Asymmetric Dearomatization

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Enantioselective Synthesis of Pyrrole-Based Spiro- and Polycyclic Derivatives by Iridium-Catalyzed Asymmetric Allylic Dearomatization and Controllable Migration Reactions**

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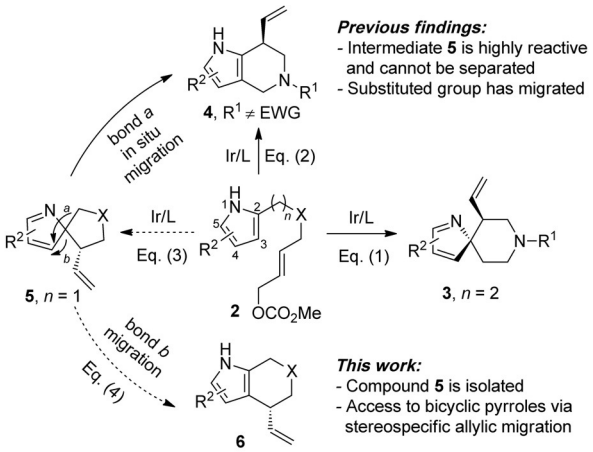
Dedicated to Professor Stephen L. Buchwald on the occasion of his 60th birthday

Abstract: *The first highly diastereo- and enantioselective synthesis of five-membered spiro-2H-pyrroles was achieved using an Ir-catalyzed asymmetric allylic dearomatization reaction. The spiro-2H-pyrrole derivatives readily undergo a controllable and stereospecific allylic migration under acid catalysis, providing polycyclic pyrrole derivatives in excellent yields and ee values. Additionally, the novel Ir-complex* ***K1****, derived from [Ir(cod)Cl]$_2$ (cod = 1,5-cyclooctadiene) and N-benzhydryl-N-phenyldinaphthophosphoramidite (BHPphos), showed excellent control of both diastereo- and enantioselectivities.*

The pyrrole moiety occurs widely as an important structural core in complex natural products and pharmaceutical agents.[1] Among those, the chiral 2*H*-pyrrole and polycyclic pyrrole derivatives are quite useful as privileged structural units in organic synthesis.[2] Thus, great efforts have been devoted to the development of new methods towards the preparation of 2*H*-pyrrole and polycyclic pyrrole derivatives.[3] In this regard, the transition-metal-catalyzed asymmetric allylic substitution reaction has been recognized as one efficient method.[4] In 2006, Bandini, Umani-Ronchi, and co-workers reported, for the first time, a highly enantioselective synthesis for pyrrolyl-based polycyclic compounds by a Pd-catalyzed intramolecular asymmetric Friedel–Crafts-type allylic alkylation reaction.[5]

As part of our continuous interest in the enantioselective functionalization of pyrroles using transition-metal-catalyzed intramolecular asymmetric allylic substitution reactions,[6–8] we found that pyrroles could undergo allylic dearomatization reactions, providing six-membered spiro-2*H*-pyrroles **3** in excellent diastereo- and enantioselectivity [Scheme 1, Eq. (1)].[7] Interestingly, when the tether in the pyrrole ring was shortened by one carbon, polycyclic product **4**, featuring the migration of the substituent from the C2 to the C3 position of pyrrole, could be obtained in excellent yield and enantioselectivity [Scheme 1, Eq. (2)].[8] The reaction was proposed to firstly proceed by an Ir-catalyzed asymmetric allylic dearomatization to furnish the five-membered spiro-2*H*-pyrrole **5**, which then underwent rapid in situ migration of the methanamine group to afford the bicyclic pyrrole compound **4**. However, the five-membered spiro-2*H*-pyrrole **5**, proposed as the key reaction intermediate, was highly reactive and could not be isolated. Thus, we envisaged that by tuning the electronic nature of the linkage X, the five-membered spiro-2*H*-pyrrole intermediate **5** might be isolated as a stable product [Scheme 1, Eq. (3)]. Furthermore, by identifying suitable reaction conditions, polycyclic pyrrole derivative **6** could be obtained by a controllable allylic group migration reaction [Scheme 1, Eq. (4); migration of bond b in **5**]. Herein, we report our efforts on the enantioselective construction and controllable migration of the five-membered spiro-2*H*-pyrrole **5**.



Scheme 1. Enantioselective syntheses of pyrrole-based spiro- and polycyclic derivatives.

The *N*-Bn tethered pyrrole substrate **2′** (Bn = benzyl) could undergo the dearomatization/in situ migration process,[8] in which the electron-donating benzyl group on the nitrogen was believed to enhance the migratory ability of the methylene portion [Scheme 2, Eq. (1)]. With this information in hand, we envisaged that the stable five-membered spiro-2*H*-pyrrole might be obtained by decreasing the migratory ability of the methylene portion. To our delight, by switching

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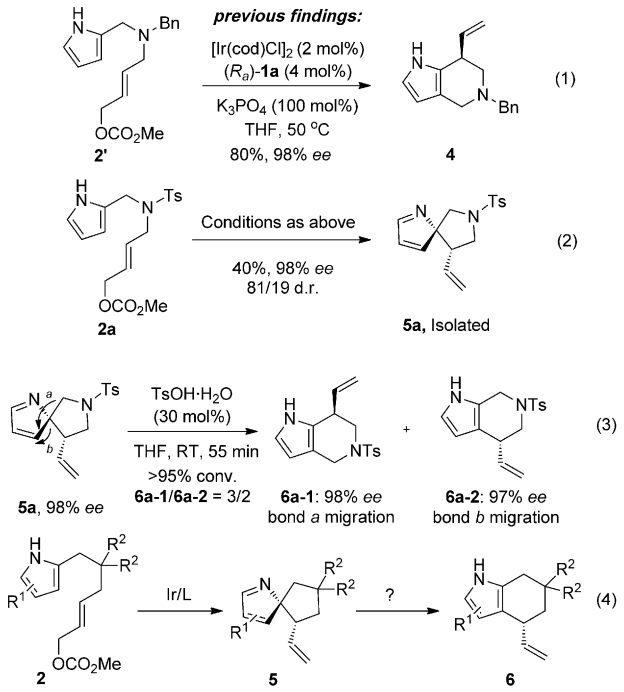
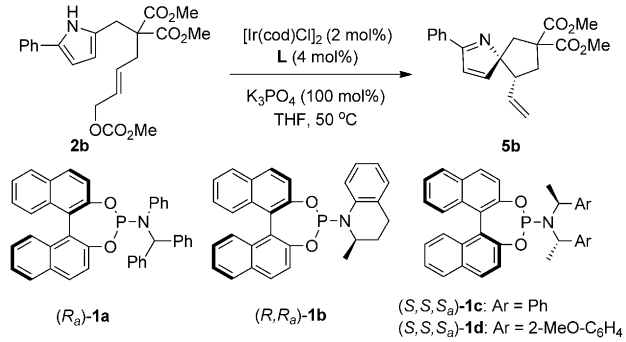


Scheme 2. Development of the controllable migration of spiro-2*H*-pyrroles. Bn = benzyl, Ts = 4-toluenesulfonyl.

Table 1: Ligand effect.[a]



entry	L	*t* [h]	conv. [%][b]	d.r.[b]	yield [%][c]	*ee* [%][d]
1	**1a**	35	>95	90/10	65	99
2	**1b**	40	95	90/10	30	88
3	**1c**	40	91	42/58	28	68
4	**1d**	40	46	45/55	14	84
5[e]	**1a**	39	>95	>95/5	73	99

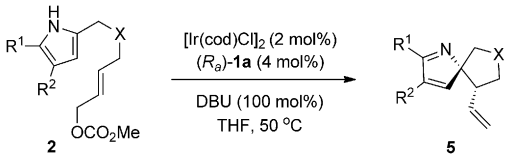
[a] Reaction conditions: $[Ir(cod)Cl]_2$ (2 mol%), ligand (4 mol%), **2b** (0.1 mmol), base (0.1 mmol) in THF (1.0 mL) at 50°C. [b] Determined by ^1H NMR spectroscopy of the crude reaction mixture. [c] Yield of the isolated major diastereoisomer. [d] Determined by HPLC analysis. [e] DBU (1 equiv) was used instead of K_3PO_4.

the substituent on the nitrogen to an electron-withdrawing group (**2a**), spiro-2*H*-pyrrole (**5a**) was obtained with an excellent *ee* value, albeit with a moderate d.r. value (d.r. = diastereomeric ratio), and yield [40% yield, 81/19 d.r., 98% *ee*; Scheme 2, Eq. (2)]. More intriguingly, upon treatment of **5a** with a catalytic amount of $TsOH{\cdot}H_2O$, both the methanamine group migration product **6a-1** and the allylic group migration product **6a-2** could be obtained (>95% conversion, **6a-1**/**6a-2** = 3/2), which indicates the -CH_2NTs group has a similar migratory ability as the allylic group [Scheme 2, Eq. (3)]. Inspired by these results, we further tested the allylic carbonate **2** with an all-carbon linker to undergo asymmetric allylic dearomatization and a subsequent chemoselective allylic group migration reaction of the dearomatized spiro-2*H*-pyrrole **5**, leading to the formation of polycyclic pyrrole derivative **6** [Scheme 2, Eq. (4)].

Our studies were initiated by an exploration of the reaction of substrate **2b** bearing an all-carbon tethered allylic carbonate with an Ir-based catalytic system derived from $[Ir(cod)Cl]_2$ and ligand **1a**, namely *N*-benzhydryl-*N*-phenyldinaphthophosphoramidite (BHPphos; Table 1).[9–11] In the presence of $[Ir(cod)Cl]_2$ (2 mol%), ligand **1a** (4 mol%), and K_3PO_4 (1.0 equiv), the reaction of **2b** in THF for 35 h led to the dearomatized product **5b**, which was isolated in good yield and diastereoselectivity and with excellent enantioselectivity (65% yield, 90/10 d.r., 99% *ee*; Table 1, entry 1). Encouraged by these results, we carried out further optimization of the reaction conditions. Ligand **1b**, developed in this group,[11] formed an efficient catalyst when combined with $[Ir(cod)Cl]_2$ to provide product **5b** with good diastereoselectivity, but with only a moderate *ee* value and yield (Table 1, entry 2). Catalysts generated from ligands **1c** and **1d** could promote the dearomatization reaction of **2b** only in poor diastereoselectivity and moderate enantioselectivity (Table 1, entry 3: 42/58 d.r., 68% *ee*; and entry 4: 45/55 d.r., 84% *ee*). After careful investigation of base and solvent, the optimum conditions were found to be: **2b** in THF (0.1M), $[Ir(cod)Cl]_2$ (2 mol%), **1a** (4 mol%), and DBU (1,8-diazabicyclo-[5.4.0]undec-7-ene; 1.0 equiv) at 50°C. Under these conditions, product **5b** was obtained in 73% yield, more than 95/5 d.r., and with 99% *ee* (Table 1, entry 5).[12]

With the optimized reaction conditions in hand, various substituted pyrrolyl allylic carbonates **2** were tested to examine the generality of the process. The results are summarized in Table 2. Reactions of allylic carbonates containing different ester groups (CO_2Me, CO_2Et, CO_2iPr, CO_2tBu) in the tether linkage all gave their corresponding products in good yields and in excellent diastereo- and enantioselectivities (Table 2, entries 1–4; 62–73% yields, 94/6–>95/5 d.r., 98–99% *ee*). Next, different substituents on the pyrrole core were investigated. Substrates bearing either electron-withdrawing (4-Cl (**2f**), 4-Br (**2g**); Table 2, entries 5,6) or electron-donating (4-Me (**2h**), 3,4-$(MeO)_2$ (**2i**); Table 2, entries 7,8) groups on the phenyl moiety (R^1) on the pyrrole core all reacted smoothly to form their corresponding products in good yields and with excellent diastereo- and enantioselectivities (56–76% yields, 91/9–>95/5 d.r., 96–99% *ee*). Notably, the reaction occurred smoothly for substrate **2j** in which an ethyl group (R^1) was present at the pyrrole core (81% yield, 89/11 d.r., 99% *ee*; Table 2, entry 9). Interestingly, when substrate **2k** bearing no substituent at the 4 or 5 position of the pyrrole core was utilized, the reaction also proceeded smoothly, affording product **5k** in good yield, and with excellent diastereo- and enantioselectivity (63% yield, 95/5 d.r., 98% *ee*; Table 2, entry 10). Moreover, the 2,4,5-tri-substituted pyrrole deriva-

Table 2: The reaction substrate scope.[a]



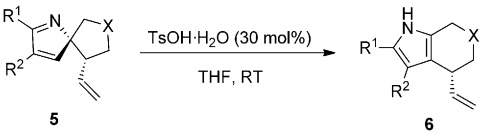
entry	2	R^1	R^2	X	t [h]	d.r.[b]	5, yield [%][c]	ee [%][d]
1	**2b**	Ph	H	$C(CO_2Me)_2$	39	>95/5	**5b**, 73	99
2	**2c**	Ph	H	$C(CO_2Et)_2$	41	>95/5	**5c**, 63	99
3	**2d**	Ph	H	$C(CO_2iPr)_2$	41	94/6	**5d**, 70	99
4	**2e**	Ph	H	$C(CO_2tBu)_2$	43	94/6	**5e**, 62	98
5	**2f**	4-Cl-C_6H_4	H	$C(CO_2Me)_2$	40	94/6	**5f**, 61	99
6	**2g**	4-Br-C_6H_4	H	$C(CO_2Me)_2$	40	>95/5	**5g**, 56	98
7	**2h**	4-Me-C_6H_4	H	$C(CO_2Me)_2$	41	91/9	**5h**, 67	99
8	**2i**	3,4-$(MeO)_2$-C_6H_3	H	$C(CO_2Me)_2$	43	92/8	**5i**, 76	96
9[e]	**2j**	Et	H	$C(CO_2Me)_2$	39	89/11	**5j**, 81	99
10[e]	**2k**	H	H	$C(CO_2Me)_2$	39	95/5	**5k**, 63	98
11	**2l**	Me	Ph	$C(CO_2Me)_2$	42	>95/5	**5l**, 67	99
12[f]	**2m**	Me	4-F-C_6H_4	$C(CO_2Me)_2$	47	>95/5	**5m**, 52	98
13	**2n**	Me	4-Me-C_6H_4	$C(CO_2Me)_2$	44	>95/5	**5n**, 51	99
14	**2o**	Me	*n*-Pentyl	$C(CO_2Me)_2$	39	88/12	**5o**, 69	98

[a] Reaction conditions: $[Ir(cod)Cl]_2$ (2 mol%), (R_a)-**1a** (4 mol%), **2** (0.2 mmol), DBU (0.2 mmol) in THF (2.0 mL) at 50°C. [b] Determined by ^1H NMR spectroscopy of the crude reaction mixture. [c] Yield of the isolated major diastereoisomer. [d] Determined by HPLC analysis. [e] Using basic Al_2O_3 flash column chromatography. [f] $[Ir(cod)Cl]_2$ (4 mol%) and (R_a)-**1a** (8 mol%) were used.

tives were also well tolerated in the dearomatization reaction. When different alkyl (**2o**) or aryl groups (**2l**, **2m**, **2n**) were installed at the 4 position of the pyrrole core (R^2), the reactions occurred smoothly to form their corresponding products in good yields and with excellent diastereo- and enantioselectivities (51–69% yields, 88/12–>95/5 d.r., 98–99% *ee*; Table 2, entries 11–14). The structure and stereochemistry of the products were confirmed unambiguously by an X-ray crystallographic analysis of a crystal of enantiopure **5m**. The absolute configuration was determined as 5*R*, 9*R*.

Next, we explored whether these five-membered spiro-2*H*-pyrroles could be chemo- and stereoselectively transformed to the bicyclic pyrrole products **6**.[13] To our delight, in the presence of $TsOH{\cdot}H_2O$ (30 mol%), spiro-2*H*-pyrrole **5b** was smoothly converted into bicyclic pyrrole **6b** in 78% yield and well-preserved enantiomeric purity (99% *ee*; Table 3, entry 1). Encouraged by these results, various spiro-2*H*-pyrroles **5** were tested. As summarized in Table 3, the reaction proceeded smoothly when there was only one substituent at the 5 position of the spiro-2*H*-pyrrole ring or no substituent on the spiro-2*H*-pyrrole core, affording the corresponding bicyclic pyrrole products **6b**–**6k** in good to excellent yields and excellent *ee* values (74–91% yields, 96–99% *ee*; Table 3, entries 1–10). However, when the sterically bulkier spiro-2*H*-pyrrole **5l** was used, the reaction proceeded in moderate yield with well-preserved enantiomeric purity (61% yield, 99% *ee*, 12 h). Interestingly, by simply switching the acid catalyst to $Sc(OTf)_3$, the migration reaction occurred smoothly with an increased rate (94% yield, 99% *ee*; Table 3, entry 11). The tri-substituted spiro-2*H*-pyrroles containing different electron-withdrawing (**5m**) or electron-donating (**5n**) aromatic rings or an alkyl group (**5o**) could also be used in the migration reaction (60–78% yields, 98–99% *ee*; Table 3, entries 12–14). More intriguingly, the NTs-tethered spiro-2*H*-pyrrole **5a** could undergo a chemoselective allylic group migration with $Sc(OTf)_3$ as the catalyst in MeCN (**6a-1**/**6a-2** = 8/92, 72% yield, 98% *ee*; Table 3, entry 15), whereas both the methanamine group and the allylic group migration products **6a-1** and **6a-2** could be obtained in a ratio of 3/2 under catalysis by $TsOH{\cdot}H_2O$ [Scheme 2, Eq. (3)].[14] Additionally, the chiral polycyclic pyrroles could be synthesized directly from the allylic carbonate substrates **2** using a one-pot procedure.[12] The structure and absolute configuration of the bicyclic pyrrole products were assigned by an X-ray crystallographic analysis of enantiopure **6g**. The absolute configuration was determined as *R*, which was found to be consistent with that of the parent compound.

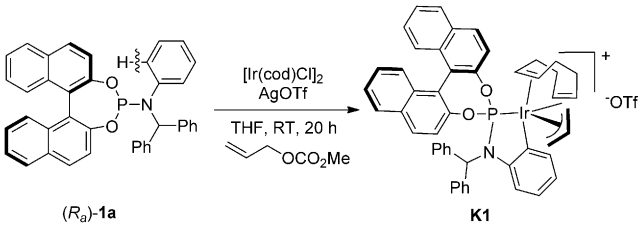
Table 3: Stereospecific allylic migration reactions of spiro-2*H*-pyrroles.[a]



entry	5, R^1, R^2, X	t [h]	6, yield [%][b]	ee [%][c]
1	**5b**, Ph, H, $C(CO_2Me)_2$	1.5	**6b**, 78	99
2	**5c**, Ph, H, $C(CO_2Et)_2$	2	**6c**, 91	99
3	**5d**, Ph, H, $C(CO_2iPr)_2$	2.5	**6d**, 81	98
4	**5e**, Ph, H, $C(CO_2tBu)_2$	1	**6e**, 89	99
5	**5f**, 4-Cl-C_6H_4, H, $C(CO_2Me)_2$	5.5	**6f**, 76	99
6	**5g**, 4-Br-C_6H_4, H, $C(CO_2Me)_2$	2	**6g**, 81	98
7	**5h**, 4-Me-C_6H_4, H, $C(CO_2Me)_2$	1.5	**6h**, 78	99
8	**5i**, 3,4-$(MeO)_2$-C_6H_3, H, $C(CO_2Me)_2$	10	**6i**, 80	96
9	**5j**, Et, H, $C(CO_2Me)_2$	4	**6j**, 81	99
10	**5k**, H, H, $C(CO_2Me)_2$	2	**6k**, 74	98
11[d]	**5l**, Me, Ph, $C(CO_2Me)_2$	1	**6l**, 94	99
12[d]	**5m**, Me, 4-F-C_6H_4, $C(CO_2Me)_2$	1	**6m**, 76	98
13[d]	**5n**, Me, 4-Me-C_6H_4, $C(CO_2Me)_2$	1.5	**6n**, 78	99
14[d]	**5o**, Me, *n*-Pentyl, $C(CO_2Me)_2$	12	**6o**, 60	99
15[d,e]	**5a**, H, H, NTs	1.5	**6a-2**, 72	98

[a] Reaction conditions: $TsOH{\cdot}H_2O$ (30 mol%), **5** (0.1 mmol) in THF (1.0 mL) at RT. [b] Yield of isolated product. [c] Determined by HPLC analysis. [d] Reaction conditions: $Sc(OTf)_3$ (30 mol%), **5** (0.15 mmol) in MeCN (1.5 mL) at RT. [e] The ratio of **6a-1**/**6a-2** was 8/92.

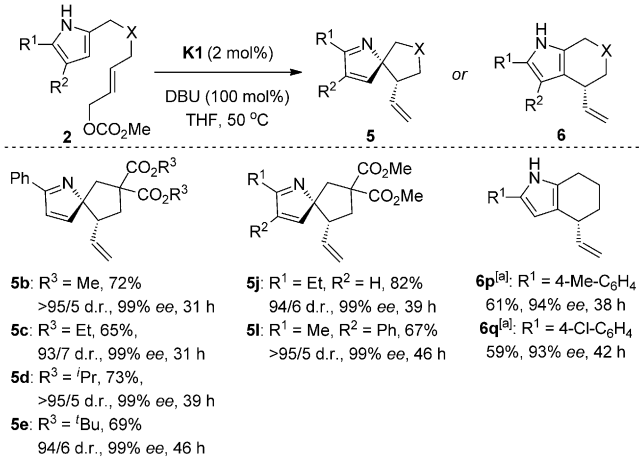
During the investigation of the reaction conditions, we found that ligand **1a** showed exceptional reactivity as well as diastereo- and enantioselectivity toward the dearomatization reaction of pyrrole substrates **2**. Thus, we focused our attention on the synthesis of the iridium complex derived from $[Ir(cod)Cl]_2$ and ligand **1a**. Fortunately, Ir complex **K1**



Scheme 3. Preparation of the Ir complex **K1**.

could be obtained in 46 % yield after a single recrystallization process following the procedure developed by Helmchen and co-workers (Scheme 3).[15] Moreover, the X-ray crystal structure analysis of the (π-allyl)Ir complex **K1** revealed that phenyl C(sp^2)–H bond activation occurred, which was different from the Ir complex generated from $[Ir(cod)Cl]_2$ the ligand **1c** (methyl C(sp^3)–H bond activation).[11b,12,16] The different activation mode of the Ir complex might attributable to the different reactivity and selectivity detected in the dearomatization reaction.

To examine the catalytic activity of the novel (π-allyl)Ir complex **K1**, various pyrrole substrates were subjected to the reaction. To our delight, the reactions proceeded smoothly with comparable results to those obtained with the iridium catalyst generated in situ, even with a decreased loading of the Ir complex **K1** (Scheme 4; **5b**–**5l**, 65–82 % yields,



Scheme 4. Catalytic activity of Ir complex **K1**. [a] **K1** (4 mol %) and K_3PO_4 (100 mol %) were used.

93/7–>95/5 d.r., 99 % *ee*). Interestingly, when substrates (**2p** and **2q**) without the malonate ester group in the tether were used in the reaction, the bicyclic pyrrole compounds **6p** and **6q** were obtained in moderate yields and with excellent *ee* values (59–61 % yields, 93–94 % *ee*; Scheme 4).

In summary, we have achieved the first highly diastereo- and enantioselective synthesis of the five-membered spiro-2*H*-pyrroles by an Ir-catalyzed asymmetric allylic dearomatization reaction. The highly enantioenriched spiro-2*H*-pyrrole derivatives **5** could undergo stereospecific allylic migration reactions with $TsOH{\cdot}H_2O$ or $Sc(OTf)_3$ as the catalyst, yielding their corresponding polycyclic pyrroles **6** without loss of the enantiomeric purity. The migratory aptitude of the methylene group and allyl group was believed to be consistent with their ability to stabilize the carbocation intermediate. Notably, BHPphos (**1a**) was the best choice for the allylic dearomatization reaction, providing the dearomatized products **5** with excellent diastereo- and enantioselectivity. Furthermore, the preparation and characterization of the novel Ir complex **K1** demonstrated that the catalytically active iridium species was formed by phenyl C(sp^2)–H bond activation.

Keywords: asymmetric catalysis · dearomatization · enantioselectivity · iridium · stereospecific migration

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[17] CCDC-1401949 (**5a**), 1401950 (**5m**), 1401951 (**6g**), and 1401952 (**K1**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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