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Enantioselective Synthesis of 1-Aryl Tetrahydroisoquinolines by the Rhodium-Catalyzed Reaction of 3,4-Dihydroisoquinolinium Tetraarylborates

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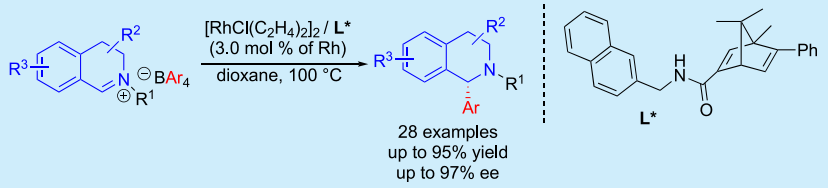

ABSTRACT: The 1-aryl tetrahydroisoquinolines (1-aryl THIQs) are omnipresent in biologically active molecules. Here we report on the direct asymmetric synthesis of these valuable compounds via the reaction of 3,4-dihydroisoquinolinium tetraarylborates. The dual roles of anionic tetraarylborates, which function as both prenucleophiles and stabilizers of 3,4-dihydroisoquinolinium cations, enable this rhodium(I)-catalyzed protocol to convergently provide enantioenriched 1-aryl THIQs in good yields (≤95%) with ≤97% ee, as demonstrated by the formal synthesis of (−)-solifenacin and the facile synthesis of (−)-Cryptostyline I.

1,2,3,4-Tetrahydroisoquinolines (abbreviated as THIQs) with a C1 stereogenic center make up a class of valuable molecules with diverse bioactivities, ranging from bradycardia, central nervous system (CNS) activation, and antidiabetic activities to the reversal of multidrug resistance.[1,2] Among these derivatives, 1-aryl THIQs have a variety of biological and pharmaceutical properties.[2] For example, Cryptostyline I (**1a**), isolated from *Cryptostylis erythroglossa* and *Cryptostylis fulva*,[3a] and **1b** have been used as probes for dopamine receptor D1.[3b] **1c** is a potent antagonist toward ionotropic glutamate receptors (iGluRs).[3c] Solifenacin (Vesicare) (**1d**), an antimuscarinic agent, is used to treat overactive bladders.[3d,e] **1e** is clinically cytotoxic against L1210 murine leukemic cells (Figure 1).[3f]

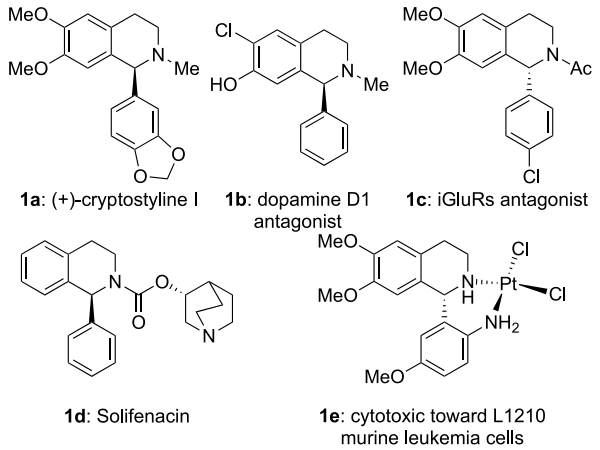

Figure 1. Alkaloids and bioactive compounds bearing 1-aryl THIQ moieties.

Consequently, optically pure 1-aryl THIQs are highly sought-after molecular targets and have stimulated the development of numerous synthetic methods.[1,4,5] Prominent among the transition metal-catalyzed methods are those based on the Ir-catalyzed enantioselective hydrogenation of 1-aryl isoquinolinium salts (Scheme 1, eq a) and their 3,4-dihydroisoquinoline analogues (eq b).[4] However, handling the high H_2 pressure and their linear-synthesis characteristic tend to be limiting factors. For these reasons, the development of a convenient method for convergently producing 1-aryl THIQs has attracted considerable interest. The asymmetric addition of carbon-based nucleophiles to a vast collection of readily available 3,4-dihydroisoquinolinium derivatives[5a,6,7] has emerged as an appealing alternative. Sato et al. published a pioneering study on the enantioselective arylation of 3,4-dihydroisoquinoline *N*-oxides.[6b] This Zn-mediated strategy, however, required a stoichiometric excess of a chiral ethylenediamine ligand to achieve a satisfactory asymmetric induction, thus thwarting its synthetic potential (eq 1c). The shortcoming shown above combined with the lack of a more

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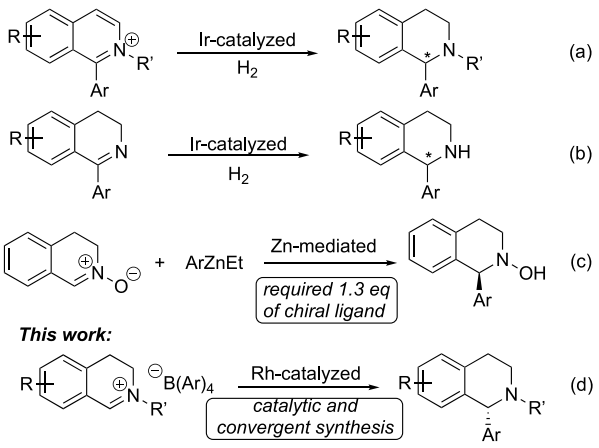
Scheme 1. Synthetic Approaches to the Formation of 1-Aryl THIQs

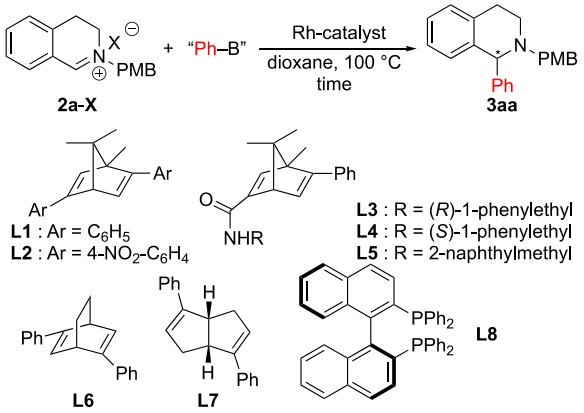


efficient method, therefore, triggered our efforts to develop a more efficient approach.[8]

Our group, recently, employed the asymmetric arylation of *N*-sulfonyl aldimines and ring cyclization reaction sequences to efficiently prepare chiral 1-phenyl THIQ. The use of a Rh catalyst comprised of a chiral bicyclo[2.2.1]heptadiene ligand to establish the stereogenic center was instrumental in our method prior to the sequential cyclization process.[9] Building upon this outcome, we envisioned a straightforward synthesis of 1-aryl THIQs via the asymmetric reaction of aryl-boron reagents with 3,4-dihydroisoquinolinium salts, which were unprecedented and challenging substrates for Rh catalysis. We report herein on the synthesis of such molecules, in which a Rh/chiral diene catalyst is used for the enantioselective reaction of 3,4-dihydroisoquinolinium tetraarylborates (eq d).

At the outset, our initial intention was to identify a suitable aryl-boron nucleophile for an addition reaction of 3,4-dihydroisoquinolinium bromide (**2a-Br**) catalyzed by 1.5 mol % $[RhCl(COD)]_2$ (Table 1). While no reaction was observed when using $PhB(OH)_2$ (entry 1) and $PhBF_3K$ (entry 2),[10] the use of $NaBPh_4$ gave a 23% yield of adduct **3aa** (entry 3).[11] This specific nucleophile led us to conceive of **2a-BPh$_4$** as a feasible substrate for this asymmetric reaction based on the assumption that the tetraphenylborate anion would not only serve as a source of a nucleophile but also enhance the stability of the 3,4-dihydroisoquinolinium cation.[12] The use of **2a-BPh$_4$**, obtained via the anion exchange of **2a-Br** with $NaBPh_4$,[13] resulted in a substantial increase in the chemical yield of **3aa** to 88% (entry 4). This pleasing result led to the subsequent optimization using a Rh catalyst comprised of a series of known chiral ligands to achieve high enantioselectivity. In initial experiments,[10] we observed the formation of **3aa** in 58% and 71% yields with 93% and 86% ee, respectively, in the presence of 3 mol % Rh catalysts derived from chiral bicyclo[2.2.1]heptadiene ligands **L1** and **L2**[14] (entries 5 and 6, respectively). A further examination of the chiral diene ligands **L3**−**L5**[15] bearing a secondary amido group resulted in relatively improved yields and selectivities (entries 7−9, respectively), with **L5** optimally giving rise to **3aa** in 82% yield with 92% ee (entry 9). Used in other Rh-catalyzed

Table 1. Optimization of Reaction Conditions[a]



entry	X	Ph-B	Rh catalyst	time (h)	yield (%)[b]	ee (%)[c]
1	Br	$PhB(OH)_2$	$[RhCl(COD)]_2$	36	nr[d]	–
2	Br	$PhBF_3K$	$[RhCl(COD)]_2$	36	nr[d]	–
3	Br	$NaBPh_4$	$[RhCl(COD)]_2$	36	23	–
4	BPh_4	–	$[RhCl(COD)]_2$	15	88	–
5	BPh_4	–	$[RhCl(C_2H_4)_2]_2$/**L1**	9	58	93
6	BPh_4	–	$[RhCl(C_2H_4)_2]_2$/**L2**	4	71	86
7	BPh_4	–	$[RhCl(C_2H_4)_2]_2$/**L3**	12	74	93
8	BPh_4	–	$[RhCl(C_2H_4)_2]_2$/**L4**	6	56	86
9	BPh_4	–	$[RhCl(C_2H_4)_2]_2$/**L5**	12	82	92
10	BPh_4	–	$[RhCl(C_2H_4)_2]_2$/**L6**	48	nr[d]	nd[e]
11	BPh_4	–	$[RhCl(C_2H_4)_2]_2$/**L7**	48	nr[d]	nd[e]
12	BPh_4	–	$[RhCl(C_2H_4)_2]_2$/**L8**	48	nr[d]	nd[e]

[a]With 0.2 mmol of **2a-X** in dioxane (1.0 mL) and $[RhCl(COD)_2]_2$ (1.5 mol %), or $[RhCl(C_2H_4)_2]_2$ (1.5 mol %) and **L** (3.6 mol %). [b]Isolated yield. [c]Determined by chiral HPLC analysis. [d]No reaction. [e]Not determined.

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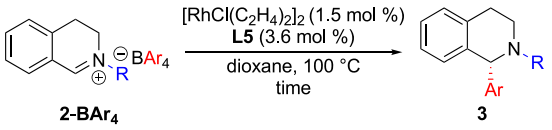
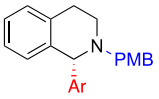
asymmetric reactions, chiral ligands **L6**−**L8** failed to produce the desired adduct (entries 10−12, respectively).

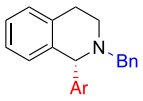
The scope of the reaction for various 3,4-dihydroisoquinolinium tetraarylborates was then explored (Scheme 2). The

Scheme 2. Substrate Scope (I)[e]

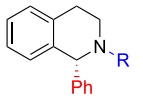




3aa, Ar = C_6H_5, 15 h, 70%, 92% ee[a]
3ab, Ar = 3-Me-C_6H_4, 8 h, 60%, 94% ee
3ac, Ar = 4-Me-C_6H_4, 8 h, 60%, 92% ee
3ad, Ar = 3-MeO-C_6H_4, 8 h, 51%, 92% ee
3ae, Ar = 4-MeO-C_6H_4, 8 h, 85%, 67% ee
12 h, 56%, 81% ee[b]
3af, Ar = 4-Cl-C_6H_4, 71 h, 21%, 94% ee
20 h, 39%, 94% ee[c]
3ag, Ar = 2-naphthyl, 15 h, 82%, 40% ee
36 h, 74%, 80% ee[d]



3ba, Ar = C_6H_5, 12 h, 73%, 93% ee
3bh, Ar = 4-*t*Bu-C_6H_4, 38 h, 55%, 94% ee
3bi, Ar = 4-F-C_6H_4, 24 h, 50%, 96% ee[c]
3bj, Ar = 4-TMS-C_6H_4, 24 h, 30%, 77% ee[c]



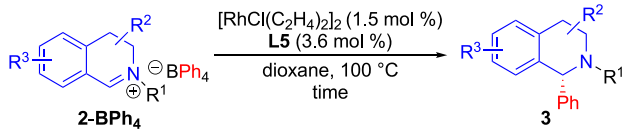
3ca, R = 4-NO_2-benzyl, 15 h, 90%, 86% ee
3da, R = CH_2CO_2Et, 13 h, 35%, 82% ee
3ea, R = Me, 43 h, 40%, 97% ee[c]

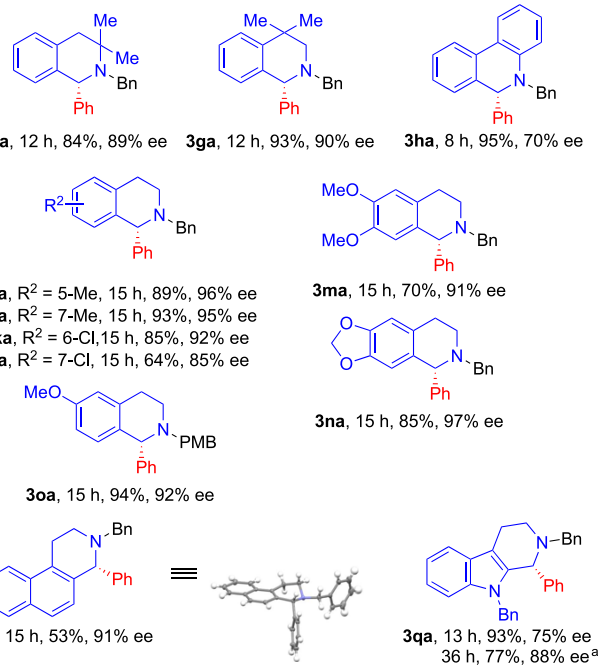
[a]On a 2 mmol (1.14 g) scale. [b]At 80 °C. [c]At 120 °C. [d]Using chiral diene ligand **L1**. [e]Reaction conditions: 0.2 mmol of **2-BAr$_4$** in dioxane (1.0 mL), $[RhCl(C_2H_4)_2]_2$ (1.5 mol %), **L5** (3.6 mol %), stirred at 100 °C.

enantioselective reactions of N-PMB 3,4-dihydroisoquinoliniums harboring diverse tetraarylborates afforded the corresponding adducts (**3aa**−**3ag**) in 21−85% yields with 80−94% ee. Notably, the reaction temperature was found to be a key factor in influencing the reactivity and enantioselectivity of the reaction. For the substrate containing tetra-4-MeO-phenyl borate, adjusting the reaction temperature to 80 °C is necessary for the corresponding product **3ae** to be produced in 81% ee, compared to the observed 67% ee at 100 °C, suggesting that the use of a lower reaction temperature resulted in a satisfactory ee for a prenucleophile containing a *para*-electron-releasing aryl group. On the contrary, the reaction of the tetraarylborate substrate harboring 4-Cl-phenyl substituents required a 120 °C reaction temperature to allow the production of **3af** in an optimal 39% yield. In addition, an enhanced 80% ee of **3ag** was observed when the reaction was carried out in the presence of the Rh(I)/**L1** catalyst for a bulkier 2-naphthyl nucleophile as opposed to the value of 40% ee when using **L5**. Asymmetric reactions with substrates bearing various N substituents provided the corresponding products (**3ba**[16]−**3ea**) in 30−90% yields along with 77−97% ee. Conducting this asymmetric reaction on a larger scale (2.0 mmol), under optimal reaction conditions, furnished **3aa** in 70% yield without the erosion of the high enantioselectivity.

Further investigations focused on substrates with varying 3,4-dihydroisoquinolinium motifs were carried out (Scheme 3). Substrates, bearing substituents on the N-containing heterocyclic ring core, underwent phenylation smoothly to

Scheme 3. Substrate Scope (II)[b]





3fa, 12 h, 84%, 89% ee
3ga, 12 h, 93%, 90% ee
3ha, 8 h, 95%, 70% ee
3ia, R^2 = 5-Me, 15 h, 89%, 96% ee
3ja, R^2 = 7-Me, 15 h, 93%, 95% ee
3ka, R^2 = 6-Cl,15 h, 85%, 92% ee
3la, R^2 = 7-Cl, 15 h, 64%, 85% ee
3ma, 15 h, 70%, 91% ee
3na, 15 h, 85%, 97% ee
3oa, 15 h, 94%, 92% ee
3pa, 15 h, 53%, 91% ee
3qa, 13 h, 93%, 75% ee
36 h, 77%, 88% ee[a]

[a]At 80 °C. [b]Reaction conditions: 0.2 mmol of **2-BPh$_4$** in dioxane (1.0 mL), $[RhCl(C_2H_4)_2]_2$ (1.5 mol %), and **L5** (3.6 mol %), stirred at 100 °C.

afford adducts (**3fa**−**3ha**) in 84−95% yields with 70−90% ee. Asymmetric phenylation with substrates containing substituted aromatic rings, regardless of whether they contained alkyl, electron-withdrawing, or electron-releasing substituents, offered the desired adducts (**3ia**−**3oa**) in 64−94% yields with 85−97% ee. 3,4-Dihydroisoquinolinium salts with extended π-conjugation or an analogue derived from 9-benzyl β-carboline were also applicable to this enantioselective reaction, furnishing **3pa** in 53% yield with 91% ee and **3qa** in 77% yield and 88% ee. The newly formed stereogenic center was unequivocally determined by a single-crystal X-ray crystallography analysis of **3pa** to possess an *R* configuration.

Although various 3,4-dihydroisoquinolinium tetraarylborates are applicable, a further investigation of the addition reaction of the 1-methyl-3,4-dihydroisoquinolinium analogue, **4-BPh$_4$**, under the optimized reaction conditions, failed to furnish the adduct bearing a quaternary stereogenic center (Scheme 4, eq 1). A diminishing asymmetric induction was observed in the case of the reaction with the isoquinolinium substrate **5-BPh$_4$**, providing **3ba**, after a subsequent reduction, in a combined 75% yield with 55% ee. This outcome suggests the 3,4-dihydroisoquinolinium ions are preferable substrates in this asymmetric transformation (eq 2). A limitation was found in the case of a tetra-heteroarylborate-containing substrate **2n-B(2-furyl)$_4$**, which afforded the desired adduct **3nb** in 46% yield with 23% ee (eq 3). While the use of $PhBF_3K$ gave no desired adduct (Table 1, entry 2), **2a-Br** underwent alkenylation with potassium octenyltrifluoroborate to afford product **3ah** in a 47% yield, but with no stereoselectivity (eq

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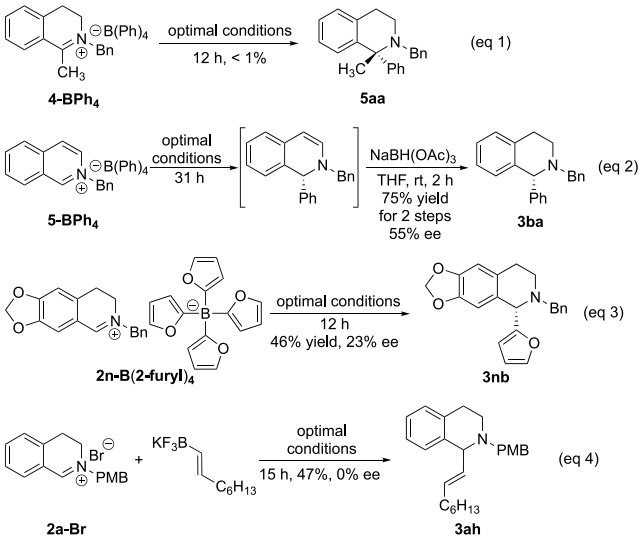
Scheme 4. Limitations



4), highlighting the stark difference in reactivity between aryl and alkenyl trifluoroborates.

Using the models shown in Figure 2, we propose a reaction pathway that explains the observed stereochemical outcomes.

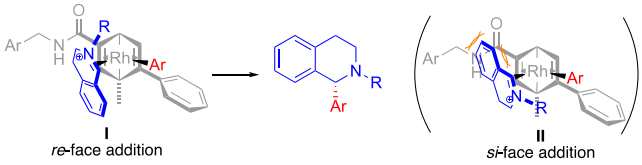
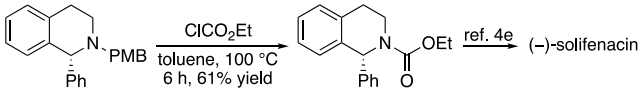


Figure 2. Proposed rationale for the stereochemical outcome of phenylation of 3,4-dihydroisoquinolinium salt.

Transmetalation of the aryl group from tetraarylborate occurs, yielding the corresponding [Rh]-Ar species to allow the addition reaction to proceed more readily via the formation of the *re*-face-coordinated transition structure (**I**) compared to that with a *si*-face coordination (**II**), which is energetically disfavored as a result of steric repulsion between the 3,4-dihydroisoquinolinium ion and the ligand backbone, giving rise to the observed *R* adducts.

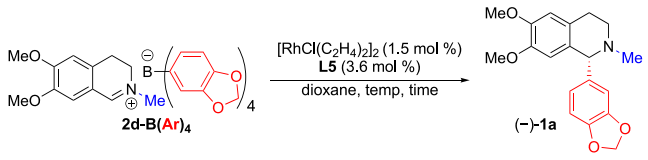
Treatment of **3aa** with ethyl chloroformate in toluene provided the resulting **6aa** in 61% without erosion of high ee, enabling a one-pot formal synthesis of (−)-solifenacin (Scheme 5).[4e]

Scheme 5. Formal Synthesis of (−)-Solifenacin



Although the successful production of **3ea** paved the way for the enantioselective synthesis of the naturally occurring Cryptostyline I (**1a**) (Figure 1), which demonstrates the synthetic utility of this reaction, the synthesis of **1a** was not encouraging at the early stage of the study. Under the optimal reaction conditions, the desired **1a** was produced in 92% yield but with only 60% ee (Table 2, entry 1). In the ensuing investigation, the ee of **1a** was increased to 73% when the

Table 2. Total Synthesis of (−)-Cryptostyline I [(−)-1a][a]



entry	ligand	temp (°C)	time (h)	yield (%)[b]	ee (%)[c]
1	**L5**	100	15	92	60
2	**L5**	80	24	90	73
3	**L1**	80	144	90	70
4	**L2**	80	48	90	79
5	**L2**	60	140	90	88

[a]With 0.2 mmol of **2d**-**B**(**Ar**)$_4$ in dioxane (1.0 mL), [RhCl(C_2H_4)$_2$]$_2$ (1.5 mol %), and **L5** (3.6 mol %). [b]Isolated yield. [c]Determined by chiral HPLC analysis.

reaction was performed at a lower temperature (80 °C) as a result of using a *para*-electron-releasing aryl prenucleophile. The comparatively weaker asymmetric induction in the formation of **1a** prompted us to reinvestigate the reaction conditions based on chiral diene ligands. Carrying out the reaction in the presence of the Rh(I)/**L1** catalyst at 80 °C for 144 h furnished **1a** in a comparable yield and ee (entry 3). Employing a Rh catalyst comprising **L2** slightly increased the enantioselectivity of **1a** in a comparatively shorter reaction time (48 h) (entry 4), and under such reaction conditions, the reaction at 60 °C ultimately afforded **1a** in a ≤88% ee (entry 5).

In conclusion, we report on the development of a method for providing enantioenriched 1-aryl THIQs based on enantioselective reaction of 3,4-dihydroisoquinolinium tetraarylborates. This protocol, in the presence of 3 mol % Rh/**L5** catalyst, proceeds smoothly to afford 1-aryl THIQs in ≤97% ee. The tetraarylborate anions not only function as stabilizers of the highly reactive but unstable 3,4-dihydroisoquinolinium countercations but also serve as readily available prenucleophiles for this asymmetric transformation to allow convenient and rapid production of a wide variety of optically active 1-aryl THIQs containing various substituents and structures. The formal synthesis of (−)-solifenacin and asymmetric synthesis of the alkaloid (−)-Cryptostyline I [(−)-**1a**] clearly confirm the synthetic applicability of this protocol.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00198.

Experimental procedures, complete characterization data, HPLC chromatograms, and NMR spectra (PDF)

Accession Codes

CCDC 2035808 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.

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