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Manganese(I)-Catalyzed H−P Bond Activation via Metal−Ligand Cooperation

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ABSTRACT: Here we report that chiral Mn(I) complexes are capable of H−P bond activation. This activation mode enables a general method for the hydrophosphination of internal and terminal α,β-unsaturated nitriles. Metal−ligand cooperation, a strategy previously not considered for catalytic H−P bond activation, is at the base of the mechanistic action of the Mn(I)-based catalyst. Our computational studies support a stepwise mechanism for the hydrophosphination and provide insight into the origin of the enantioselectivity.

Homogeneous catalysis is a powerful methodology in organic chemistry that supports countless reactions and applications.[1] It owes this privileged position largely to the power of a subset of catalysts that contain both noble transition metals and (chiral) phosphine ligands (Figure 1a).[2] Unfortunately, noble metals are scarce and often toxic and since general methods for catalytic synthesis of chiral phosphine ligands are lacking, their synthesis is often expensive. Developing competitive catalysts that contain earth-abundant transition metals instead, such as iron or manganese, is attractive[3] both for the chemical/pharmaceutical industry because of the economic advantages and much reduced toxicity,[4] as well as for academia as this represents largely uncharted territory. The quest for sustainable homogeneous catalysis is 2-fold: replacing noble metals with both cheap and readily available metals as well as finding cost-efficient ways to access chiral ligands. The past decade has witnessed significant progress in this regard, for example, for (de)hydrogenation reactions, arguably the most important class of chemical transformations that rely on noble metal catalysts.[5] In 2016, the first examples of hydrogenation using manganese(I) catalysts were reported by the groups of Milstein and Beller and extended to catalytic asymmetric reactions a year later with the initial reports from the groups of Clarke and Beller (Figure 1a).[6] These new catalysts still require the same type of chiral phosphine ligands and the lack of efficient catalytic methods for their synthesis still persists.

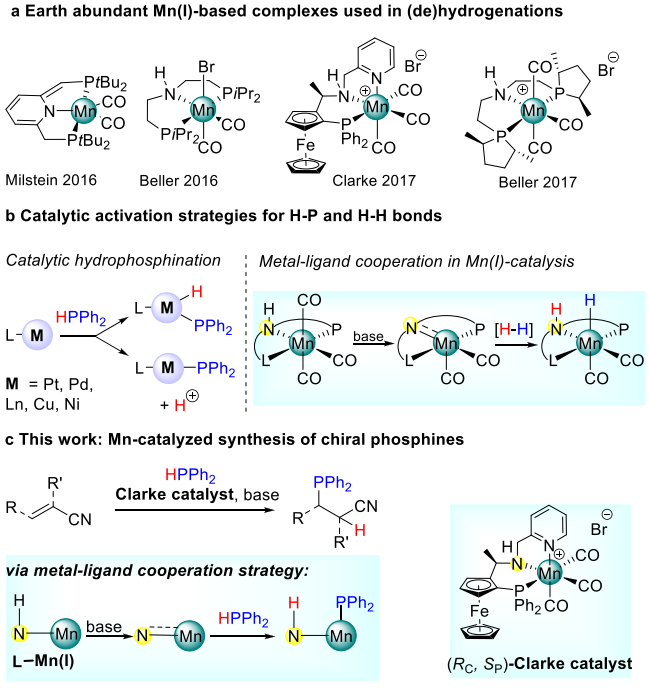

Figure 1. State of the art and this work.

Catalytic asymmetric hydrophosphination is a highly attractive path for generating optically active chiral phosphines.[7] Inspired by the recent successes of chiral Mn(I) complexes in reductive transformations via H−X bond activation,[5a] we decided to explore whether Mn(I) catalysts could play a role in the enantioselective, catalytic formation of chiral phosphines via H−P bond activation. As with other chemical transformations, catalytic asymmetric hydrophosphination relies heavily on noble metal catalysis,[7a−d] although excellent examples using Ni-[7e−g] and Cu-catalysis[7h] have also been reported.

The mechanisms invoked in metal-catalyzed asymmetric hydrophosphinations follow the classical transition metal catalysis concept where the ligand bound to the metal acts

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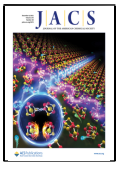

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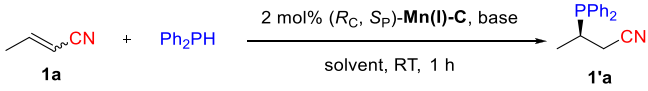
as a spectator, and all crucial catalytic steps, including changes in metal oxidation state, occur at the metal center (Figure 1b).[7b] However, in an alternative mechanistic path exploited in homogeneous catalysis, the so-called metal−ligand cooperation (MLC), the ligand participates in bond activation in cooperation with the metal, leading to chemical modifications of both.[7b] Application of H−P bond activation via MLC is unprecedented in catalysis,[8] although the ability to split the H−P through the cooperation between carbene ligand and Ru- (and Ir-) complexes has been demonstrated by Gessner and co-workers.[9]

We envisioned that the mechanism responsible for the heterolytic cleavage of H−H (H−X) bonds by Mn(I)-catalysts could also be effective to cleave H−P bonds with earth-abundant metals and trigger catalytic hydrophosphinations (Figure 1c). Our main focus was on α,β-unsaturated nitriles because chiral phosphine products derived from nitriles provide an unique opportunity for quick access (in 2−3 synthesis steps) to structural motifs resembling known chiral ligands. The feasibility of catalytic asymmetric hydrophosphination was already demonstrated 20 years ago for acrylonitrile by Glueck and co-workers.[7a,10] Interestingly, while general methodologies for various substrate classes have been developed afterward, the application of this approach to nitriles is limited to a report from Togni's group, who demonstrated excellent enantioselectivity with methacrylonitrile.[7e,f,11]

Crotonitrile (**1a**) was selected for our initial studies in Mn(I)-promoted hydrophosphination. Typical conditions for Mn(I)-catalyzed reductive transformations of carbonyl compounds include elevated temperatures and superstoichiometric amounts of a base with respect to the Mn(I) complex to activate the catalyst. However, an excess of base and elevated temperatures are not desirable, as these conditions are known to be favorable for competing nonenantioselective, base-catalyzed, or heat triggered hydrophosphination, leading to racemic phosphines. The blank reaction between **1a** and diphenylphosphine in toluene without a base or a catalyst did not proceed at room temperature, but adding 10 mol % of a base (*t*BuOK) gave 22% conversion toward the phosphine product **1′a** within 1 h (Table 1, entries 1 and 2). To study the asymmetric reaction using chiral Mn(I)-complexes, we chose the (R_C,S_P)-Clarke catalyst (**Mn(I)-C**), known for its excellent performance in asymmetric hydrogenation reactions and whose chiral ligand is relatively easy to synthesize.[6c,g,h] Right off the bat, we observed that in the presence of 2 mol % (R_C,S_P)-**Mn(I)-C** and 4 mol % *t*BuOK in toluene, diphenylphosphine addition product **1′a** was obtained with 96% conversion after 1 h and, even more importantly, with an enantiomeric ratio (er) of 90:10 (entry 3). Further experiments were carried out to optimize the reaction conditions, evaluating the solvent, type of base, catalyst and base loadings, and the temperature.[12] We found that nearly full conversion toward enantioenriched product **1′a** with high er was obtained in toluene, diethyl ether, and isopropanol (entries 3, 5 and 6).

Similarly, the reaction accommodates several bases, providing the best results with *t*BuOK and *t*PentOK (entries 3, 7−10). Loading of 1.5−2 equiv of *t*PentOK with regard to (R_C,S_P)-**Mn(I)-C** gives optimal performance. A higher amount results in lower enantioselectivity due to the competing base catalyzed reaction (entry 11). However, only traces of product were obtained with less than 1.5 equiv of base, most likely due to the Mn(I)-catalyst not being activated (entry 12). On the basis of these studies, we selected toluene, 2 mol % (R_C,S_P)-**Mn(I)-C**, 4 mol % *t*PentOK, and room temperature as the optimal reaction conditions (entry 10).

Table 1. Optimization and Control Studies[a]



1a 1′a

entry	base [mol %][b]	solvent	conv. [%][c]	er[d]
1[e]	none	toluene	0	
2[e]	*t*BuOK [10]	toluene	22	
3	*t*BuOK [4]	toluene	96	90:10
4	*t*BuOK [4]	CH_2Cl_2	0	-
5	*t*BuOK [4]	Et_2O	99	91.5:8.5
6	*t*BuOK [4]	*i*PrOH	96	90:10
7	K_2CO_3 [10]	toluene	0	
8	LDA [10]	toluene	56	88.5:11.5
9	NaH (25)	toluene	99	89:11
10	*t*PentOK [4]	toluene	99	91.5:8.5
11	*t*PentOK [10]	toluene	99	50:50
12	*t*PentOK [2]	toluene	<5	n.d.

[a]Reaction conditions: 0.1 mmol scale, 2 mol % (R_C, S_P)-**Mn(I)-C**, 0.1 M solution of **1a** (2/1 mixture of *Z*/*E*), Ph_2PH (1.0 equiv). [b]*t*BuOK was used as a solid; *t*PentOK was used as 1.7 M solution in toluene. [c]Determined by NMR of reaction crude. [d]Determined by chiral HPLC. [e]No **Mn(I)-C** was used in this case.

Next, we embarked on evaluating the scope in alkenes (Scheme 1). α,β-Unsaturated nitriles bearing an aliphatic substituent in the β-position (**1a−1c**) were found to provide full conversion to the desired products (**1′a−1′c**) with er values in the range of 90:10−92.5:7.5 (Scheme 1). Variation of the substituents at the β-position of α,β-unsaturated aromatic nitriles revealed that both aryl groups with electron-donating and -withdrawing functionalities are compatible with this catalytic system and afford the corresponding products (**1′d−1′m**) with excellent yields and er values. Hydrophosphination of nitriles with heteroaromatic substituents at the β-position provided corresponding chiral phosphine products **1′n−1′p** with excellent outcome, thus opening up a convenient path to valuable precursors for new tridentate chiral ligands.

The β-substituted nitriles discussed so far generate a carbon stereocenter upon forming a bond with a phosphorus atom. In contrast, when using α-substituted terminal alkene, the carbon stereocenter is formed upon C−H bond formation (formal stereospecific protonation) similar to the example reported by Togni and co-workers for methacrylonitrile.[7e,f] Addressing such stereochemical nuances often requires different catalytic systems; however, we found that the same (R_C,S_P)-**Mn(I)-C** Clarke catalyst provides high asymmetric inductions for products derived from vinyl nitriles as well (**2′a−2′c**).

In view of potential future applications of this methodology in chiral phosphine ligand synthesis, we validated the robustness of the methodology for larger scale synthesis. The preparative scale (1−1.5 mmol) reaction furnished products **1′d** and **2′c** with the same isolated yields and er values as those obtained in small-scale reactions. To showcase the potential of our novel catalytic protocol for ligand synthesis we transformed chiral phosphine product **2′c** into various PN- and PNN-type novel chiral ligands (**L1−L4**). Chiral **Mn(I)-L4** complex prepared from **L4** was found to be an efficient catalyst for both enantioselective hydrophosphination and transfer hydrogenation reactions (Scheme 2).

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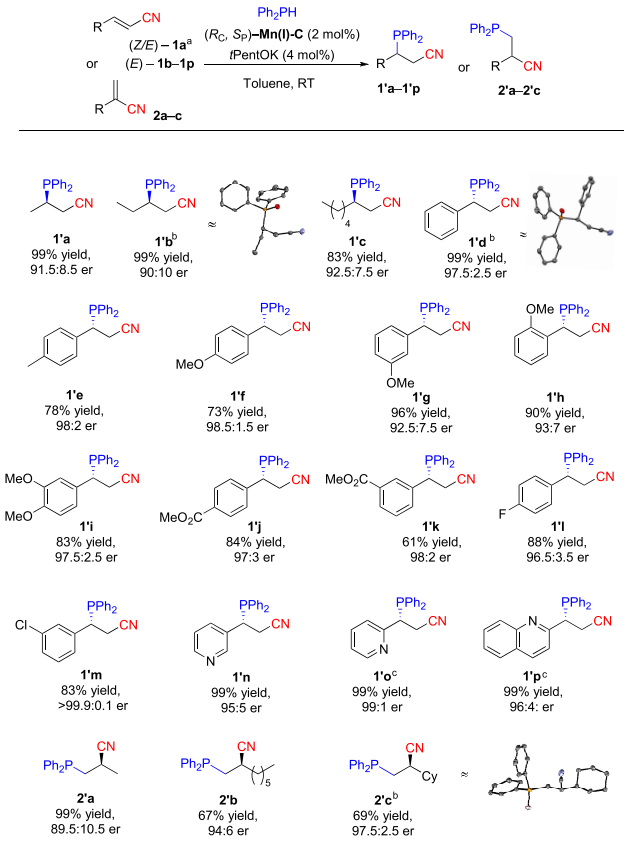
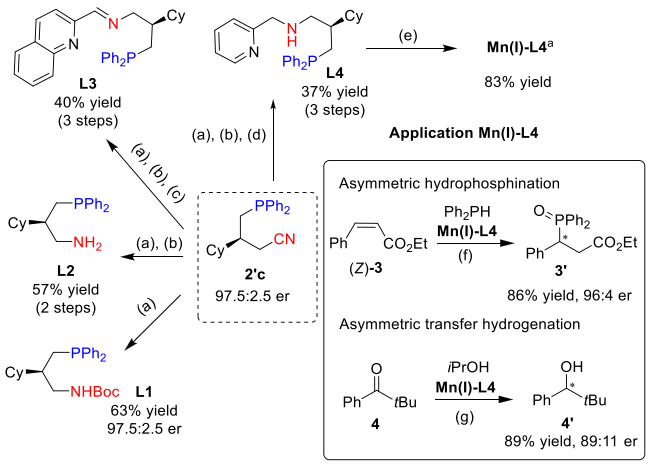
Scheme 1. Scope of α,β-Unsaturated Nitriles



[a]**1a** was used as a 2/1 mixture of *Z*/*E* stereoisomers. [b]Oxidized or borane protected compound was used for X-ray crystallography. [c]Reaction carried out at 0 °C.

Scheme 2. Synthesis Applications[a]



[a]Synthesis of PN, PNN ligands, a novel Mn(I) catalyst, and its application in asymmetric catalysis. Reaction conditions: (a) $NiCl_2$, $(Boc)_2O$, $NaBH_4$, MeOH, RT. (b) TFA, CH_2Cl_2, RT. (c) Quinoline-2-carboxaldehyde, Na_2SO_4, RT. (d) Picolinaldehyde, $NaBH_4$, MeOH, RT to 40 °C. (e) $Mn(CO)_5Br$, toluene, 110 °C. (f) **Mn(I)-L4**, *t*PentOK, toluene, 0 °C, quenched with H_2O_2. (g) **Mn(I)-L4**, *t*PentOK, *i*PrOH, RT.

The ability of the Mn(I) complex to catalyze hydrophosphinations of α,β-unsaturated nitriles is mechanistically intriguing. In Mn(I)-catalyzed (de)hydrogenations MLC has been proposed to play an important role in the catalytic cycle.[13] To glean insight into the underlying mechanism of our system, we conducted computational studies, focusing on nitrile substrate (*E*)-**1d**. Our computational data indicate that the base deprotonates the Mn(I) complex twice: first the amino group on catalyst (**I**), forming **II**, and subsequently the benzylic position adjacent to the pyridine moiety of the ligand with concomitant dearomatization of the pyridine ring, resulting in **III** (Figure 2a,b). This double deprotonation explains why the optimal ratio of base versus **Mn(I)-C** was found to lie between 1.5:1 and 2:1 in our optimization studies.

Species **III** then evolves to **IV** via the release of a CO molecule. The resulting coordination vacancy can be occupied either by the nitrile or the Ph_2PH, with the latter found to be the thermodynamically and kinetically preferred path. This interaction involves reprotonation of the ligand followed by coordination of the resulting phosphide and subsequent protonation of the amide moiety by another Ph_2PH molecule, rendering **VI**. Species **VI** can also be formed with only 1 equiv of the base, but this path involves a higher energy barrier resulting in lower conversion (Figure S6), as confirmed experimentally (Table 1, entry 12). The formation of species **II**–**VI** was followed by ^{31}P NMR spectroscopy (Figure S13).[12] Once **VI** is formed, the reaction with the nitrile can take place, promoting the catalyzed enantioselective hydrophosphination. According to the computational data the first step in this catalytic reaction entails the nucleophilic addition of the phosphide moiety of **VI** to the C-4 position of the alkene, resulting in **VII** and fixing the stereochemistry ((*R*)-configured product) (Figure 2c). Species **VII** spontaneously evolves toward **VIII** via a barrierless protonation of the C-3 position of the nitrile by the *N*–*H* moiety from the same face. This is consistent with the experimental observation that both P and H atoms are added from the same face of the alkene (formal *syn*-addition, Figures S16 and S17).[12] Species **VIII** releases the phosphine product, resulting in **IX** that binds to a second phosphine molecule, followed by a series of acid–base reactions, re-establishing **VI**, the active catalyst (Figures 2c and S10).[12]

With the general mechanism outlined, we wanted to shed more light on the origin of the enantioselection (Figure 2d). The stereodetermining step of the reaction is the addition of nitrile (*E*)-**1d** to **VI**. Two factors determine which face of nitrile (*E*)-**1d** is approached by the Mn(I)-catalyst: (i) the minimization of the steric clash between the phenyl groups of the alkene and the phosphide moiety of **VI** and (ii) the establishment of a hydrogen bond between the N–*H* group of the Mn(I) complex ligand and the C-3 atom of the alkene at **TS-(VI–VII)**. The latter ensures the stabilization of the putative carbanion formed on the C-3 position of (*E*)-**1d**, while the minimization of the steric constrains at the phenyl moiety ensures the formation of only the (*R*)-product. This stereochemical description suggests that for (*E*)-**1d** complete enantioselectivity should be achieved since the difference in energy between the *proR* and *proS* transition states is 4.97 kcal/mol, thus aligning with the experimentally observed high er of 97.5:2.5. The proposed mechanism also accounts for the er values obtained with terminal alkenes, since the formation of the C-4-P bond of the product is followed by a fast stereospecific intramolecular protonation of the C-3 carbanion by the N–*H* moiety of the Mn(I) complex, thereby ensuring the formation of predominantly one enantiomer of the addition product.

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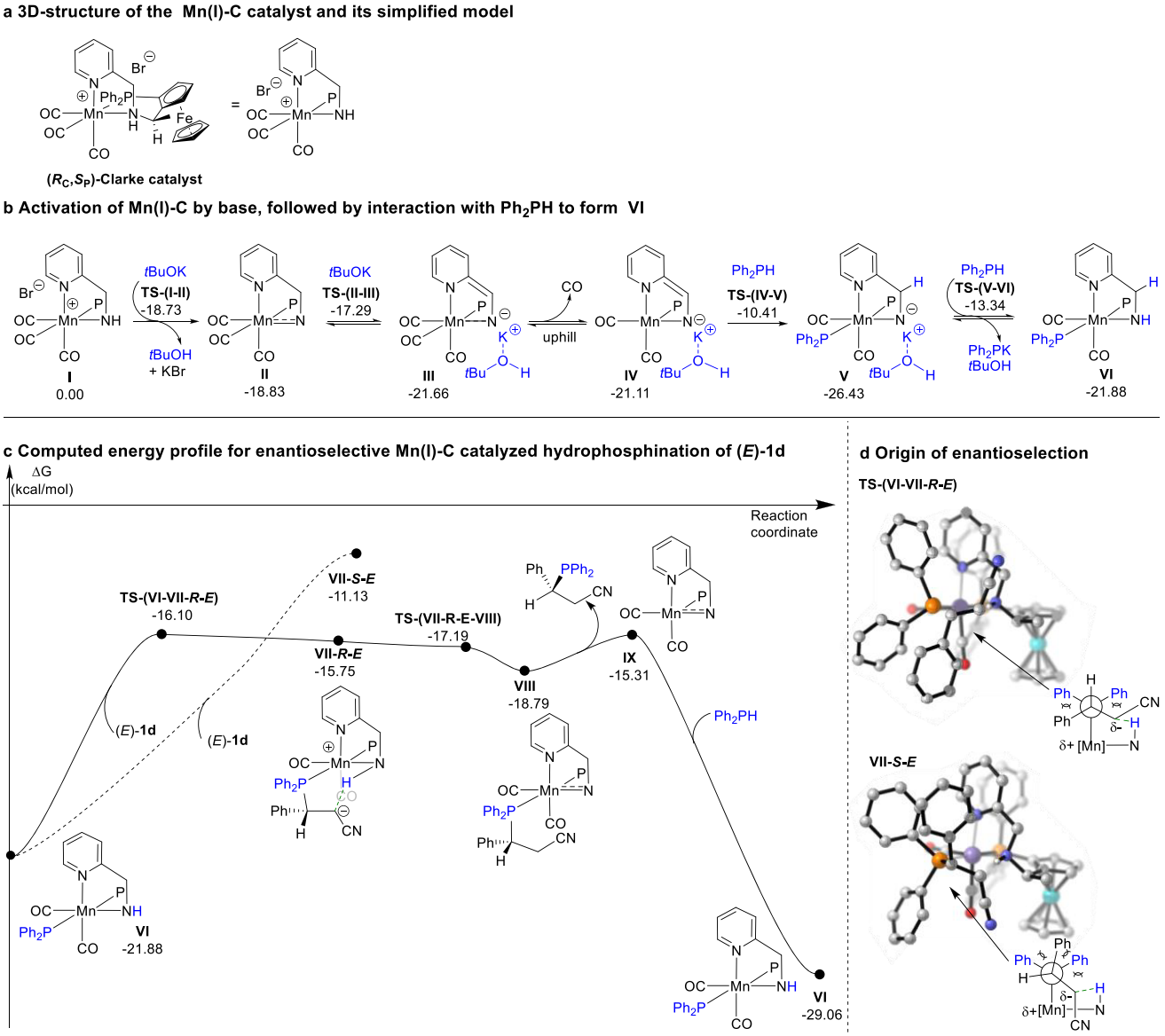

Figure 2. Computational studies. DFT studies were performed at the PCM (toluene)[14]–B3LYP[15]–GD3[16]–def2svpp[17] computational level. The energies reported correspond to relative Gibbs free energies and are expressed in kcal/mol. The reference point in energy is **I** + 2*t*BuOK + 3Ph_2PH + (*E*)-**1d**.

In summary, we have demonstrated that chiral (R_C,S_P)-**Mn(I)-C** is capable of H–P bond activation and consequently enables highly enantioselective hydrophosphination of internal and terminal α,β-unsaturated nitriles. Metal–ligand cooperation is at the basis of the H–P bond activation. We believe that our method further highlights the untapped possibilities for Mn(I) complexes in homogeneous catalysis. Studies to expand the scope of this new catalytic system and to get detailed mechanistic insights are underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c10756.

Experimental procedures, characterization data, computational details and NMR spectra (PDF)

Crystallographic data in CIF format for compounds **1′b**, **1d′** and **2′c** (PDF)

X-ray crystallographic data (PDF)

Accession Codes

CCDC 2085290, 2085460, and 2120248 contain 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.

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