OL | Organic Letters

Letter

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

pubs.acs.org/OrgLett

Synthesis of Medium-Sized Carbocycles by Gallium-Catalyzed Tandem Carbonyl−Olefin Metathesis/Transfer Hydrogenation

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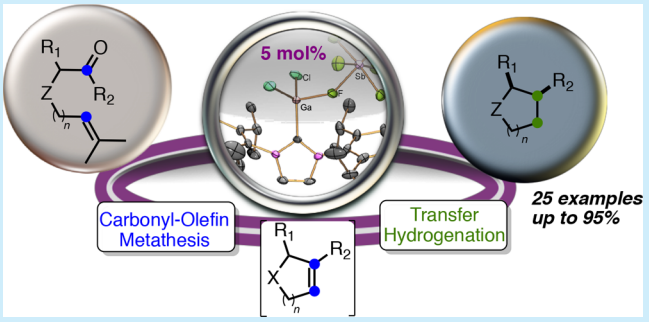
Supporting Information

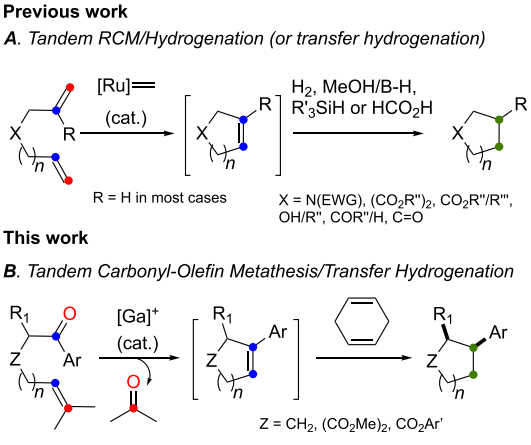
ABSTRACT: The first examples of a catalytic tandem process involving a ring-closing carbonyl-olefin metathesis and a transfer hydrogenation are described. 1,4-Cyclohexadiene has been used as an H_2 surrogate to reduce the cyclic alkenes formed after the metathesis step. The same cationic gallium(III) complex, [IPr·$GaCl_2$][SbF_6], performs the two steps with functional group tolerance. This stereoselective reaction leads to 1,2-*cis*-disubstituted cyclopentanes and various cyclohexanes. DFT computations support an unexpected mechanism involving activation of 1,4-cyclohexadiene by superelectrophilic gallium(III) dimers.



The synthesis of substituted carbocycles from simple substrates is a major objective in organic chemistry. Among the medium-sized ones, 1,2-*cis*-disubstituted cyclopentanes are a target of choice, notably because this particular scaffold can be found in a variety of biologically active compounds.[1] A practical and chemoselective route to large- and medium-sized carbocycles is the tandem ring-closing metathesis (RCM)/hydrogenation (or transfer hydrogenation) of dienes (Scheme 1A).[2] So far, this strategy has always involved ruthenium-based catalysts and H_2,[3] MeOH/borohydride,[4] silanes,[5] or formic acid[6] as reducing agents. Owing to the difficulty of reducing the RCM intermediate when the endocyclic alkene is substituted (R ≠ H), all of the studies directed toward this tandem process have been limited to the synthesis of 1,1-disubstituted cycloalkanes (for instance, X = $(CO_2R)_2$, no other substituents) or to a very few 1,1,3-trisubstituted cycloalkanes (for instance, X = $(CO_2R)_2$ and R = Me). In no report has the stereoselectivity of the reduction step been addressed. Actually, only one paper describes the synthesis of a 1,2-*cis*-disubstituted cyclopentane based on a Ru-catalyzed RCM, but the hydrogenation step was achieved independently by Pd/C-catalyzed hydrogenation.[7]

The carbonyl-olefin metathesis reaction is also an expedient way to generate cyclic alkenes.[8] In contrast with the diene RCM, it is achieved from readily available ene−aryl ketones, or more recently using aliphatic ketones,[9h] using simple Lewis acids (particularly $FeCl_3$ or $GaCl_3$ by Schindler et al),[9] Brønsted acids,[10] tropylium cations,[11] or organic reagents.[12,13] Due to our interest in the development of gallium-catalyzed transformations,[14] and our recent work on the gallium-catalyzed transfer hydrogenation of alkenes using 1,4-cyclohexadiene as hydrogen donor,[15,16] we decided to investigate a tandem process combining a carbonyl-olefin metathesis and a transfer hydrogenation to form cycloalkanes (Scheme 1B). We kept in mind that the judicious installation of substituents (R^1 and Ar) could allow the formation of two contiguous stereocenters and possibly address the issue of the formation of 1,2-*cis*-disubtituted cyclopentanes.

Scheme 1. Tandem Metathesis/Hydrogenation Routes to Cyclic Compounds

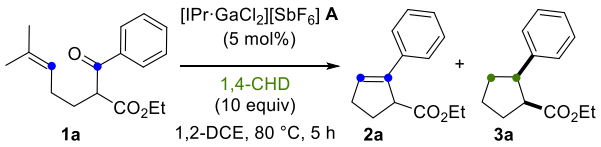


Received: September 13, 2019

DOI: 10.1021/acs.orglett.9b03240
Org. Lett. XXXX, XXX, XXX−XXX

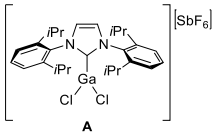
Our catalyst of choice for the development of gallium-catalyzed reactions is the cationic NHC-stabilized gallium dichloride $[IPr{\cdot}GaCl_2]^+[SbF_6]^-$ **A** (IPr = 1,3-bis(2,6-diisopropylphenyl)-imidazol-2-ylidene, see bottom of Table 1 for its

Table 1. Catalyst Screening and Optimization



entry	modifications from the above conditions[a]	1a/2a/3a ratio[b]			yield of 3a[c] (%)
1	none	0	16	84	68[d]
2	1,4-CHD added after 1 h	0	64	36	
3	1 mol % of **A**	0	96	4	
4	40 °C	0	91	9	
5	$GaCl_3$ instead of **A**	7	92	1	
6	$GaCl_3/GaBr_3$ (2.5/2.5 mol %) instead of **A**	0	50	50	
7	$GaCl_3/AgSbF_6$ instead of **A**	0	12	82	27
8	$AlCl_3$ instead of **A**	99	1	0	
9	$B(C_6F_5)_3$ instead of **A**	100	0	0	
10	$FeCl_3$ instead of **A**	68	32	0	
11	$BF_3{\cdot}OEt_2$ instead of **A**	0	10	90	50
12	$[IPr{\cdot}InBr_2][SbF_6]$ instead of **A**	0	67	33	
13	$[Ph_3PAu][SbF_6]$[e] instead of **A**	51	49	0	
14	HOTf instead of **A**	0	100	0	
15	$HNTf_2$ instead **A**	0	34	66[f]	
16	2,4,6-Me_3-1,4-CHD instead of 1,4-CHD	0	96	4	
17	Et_3SiH instead of 1,4-CHD	0	94	6	
18	Hantzsch ester instead of 1,4-CHD	0	100	0	
19	toluene instead of 1,2-DCE	0	96	4	
20	HFIP instead of 1,2-DCE	0	0	100	92

[a]Generated in situ from $IPr{\cdot}GaCl_3$ (5 mol %) and $AgSbF_6$ (7 mol %); 0.1 mmol of **1a**, 0.2 M. [b]Estimated by ^1H NMR, diastereomeric ratio *cis*/*trans* 4/1. [c]Isolated yield. [d]Same yield on a 10 mmol scale. [e]Generated in situ from Ph_3PAuCl (5 mol %) and $AgSbF_6$ (7 mol %). [f]Complex mixture.



A

structure),[17] which can be employed as such or prepared in situ from the air-stable $IPr{\cdot}GaCl_3$ complex[18] and $AgSbF_6$.[19] This protocol is much more practical than the use of $GaCl_3$, which is very sensitive toward moisture and usually less efficient than **A**. After screening several experimental parameters (see Table S1), we found that the reductive cyclization of β-ketoester **1a**, bearing a dimethyl substitution at the olefin terminus, could be efficiently carried out in the presence of a catalytic amount of in situ generated $[IPr{\cdot}GaCl_2][SbF_6]$ **A** (5 mol %) and 1,4-cyclohexadiene (1,4-CHD, 10 equiv) in 1,2-dichloroethane at 80 °C for 5 h (Table 1, entry 1). Ethyl 2-phenylcyclopentane-carboxylate **3a** was obtained in 68% isolated yield with a *cis*/*trans* diastereomeric ratio of 4:1. The relative *cis* configuration was ascertained by NOE experiments and is consistent with the data available in the literature.[20] The presence of the cycloalkene **2a** as side product, and the monitoring of the **2a**/**3a** ratio over time, confirmed its intermediacy toward **3a**. The reaction could be scaled up to 10 mmol without affecting the yield (68% on a 0.1 or 10 mmol scale). No conversion was observed without $AgSbF_6$ to activate $IPr{\cdot}GaCl_3$, nor with $AgSbF_6$ alone (see Table S1). Adding 1,4-CHD after 1 h drastically decreased the proportion of **3a** (entry 2). Lowering the catalytic amount of gallium to 1 mol % (entry 3) or the temperature to 40 °C (entry 4) also clearly disfavored the transfer hydrogenation step. Running the reaction with $GaCl_3$ gave good conversion toward **2a** and very little reduction (entry 5). Using a catalytic amount of an equimolar mixture of $GaCl_3/GaBr_3$ (entry 6) increased the proportion of **3a**, suggesting the formation of a heterobimetallic superelectrophile known to have a higher Lewis acidity than the homobimetallic $(GaCl_3)_2$ superelectrophilic dimer.[9h] The intervention of superelectrophilic species in this chemistry will be further discussed below and in the Supporting Information (IR and DFT studies). When using a catalytic mixture of $GaCl_3$ and $AgSbF_6$, the desired product **3a** was observed as a major component of the mixture, but significant decomposition lowered the isolated yield to 27% (entry 7). Among the other Lewis acids tested (entries 8–13), $BF_3{\cdot}OEt_2$ proved to be the only catalyst offering a reactivity apparently similar to **A**, yet the isolated yield was lower due to substantial degradation (entry 11). Importantly, while $B(C_6F_5)_3$ has been demonstrated to be a good transfer hydrogenation catalyst,[21] it failed at promoting the carbonyl-olefin metathesis step (entry 9).

It is also striking that $FeCl_3$, shown to be an excellent carbonyl-olefin metathesis catalyst[9a−e,h] did not perform well in the presence of 1,4-CHD and failed at promoting the transfer hydrogenation step (entry 10). The softer Lewis acid $[IPr{\cdot}InBr_2][SbF_6]$[22] formed the desired product in only 33% yield (entry 12), while $[Ph_3PAu][SbF_6]$ did not deliver **3a** (entry 13). Regarding the Brønsted acids, although TfOH led to **2a**, it proved ineffective for the transfer hydrogenation step (entry 14). The desired product was observed when the stronger acid Tf_2NH was used, but it was admixed to many other unidentified products (entry 15). With other H_2 surrogates such as 2,4,6-Me_3-1,4-CHD,[21] Et_3SiH, or Hantzsch ester, no hydrogen transfer to the intermediate **2a** was observed (entries 16–18). The transfer hydrogenation step did not proceed in toluene (entry 19), but the tandem process worked very well in hexafluoroisopropanol (HFIP) (entry 20).[23]

The scope of the reaction was then studied. With a *p*-methoxyphenyl group, **3b** was obtained in 53% and 70% yield in 1,2-DCE and HFIP, respectively (Scheme 2).

The electron-withdrawing *p*-fluoro and -chloro substituents were also well-tolerated, giving **3c** and **3d** in up to 81% yield in HFIP. The tricyclic compound **3f** was also isolated in good yield from α-tetralone **1f** in HFIP.[24] In contrast, the desired products were not formed when α-indanone **1e** or α-benzosuberone **1g** was subjected to the reactions conditions. For the latter, only the metathesis product **2g** was isolated in quantitative yield when 1,2-DCE was employed. In HFIP, only the reduction of the alkene function of **1e** and **1g** was observed. According to the work of Schindler,[9a] in the absence of a substituent in the β position of the ketone ($R^2 = CO_2R$ for instance), the carbonyl-olefin metathesis tends to be less efficient. However, under our conditions, **1h** transformed into the *cis*-1,2-diphenylcyclopentane product **3h** in 61% yield with an excellent *cis*/*trans* selectivity in 1,2-DCE (20:1).[25] The

DOI: 10.1021/acs.orglett.9b03240
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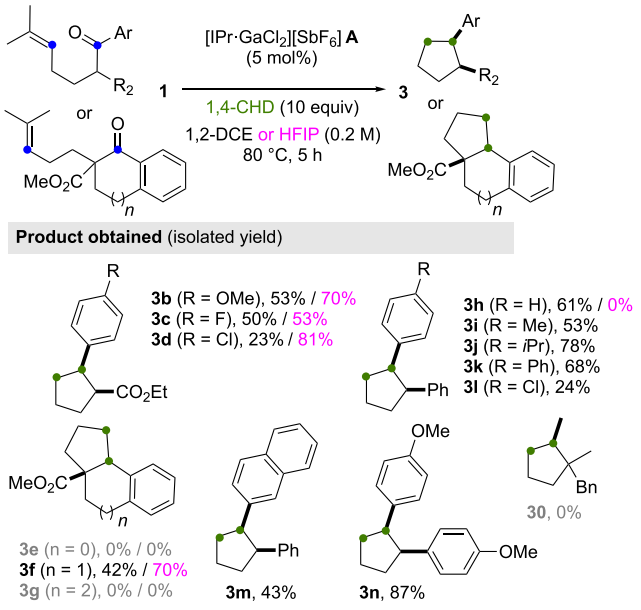
Scheme 2. Substrate Scope: Part 1

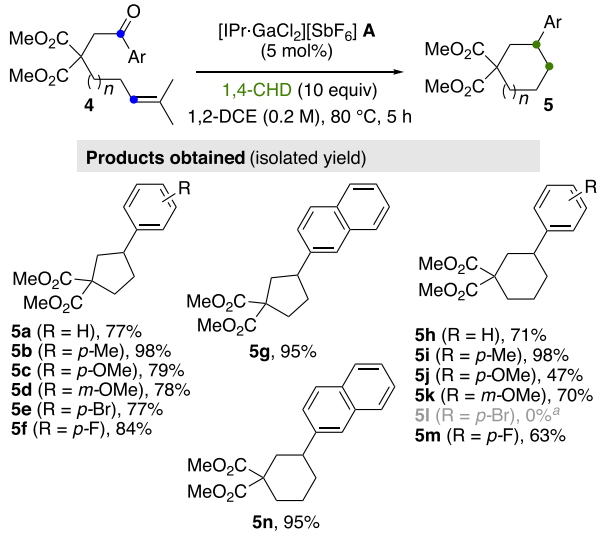


[a] *cis/trans* dr: **3b–d**, 4:1; **3h–n**, > 20:1.

structure of *cis*-**3h** was ascertained by X-ray crystallography analysis.[26] In HFIP, only the reduction of the alkene moiety of the starting material was observed. Other 1,2-diarylpropan-2-ones bearing different substituents at the arene moiety were converted into the corresponding 1,2-*cis*-diarylcyclopentanes (**3i–n**), which were isolated in moderate to good yields. The best yield was actually obtained with two electron-rich *p*-methoxyphenyl groups (**3n**, 87%).

Substrates exhibiting a *gem*-dimethyl ester tether located at the *β*-position of the ketone were also well-tolerated (Scheme 3). Most products (cyclopentanes or cyclohexanes) were obtained in good to excellent yields (up to 98%) with electron-donating or -withdrawing substituents. Surprisingly, enone **4l**, displaying a *p*-bromo substituent, transformed quantitatively into the corresponding metathesis product, which proved

Scheme 3. Substrate Scope: Part 2

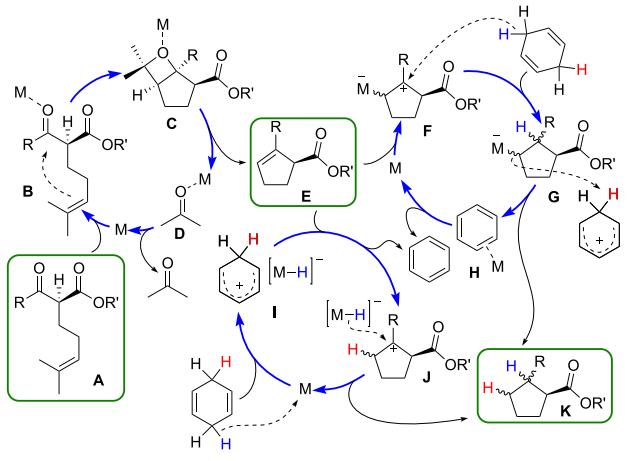


[a] Metathesis product obtained quantitatively.

reluctant to undergo the transfer hydrogenation step. This was yet not an issue with one less carbon in the tether (**4e**) or with a *p*-fluoro substituent (**4m**).

The mechanism of the tandem process can be hypothesized as follows (Scheme 4). With $FeCl_3$ as catalyst, the formation of

Scheme 4. Discarded Mechanistic Hypotheses



the metathesis product **E** from **A** was shown to be a noncationic process through just **B** and the [2 + 2] cycloadduct **C**.[9h] The formation of **C** and its scission were described as concerted. Two catalytic cycles can be envisaged for the reduction of **E** into the final product **K**. According to our previous proposal in the case of gallium catalysis,[15] it could be the result of a hydride transfer from 1,4-CHD to carbocation **F**, followed by protodegallation of **G**. Alternatively, as suggested in the case of boron catalysis,[21d] 1,4-CHD could react with the catalyst to form species **I**. Its cationic part could be used to protonate **E**, and its metal hydride moiety could then react with **J** to give **K**.

To gain a deeper insight into the mechanism of this novel hydrogenative carbonyl-olefin metathesis by a gallium catalyst,[27] we performed DFT calculations at the *ω*B97-XD/6-31G(d) level of theory using **1a** as a model substrate and 1,3-dimethylimidazol-2-ylidene as the model NHC (noted IMD, see the SI for details). However, with $[(IMD)GaCl_2]^+$ as active species, none of the above hypotheses proved energetically favorable.

Instead of $[(IMD)GaCl_2]^+$ as the active species, we then used the homodimer $\{[(IMD)GaCl](\mu\text{-}Cl)[GaCl_2(IMD)]\}^{2+}$.[28] Schindler et al. have recently shown that in the case of the $FeCl_3$-catalyzed carbonyl-olefin metathesis reaction the superelectrophilic homodimer $[Cl_2Fe(\mu\text{-}Cl)FeCl_3]$ was more active than $FeCl_3$.[9h] The mechanism remained concerted in their case, i.e., no carbocationic intermediate involved. With the Ga(III) homodimer, the carbonyl-olefin metathesis became much more favorable indeed, but it was found to involve carbocationic intermediates (Scheme 5). In particular, the presence of a second $[(IMD)GaCl_2]^+$ unit allowed the formation of pentacoordinated gallium species (Figure 1) and the formation of carbocations **D2** and **D4**.

However, even using the gallium(III) homodimer, the two transfer hydrogenation hypotheses presented in Scheme 4 remained unfavorable (see **D6–D9** in the SI). The main issue with one or two gallium atoms is the high free energy of activation associated with the protonolysis of the strong Csp^3–

DOI: 10.1021/acs.orglett.9b03240
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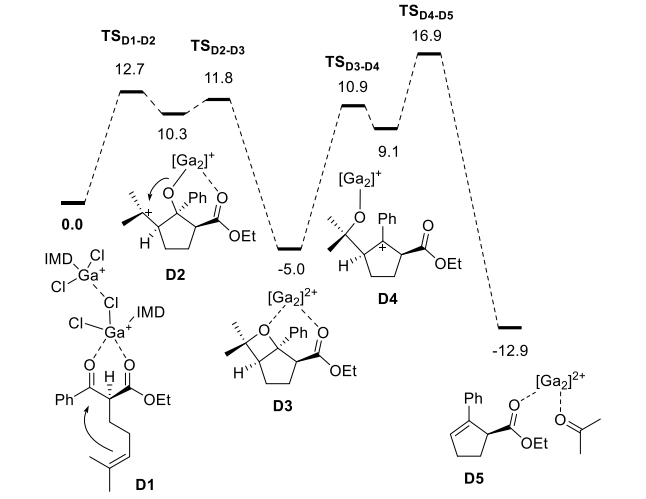
Scheme 5. Free Energies Profile of the $\{[(IMD)GaCl_2]_2\}_2^{+}$-Catalyzed Carbonyl-Olefin Metathesis (ΔG, kcal/mol)



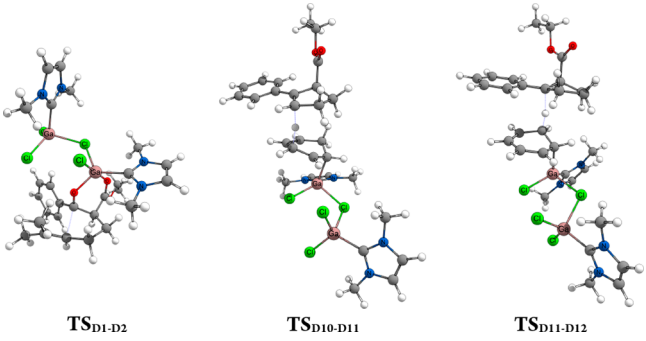
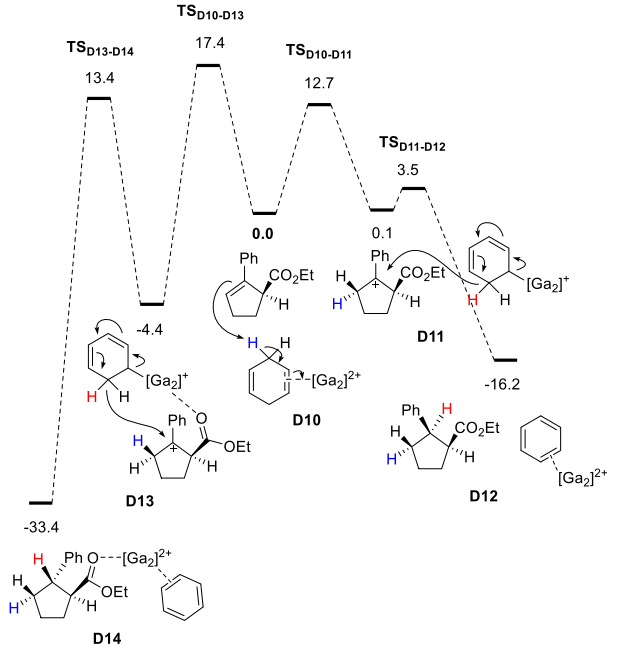


Figure 1. Geometries of selected transition states.

Ga bond in **G** displayed in Scheme 4 or the unfavorable formation of the gallium hydride **I**. We thus visited a new mechanistic hypothesis that involves the activation of cyclohexadiene by coordination (Scheme 6). The pathway leading to the *cis* product **D12** from **D10** starts with a thermoneutral step giving **D11**, which contains a σ-dienyl gallium complex. It easily transfers a hydride to the carbocationic counterpart through $\mathbf{TS_{D11\text{-}D12}}$. The formation of the *trans* product **D14** is thermodynamically more favorable but involves highest lying transition states since it takes place on the more bulky side of the carbonyl-olefin metathesis product. This mechanism, which does not involve any proto-degallation, rationalizes the *cis* selectivity observed and also explains why the more sterically congested 2,4,6-Me_3-CHD was not efficient, as it would be more difficult to activate by the gallium(III) homodimer (Table 1, entry 16).

In summary, we have devised an efficient gallium-catalyzed tandem carbonyl-olefin metathesis/transfer hydrogenation protocol. It represents a main group metal catalyzed version of the Ru-catalyzed diene RCM/transfer hydrogenation. It allows the synthesis of medium-sized carbocycles, notably 1,2-*cis*-disubstituted cyclopentanes. Computations support the role of gallium(III) homodimers in the two steps and reveal an unexpected activation of 1,4-cyclohexadiene.

Scheme 6. Free Energies Profile of the $\{[(IMD)GaCl_2]_2\}_2^{+}$-Catalyzed Transfer Hydrogenation (ΔG, kcal/mol)



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03240.

Experimental procedures and characterization data (PDF)

^{1}H and ^{13}C NMR spectra (PDF)

Coordinates and energy of the computed species (XYZ)

Accession Codes

CCDC 1920340 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

An early preprint of this work appeared on ChemRxiv.[29]

■ ACKNOWLEDGMENTS

We are grateful to the China Scholarship Council (CSC), CNRS, MESRI, Université Paris-Sud, ANR ANR-18-CE07-0033-01 (HICAT), and Ecole Polytechnique for their support of this work.

DOI: 10.1021/acs.orglett.9b03240
Org. Lett. XXXX, XXX, XXX−XXX

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