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Cassandre Bories, Geoffrey Gontard, Marion Barbazanges, Etienne Derat, Marc Petit. Hydrido-Cobalt Complexes for the Chemo- and Regioselective 1,2-Silylative Dearomatization of N-Heteroarenes. *Organic Letters*, 2023, 25 (5), pp.843-848. 10.1021/acs.orglett.3c00022 . hal-04095225

HAL Id: hal-04095225

<https://hal.science/hal-04095225>

Submitted on 13 Nov 2023

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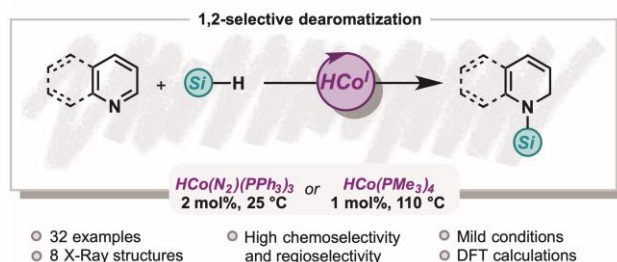
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Hydrido-Cobalt Complexes For the Chemo- and Regioselective 1,2-Silylative Dearomatization of *N*-Heteroarenes.

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Supporting Information Placeholder

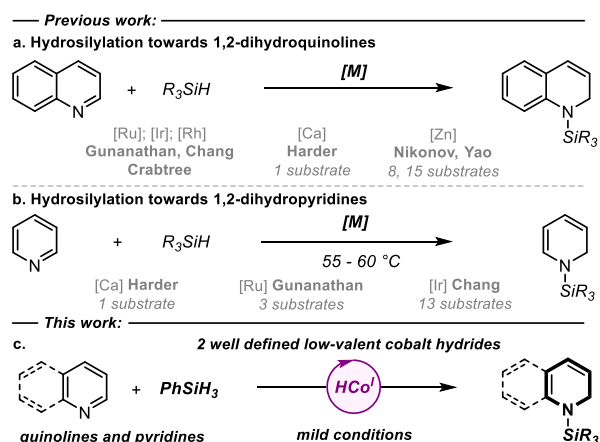


ABSTRACT: We describe an efficient regio- and chemoselective dearomatization of *N*-heteroarenes using hydrido-cobalt catalysts. Reactions were performed under mild conditions on a wide range of *N*-heteroarenes leading exclusively to the silyl-1,2-dihydroheteroarene. Various quinolines and pyridines bearing electron-donating and electron-withdrawing substituents are compatible with this methodology. DFT calculations, NMR spectroscopic studies, and X-ray diffraction analysis underlined the importance of a second silane for the final step of the reaction.

N-heterocyclic derivatives are important synthons in pharmaceutical and agrochemical industries. Among them, dihydropyridines and dihydroquinolines (DHP and DHQ) appeared as important scaffolds with the discovery of unprecedented biological properties.¹ Many synthesis of such moieties have been described,² one of the most elegant is based on the partial and selective reduction of *N*-heteroarenes.³ However, the slight difference in term of thermodynamic stability between the 1,2- and 1,4-isomers often drives to a mixture of both in harsh conditions. Moreover, dihydropyridines or quinolines are sensitive compounds that undergo rearomatization, disproportionation and other side reactions.⁴ Traditional methods using stoichiometric metal hydride reactions are facing drawbacks such as low selectivity, problem of group tolerance and a large amount of waste. To avoid it, hydrogenation appeared as the simplest solution, however high-pressure have to be employed and trouble of over-reduction and selectivity are still present. During the last decades the development of silanes and boranes as mild reducing reagents emerged as an appealing solution. Since the first results on hydroboration by Hill,⁵ numerous reports demonstrated that hydroboration is the most selective hydroelementation system of *N*-heteroarenes. Indeed, it is possible to reach the desired 1,2- or 1,4-isomer of DHPs and DHQs.^{3a-e} On the other hand, for hydrosilylation, since the non-selective report by Harrod⁶ and except the reports from Oestreich and Nikonov on 1,4-selective ruthenium catalyzed hydrosilylation,^{7,8} examples of selective 1,2-hydrosilylation of both pyridines and quinolines remain scarce. Indeed, few reports using non noble metal such as Ca⁹ and Zn^{11,12} are described with a narrow scope.

Only the use of expensive metal such as Ir¹⁰ and Ru¹³ allows larger scope on quinolines and pyridines (Scheme 1a and 1b).

Scheme 1. 1,2-Silylative dearomatization



Thus, 1,2-hydrosilylation of *N*-heteroarenes remains understudied and it appears mandatory to develop simple, efficient and selective non-noble metal catalysis. Our group¹⁴ and others¹⁵ have explored the reactivity of two simple cobalt complexes $\text{HCo}(\text{PMe}_3)_4$ and $\text{HCo}(\text{N}_2)(\text{PPh}_3)_3$ for bonds activation,^{14b-e} hydroelementation^{14f,h} and recently imines reduction.¹⁶ Herein, we described for the first time an efficient 1,2-hydrosilylation of

both quinolines and pyridines on a large scope using these two well-defined cobalt hydrides (Scheme 1c).¹⁷

Table 1. Optimization of the conditions

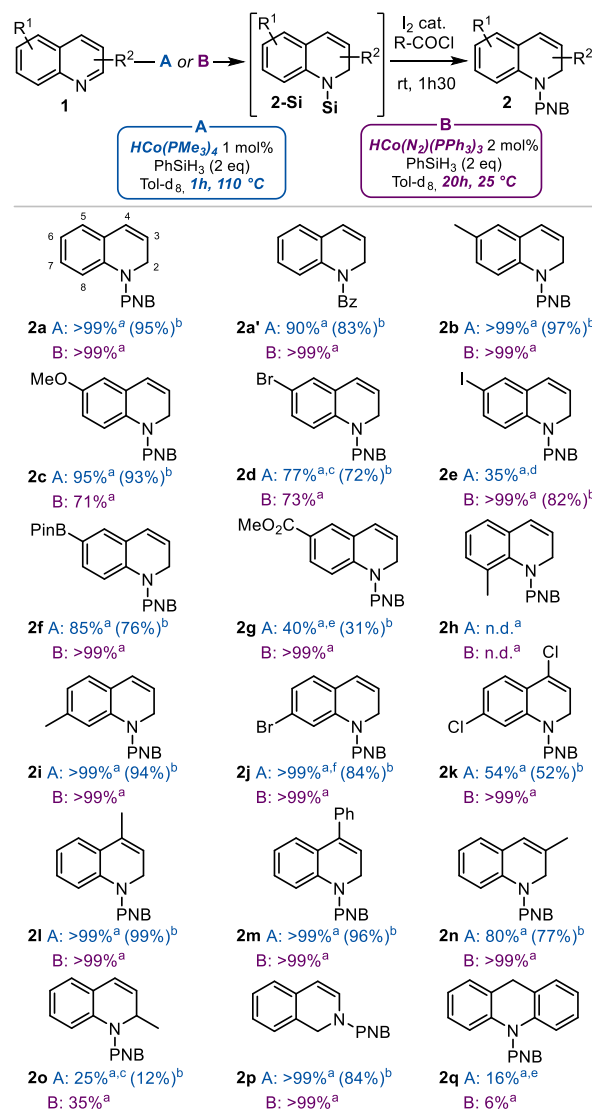
Entry	cat.	x	R ₃ SiH	y	T(°C)	time	conv. ^a
1	Co-1	1	PhSiH ₃	2	50	1h (20h)	0% (63%)
2	Co-1	1	PhSiH ₃	2	110	1h	100%
3	Co-1	1	PhSiH ₃	1.1	110	1h	45%
4	Co-2	2	PhSiH ₃	2	25	20h (6h)	100% (97%)
5	Co-2	2	PMHS	2	25	20h	12%
6	Co-2	2	Ph ₂ SiH ₂	2	25	20h	20%
7	Co-2	2	PhMeSiH ₂	2	25	20h (6h)	100% (29%)
8	Co-2	2	PhSiH ₃	1.1	25	20h	97%
9	Co-2	1	PhSiH ₃	2	25	20h	72%
10	Co-3	2	PhSiH ₃	2	25	24h	17%

^aConversion of **1a** measured by ¹H NMR spectroscopy

We first evaluated **Co-1** as the catalyst and phenylsilane as the hydride source.¹⁶ The reaction, at 50°C, is slow with no conversion after 1h. Extending the reaction time to 20h, drives to a conversion of 63% (Table 1, Entry 1). Increasing the temperature to 110°C allows to achieve full conversion in 1h (Entry 2). Decreasing the amount of silane is detrimental to the reaction with lower conversion (Entries 2 vs 3). To reach milder conditions, we tested a well-defined cobalt complex bearing more labile ligands. Thus using **Co-2**¹⁸ allows full conversion at 25 °C after 20h (Entry 4). Other silanes such as PMHS, Ph₂SiH₂ or PhMeSiH₂ gave respectively 12%, 20% and 100% conversion (Entries 5-7). To determine the most efficient one, the reaction time was decreased to 6h and PhSiH₃ with a 97% conversion versus 29% for PhMeSiH₂ appeared the best candidate (Entries 4 vs 7). Decreasing the amount of silane does not really affect the conversion (Entries 8 vs 4), but decreasing the catalyst loading from 2 mol% to 1 mol% results in lower conversion of 72% (Entry 9). *In-situ* formation a low-valent cobalt(I) hydride **Co-3** by using Co(OAc)₂ or Co(acac)₂ only led to conversion of 0% and 17%, respectively (Entry 10).^{18b,19} We then investigated the scope and limitations first on quinolines moieties, by using respectively conditions **A** with **Co-1** (Entry 2) and **B** with **Co-2** (Entry 4). In each case, the regioselectivity (1,2- vs 1,4-hydroxylation) and the conversion were evaluated by *in-situ* ¹H NMR spectroscopy on the crude intermediates **2-Si** (Figure S1). Due to its high sensitivity, **2-Si** was trapped by *p*-nitrobenzoylchloride (PNB-Cl) or benzoylchloride (Bz-Cl) to form the purifiable acylated product **2** (Scheme 2). Following these sequences, quinoline **1a** was selectively dearomatized into 1,2-DHQ **2a** or **2a'** in quantitative yield regardless of the conditions **A** or **B**, showing the efficiency of both catalysts. Substitution of the benzenic ring at C6 to C8 were well tolerated with the 6-methylquinoline **1b** leading to quantitative formation of the 1,2-DHQ **2b-Si** together with a 97% isolated yield of acylated 1,2-DHQ **2b**. Electron-donating and withdrawing groups were tested with the 6-methoxy and 6-bromo quinolines that yielded **2c** and **2d** in 93% and 72% isolated yields. The 6-iodoquinoline **1e** gave 35% conversion as a 1/1 mixture of **2a-Si/2e-Si** due to partial oxidative addition. High functional group tolerance was observed since the 6-substituted pinacol boronic ester **2f** and methylester **2g** led to 85% and 40% conversions, with a total

chemo- and regioselectivity. Substitutions in C7 were well tolerated as the 7-methylquinoline allowed the isolation of 1,2-DHQ **2i** in a 94% yield, and the 7-Br substituted **2j** was obtained in 84% yield. **1k** Bearing two chlorine substituents in C7 and C4, precursor of the famous hydroxychloroquine,²⁰ was selectively reduced to the 1,2-DHQ albeit with a lower 52% yield.

Scheme 2. Scope of the quinolines

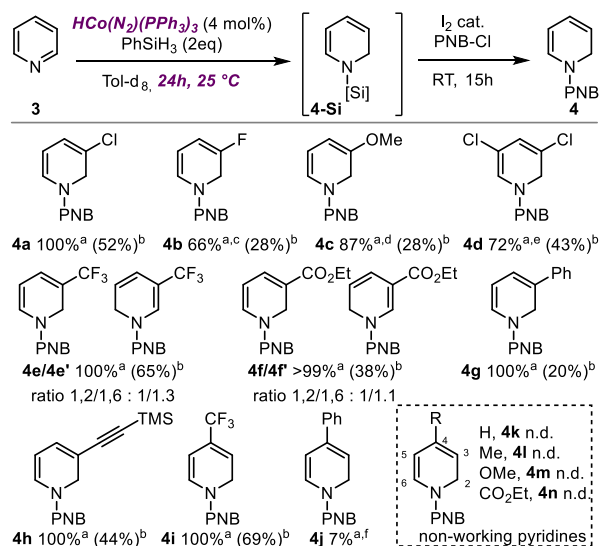


^aConversion of **1** measured by ¹H NMR spectroscopy. ^bIsolated yield of **2**. ^cTime: 2 h 45 min. ^d1/1 mixture of **2e-Si/2a-Si**. ^eTime: 18h. ^f9/1 mixture of **2j-Si/2a-Si**

Dehalogenation was slightly observed for 7-bromoquinoline **1j**, with the obtention of 10% of **2a** along with 90% of the desired **2j**. Substitution at C8 was dramatical as quinoline **1h** was unreactive, showing that steric hindrance around the nitrogen affects the reactivity. Substitution at the heteroaromatic ring was also studied. Substitution at C4 had no impact as 4-methyl- and 4-phenylquinolines provided selectively 1,2-DHQs **2l** and **2m** in excellent isolated yields. Same observation was made at C3 as 1,2-DHQ **2n** is obtained in 77% yield. Substrate **1o** substituted by a methyl at C2 gave poorer yield, even after 18h, probably because of the steric hindrance. Other aromatic *N*-heterocycles

were explored such as isoquinoline **1p** that gave good result with 84% yield. Acridine **1q** led to a low conversion of the dearomatized product **2q**, which is consistent with the substitution at C2. X-Ray analysis were obtained for **2a**, **2c**, **2f**, **2i**, **2k**, **2l**, **2m** and **2n** and confirmed the 1,2-selectivity (See Supporting Information). Conditions **A** appeared efficient with total regioselectivity, good yields, short reaction time and low catalyst loading. Using the milder conditions **B** with **Co-2** (room temperature, 2 mol% loading), identical or even better conversions were observed. For instance, no oxidative addition was observed for 7-bromo **1j** and only 10 % for the 6-iodo **1e**. Increased conversions were obtained for the functionalized quinolines **1f** and **1g**. The efficiency of **Co-2** compared to **Co-1**, together with milder conditions led us to pursue with this catalyst to the more challenging pyridines.

Scheme 3. Scope of the pyridines

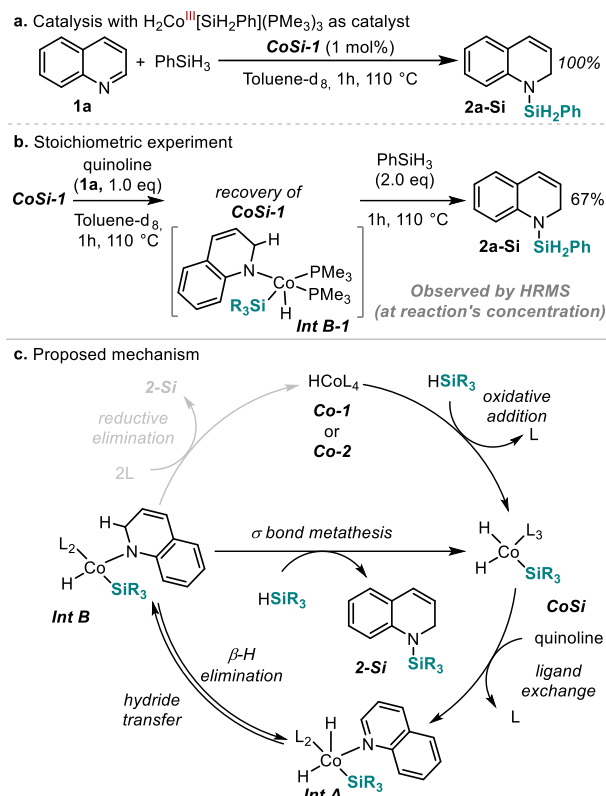


^aConversion of **3** measured by ¹H NMR spectroscopy. ^bIsolated yield of **4**. ^cTime: 72h. ^dTime: 30h; 66% conversion after 24h. ^eratio (4d/4a): 1/3.5 due to reductive dehalogenation. n.d.: non detected

Using conditions **B** with 4 mol% of catalyst we succeeded in reducing substituted pyridines (Scheme 3). These mild conditions are highly competitive compared to the few existing reports in terms of both catalyst/ligand cost and temperature of reaction.^{9,10,13} Conversion and selectivity were assessed on the crude intermediate **4-Si** or **4** by *in-situ* NMR spectroscopy, and product isolation was performed after trapping with PNB-Cl. The difference between conversions and isolated yields is explained by the sensitivity of the products which, even protected, rearomatize into pyridines during purification.¹⁰ Substitution at C3 was first explored with 3-chloro and 3-fluoropyridines that led selectively to the 1,2-DHPs **4a** and **4b** in good conversions. Double chlorine substitution at C3 and C5 was also studied with **3d**. It was converted into a mixture of **4d** and the dechlorinated compound **4a** with a 72% global conversion. Both electron-donating and electron-withdrawing groups were tolerated in C3. Indeed, 3-methoxypyridine **3c** was selectively hydrosilylated to give the corresponding 1,2-DHP **4c** with good conversion of 87%. For 3-trifluoromethyl and 3-ethylcarboxylate pyridines **3e** and **3f**, the system is very efficient with quantitative conversions to the DHPs. As observed by others the regioselectivity

was changed and a mixture of the minor 1,2- and the major 1,6-DHPs was obtained.^{10,21} Substituents such as phenyl and trimethylsilylacetylene were introduced at C3 to give 1,2-DHPs **4g** and **4h** with high conversions. Substitution in C4 was studied with 4-CF₃ pyridine **3i** that gave quantitative conversion to the 1,2-isomer and the acylated analog was isolated in 69% yield. Pyridine **3j** with phenyl at C4 was less reactive with 7% conversion into the 1,2-DHP. Pyridines **3k-n** were not reactive.

Scheme 4. NMR experiments and plausible mechanism



We then worked on the mechanism and based on our previous work, the first step is the oxidative addition of silane into **Co-1**. Indeed, using $\text{H}_2\text{Co}[\text{SiH}_2\text{Ph}](\text{PMe}_3)_3$ **CoSi-1** as catalyst,¹⁶ the full conversion towards the silylated 1,2-DHQ **2a-Si** (Scheme 4a) confirmed that it is an active catalyst. Adding phenylsilane to $\text{HCo}(\text{N}_2)(\text{PPh}_3)_3$ we observed by ¹H NMR, like Parish,^{18a} a shift of the hydride consistent with the oxidative addition. However, the lack of fine structure and the appearance of free phosphines suggest dissociations and the formation of new silyl hydride cobalt species (Scheme S7 and S8). Then, these silylcobalt(III) dihydride **CoSi** can undergo a ligand exchange between the substrate and a phosphine followed by hydride transfer.^{13,22} **Int B** can then undergo reductive elimination to regenerate the hydrido-cobalt(I) or σ -bond metathesis with another PhSiH_3 (Scheme 4c).¹⁶ ¹H NMR showed no new signal when heating **CoSi-1** in presence of quinoline **1a**. The same experiment at the reaction's concentration allowed the observation of **Int B-1** by HRMS. Moreover, formation of 1,2-DHQ was observed after subsequent addition of phenylsilane (Scheme 4b), suggesting that a second silane is mandatory for the final step. Furthermore, ¹H NMR monitoring (Figures S2&S3) revealed that once the oxidative addition has occurred, the regeneration of **Co-1** never happens. DFT calculations were performed to rationalize these observations.

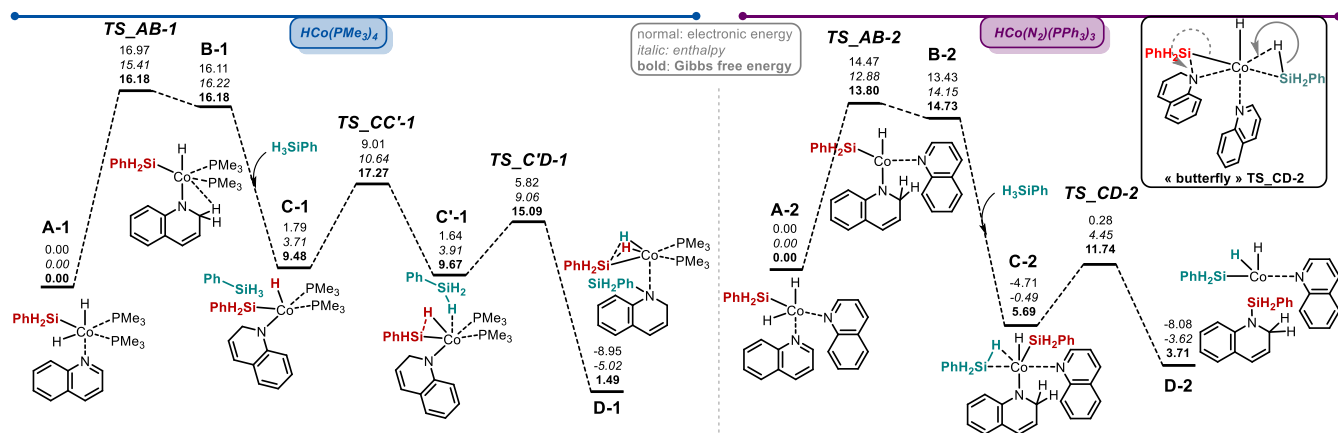


Figure 1. DFT calculated potential energy surfaces (kcal.mol⁻¹) of the hydrosilylation of **2a** starting from Left: **Co-1**; Right: **Co-2**.

Based on the experimental and previous work,¹⁶ **Co-1** and **Co-2** seem to be pre-catalysts and due to the large excess of silane a fast oxidative addition with loss of phosphines occurs to form **CoSi**. For **Co-1** a phosphine is then exchanged by a quinoline to give **A-1**, with an electronic energy of 16.43 kcal/mol, explaining the higher temperature required for this catalyst (Figure S14). Thus, starting from **A-1**, a hydrocobaltation process is found with a barrier of 16.18 kcal/mol (**TS_AB-1**, Figure 1). Metastable intermediate **B-1** is then localized but direct reductive elimination is not possible (barrier of 27.04 kcal/mol), confirming the experiment (Scheme 4b) where a second silane is necessary. From here, the approaching silane (blue) is weakly interacting with the metal but is stacked through dispersive interactions. A transition state is needed to create agostic interaction between the second silane (blue) and the cobalt (barrier of 7.79 kcal/mol). It leads to **C'-1** as starting point for the final transition state, where the second silane (blue) is directly coordinated to the cobalt through an agostic bond and where the first silane (red) is now coordinated through a η^2 -interaction (Si...H distance: 1.70 Å). Finally, in **TS C'D-1**, the second silane (blue) transfers its hydrogen to the cobalt and creates the N-Si bond, with a small barrier of 5.42 kcal/mol. The two hydrogens in **D-1** are in between the silicon and the cobalt (μ_2 -coordination). For **Co-2**, the observation of free phosphines during the reaction let us envision several phosphines exchanges (Figure S14). Intermediate **B-2**²³ is also stabilized (9.04 kcal/mol) by interacting with a second silane (blue). It creates an intermediate **C-2** where the silane (blue) strongly interacts with the cobalt: this second silane is found at a Si-Co bond distance of 2.31 Å whereas the first one (in red) is at 2.21 Å. With no phosphine remaining on the cobalt, no reorganization is needed to create strong agostic interaction between the second silane and the cobalt. This leads to an original "butterfly" transition state (**TS_CD-2**) in which the first silane (red) creates a bond with the nitrogen of the reduced quinoline (barrier of 6.05 kcal/mol) and the second silane (blue) transfers its hydrogen to the metal to regenerate the catalyst (Figure 1).

In conclusion, we developed a cobalt-catalyzed selective dearomatization of *N*-heteroarenes towards 1,2-DHQs and 1,2-DHPs. Two conditions were developed for the hydrosilylation of quinolines using simple well-defined hydride complexes **HCo(PMe₃)₄** and **HCo(N₂)(PPh₃)₃**. The latter allows the hydrosilylation of pyridines in mild conditions at room temperature. Finally, we propose a mechanism through the isolation of a silyl-

cobalt dihydride complex, NMR analysis and DFT calculations. We highlighted the importance of a second silane to end the catalytic cycle. Notably, we showed that if the mechanism looks like a σ -bond metathesis, the last step depends on the ligands around the cobalt.

ASSOCIATED CONTENT

The data underlying this study are available in the published article and its Supporting Information.

The Supporting Information is available free of charge on the ACS Publications website. Experimental and computational details, characterization and spectral data, and crystallographic data.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

We warmly thank Denis Lesage (Sorbonne Université) for the HRMS analysis of Int B-1. This work was supported by CNRS, MRES and Sorbonne Université which we gratefully acknowledge.

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