (d of d, $^3J_{PH}$ = 7.0 Hz, $^4J_{HH}$ = 2.5 Hz, 1H, Ar-H), 4.96 (s, 2H, CH_2 (MOM)), 3.97 (d, $^1J_{PH}$ = 202.1 Hz, 2H, $-PH_2$), 3.40 (s, 3H, CH_3 (MOM)), 1.48 (s, 9H, $C(CH_3)_3$), 1.23 (s, 9H, $C(CH_3)_3$). $^{13}C\{^1H\}$ NMR (C_6D_6) δ: 155.7 (d, J_{PC} = 10.9 Hz, Ar-quaternary), 145.4 (d, J_{PC} = 3.0 Hz, Ar-quaternary), 141.9 (d, J_{PC} = 1.5 Hz, Ar-quaternary), 130.7 (d, $^2J_{PC}$ = 7.4 Hz, Ar-CH), 124.5 (Ar-CH), 123.0 (d, J_{PC} = 11.4 Hz, Ar-quaternary), 98.8 (d, $^4J_{PC}$ = 7.9 Hz, CH_2 (MOM)), 56.2 (d, J_{PC} = 1.5 Hz, CH_3 (MOM)), 34.6 (d, $^2J_{PC}$ = 0.75 Hz, $C(CH_3)_3$)), 33.5 ($C(CH_3)_3$), 30.5 ($C(CH_3)_3$), 30.3 ($C(CH_3)_3$). $^{31}P\{^1H\}$ NMR (C_6D_6) δ: –128.6.

Preparation of 5

To a magnetically stirred solution of **4** (0.244 g, 0.860 mmol) in THF (5 mL) was added a 1.45 mol/L solution of *n*-BuLi in hexanes (0.600 mL, 0.860 mmol). The reaction mixture went from colorless to yellow in appearance and was magnetically stirred at ambient temperature for 1.5 h, followed by the addition of a THF (2 mL) solution of (2*S*,5*S*)-2,5-hexanediol cyclic sulfate (0.156 g, 0.860 mmol). The reaction went colorless and was magnetically stirred at ambient temperature for 2 h followed by the addition of a 1.45 mol/L solution of *n*-BuLi in hexanes (0.60 mL, 0.860 mmol). The mixture went yellow and remained that color for the subsequent 2 h of magnetic stirring. The solvent and other volatiles were removed in vacuo affording an off-white solid that was washed with pentane (2 × 3 mL) to effect the precipitation of a gelatinous white solid, which was separated by filtration through Celite. The remaining solvent was removed in vacuo affording **5** as a yellow oil that was used without further purification (0.215 g, 0.59 mmol, 68%). ^1H NMR (C_6D_6) δ: 7.53 (d, $^4J_{HH}$ = 2.0 Hz, 1H, Ar-H), 7.39 (m, 1H, Ar-H), 5.81 (t, $^5J_{PH}$ = 4.0 Hz, 1H, CH_2 (MOM)), 5.11 (d, 1H, $^5J_{PH}$ = 3.5 Hz, 1H, CH_2 (MOM)), 3.56 (s, 3H, CH_3 (MOM)), 2.62 (m, 1H, CH (phospholane)), 2.27 (m, 1H, CH (phospholane)), 2.13 (m, 1H, CH_2 (phospholane)), 1.84 (m, 1H, CH_2 (phospholane)), 1.57 (s, 9H, $C(CH_3)_3$), 1.41 (m, 1H, CH_2 (phospholane)), 1.33 (d of d, $^3J_{PH}$ = 19.0 Hz, $^3J_{HH}$ = 6.0 Hz, 3H, CH_3 (phospholane)), 1.31 (s, 9H, $C(CH_3)_3$), 1.25 (m, 1H, CH_2 (phospholane)), 0.93 (d of d, $^3J_{PH}$ = 9.5 Hz, $^3J_{HH}$ = 7.0 Hz, 3H, CH_3 (phospholane)). $^{13}C\{^1H\}$ NMR (C_6D_6) δ: 156.6 (d, $^2J_{PC}$ = 18.5 Hz, Ar-quaternary), 144.4 (Ar-quaternary), 141.6 (d, J_{PC} = 0.9 Hz, Ar-quaternary), 130.0 (d, J_{PC} = 31.6 Hz, Ar-quaternary), 127.3 (d, $^2J_{PC}$ = 2.3 Hz, Ar-CH), 124.4 (Ar-CH), 98.7 (d, $^3J_{PC}$ = 21.0 Hz, CH_2 (MOM)), 56.2

(d, J_{PC} = 1.9 Hz, CH_3 (MOM)), 35.9 (d, $^2J_{PC}$ = 2.4 Hz, CH_2 (phospholane)), 35.3 (d, $^2J_{PC}$ = 2.3 Hz, CH_2 (phospholane)), 34.6 (d, J_{PC} = 1.1 Hz, $C(CH_3)_3$), 34.1 (d, $^2J_{PC}$ = 14.7 Hz, CH (phospholane)), 33.7 ($C(CH_3)_3$), 33.6 (d, $^2J_{PC}$ = 10.9 Hz, CH (phospholane)), 30.7 ($C(CH_3)_3$), 30.2 ($C(CH_3)_3$), 20.4 (d, $^3J_{PC}$ = 35.5 Hz, CH_3 (phospholane)), 15.0 (d, $^3J_{PC}$ = 0.9 Hz, CH_3 (phospholane)). $^{31}P\{^1H\}$ NMR (C_6D_6) δ: 2.3.

Preparation of 6

To a magnetically stirred solution of **5** (0.382 g, 1.05 mmol) in THF (10 mL) was added 5 mol/L HCl (aq.) (5 mL) followed by heating at 50 °C in an oil bath for 16 h. Subsequent removal of the solvent afforded a white solid that was suspended in diethyl ether (10 mL) followed by the addition of 7 mol/L NH_4OH (aq.) (5 mL), which caused the solution to become homogeneous. The solution was magnetically stirred for 5 h at ambient temperature followed by removal of the solvent and extraction of the residue into pentane (3 × 3 mL). Upon removal of the pentane in vacuo, **6** was obtained as a colorless oil that was used without further purification (0.246 g, 0.767 mmol, 73%). ^1H NMR (C_6D_6) δ: 7.72 (d, $^4J_{PH}$ = 13.5 Hz, 1H, O*H*), 7.52 (d, $^4J_{HH}$ = 2.0 Hz, 1H, Ar-H), 7.27 (m, 1H, Ar-H), 2.53 (m, 1H, CH (phospholane)), 2.05 (m, 2H, CH and CH_2 (phospholane)), 1.78 (m, 1H, CH_2 (phospholane)), 1.60 (s, 9H, $C(CH_3)_3$), 1.53 (m, 1H, CH_2 (phospholane)), 1.32 (s, 9H, $C(CH_3)_3$), 1.15 (d of d, $^3J_{PH}$ = 19.5 Hz, $^3J_{HH}$ = 7.0 Hz, 3H, CH_3 (phospholane)), 1.12 (m, 1H, CH_2 (phospholane)), 0.79 (d of d, $^3J_{PH}$ = 11.5 Hz, $^3J_{HH}$ = 7.0 Hz, 3H, CH_3 (phospholane)). $^{13}C\{^1H\}$ NMR (C_6D_6) δ: 156.8 (d, J_{PC} = 19.4 Hz, Ar-quaternary), 140.4 (Ar-quaternary), 134.4 (Ar-quaternary), 134.3 (d, J_{PC} = 15.8 Hz, Ar-quaternary), 126.9 (d, $^2J_{PC}$ = 2.1 Hz, Ar-CH), 124.9 (Ar-CH), 36.5 (d, $^2J_{PC}$ = 4.2 Hz, CH_2 (phospholane)), 36.4 (CH_2 (phospholane)), 35.8 (d, $^1J_{PC}$ = 4.8 Hz, CH (phospholane)), 34.4 ($C(CH_3)_3$), 33.5 ($C(CH_3)_3$), 33.2 (d, $^1J_{PC}$ = 5.7 Hz, CH (phospholane)), 30.8 ($C(CH_3)_3$), 28.8 ($C(CH_3)_3$), 19.6 (d, $^2J_{PC}$ = 31.7 Hz, CH_3 (phospholane)), 13.8 (CH_3 (phospholane)). $^{31}P\{^1H\}$ NMR (C_6D_6) δ: –25.6.

Preparation of 7

To a magnetically stirred solution of $[Ir(COD)Cl]_2$ (0.14 g, 0.20 mmol) in THF (2 mL) was added a THF (2 mL) solution of **6** (0.13 g, 0.41 mmol). After 3 h of magnetic stirring, NEt_3 (57 μL, 0.41 mmol) was added, which resulted in an immediate color change from yellow-orange to bright orange. After 2 h of magnetic stirring at ambient temperature, ^{31}P NMR analysis of the reaction mixture confirmed the consumption of **6** and the quantitative formation of a new product (**7**). The solvent and other volatiles were removed in vacuo and the residual solid was extracted into pentane (3 × 2 mL). Subsequent removal of the solvent afforded **7** as an analytically pure orange solid (0.17 g, 0.28 mmol, 68%). ^1H NMR (C_6D_6) δ: 7.57 (d, $^4J_{HH}$ = 2.0 Hz, 1H, Ar-H), 7.05 (d of d, $^3J_{PH}$ = 8.5 Hz, $^3J_{HH}$ = 2.5 Hz, 1H, Ar-H), 5.36 (m, 2H, 2 x CH (COD)), 3.56 (m, 1H, CH (COD)), 3.13 (m, 1H, CH (COD)), 2.54 (m, 1H, CH (phospholane)), 2.27 (m, 3H, CH_2 (COD) and CH (phospholane)), 2.13 (m, 2H, CH_2 (COD)), 1.88 (m, 2H, CH_2 (COD)), 1.83 (m, 1H, CH_2 (phospholane)), 1.78 (m, 1H, CH_2 (phospholane)), 1.72 (m, 2H, CH_2 (COD)), 1.70 (s, 9H, $C(CH_3)_3$), 1.39 (s, 9H, $C(CH_3)_3$), 1.35 (m, 1H, CH_2 (phospholane)), 1.12 (d of d, $^3J_{PH}$ = 17.5 Hz, $^3J_{HH}$ = 7.5 Hz, 3H, CH_3 (phospholane)), 1.03 (m, 1H, CH_2 (phospholane)), 0.93 (d of d, $^3J_{PH}$ = 14.5 Hz, $^3J_{HH}$ = 7.0 Hz, 3H, CH_3 (phospholane)). $^{13}C\{^1H\}$ NMR (C_6D_6) δ: 176.6 (d, J_{PC} = 18.7 Hz, Ar-quaternary), 137.1 (d, J_{PC} = 6.7 Hz, Ar-quaternary), 136.7 (d, J_{PC} = 8.8 Hz, Ar-quaternary), 126.6 (d, J_{PC} = 2.0 Hz, Ar-CH), 125.0 (Ar-CH), 116.8 (d, J_{PC} = 45.1 (Ar-quaternary), 92.5 (d, $^2J_{PC}$ = 12.7 Hz, CH (COD)), 91.5 (d, $^2J_{PC}$ = 5.4 Hz, CH (COD)), 51.4 (CH (COD)), 45.9 (CH (COD)), 39.1 (d, $^1J_{PC}$ = 43.4 Hz, CH (phospholane)), 35.7 (CH_2 (phospholane)), 35.3 (d, $^2J_{PC}$ = 4.9 Hz, CH_2 (phospholane)), 34.0 (d, $^3J_{PC}$ = 2.9 Hz, CH_2 (COD)), 33.5 (d, $^3J_{PC}$ = 2.8 Hz, CH_2 (COD)), 33.1 ($C(CH_3)_3$), 33.0 (d, $^1J_{PC}$ = 30.3 Hz, CH (phospholane)), 31.1 ($C(CH_3)_3$), 29.0 ($C(CH_3)_3$), 28.2 (d, $^3J_{PC}$ = 2.3 Hz, CH_2 (COD)), 28.1 (d, $^3J_{PC}$ = 2.0 Hz, CH_2 (COD)), 21.7 ($C(CH_3)_3$), 16.4 (d, $^2J_{PC}$ = 8.2 Hz, CH_3 (phospholane)), 13.9 (d, $^2J_{PC}$ = 1.6 Hz, CH_3 (phospholane)). $^{31}P\{^1H\}$ NMR (C_6D_6) δ: 40.1. Anal. calcd. for $C_{28}H_{44}IrOP$: C 54.23, H 7.16, N 0.00; found: C 54.44, H 7.52, N < 0.3. Crystals suitable for X-ray crystallographic analysis were grown from a concentrated solution of **7** in pentane at –35 °C.

Representative procedure for the intramolecular hydroamination of unactivated alkenes by secondary alkylamines catalyzed by 1

To a screw-capped vial containing **2a** (82 mg, 0.25 mmol) and a stir-bar was added 0.220 mL of a stock solution of **1** (5.8 mg in 1.000 mL of 1,4-dioxane) and 0.280 mL of 1,4-dioxane (total reaction volume = 0. 5 mL). The vial was sealed under N_2 with a cap containing a PTFE septum and, once all the material had dissolved, was removed from the glovebox and was placed in a temperature-controlled aluminum heating block set at 110 °C. After 16 h of magnetic stirring, the vial was removed from the temperature-controlled aluminum heating block, cooled to ambient temperature, diluted with CH_2Cl_2 (2 mL), and was washed with brine (2 × 2 mL). The organic extracts were combined, dried over Na_2SO_4, and concentrated. The resulting residue was purified by flash column chromatography on silica gel (hexanes/EtOAc = 20:1) to yield **2b** as a white solid (74 mg, 0.23 mmol, 92%) that afforded analytical data in agreement with data reported in the literature.[7f]

1-Benzyl-2-methyl-4,4-diphenylpyrrolidine (Table 1, entry 1)

The indicated compound was purified by flash chromatography on silica gel (EtOAc/hexanes = 20:1) in a 92% yield (74 mg) as a white solid.[7f] ^1H NMR ($CDCl_3$) δ: 7.53–7.19 (m, 15H), 4.21 (d, J = 13.5 Hz, 1H), 3.77 (d, J = 9.5 Hz, 1H), 3.38 (d, J = 13.5 Hz, 1H), 3.07–2.89 (m, 3H), 2.34 (d of d, J = 13.0, 8.0 Hz, 1H), 1.29 (d, J = 6.5 Hz, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ: 150.6, 148.7, 140.1, 128.6, 128.2, 128.1, 127.8, 127.4, 127.2, 126.7, 125.8, 125.4, 66.4, 59.6, 58.0, 52.5, 48.0, 19.5.

1-(4-Chlorobenzyl)-2-methyl-4,4-diphenylpyrrolidine (Table 1, entry 2)

The indicated compound was purified by flash chromatography on silica gel (*n*-pentane/Et_2O = 30:1) in an 86%

yield (78 mg) as a white solid.[2a] ^{1}H NMR ($CDCl_3$) δ: 7.43–7.17 (m, 14H), 4.12 (d, J = 13.5 Hz, 1H), 3.71 (d, J = 10.0 Hz, 1H), 3.33 (d, J = 13.5 Hz, 1H), 3.05–2.89 (m, 2H), 2.87 (d, J = 9.5 Hz, 1H), 2.33 (d of d, J = 12.5, 7.9 Hz, 1H), 1.26 (d, J = 6.5 Hz, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$) δ: 150.4, 148.6, 138.6, 132.4, 129.8, 128.3, 128.1, 127.8, 127.3, 127.1, 125.8, 125.5, 66.3, 59.6, 57.2, 52.5, 47.8, 19.5.

Methyl 4-(2-methyl-4,4-diphenylpyrrolidin-1-ylmethyl)-benzoate (Table 1, entry 3)

The indicated compound was purified by flash chromatography on silica gel (n-pentane/Et_2O = 8:1) in a 85% yield (82 mg) as a colorless oil.[7f] ^{1}H NMR ($CDCl_3$) δ: 8.07 (d, J = 8.0 Hz, 2H), 7.50 (d, J = 8.5 Hz, 2H), 7.35–7.15 (m, 10H), 4.16 (d, J = 14.0 Hz, 1H), 3.98 (s, 3H), 3.68 (d, J = 10.0 Hz, 1H), 3.39 (d, J = 13.5 Hz, 1H), 3.02–2.88 (m, 2H), 2.86 (d, J = 10.0 Hz, 1H), 2.31 (d of d, J = 13.0, 7.5 Hz, 1H), 1.23 (d, J = 5.5 Hz, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$) δ: 167.1, 150.3, 148.5, 145.7, 129.6, 128.7, 128.4, 128.1, 127.8, 127.3, 127.1, 125.8, 125.5, 66.4, 59.7, 57.7, 52.6, 51.9, 47.8, 19.5.

1-(4-Methoxybenzyl)-2-methyl-4,4-diphenylpyrrolidine (Table 1, entry 4)

The indicated compound was purified by flash chromatography on silica gel (n-pentane/Et_2O = 15:1) in a 87% yield (77 mg) as a colorless oil.[2a] ^{1}H NMR ($CDCl_3$) δ: 7.29 (m, 1H), 7.00–6.95 (m, 2H), 4.13 (d, J = 13.0 Hz, 1H), 3.90 (s, 3H), 3.74 (d, J = 10.0 Hz, 1H), 3.30 (d, J = 13.0 Hz, 1H), 3.02 (d of d, J = 13.0, 7.5 Hz, 1H), 2.96–2.85 (m, 2H), 2.30 (d of d, J = 13.0, 7.5 Hz, 1H), 1.27 (d, J = 6.0 Hz, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$) δ: 158.5, 150.6, 148.7, 132.0, 129.6, 128.1, 127.8, 127.4, 127.2, 125.7, 125.3, 113.5, 66.3, 59.5, 57.2, 55.2, 52.4, 48.0, 19.5.

1-Cyclohexylmethyl-2-methyl-4,4-diphenylpyrrolidine (Table 1, entry 5)

The indicated compound was purified by flash chromatography on silica gel (hexanes/EtOAc = 8:1) in a 89% yield (75 mg) as a white solid.[7d] ^{1}H NMR ($CDCl_3$) δ: 7.38–7.21 (m, 9H), 7.16 (m, 1H), 3.87 (d, J = 9.5 Hz, 1H), 2.87 (d of d, J = 13.0, 7.5 Hz, 1H), 2.82 (d, J = 10.0 Hz, 1H), 2.66 (m, 1H), 2.56 (m, 1H), 2.18–2.03 (m, 3H), 1.82–1.63 (m, 4H), 1.53 (m, 1H), 1.36–1.15 (m, 3H), 1.10 (d, J = 6.0 Hz, 3H), 1.02–0.87 (m, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$) δ: 151.3, 148.9, 128.1, 127.8, 127.6, 127.3, 125.7, 125.4, 67.6, 61.4, 60.3, 52.8, 48.1, 37.3, 32.2, 31.9, 26.9, 26.3, 26.1, 19.6.

2-Benzyl-3-methyl-2-aza-spiro[4,5]decane (Table 1, entry 6)

The indicated compound was purified by flash chromatography on silica gel (hexanes/EtOAc = 20:1) in a 85% yield (52 mg) as a colorless oil.[7f] ^{1}H NMR ($CDCl_3$) δ: 7.40–7.24 (m, 5H), 4.06 (d, J = 13.0 Hz, 1H), 3.14 (d, J = 13.5 Hz, 1H), 2.82 (d, J = 9.5 Hz, 1H), 2.54 (m, 1H), 1.91 (d, J = 9.5 Hz, 1H), 1.80 (d of d, J = 12.0, 7.0 Hz, 1H), 1.56–1.27 (m, 11H), 1.19 (d, J = 6.0 Hz, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$) δ: 140.0, 128.6, 128.0, 126.5, 66.6, 59.0, 58.0, 47.0, 39.3, 39.2, 38.5, 26.1, 23.6, 23.5, 19.3.

1-Benzyl-2,4,4-trimethylpyrrolidine (Table 1, entry 7)

The indicated compound was purified by flash chromatography on silica gel (hexanes/EtOAc = 20:1) in a 86% yield (44 mg) as a colorless oil.[7f] ^{1}H NMR ($CDCl_3$) δ: 7.39–7.23 (m, 5H), 4.05 (d, J = 14.5 Hz, 1H), 3.15 (d, J = 13.5 Hz, 1H), 2.67 (d, J = 9.0 Hz, 1H), 2.59 (m, 1H), 1.98 (d, J = 9.0 Hz, 1H), 1.76 (d of d, J = 12.0, 7.5 Hz, 1H), 1.35 (d of d, J = 12.5, 9.0 Hz, 1H), 1.19 (d, J = 6.0 Hz, 3H), 1.11 (s, 3H), 1.01 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$) δ: 140.1, 128.7, 128.0, 126.5, 68.4, 59.7, 58.0, 49.1, 35.4, 30.9, 29.2, 19.4.

1-Benzyl-2-methyl-4-isopropylpyrrolidine (Table 1, entry 8)

The indicated compound was obtained in 87% yield with a diastereomeric ratio of 1.3:1 on the basis of ^{1}H NMR using 1,4-bis(trifluoromethyl)benzene as an internal standard.[7f]

1-Benzyl-2-methyl-5,5-diphenylpiperidine (Table 1, entry 9)

The indicated compound was purified by flash chromatography on silica gel (hexanes/EtOAc = 20:1) in a 85% yield (73 mg) as a colorless oil.[7d] ^{1}H NMR ($CDCl_3$) δ: 7.46–7.14 (m, 15H), 4.13 (d, J = 13.5 Hz, 1H), 3.43 (d, J = 12.5 Hz, 1H), 3.21 (d, J = 13.5 Hz, 1H), 3.60–2.50 (m, 3H), 2.25 (m, 1H), 1.70 (m, 1H), 1.45 (m, 1H), 1.21 (d, J = 6.0 Hz, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$) δ: 148.6, 146.7, 139.4, 129.5, 128.4, 128.0, 127.9, 127.6, 127.0, 126.9, 125.6, 125.3, 61.0, 58.9, 56.1, 46.5, 34.2, 31.0, 18.6.

1-Benzyl-2–2-dimethyl-4,4-diphenylpyrrolidine (Table 1, entry 10)

The indicated compound was purified by flash chromatography on silica gel (EtOAc/hexanes = 20:1) in a 92% yield (78 mg) as a white solid.[15] ^{1}H NMR ($CDCl_3$) δ: 7.52–7.20 (m, 15H), 3.73 (s, 2H), 3.41 (s, 2H), 2.74 (s, 2H), 1.26 (s, 6H). ^{13}C{^{1}H} NMR ($CDCl_3$) δ: 149.7, 140.9, 128.5, 128.1, 127.8, 127.2, 126.7, 125.4, 6.1, 60.4, 54.4, 52.4, 51.6, 25.1.

Crystallographic characterization of 7

Crystallographic data were obtained at 193 (±2) K on a Bruker PLATFORM/SMART 1000 CCD diffractometer using a graphite-monochromated Mo Kα (λ = 0.71073 Å) radiation, employing a sample that was mounted in inert oil and transferred to a cold gas stream on the diffractometer. Programs for diffractometer operation, data collection, and data reduction were supplied by Bruker. SADABS was employed as the absorption correction method. The structure was solved by use of a Patterson search/structure expansion and refinement was carried out by use of full-matrix least-squares procedures (on F^2) with R_1 based on $F_o^2 \geq 2\sigma(F_o^2)$ and wR_2 based on $F_o^2 \geq -3\sigma(F_o^2)$. All hydrogen atoms were added at calculated positions and refined by use of a riding model employing isotropic displacement parameters based on the isotropic displacement parameter of the attached atom. The near-zero final refined value of the absolute structure parameter (0.000(5)) supported that the correct absolute structure had been chosen.[16] See the Supplementary data section for information on obtaining the complete supplementary crystallographic data for this paper. The thermal ellipsoid plot of **7** was generated by use of ORTEP-3 for Windows.[17]

Supplementary data

Supplementary data for this article are available on the journal Web site (canjchem.nrc.ca). CCDC 744698 contains the X-ray data in CIF format for this manuscript. These data can be obtained, free of charge, via www.ccdc.cam.ac.uk/conts/retrieving.html (Or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax +44 1223 336033; or deposit@ccdc.cam.ac.uk).

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