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Communication

Rhodium-Catalyzed Regio- and Enantioselective Allylic Amination of Racemic 1,2-Disubstituted Allylic Phosphates

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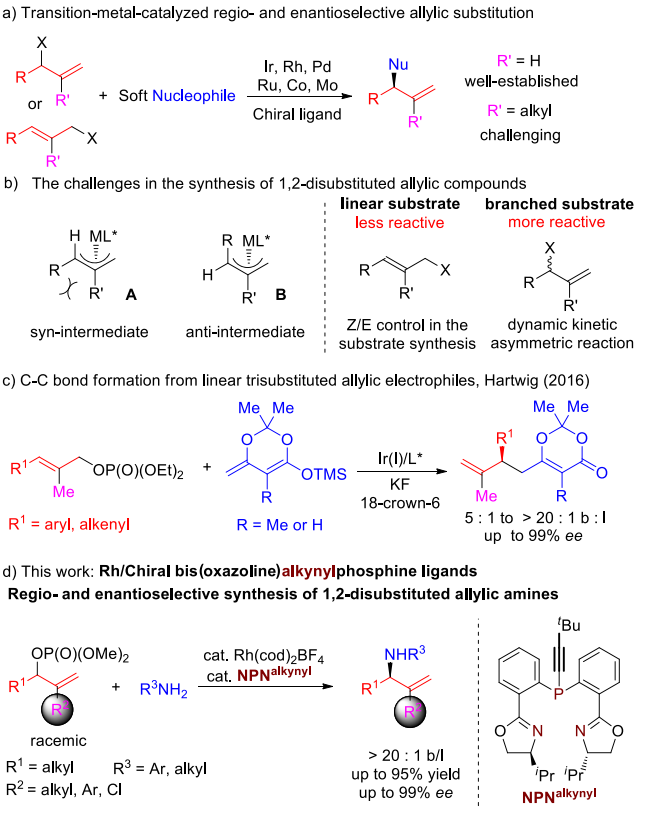
ABSTRACT: Alkynylphosphines are rarely used as ligands in asymmetric metal catalysis. We synthesized a series of chiral bis(oxazoline)alkynylphosphine ligands and used them in Rh-catalyzed highly regio- and enantioselective allylic amination reactions of 1,2-disubstituted allylic phosphates. Chiral 1,2-disubstituted allylic amines were synthesized in up to 95% yield with >20:1 branched/linear (b/l) ratio and 99% *ee* from racemic 1,2-disubstituted allylic precursors. The sterically smaller linear alkynyl group on the P atom in the bis(oxazoline)alkynylphosphine ligands was the key to fit the new requirements of the introduction of bulky 2-R′ groups.

Transition-metal-catalyzed asymmetric allylic substitution of monosubstituted allylic substrates with soft nucleophiles has been well-established for the regio- and enantioselective preparation of chiral allylic products in the presence of Ir, Rh, Pd, Ru, Mo, Co, and other metal complexes.[1] However, the synthesis of chiral acyclic 1,2-disubstituted allylic products is much less explored and challenging when an extra 2-alkyl group is introduced (Scheme 1a). In the 1,2-disubstituted π-allylmetal complexes, the energy difference between the syn π-allylmetal complex **A** and the anti complex **B** becomes smaller because of steric repulsion between the R and R′ groups.[2] Moreover, *Z*/*E* control in the substrate synthesis and the lower reactivity of linear trisubstituted allylic precursors make it more difficult to get high efficiency and enantioselectivity (Scheme 1b). Reactions starting from the more reactive branched racemic allylic substrates require a challenging dynamic kinetic asymmetric transformation process after the introduction of the 2-R′ group. To the best of our knowledge, with the well-explored Ir and Rh catalysts, the only successful example was the allylic alkylation of dioxinone-derived enol silanes from linear 2-methyl-substituted allylic precursors reported by Hartwig[3] (Scheme 1c). The synthesis of chiral allylic compounds with 2-alkyl groups bulkier than methyl has rarely been reported.[4−7] The development of new efficient catalysts for the preparation of such compounds is highly desired. In the present work, we synthesized a series of chiral tridentate bis(oxazoline)-alkynylphosphine ligands, which could be used in highly regio- and enantioselective allylic amination of racemic 1,2-disubstituted allylic phosphates (Scheme 1d). Chiral 1,2-disubstituted allylic amines could be obtained in up to 95% yield with >20:1 branched/linear (b/l) ratio and 99% *ee*.

Recently, our group developed new catalyst systems based on Co/Rh and bis(oxazoline)phosphine ligands for highly branch- and enantioselective synthesis of monosubstituted allylic compounds.[8] The excellent enantioselectivity obtained for this reaction was assigned to the high exo/endo ratio in the π-allylmetal intermediate. Analysis of the crystal structure of

Scheme 1. Transition-Metal-Catalyzed Regio- and Enantioselective Synthesis of Acyclic 1,2-Disubstituted Allylic Products



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the π-allylrhodium−NPN* complex indicates that the 2-H of the allyl group is located very close to the ortho hydrogen of the phenyl group on the P atom (2.024 Å; dashed cyan line in Figure 1a).[8c] The introduction of a bulky R^2 group to replace

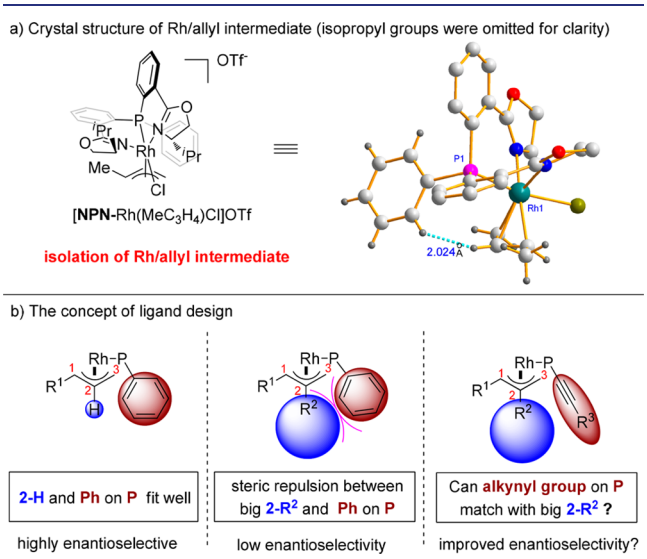
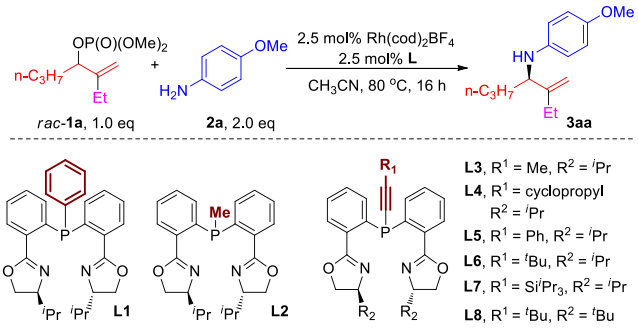


Figure 1. Rational modification of the ligand to fit the requirement of the bulky 2-alkyl group.

the hydrogen atom at the 2-position of the allyl group in the π-allylrhodium complex may cause repulsion between this R^2 group and the phenyl group in the ligand and result in the low exo/endo selectivity and enantioselectivity (Figure 1b). We envisioned that rational modification of the phenyl group on the P atom to a smaller group would lead to a new balance for the 2-R^2 group, giving the same exo/endo selectivity in the new 1,2-disubstituted π-allylrhodium complex as in the monosubstituted π-allylrhodium complex. In this work, we present our result that a smaller alkynyl group on the P atom was identified to be a perfect solution to realize the dynamic kinetic asymmetric allylic amination of racemic 1,2-disubstituted allylic phosphates.

We started the investigation with racemic 1-*n*-propyl-2-ethylallylic phosphate **1a** and 4-methoxyaniline (**2a**) as the model substrates (Table 1). In the presence of $Rh(cod)_2BF_4$ and NPN ligand **L1** with phenyl on the P atom, after 12 h of heating in CH_3CN at 80 °C, the desired product **3aa** was obtained in 39% yield with a moderate 47% *ee* (entry 1). When less reactive allylic methyl carbonate **1a′** was used under the same conditions, no conversion was observed. The extra ethyl group at the 2-position retards the oxidative addition of the rhodium complex with allylic carbonates. As predicted, when the phenyl group on the P atom was replaced by a smaller methyl group, a higher 80% *ee* was obtained (entry 2), which supports our hypothesis that the size of the group on the P atom has a significant effect on the enantioselectivity. Although hydrogen is smaller than the methyl group, the possible air sensitivity of the ligand turned our attention to other less bulkier groups. Inspired by the triethynylphosphine ligands developed by the Sawamura group[9] and the alkynylP* ligands reported by Imatomo,[10] **L3**−**L8** with an alkynyl group were synthesized. To our delight, 90% *ee* was observed with **L3** or **L4**, although the yields were lower (entries 3 and 4). The substituent on the alkyne plays a key role in the enantioselectivity as well. The reaction in the presence of **L6**

Table 1. Optimization of Rh-Catalyzed Asymmetric Allylic Amination of Racemic 1,2-Disubstituted Allylic Phosphates[a]



entry	ligand	yield of **3aa** (%)[b]	*ee* of **3aa** (%)[c]
1	**L1**	39	47
2	**L2**	49	80
3	**L3**	32	90
4	**L4**	41	90
5	**L5**	48	63
6	**L6**	72	96
7	**L7**	52	82
8	**L8**	67	86
9[d]	**L6**	91	97

[a]Conditions: **1a** (0.4 mmol, 1.0 equiv), **2a** (0.8 mmol, 2.0 equiv), $Rh(cod)_2BF_4$ (0.01 mmol, 0.025 equiv), and the ligand (0.01 mmol, 0.025 equiv) in CH_3CN (2 mL). [b]Isolated yields. [c]Determined by HPLC with a chiral column. [d]The reaction time was 40 h.

with a *tert*-butyl group afforded the **3aa** in the highest yield of 72% with 96% *ee* (entry 6), while **L5** with a phenyl group and **L7** with a triisopropylsilyl group led to 62% and 82% *ee*, respectively (entries 5 and 7). The substituents on the oxazoline rings can also influence the enantioselectivity. **L8** with *tert*-butyl groups at R^2 led to a lower 86% *ee* (entry 8). Finally, when the reaction time was extended to 40 h, **3aa** was isolated in 91% yield with 97% *ee* (entry 9). In all cases, a >20:1 b/l ratio was obtained.

With the optimized conditions in hand (Table 1, entry 9), the reaction scope of anilines and allylic phosphates was examined. (Scheme 2). The synthesis of **3aa** could be conducted on a 10 mmol scale, and the enantioselectivity remained at 97% *ee*. The absolute configuration of **3aa** was assigned to be *R* by single-crystal X-ray diffraction analysis of the HCl salt of **3aa**. The *R* configuration of **3aa** is consistent with the hypothesis that the same exo/endo selectivity could be expected when a smaller alkynyl group is used to fit the size of the 2-ethyl group. Electron-neutral, electron-donating, and electron-withdrawing groups could be tolerated at the para position of the aniline (**3ab**−**af**). A high yield was obtained when *o*-methoxyaniline (**2g**) was used as the nucleophile, although a slightly reduced 92% *ee* was observed. The allylic phosphate side was further examined. Besides a 2-ethyl group, 2-methyl-, 2-benzyl-, and 2-*n*-decanyl-substituted allylic phosphates reacted smoothly to give the corresponding allylic amines with high *ees* (**3ba** to **3da**). However, the allylic phosphate with a more sterically hindered 2-isopropyl group failed to give the desired product.[11] Functional groups of olefin and benzyl ether could be tolerated, giving **3ea** and **3fa**. Cyclic allylic amine **3ga** was prepared in 69% yield with 99% *ee* by further intramolecular amination of the chloride-containing substrate. The substituent at R^2 could be further extended to

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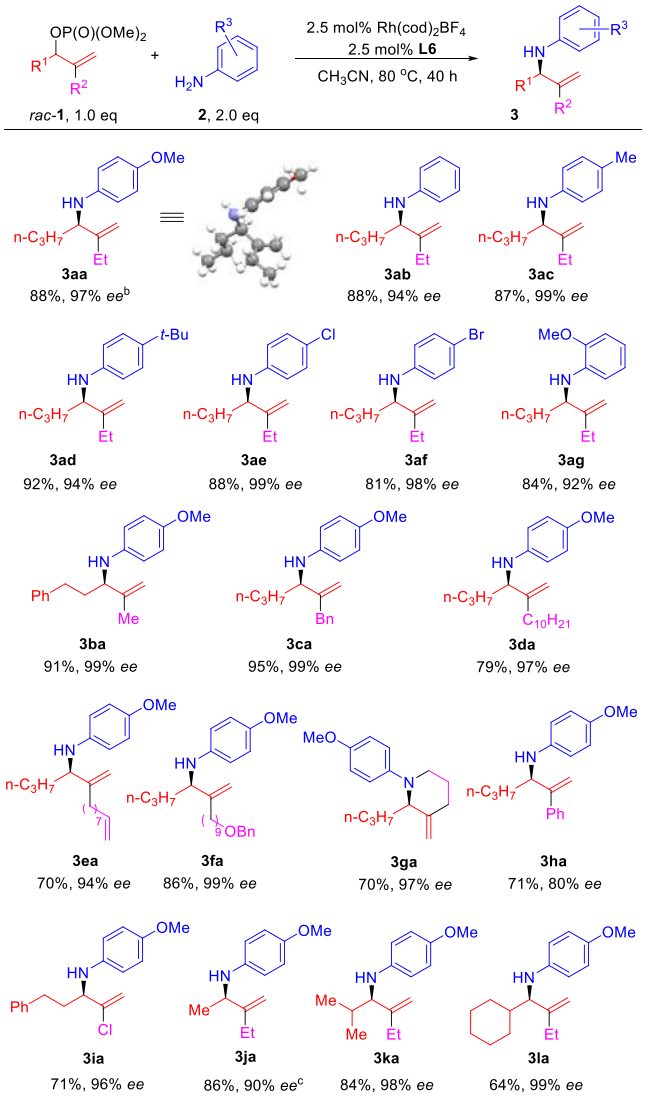
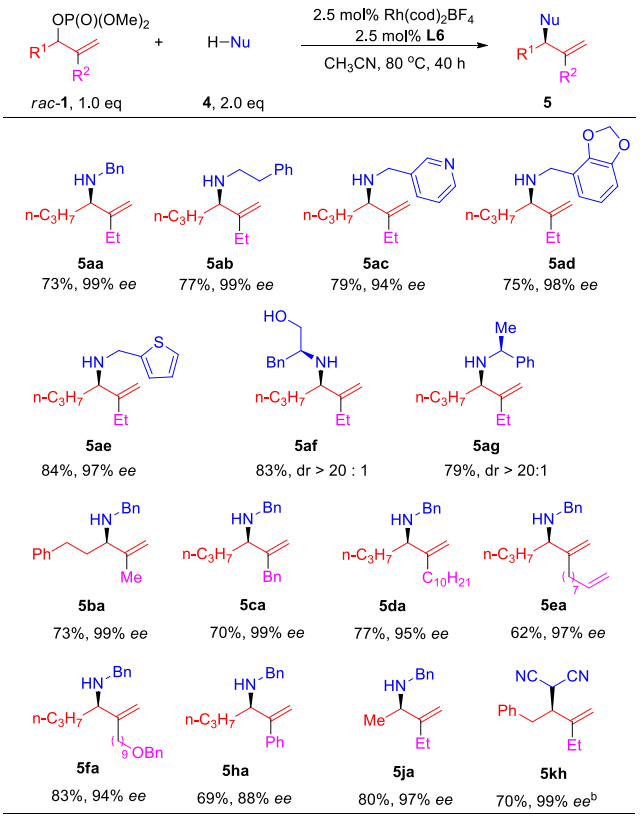
Scheme 2. Scope of Anilines and Allylic Phosphates[a]



[a]Conditions: **1** (0.4 mmol, 1.5 equiv), **2** (0.8 mmol, 2.0 equiv), $Rh(cod)_2BF_4$ (0.01 mmol, 0.025 equiv), and **L6** (0.01 mmol, 0.025 equiv) in CH_3CN (2 mL). [b]The reaction was run on a 10 mmol scale. [c]**L8** was used instead of **L6**.

Scheme 3. Scope of Other Nucleophiles[a]



[a]Conditions: **1** (0.4 mmol, 1.5 equiv), **2** (0.8 mmol, 2.0 equiv), $Rh(cod)_2BF_4$ (0.01 mmol, 0.025 equiv), and **L6** (0.01 mmol, 0.025 equiv) in CH_3CN (2 mL). [b]The methyl allyl carbonate was used.

phenyl and chloride under the identical conditions (**3ha** and **3ia**). In addition to the *n*-propyl and phenylethyl groups, substrates bearing methyl, isopropyl, and cyclohexyl groups as R^1 were also converted to allylic amines **3ja**–**la** in high yields and enantioselectivities.

The scope of more basic aliphatic amines was also examined under the optimized conditions (Scheme 3). Benzylamine and 2-phenylethylamine were good nucleophiles, giving the secondary amines **5aa** and **5ab**, respectively, with 99% *ee*. Amines with heterocyclic pyridine, 1,3-benzodioxolane, and thiophene were transformed to the corresponding products **5ac**–**ae** in high yields and *ee*'s. Chiral (*S*)-2-amino-3-phenylpropan-1-ol and (*S*)-1-phenylethanamine reacted under the optimized conditions to give amines **5af** and **5ag**, respectively, with >20:1 dr. Variation of the group at the R^2 position to methyl, benzyl, and *n*-decanyl as well as olefin- and ether-containing groups had little influence on the results of the allylic substitution reaction (**5ba**–**fa**). However, the *ee* of phenyl-substituted allylic amine **5ha** dropped to 88% under the unoptimized conditions. Finally, malononitrile (**4h**) could be utilized as the nucleophile to give **5kh** in 70% yield with 94% *ee* under neutral conditions.

Some control experiments were conducted to gain mechanistic insight into the Rh-catalyzed asymmetric allylic amination. The reactivity of branched 1,2-disubstituted allylic phosphate **1a** toward a stoichiometric amount of Rh-$(cod)_2BF_4$/**L6** complex was examined (Scheme 4a). After 12 h of heating in CH_3CN, π-allylrhodium complex **6** was isolated in 97% yield. This complex was characterized as a single isomer in solution according to ^1H and ^{31}P NMR spectroscopy. Unfortunately, no crystal of **6** suitable for X-ray analysis could be obtained. The coordination of the $OP(O)(OMe)_2$ group to the metal center was confirmed by the dd peaks at 26.1 and 2.8 ppm in the ^{31}P NMR spectrum, which were assigned to be the P atoms in the NPN ligand and the phosphate, respectively. The reaction of **6** with 2 equiv of **2a** afforded **3aa** in 84% yield with 94% *ee* (Scheme 4b). **6** can also be used as the catalyst to convert **1a** and **2a** to **3aa** in high yield (Scheme 4c), which indicates that **6** is involved as the reactive intermediate in the catalysis. Finally, when bulky nucleophiles are used, the *E*-linear product is expected to be formed from the *syn*-π-allylrhodium intermediate, while the *Z*-linear product can be generated from the *anti*-π-allylrhodium complex (Scheme 4d).[12] *N*-Methylaniline (**2h**) reacted with **6** as the nucleophile to give exclusively *E*-linear **3ah′** in 80% yield (as confirmed by NOE experiment). The *E* configuration of **3ah′**, the *R* configuration of **3aa**, and the nuclear Overhauser effect spectroscopy (NOESY) analysis of complex **6** (see the

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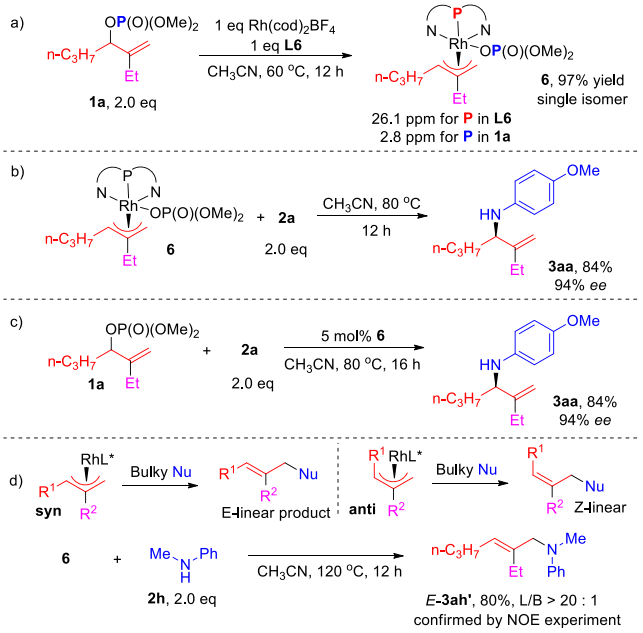
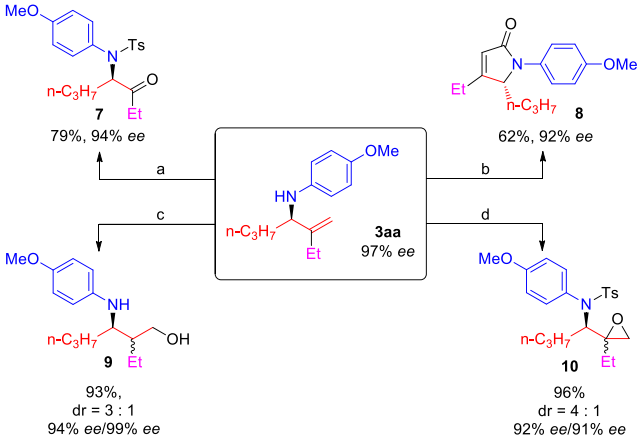
Scheme 4. Control Experiments



Supporting Information) support that the *syn*-π-allylrhodium−NPN* complex exists as the reactive intermediate.

The chiral 1,2-disubstituted allylic amines could be transformed into different chiral products after further functional group manipulations (Scheme 5). Compound **7** was isolated in

Scheme 5. Synthetic Applications of Chiral 1,2-Disubstituted Allylic Amine Derivatives[a]



[a]Conditions: (a) (1) TsCl, pyridine, DCM, 0 °C to rt, 12 h; (2) $NaIO_4$, $RuCl_3$, 2,6-lutidine, DCM/CH_3CN/H_2O (1:1:1.5), rt, 12 h. (b) (1) Acryloyl chloride, pyridine, DCM, 0 °C to rt, 12 h; (2) Grubbs-II, toluene, 100 °C, 40 h. (c) 9-BBN, 0 °C to rt, 12 h, then EtOH, NaOH, H_2O_2 (30%). (d) (1) TsCl, pyridine, DCM, 0 °C to rt, 12 h; (2) *m*-CPBA, DCM.

79% yield with 94% *ee* by *N*-Ts protection and oxidative cleavage of the C−C double bond (route a). Chiral lactam **8** was produced in 62% overall yield by N-protection with acryloyl chloride followed by ring-closing metathesis (route b). Oxidation of the double bond in **3aa** with 9-BBN/H_2O_2 (route c) and *m*-CPBA (route d) produced **9** and **10**, respectively, with moderate dr and high *ee*, which can be used to prepare molecules with two consecutive chiral centers.

In conclusion, we have designed and synthesized novel bis(oxazoline)phosphine ligands with alkynyl functions on the P atom after analysis of the monosubstituted allylrhodium−NPN complex. These ligands could be used to fit the new requirements of the bulky 2-R′ groups in Rh-catalyzed regio- and enantioselective allylic amination reactions of challenging 1,2-disubstituted allylic precursors. Chiral 1,2-disubstituted allylic amines were synthesized in up to 95% yield with >20:1 branched/linear ratio and 99% *ee*.[13] Rational modification of the NPN ligands to solve the other problems in enantioselective allylic substitution reactions is under investigation in our group.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c04016.

Detailed experimental procedures, characterization data, and copies of ^1H and ^{13}C NMR and HPLC spectra (PDF)

Accession Codes

CCDC 2078097 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, U.K.; fax: +44 1223 336033.

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Author Contributions

†W.-B. Xu and M. Sun contributed equally.

Notes

The authors declare no competing financial interest.

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