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Indium Mediated Reformatsky-Type Allylation of N-*tert*-Butanesulfinyl Iminoester with 1,3-Butadiene

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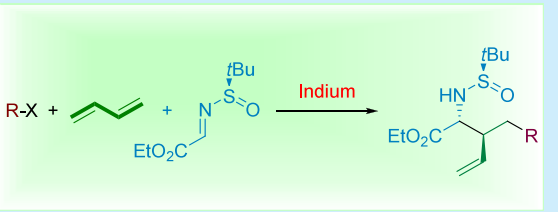
ABSTRACT: This study presents the indium-mediated three-component radical Reformatsky-type allylation of *N-tert*-butanesulfinyl iminoester with 1,3-butadiene. This novel approach offers a rapid synthesis pathway to valuable homoallylic noncanonical amino acids, demonstrated with over 30 examples showing nice regio- and diastereoselectivity. Mechanism studies revealed that allylindium complexes served as key intermediates, formed through a single-electron reduction of allylic radicals by Indium species.



The commercial availability of peptides, estimated at US $25.4 billion in 2018, has sparked growing interest in pharmaceutical research and development focusing on peptides and modified peptides.[1] Standard proteinogenic amino acids have historically been crucial in peptide drug discovery. Nonetheless, there has been a burgeoning interest in noncanonical amino acids (ncAAs) due to research shedding light on their significance as precursors to pharmaceuticals, biological probes, natural products, and various other applications.[2] Particularly, the biological activity of α-amino acids with an allyl side chain has garnered significant attention in the scientific community. Homoallylic α-amino acids, such as Allylglycine, Crotylglycine, and Methallylglycine, have been identified as biologically active compounds.[3] Moreover, these motifs are also commonly found in bioactive molecules, including Eponemycin and Renin inhibitor (Figure 1a).[2,4] In addition, the double bond of the allylic moiety can participate in various synthetically valuable transformations to other α-amino acids.[5] Therefore, the development of economically efficient synthesis routes for homoallylic α-amino acids has attracted widespread attention.

Various effective methods for accessing noncanonical homoallylic α-amino acids have been developed.[5,6] An important approach is the allylic addition to N-sulfinyl-α-iminoester, which was first reported by Davis.[7] In this process, the diastereoselectivity is influenced by the chiral auxiliary group attached to the nitrogen atom. Subsequently, *N*-sulfinyl-α-iminoesters, serving as electrophiles precursors, have found widespread application in the synthesis of complex molecules.[8] However, prefunctionalized allyl reagents, such as allyl-aluminum, allyl-zinc, allyl-tin, allyl-silicon, and allyl-boron, are necessarily involved (Figure 1b).[9]

Alternatively, 1,3-butadiene, a cost-effective feedstock derived from petroleum cracking, offers economically and environmentally attractive raw materials as allyl precursors for the production of high-value fine chemicals. Many research groups have made significant progress in this area.[10]

Specifically, the recent advances in radical generation of allyl-metal from butadiene for carbonyl allylation demonstrate a high level of atom efficiency and have the potential to serve as a general platform for constructing complex homoallylic alcohol motifs.[11] Additionally, butadiene has been utilized for the generation of linear homoallylamine via the 1,4-functionalization pathway by Gong[12] and our group[13] respectively. However, as far as our knowledge extends, the stereoselective allylation of imines with 1,3-butadiene through the 1,2-functionalization pathway has not yet been achieved.

Building upon prior advancements in the field, we aim to investigate the feasibility of a stereoselective three-component radical allylation of *N-tert*-butanesulfinyl iminoester with butadiene for the asymmetric synthesis of homoallylic amino acids. Indium's pronounced redox properties (First ionization potential: 5.8 eV, lower than zinc or tin and close to that of alkali metals such as sodium) render it particularly appealing for its role in single-electron transfer processes.[14] In this context, we propose that the single-electron-transfer (SET) reduction of alkyl halides by indium would generate an alkyl radical, which would subsequently add to butadiene. This reaction yields a highly reactive allyl radical that is anticipated to react with indium, forming a nucleophilic allyl-indium species. This intermediate could then participate in successive coupling reactions with *N-tert*-butanesulfinyl iminoester (Figure 1c). Existing literature has reported that alkyl radicals

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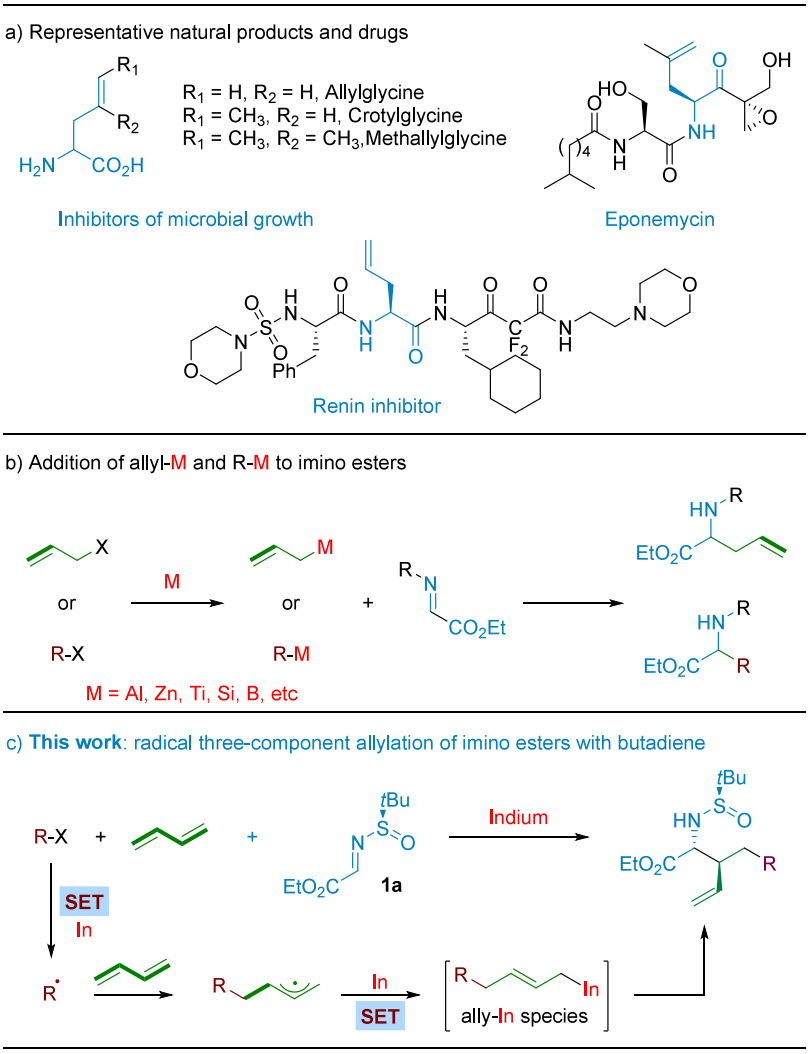
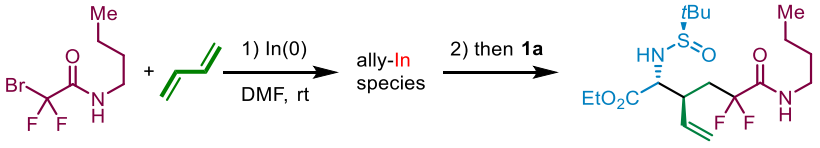


Figure 1. (a) Drug molecules with homoallylic α-amino acid building blocks; (b) Addition of allyl-M and R-M to iminoester; (c) Radical three-component allylation of iminoester with butadiene.

Table 1. Reaction Optimization[a,b,c]



2a **3a**

entry	variation from standard conditions	yields (%)	d.r.
1	none	91	>20:1
2	**2a** (1 equiv)	18	>20:1
3	**2a** (3 equiv)	61	>20:1
4	In (1 equiv)	38	>20:1
5	$InCl_3$ instead of In(0)	0	
6	InCl instead of In(0)	56	>20:1
7	Zn instead of In(0)	0	
8	Mg instead of In(0)	0	
9	−10 °C	0	
10	No In	0	
11	Gram-scale, **3a** 1.82 g	83	>20:1

[a]Reactions were performed on a 0.5 mmol scale of **1a** (1 equiv of DMF 0.05 M), **2a** (5 equiv), In (3 equiv), butadiene (gas), 1 h. [b]Isolated yields. [c]Diastereomeric ratios were determined by ^{1}H NMR and ^{19}F NMR.

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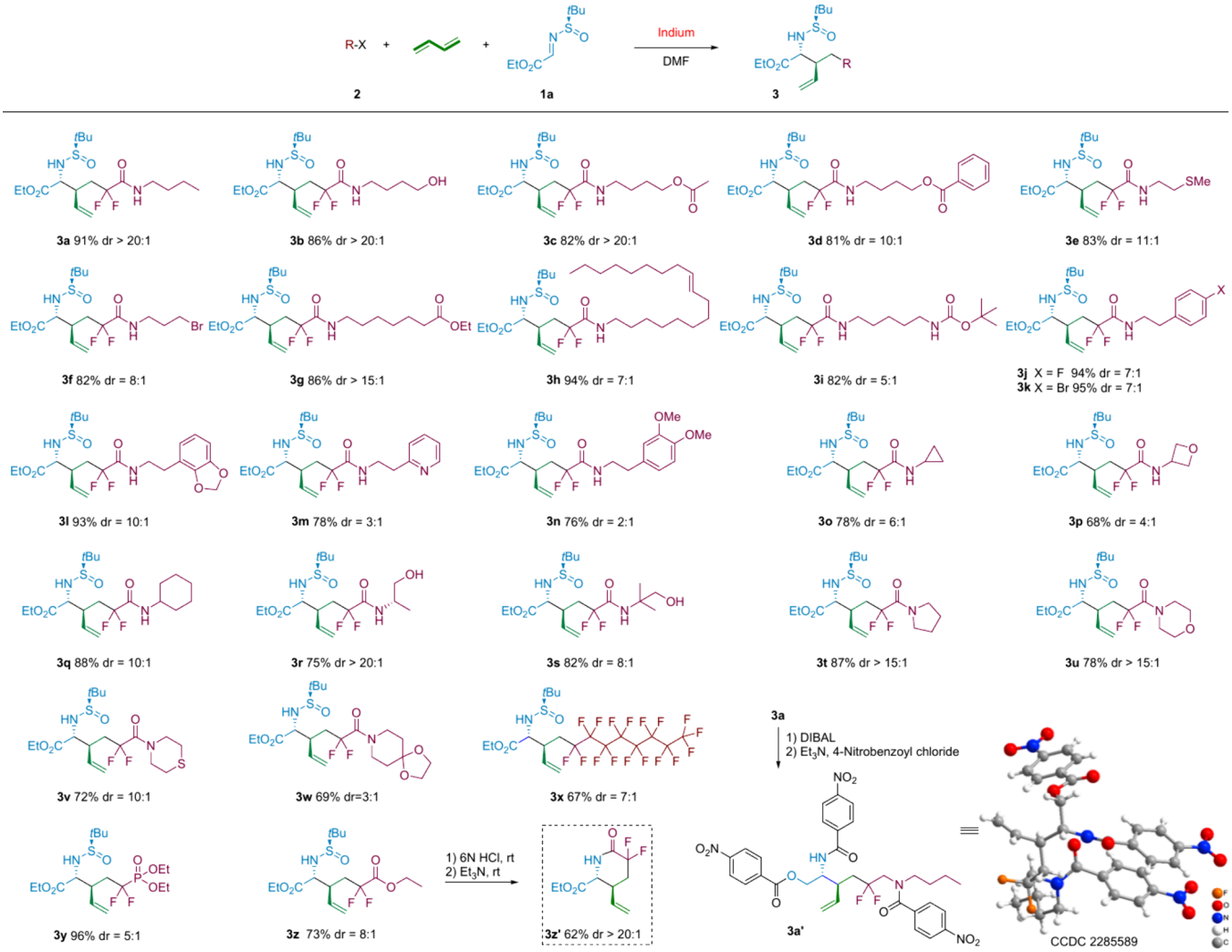
Scheme 1. Scope of Allylation Reactions[a,b,c]



[a]Reactions were performed on a 0.5 mmol scale of **1a** (1 equiv of DMF 0.05 M), **2** (5 equiv), In (3 equiv), 1,3-butadiene, 1 h. [b]Isolated yield. [c]Diastereomeric ratios were determined by ^{1}H NMR and ^{19}F NMR spectroscopy.

can directly add to imine esters;[14,15] however, this reaction requires that the alkyl radicals react rapidly with butadiene. Additionally, indium must selectively react with allyl radicals instead of alkyl radicals. Finally, metallic indium can serve as both a two-electron-reducing agent and a one-electron-reducing agent; therefore, how to control this process is of utmost importance.

With the aforementioned challenges in mind, we started the study by examining 1,3-butadiene, iminoester **1a**, and difluorobromoacetamides **2a** as radical precursors. Given the significant influence of the solvent on the reduction process of indium, we conducted initial screening of solvents including tetrahydrofuran, acetonitrile, toluene, brine solutions, etc. The results indicated that none of these conditions yielded any **3a** product. Intriguingly, desired product **3a** was observed when dimethylformamide (DMF) was employed as the solvent, probably due to solvent effect that the coordination of DMF with metal indium ions results in the formation of a more stable complex, which reduces the concentration of free In^{3+} ions, and consequently raises the reduction potential of the In^{3+}/In couple.[16] Subsequently, through a systematic variation of various reaction parameters, we successfully identified the optimal reaction conditions. Specifically, a mixture of In(0) powder (3 equiv), 1,3-butadiene and **2a** (5 equiv) in DMF was reacted at room temperature for 30 min. Subsequently, **1a** was added to the reaction mixture and allowed to react for an additional 30 min, resulting in the formation of the desired product **3a** with an excellent yield of 91% and notable diastereoselectivity (d.r. > 20:1, Table 1, entry 1). The yield of **3a** was lower when the stoichiometric ratio of **2a** or indium powder was reduced (Table 1, entries 2−4). When $InCl_3$ was used instead of In, the reaction afforded no product (Table 1, entry 5). In contrast, when InCl was used instead of In(0) powder, the reaction resulted in a lower yield of 56% (Table 1, entry 6). Other metals, such as zinc and magnesium instead of In, were tested and produced no product (Table 1, entries 7−8). The reaction is highly sensitive to temperature. When the reaction was conducted at a lower temperature of −10 °C (Table 1, entry 9), no product was obtained. Notably, the allylation did not proceed without In powder (Table 1, entry 10). The preparation of **3a** was performed on a gram-scale and a pleasing yield of 83% (1.82 g) was obtained, demonstrating the scalability of the reaction (Table 1, entry 11). It should be noted that the reaction procedure is carried out in two steps.

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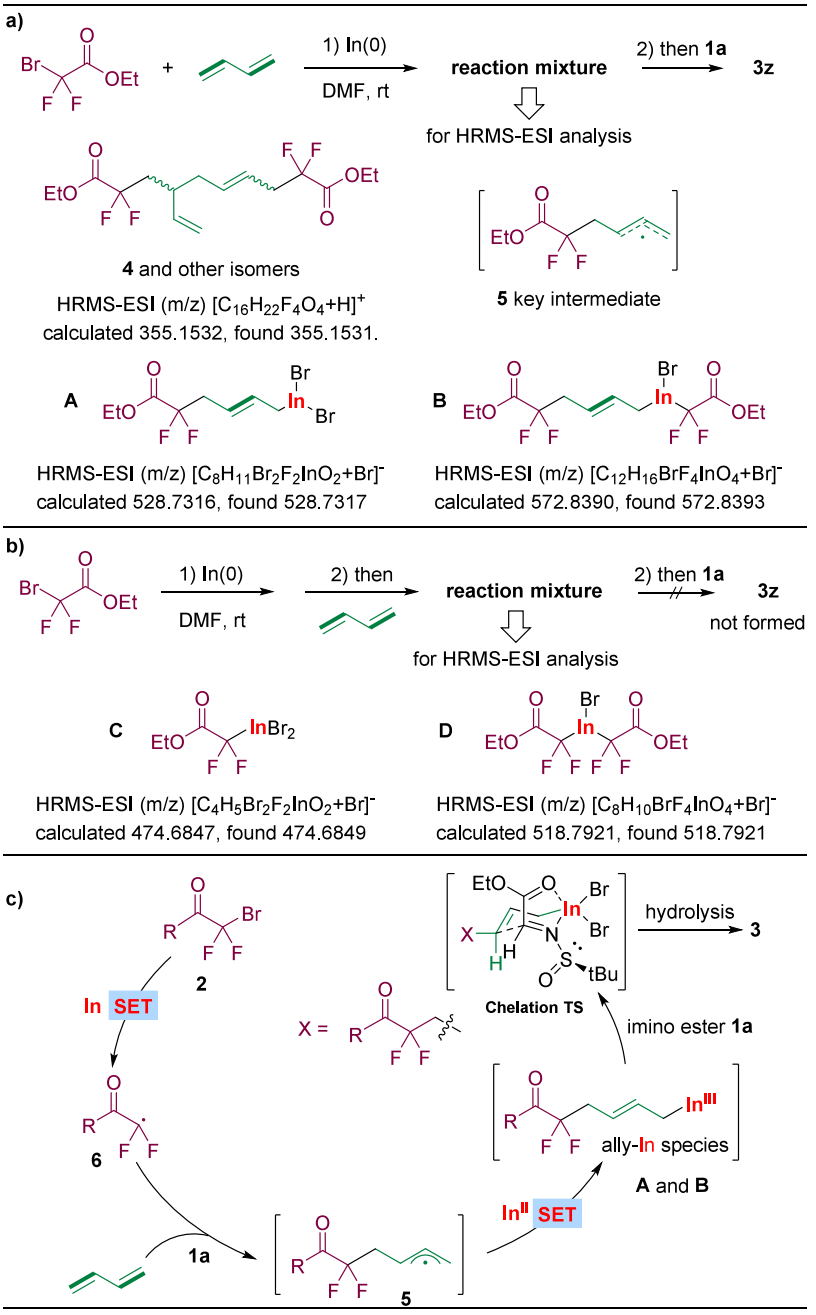
Scheme 2. Mechanism Studies and the Intermediates in the Reaction Mixture



The first step involves the synthesis of the allylindium species, after which iminoester **1a** is added. If the substrates are mixed and added to the reaction all at once, the reaction system will not yield any products.

Following the determination of the ideal conditions, we explored the scope of the three-component reaction (Scheme 1). The reaction exhibited excellent performance with diverse difluorobromide compounds, resulting in the synthesis of ncAAs with nice yields, regioselectivity, and diastereoselectivity. It has been observed that the diastereoselectivity can be affected by the flexibility and steric hindrance of amide substrates. Basically, both primary and secondary amides can provide satisfactory diastereoselectivity (**3a**-**3c**, and **3t**-**3v**). Remarkably, an amide substrate with a long linear chain containing 18 carbon atoms still exhibits excellent diastereoselectivity (**3h**). The reaction can accommodate a variety of functional groups at the end of the carbon chain, such as ester (**3c** and **3d**), free hydroxyl (**3b**), thioether (**3e**), bromine atom (**3f**), and olefins (**3h**). However, if a phenyl group is present at the end of the carbon chain, then the diastereoselectivity may be slightly reduced (**3i**−**3k**, **3n**). In particular, when a pyridine ring is located at the end of the carbon chain, it significantly impacts the diastereoselectivity (**3m**). The reactions proceeded with amides containing rigid cyclopropyl and oxetan, resulting in the formation of products **3o** and **3p** with diastereoselectivity of 6:1 and 4:1, respectively.

Interestingly, when the amide substrate contains a larger and more flexible cyclohexane moiety, the diastereoselectivity of product **3q** is slightly enhanced, reaching up to 10:1. Amides containing heterocycles including pyrrolidine (**3t**), morpholine

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(**3u**), and thiomorpholine (**3v**), served as effective flexible substrates for stereoselective allylation, resulting in the desired products in good yield and nice diastereoselectivity. Amino acids containing fluorinated carbon chains can also be rapidly synthesized with high stereoselectivity through this approach (**3x**). In addition, phosphates can also be successfully introduced into the corresponding amino acids (**3y**). Compound **3a** underwent DIBAL-H reduction, leading to the formation of an amino alcohol intermediate, which was subsequently reacted with nitrobenzoyl chloride. The X-ray structure of the resultingproduct **3a′** was provided to confirm its stereochemistry. Interestingly, amino acid **3z** could be smoothly transformed to optically active δ-lactam **3z′** in two steps smoothly.

It is essential to elucidate the reaction pathway and clarify the nature of the allylindium species. The experimental procedure consists of two main steps: first, the generation of allylindium species followed by their addition to imino ester. With this in mind, several experiments were conducted to further understand the single electron transfer (SET) process mediated by indium and the allylindium species. Initially, reactions were conducted with bromodifluoroacetate, butadiene, and indium but without imino esters. The resulting mixture was directly analyzed using mass spectrometry (MS) as depicted in Scheme 2a. Electrospray ionization mass spectrometry (ESI-MS) revealed the formation of allyl-indium species **A** and **B**, along with the detection of dimers **4**. This result suggests that allyl radical **5** may be a key intermediate in the reaction. Contrastingly, when bromodifluoroacetate was premixed with indium before the introduction of butadiene, mass spectrometry analysis revealed the absence of species **A** and **B**, but with the detection of species **C** and **D** instead (Scheme 2b). This observation indicates that species **C** and **D** do not undergo a reaction with butadiene to form species **A** and **B**. As a result, no products **3z** were observed upon the addition of **1a** to the reaction system. The experimental results above suggest that indium can rapidly react with the allyl radical to generate a nucleophilic allyl-indium species.

Based on these results, a reaction pathway is proposed, as shown in Scheme 2c. The In(0) species ($E^{red}_{In(III)/In(0)}$ = −1.18 V vs SCE)[17] initiates the formation of alkyl radicals **6** with difluorobromide derivatives ($E^{red}_{1/2} \approx$ −0.82 V vs SCE)[18] through a single-electron transfer process. The resulting alkyl radicals can quickly be added to 1,3-butadiene to generate fluorinated allyl radical species **5**. Meanwhile, a portion of the alkyl radicals is trapped by In to form the inactive species **C** and **D**.

Transient allyl radicals are also trapped by indium to generate nucleophilic allyl-indium intermediates **A** and **B**, which subsequently couple with iminoester through a well-known chelation controlled TS model.[14,19,20] In this model, the ethyl ester group occupies the axial position where the carbonyl moiety may coordinate with In, thereby forming a five-membered ring. Upon hydrolysis, the antiselective homoallylic amino acids are produced.

In summary, we have developed a novel and efficient method for synthesizing allyl-indium complexes using a radical strategy. The efficacy of this synthetic approach was demonstrated through a three-component allylation of an iminoester with feedstock butadiene. This environmentally friendly and operationally straightforward methodology facilitates the synthesis of a diverse range of novel and valuable noncanonical amino acids, showcasing nice regio- and diastereoselectivity. Mechanistic studies reveal that the allyl radical can be selectively captured by indium via a single-electron-transfer (SET) process, with the resulting allyl-indium complexes acting as crucial intermediates in the reaction.

■ ASSOCIATED CONTENT

Data Availability Statement

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

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.4c04086.

Experimental details, characterization data of compounds, Crystallographic Information, DFT Calculations, NMR spectra. (PDF)

Accession Codes

Deposition Number 2285589 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via the joint Cambridge Crystallographic Data Centre (CCDC) and Fachinformationszentrum Karlsruhe Access Structures service.

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Notes

The authors declare no competing financial interest.

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