

Article

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Ramarao Parella, and Srinivasarao Arulananda Babu

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Regio- and Stereoselective Pd-Catalyzed Direct Arylation of Unactivated sp^3 C(3)-H Bonds of Tetrahydrofuran and 1,4-Benzodioxane Systems

Ramarao Parella and Srinivasarao Arulananda Babu*

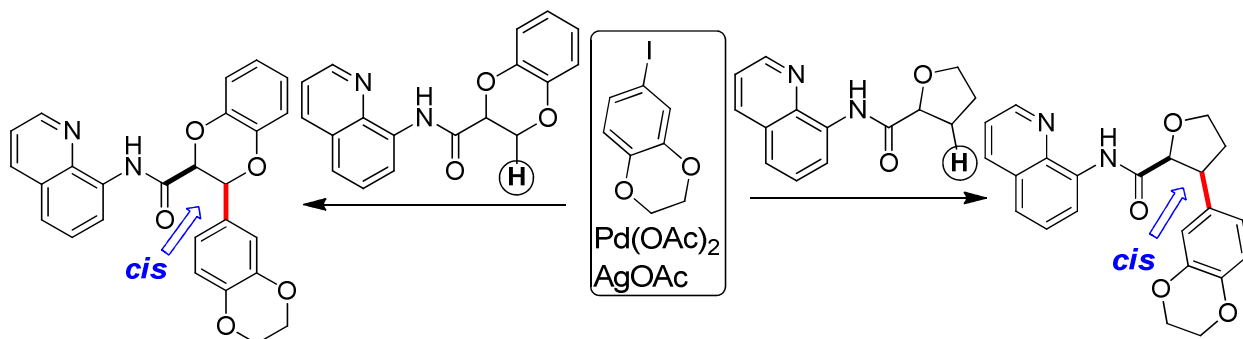
Department of Chemical Sciences, Indian Institute of Science Education and Research (IISER)

Mohali, Manauli P.O., Sector 81, SAS Nagar, Mohali, Knowledge City, Punjab 140306, India

sababu@iisermohali.ac.in

ABSTRACT

sp^3 C-H activation and direct C(3)-H arylation of THF and benzodioxane



- regio- and stereoselective arylation of sp^3 C-H at C-3

- neolignan & norlignan analogues with *cis* stereochemistry

An auxiliary-enabled Pd-catalyzed highly regio- and stereoselective sp^3 C-H activation and the direct arylation of the C3-position of oxygen heterocycles, such as tetrahydrofuran and 1,4-benzodioxane systems are reported. An efficient stereoselective construction of *cis* 2,3-disubstituted tetrahydrofuran derivatives (analogues of norlignans) and *cis* 2,3-disubstituted 1,4-benzodioxane derivatives (analogues of neolignans) is described. The direct C(sp^3)-H arylation of the C3-position of (*R*)- or (*S*)- tetrahydrofuran-2-carboxamides furnished the corresponding (2*R*,3*R*) and (2*S*,3*S*) C3-arylated THF scaffolds as major compounds with very high regio- and diastereoselectivities. The stereochemistry of the products obtained in this work were

unambiguously assigned on the basis of the X-ray structure analyses of representative compounds **3b**, **3e**, **4p** and **7**.

INTRODUCTION

Saturated oxygen heterocycles, especially, tetrahydrofuran (THF) and benzodioxane based motifs are recurrently encountered in nature (e.g., lignans, annonaceous acetogenins, polyether ionophores/antibiotics and macrodiolides), pharmaceuticals and bioactive synthetic compounds.^{1,2} Several substituted THF- and benzodioxane-based synthetic molecules and naturally occurring lignan-, neolignan- and norlignan oxygen heterocycles were found to exhibit a wide range of biological activities (e.g., anticancer, antioxidant, antimicrobial, anti-inflammatory and immunosuppressive activities).¹⁻⁴ There exist several naturally occurring THF-norlignan and benzodioxane-neolignan motifs possessing an aryl group at the C3-position (Figure 1) and many of them were found to exhibit various biological activities.^{1,2} For example, recently, a family of THF-norlignans, such as metasequirins A, B, E, F, G and H were isolated^{2a-c} and metasequirins E and F were evaluated for cytotoxicity against five human tumor cell lines.^{2a} Further, benzodioxane-neolignan molecules, such as isoamericanol A, americanol A, isoamericanin A and americanin A were found to show neurotropic and acetylcholine enhancing activities.^{2d,e} The present investigation deals on the synthesis of analogues of norlignans and neolignans.

Due to their prevalence in natural products, biological activities and ability to serve as building blocks in organic chemistry, numerous classical and modern stereoselective synthetic methods¹⁻⁴ including the α -C-H functionalization⁵ have been developed for producing bioactive and

synthetic tetrahydrofuran and benzodioxane derivatives. In general, majority of the tetrahydrofuran and benzodioxane derivatives were assembled mainly via the cyclization reaction^{3,4} of pre-designed starting materials having the required functional groups.

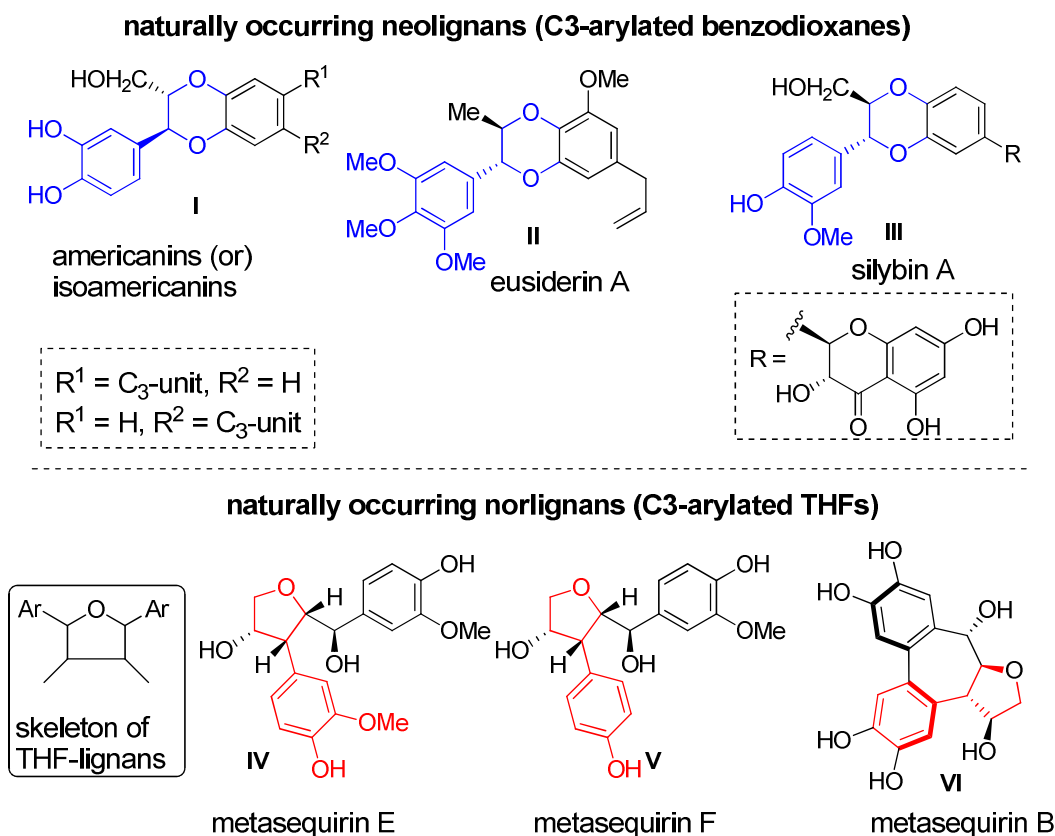


Figure 1. Representative examples of lignan natural products.

The direct functionalization of the unactivated C(sp³)-H bonds of organic molecules is known to be a challenging task in the past decades. However, from the recent past decade, several exceptional reports appeared on the transition metal-catalyzed direct functionalization of C-H bonds present in organic molecules and indeed, functionalization of organic molecules via the C-H activation is emerging as one of the important strategies.⁶⁻¹⁵ There exist several outstanding reports which are dealing on the direct functionalization of C(sp²)-H bonds present in organic

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2
3 molecules. On the other hand, the direct functionalization of the unactivated C(sp³)-H bonds
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5 present in organic molecules is one of the emerging research areas.⁶⁻¹⁵ Notably, an auxiliary-
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7 enabled, Pd-catalyzed arylation reaction of alkyl C(sp³)-H bonds instigated by Daugulis, Yu,
8
9 Chen and others is emerging as one of the seminal methods for constructing C-C bonds. In this
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11 line, the direct arylations of C(sp³)-H bonds present in the carbocyclic systems, such as
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13 cyclopropane, cyclobutane, medium-sized rings, norbornane framework and acyclic amino acid
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15 derivatives have been successfully demonstrated by various research groups.^{14,15}
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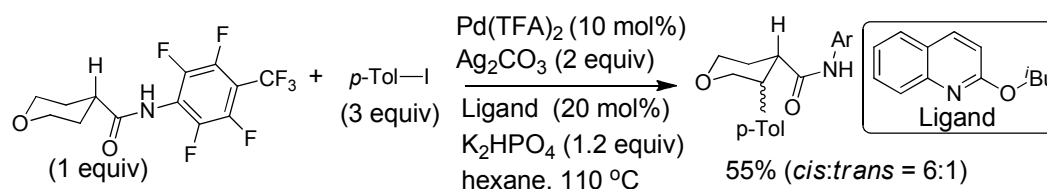
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19 Along this line, we envisioned the selective C-H functionalization and the direct arylation of the
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21 unactivated C(sp³)-H bonds present in the THF and 1,4-benzodioxane systems for assembling
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23 new neolignan/norlignan scaffolds. To the best of our knowledge, there exist only rare papers
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25 dealing on the directing group-enabled, Pd-catalyzed C-H functionalization of the unactivated
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27 C(sp³)-H bonds of saturated heterocycles and a literature survey revealed that there is no report
28
29 dealing on the Pd-catalyzed direct arylation of the C3-position of the tetrahydrofuran and
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31 benzodioxane systems.⁶⁻¹⁵ With regard to the functionalization of C(sp³)-H bonds of saturated
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33 oxygen heterocycles, there exist only two examples reported by Yu *et al.*, which include the
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35 arylation^{15a} and alkynylation^{15b} of the C3-position of a tetrahydropyran derivative (Scheme 1).
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37 On the other hand, with regard to the functionalization of the unactivated C(sp³)-H bonds of
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39 saturated nitrogen heterocycles, recently, Bull *et al.* reported the direct arylation of the C(3)-H
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41 bond of a proline derivative.^{15c} Wu *et al.* revealed the amination reaction involving the C(3)-H
42
43 bond of a proline derivative.^{15d} Earlier, Chen's group reported an example of the direct alkylation
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45 of the C(3)-H bond of a piperidine derivative.^{15e}
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53 In continuation of our lab's interest on the C-H activation reactions, herein, we report an
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55 auxiliary-enabled, Pd-catalyzed highly regio- and stereoselective C(sp³)-H
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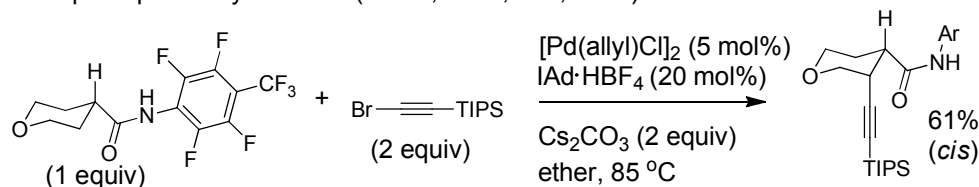
activation/functionalization of the tetrahydrofuran and 1,4-benzodioxane systems. This work demonstrates a new route for the direct arylation of the of C(3)-H position of oxygen heterocycles, such as tetrahydrofuran and 1,4-benzodioxane systems and highly stereoselective construction of novel norlignan-type *cis* 2,3-disubstituted tetrahydrofurans and neolignan-type *cis* 2,3-disubstituted 1,4-benzodioxanes.

Scheme 1. Theme of This Work.

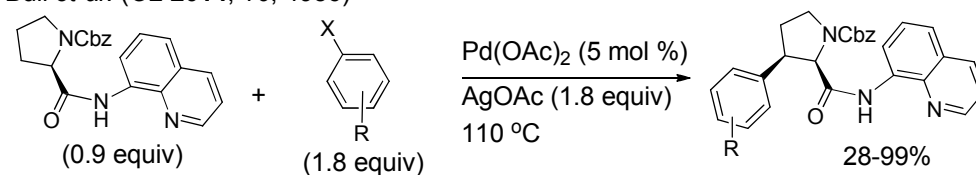
an example reported by Yu *et al.* (JACS, 2012, 134, 18570)



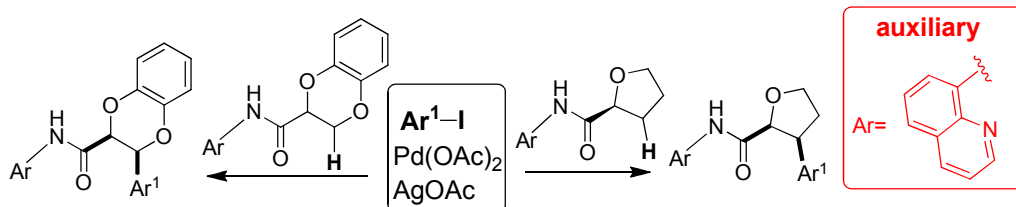
an example reported by Yu *et al.* (JACS, 2013, 135, 3387)



Bull *et al.* (OL 2014, 16, 4956)



this work: direct C(3)-H arylation of THF and benzodioxane systems



- highly regio- and stereoselective arylation of sp^3 C(3)-H bond
- construction of neolignan & norlignan scaffolds

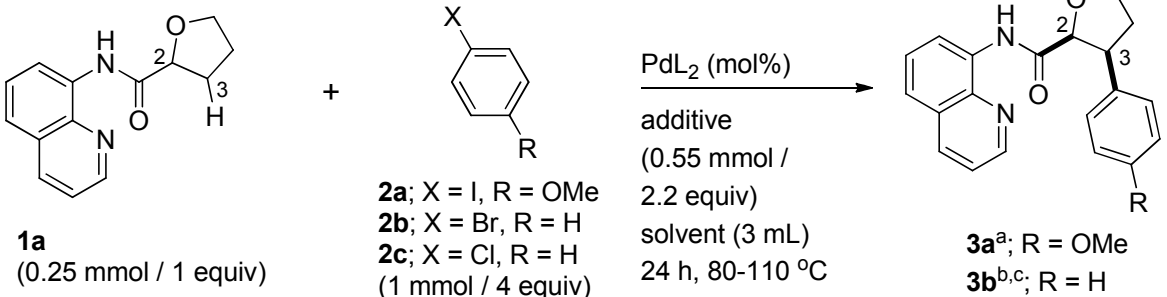
RESULTS AND DISCUSSION

To examine the arylation of methylene C(sp³)-H bond of oxygen heterocycles, such as tetrahydrofuran and 1,4-benzodioxane systems, initially, we prepared the substrate **1a** by linking tetrahydrofuran-2-carboxylic acid chloride with the Daugulis's bidentate directing group (8-aminoquinoline).^{14a,b} Then, to find out the best reaction conditions for achieving the C(3)-H arylation of substrate **1a**, we performed several reactions as shown in Table 1. We found the best reaction conditions comprising the reaction of substrate **1a**, aryl iodide **2a** and AgOAc (additive) in the presence 5 or 10 mol% of the Pd(OAc)₂ catalyst, which afforded the C3-arylated product, *cis* 2,3-disubstituted tetrahydrofuran **3a** (norlignan analogue) in 70 and 81% yields, respectively (entries 3 and 4, Table 1). The C-H arylation of the substrate **1a** with **2a** in the presence of Ag₂CO₃ as an additive instead of AgOAc also gave the product **3a** in 69% yield (entry 5, Table 1).

The Pd-catalyzed C(3)-H arylation of substrate **1a** with **2a** in the presence of various other additives, such as K₂CO₃ or KOAc or PhI(OAc)₂ did not give the product **3a** (entries 6-8, Table 1). The C-H arylation of substrate **1a** in the presence of other palladium catalysts, such as PdCl₂ or Pd(TFA)₂ instead of Pd(OAc)₂ did not give satisfactory yields (entries 9 and 10, Table 1). However, the C-H arylation of **1a** in the presence of Pd(CH₃CN)₂Cl₂ and Pd(PPh₃)₄ instead of Pd(OAc)₂ furnished the product **3a** in 69 and 30% yields, respectively (entries 11 and 12, Table 1). The Pd-catalyzed C-H arylation of **1a** with **2a** in other solvents, such as MeCN or 1,2-DCE or *tert*-butyl alcohol failed to afford the product **3a** (entries 13-15, Table 1). However, the Pd-catalyzed reaction of **1a** with **2a** in 1,4-dioxane or *tert*-amyl alcohol gave the product **3a** in 46

and 57% yields, respectively (entries 16 and 17, Table 1). Employing coupling partners **2b** or **2c** instead of **2a** was ineffective (entry 18, Table 1).

Table 1. Optimization of Reaction Conditions.



1a
(0.25 mmol / 1 equiv)

2a; X = I, R = OMe
2b; X = Br, R = H
2c; X = Cl, R = H
(1 mmol / 4 equiv)

PdL₂ (mol%)
additive
(0.55 mmol /
2.2 equiv)
solvent (3 mL)
24 h, 80-110 °C

3a^a; R = OMe
3b^{b,c}; R = H

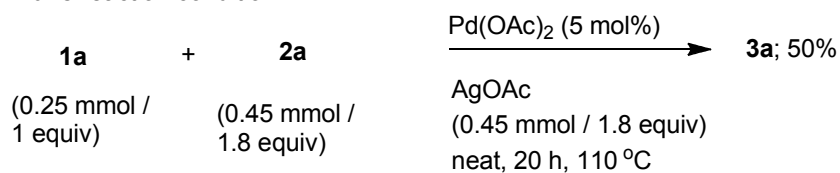
entry	PdL ₂ (mol%)	additive (mmol)	solvent (3 mL)	T (°C)	3a ; yield (%) ^a
1	nil	AgOAc (0.55)	toluene	110	0
2	Pd(OAc) ₂ (10)	nil	toluene	110	<15
3	Pd(OAc) ₂ (5)	AgOAc (0.55)	toluene	110	70
4	Pd(OAc)₂ (10)	AgOAc (0.55)	toluene	110	81
5	Pd(OAc) ₂ (10)	Ag ₂ CO ₃ (0.55)	toluene	110	69
6	Pd(OAc) ₂ (10)	K ₂ CO ₃ (0.55)	toluene	110	0
7	Pd(OAc) ₂ (10)	KOAc (0.55)	toluene	110	traces
8	Pd(OAc) ₂ (10)	PhI(OAc) ₂ (0.55)	toluene	110	0
9	PdCl ₂ (10)	AgOAc (0.55)	toluene	110	<10
10	Pd(TFA) ₂ (10)	AgOAc (0.55)	toluene	110	0
11	Pd(CH ₃ CN) ₂ Cl ₂ (10)	AgOAc (0.55)	toluene	110	69
12	Pd(PPh ₃) ₄ (10)	AgOAc (0.55)	toluene	110	30
13	Pd(OAc) ₂ (10)	AgOAc (0.55)	CH ₃ CN	80	0
14	Pd(OAc) ₂ (10)	AgOAc (0.55)	1,2-DCE	80	0
15	Pd(OAc) ₂ (10)	AgOAc (0.55)	<i>t</i> BuOH	85	0
16	Pd(OAc) ₂ (10)	AgOAc (0.55)	1,4-Dioxane	100	46
17	Pd(OAc) ₂ (10)	AgOAc (0.55)	<i>t</i> AmylOH	110	57
18	Pd(OAc) ₂ (10)	AgOAc (0.55)	toluene	110	0 ^{b,c}

^a The yield corresponds to the reaction of **1a** with **2a**. ^b The yield corresponds to the reaction of **1a** with **2b**. ^c The yield corresponds to the reaction of **1a** with **2c**.

Table 2. Optimization of Reaction Conditions.

$ \begin{array}{ccc} \text{1a} & + & \text{2a} \\ (0.25 \text{ mmol} / & & (0.25 - 1.0 \text{ mmol} / \\ 1 \text{ equiv}) & & 1-4 \text{ equiv}) \end{array} \xrightarrow[\text{24 h, 110 }^\circ\text{C}]{\text{Pd(OAc)}_2 (10 \text{ mol}\%), \text{ AgOAc} (0.55 \text{ mmol} / 2.2 \text{ equiv}), \text{ toluene (3 mL)}} \text{3a} $				
entry	2a (mmol)	2a (equiv)	ratio of 1a : 2a	3a: yield (%)
1	0.25	1	1 : 1	35
2	0.5	2	1 : 3	59
3	0.75	3	1 : 3	68
4	1.0	4	1 : 4	81

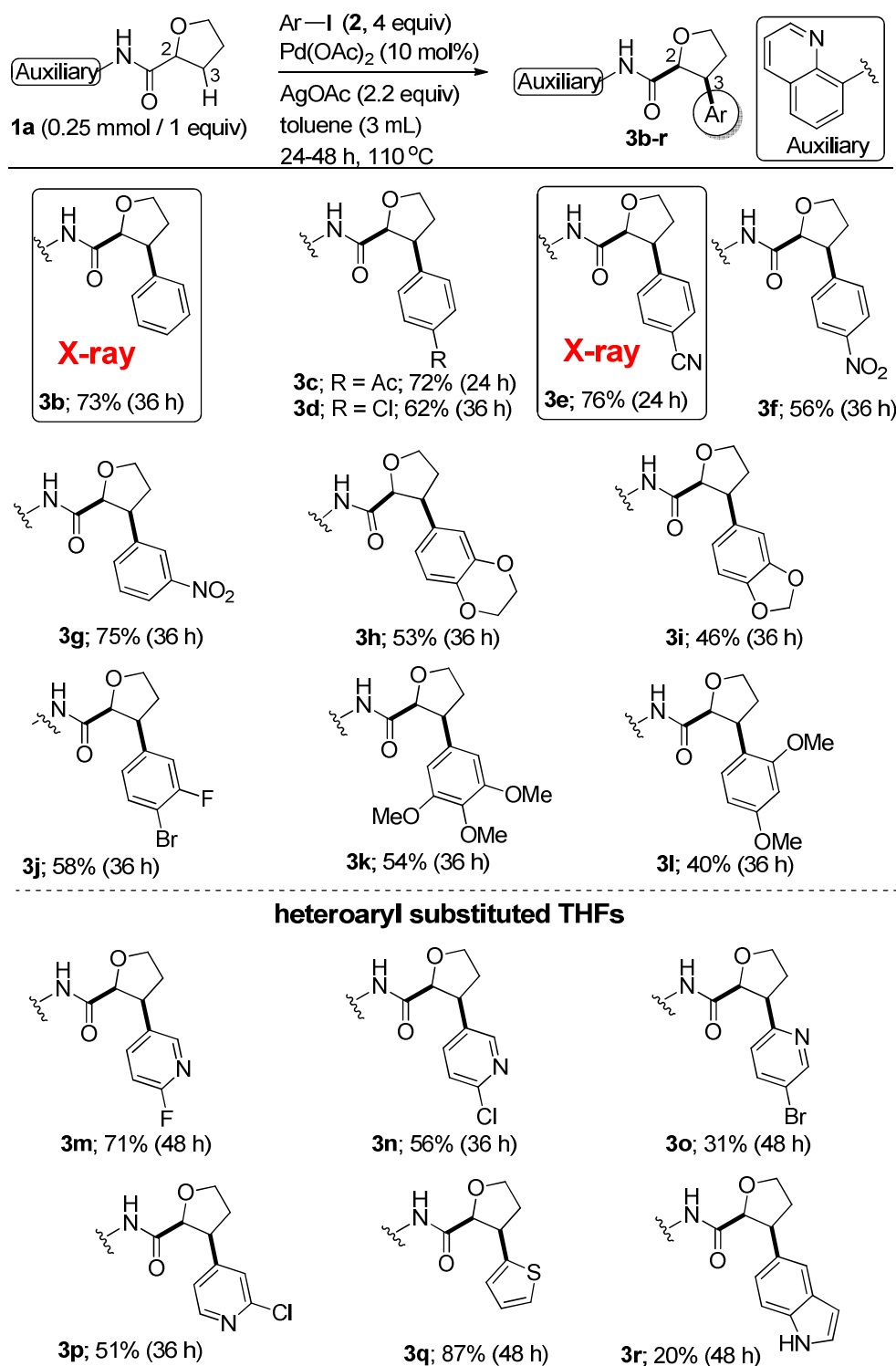
Bull's reaction condition



In order to find out how many equivalents of aryl iodide **2a** are required for producing the C3-arylated product **3a** with better yield, we investigated the C-H arylation of substrate **1a** by varying the quantity of **2a** (Table 2). The Pd-catalyzed C-H arylation of substrate **1a** with one equivalent of **2a** gave the C3-arylated product **3a** in low yield (35%, entry 1, Table 2). Next, the Pd-catalyzed C-H arylation of substrate **1a** with two or three equivalents of **2a** gave the C3-arylated product **3a** in 59% and 68% yields, respectively (entries 2 and 3, Table 2). The usage of four equivalents of **2a** gave the C3-arylated product **3a** in very good yield (81%, entry 4, Tables 1 and 2). In this line, we have also performed the Pd-catalyzed C-H arylation of substrate **1a** with 1.8 equivalents of **2a** by using the Bull's reaction conditions,^{15c} which gave the C3-arylated product **3a** in 50% yield (Table 2).

Scheme 2. Arylation of sp^3 C(3)-H Bond of **1a** and Construction of Norlignan-THF

Scaffolds.

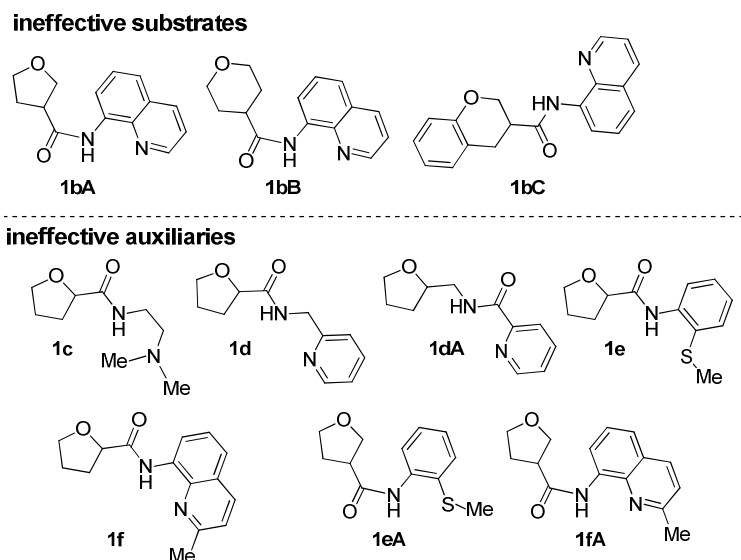


Subsequently, the generality of this bidentate directing group-enabled, Pd-catalyzed direct arylation of C(3)-H bond of the THF derivative **1a** was elaborated using a variety of aryl iodides (Scheme 2). The direct arylation of the methylene sp^3 C(3)-H bond of the substrate **1a** with various aryl iodides containing a substituent at the *para* or *meta* position (e.g., Ac, Cl and NO_2) afforded the corresponding *cis* 2,3-disubstituted tetrahydrofurans **3b-3g** in 56-76% yields. Similarly, the C3-arylated THF scaffolds **3h** and **3i** were obtained from the Pd-catalyzed C-H arylation of the substrate **1a** by using the corresponding benzodioxane- or benzodioxole-based aryl iodides as the coupling partners. Further, the arylation of the substrate **1a** with multi substituted aryl iodides gave the corresponding products **3j-l** in 40-58% yields. We have also carried out the Pd-catalyzed direct arylation of the C(3)-position of the THF derivative **1a** with a variety of hetero aryl iodides, which furnished the corresponding THF scaffolds **3m-3r** possessing heteroaryl groups at the C3-position in 20-87% yields.

Representatively, recrystallization of C-H arylated products **3b** and **3e** formed single-crystals, which were subjected to the single-crystal X-ray structure analyses. The X-ray structures of the representative compounds **3b** and **3e** (see SI for the X-ray structures of **3b** and **3e**)¹⁶ unambiguously confirmed that all these reactions were highly regio- and stereoselective and the direct C-H arylation occurred only at the C3-position of the substrate **1a** and selectively gave the 2,3-disubstituted tetrahydrofurans **3a-r** having the *cis* stereochemistry (C2-C3 stereocenters). In addition, characteristically, the C2 proton of all the compounds (**3a-r**) appeared as a doublet (chemical shift value range, δ = 4.71-4.91 ppm) due to its coupling with the C3 proton. The coupling constants (J) of the doublet peaks of the C2 proton of all the compounds **3a-r** were calculated from their respective 1H NMR spectra and found to be in the range of 6.6-8.2 Hz (except the compound **3q** having a thiophene moiety at the C3-position, C2H, doublet, J = 6.3

Hz).^{17a} Accordingly, the stereochemistry of all the compounds **3a-r** were assigned as *cis* on the basis of the X-ray structure analyses of the compounds **3b** and **3e** coupled with the similarity in the NMR spectral pattern of the compounds **3a-r**.

Figure 2. Investigation of C(sp³)-H Arylation Reactions Using Other Substrates and Auxiliaries.^{a,b}



^a Conditions: Substrate (0.25 mmol), **2a** or 1-iodo-4-methylbenzene (1 mmol, 4 equiv), (Pd(OAc)₂ (5-10 mol%), AgOAc (0.55 mmol, 2.2 equiv), toluene (3 mL), 24 h and 110 °C. ^b See the SI for additional information and individual reaction conditions (Tables 3-5).

Successively, we investigated the Pd-catalyzed C-H arylation of other substrates, such as **1bA**, **1bB** and **1bC** (Figure 2). It is a limitation that the Pd-catalyzed C-H arylation reactions of substrates **1bA**, **1bB** and **1bC** with **2a** were not successful (see the SI for additional information and individual reaction conditions). Furthermore, to find out the other working auxiliaries for selectively arylating the C(3)-H bond of THF derivatives, we performed the Pd-catalyzed reactions of substrates **1c-f**, **1dA**, **1eA** and **1fA** with **2a** (Figure 2) and in these reactions we did not get any of the corresponding C-H arylated THF products. These reactions indicated that 8-

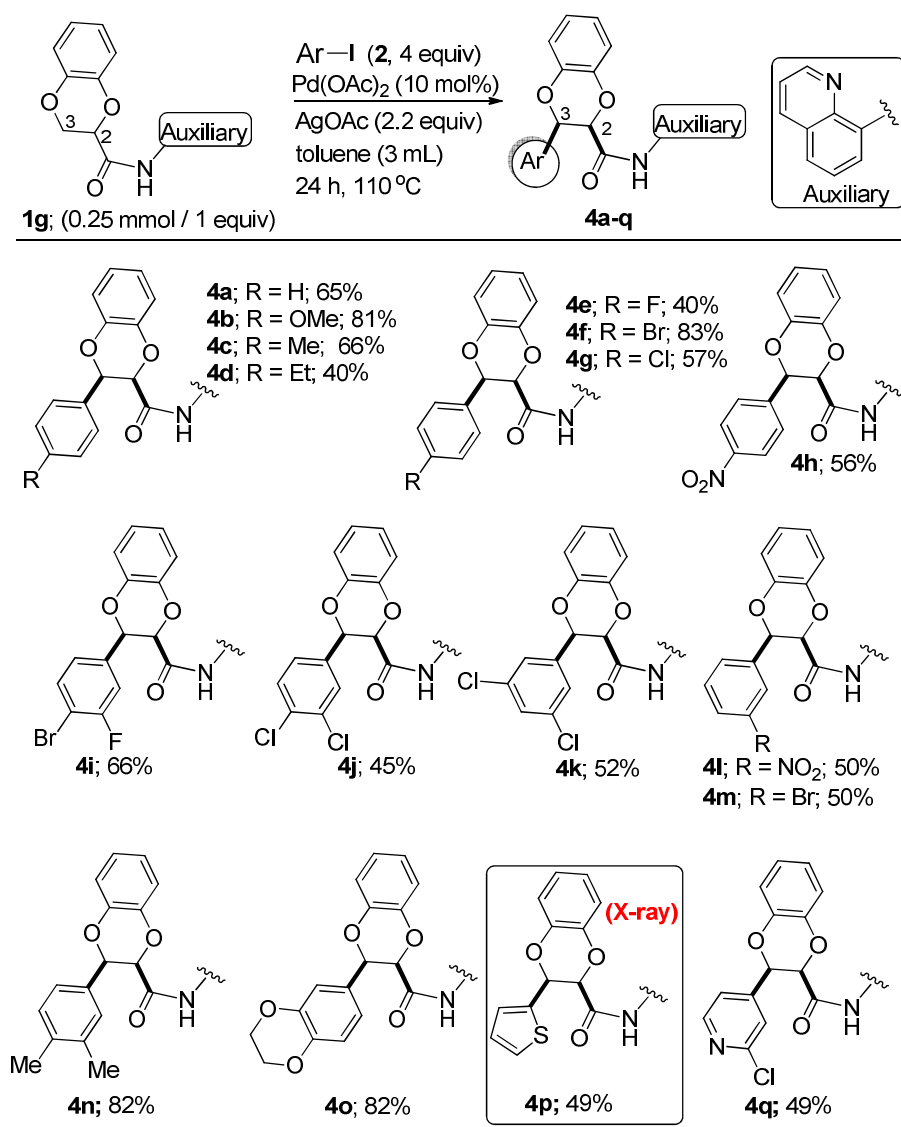
aminoquinoline (Daugulis's auxiliary^{14a,b}) is an effective auxiliary as the substrate **1a** underwent the Pd-catalyzed C-H arylation smoothly than the other substrates **1c-f**, **1dA**, **1eA** and **1fA**.

Furthermore, we focused our attention to further extend the generality of this protocol and we decided to investigate the Pd-catalyzed direct C-H arylation of the methylene C(sp³)-H bond of 1,4-benzodioxane system (Scheme 3). Along this line, initially, we assembled the substrate **1g** by linking the corresponding 1,4-benzodioxane carboxylic acid chloride with the Daugulis's bidentate directing group (8-aminoquinoline). Then, we performed the reaction of the substrate **1g** with phenyl iodide in the presence of AgOAc (2.2 equiv) and 10 mol% of the Pd(OAc)₂ catalyst, which successfully gave the C3-arylated product, *cis* 2,3-disubstituted 1,4-benzodioxane scaffold **4a** (neolignan analogue) in 65% yield (Scheme 3). Thenceforth, we capitalized this success and synthesized of a wide range neolignan-type *cis* 2,3-disubstituted 1,4-benzodioxane scaffolds **4b-q** (40-83%) from the Pd-catalyzed direct arylation of the methylene sp³ C(3)-H bond of 1,4-benzodioxane system **1g** by using the corresponding aryl iodides, such as mono- and disubstituted aryl iodides, benzodioxane-based aryl iodide and heteroaryl iodides.

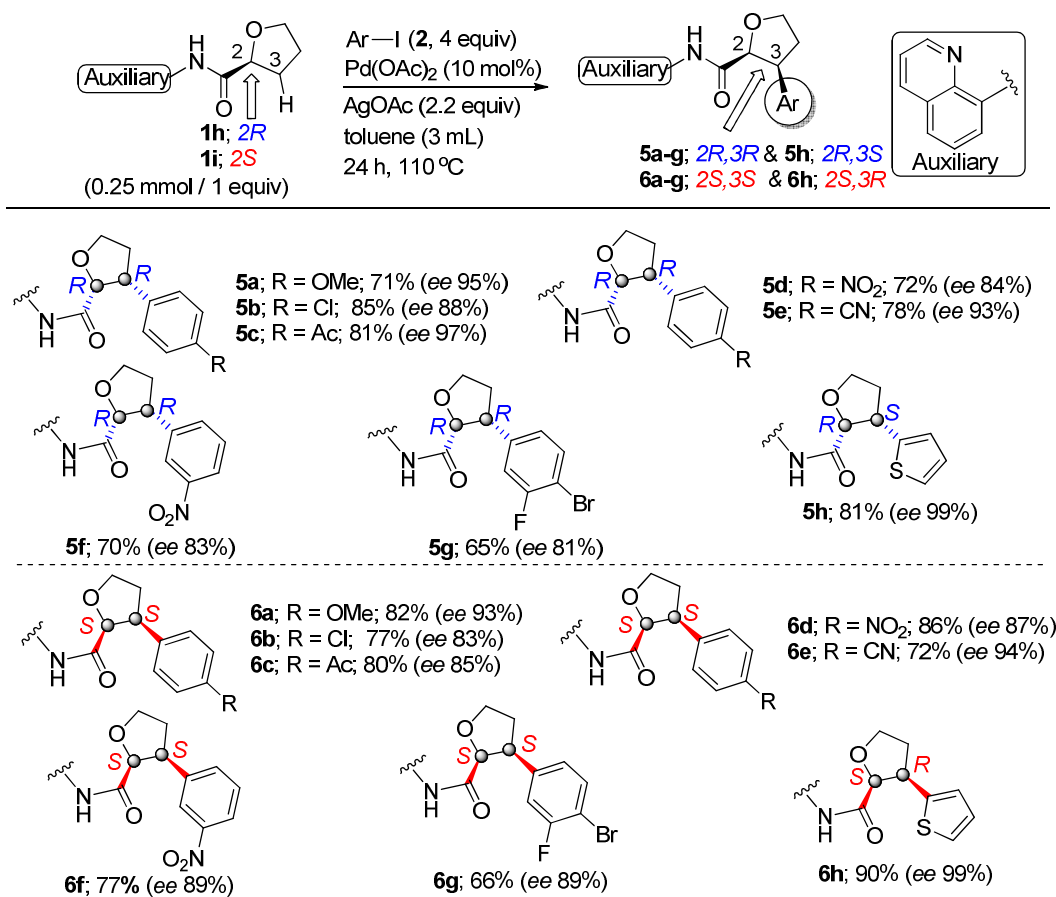
In a representative case, the C-H arylated product **4p** was recrystallized and subjected to the single-crystal X-ray structure analysis. The X-ray structure of the representative compound **4p** (see SI for the X-ray structure of **4p**¹⁶) clearly confirmed that the C-H arylation of the substrate **1g** was highly regio- and stereoselective and the direct C-H arylation occurred only at the C3-position of the substrate **1g** and selectively gave the 2,3-disubstituted 1,4-benzodioxanes **4a-q** with the *cis* stereochemistry (C2-C3 stereocenters). Characteristically, the C2 and C3 protons in all the compounds (**4a-q**) appeared as doublets and the coupling constants (*J*) of the doublet peaks of C2 and C3 protons of all the compounds **4a-q** were calculated from their respective ¹H NMR spectra and found to be in the range of 2.8-3.1 Hz.¹⁸ Accordingly, the stereochemistry of

the 2,3-disubstituted 1,4-benzodioxanes **4a-q** were assigned as *cis* on the basis of the X-ray structure analysis of the compound **4p** coupled with the similarity in their NMR spectral pattern and the characteristic coupling constant values of the doublet peaks of the C2 protons and C3 protons of all the compounds **4a-q**.

Scheme 3. Arylation of sp^3 C(3)-H Bond of **1g and Construction of Benzodioxane-Neolignan Motifs.**



Scheme 4. Arylation of sp^3 C(3)-H Bond of **1h,i** and Construction of Norlignan-THF Scaffolds.



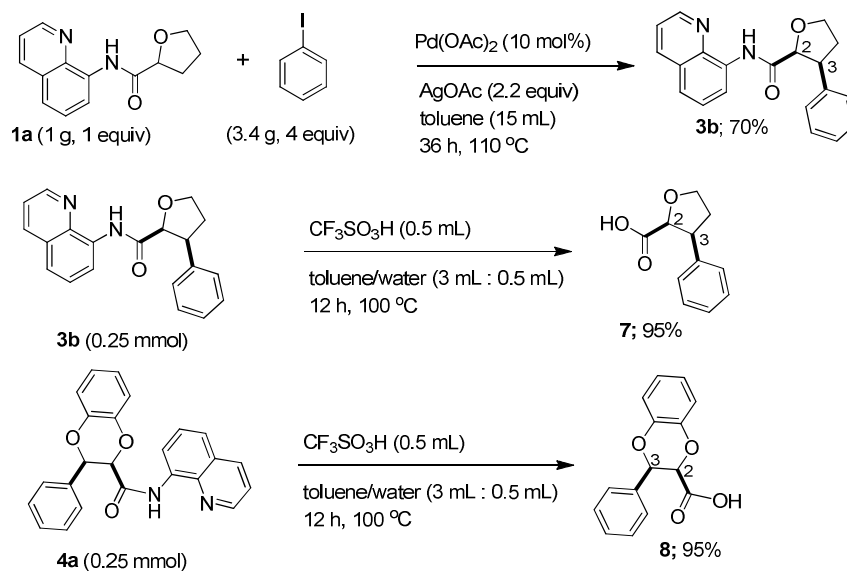
Subsequently, we decided to explore the direct C-H arylation of the unactivated sp^3 C(3)-H bond of chiral tetrahydrofuran-2-carboxamides and synthesize chiral C3-arylated tetrahydrofuran-2-carboxamides. In this regard, we assembled the chiral tetrahydrofuran-2-carboxamide substrates **1h** (*R*-isomer) and **1i** (*S*-isomer, Scheme 4). Then, we performed the Pd-catalyzed direct C(sp^3)-H arylation of the substrates **1h** and **1i** with various aryl iodides. These reactions successfully furnished the corresponding chiral 2,3-disubstituted tetrahydrofurans **5a-g** (2*R*,3*R*, major isomer) and **6a-g** (2*S*,3*S*, major isomer) in 70-86% yields. Similarly, the C-H arylation of substrates **1h** and **1i** with 2-iodothiophene gave the products **5h** (2*R*,3*S*, major isomer) and **6h** (2*S*,3*R*, major

isomer) in 81 and 90% yields, respectively (Scheme 4). The HPLC analyses of the compounds **5a-h** and **6a-h** revealed that the C-H arylation of the chiral substrates **1h** and **1i** resulted the chiral products **5a-h** with *ee* 81 to >99% and **6a-h** with *ee* 83 to >99% and perceptibly, partial racemizations were observed in most of the reactions under the experimental conditions. The direct C-H arylation of chiral substrates **1h** and **1i** occurred only at the C3-position and selectively gave the chiral 2,3-disubstituted tetrahydrofurans **5a-h** and **6a-h** with *cis* stereochemistry (C2 and C3 stereocenters). The compounds **5a-h** and **6a-h** were isolated in pure form as single diastereomers and characterized by NMR spectral data, mass and HPLC analyses. The stereochemistry of all the compounds **5a-h** and **6a-h** (*cis* isomers) were assigned on the basis of the X-ray structure analyses of the compounds **3b** and **3e** and deliberations given for establishing the stereochemistry of the compounds **3a-r**.^{17a}

We also performed the Pd-catalyzed direct arylation of C(3)-H bond of the substrate **1a** with iodobenzene in a gram scale. This reaction gave the C3-arylated product **3b** in 70% yield (Scheme 5). Finally, we have attempted the removal of the bidentate directing group (8-aminoquinoline) from the C3-arylated *cis* 2,3-disubstituted THF and benzodioxane systems. Representatively, we carried out the hydrolysis of the carboxamides **3b** and **4a**. The hydrolysis of the carboxamides **3b** and **4a** under the standard hydrolysis reaction conditions (e.g., Con. HCl or NaOH-mediated hydrolysis) failed to afford the corresponding carboxylic acids **7** and **8**. Later, we found that the hydrolysis of carboxamides **3b** and **4a** in the presence of triflic acid (TfOH) successfully gave the corresponding carboxylic acids **7** and **8** (Scheme 5). The stereochemistry of the compound **7** (C2-C3 stereocenters) was unambiguously found to be *cis* (see SI for the X-ray structure of **7**)¹⁶ and no significant epimerization was observed under the experimental condition

employed for hydrolyzing the carboxamide **3b**. Additionally, the C2 proton in the compound **7** appeared as a doublet ($\delta = 4.65$ ppm) due to its coupling with the C3 proton similar to its parent compound **3b** (C2H, doublet, $\delta = 4.78$, $J = 7.0$ Hz). The coupling constant (J) of the doublet peak of the C2 proton of the compound **7** (*cis* isomer) was found to be 7.7 Hz similar to its parent compound **3b** (*cis* isomer).^{17a} Likewise, the stereochemistry of the C2-C3 stereocenters of the compound **8** was assigned as *cis* based on the coupling constant ($J = 3.2$ Hz) of the doublet peaks of the C2/C3 protons, which was found to be in agreement with the literature and its parent compound **4a** (*cis* isomer), in which the coupling constant (J) of the doublet peaks of the C2/C3 protons was 3.1 Hz.¹⁸

Scheme 5. Gram Scale Reaction and Removal of the Directing Group.



In summary, we have shown the bidentate directing group-aided Pd-catalyzed highly regio- and stereoselective sp^3 C-H activation and direct arylation of the C(3)-H position of tetrahydrofuran and 1,4-benzodioxane systems. The direct C-H arylation occurred only at the C3 position of

racemic tetrahydrofuran-2-carboxamides and gave the corresponding racemic C3-arylated THF derivatives with excellent regio- and diastereoselectivities. Similarly, the C-H arylation of chiral (*R*)- or (*S*)- tetrahydrofuran-2-carboxamides resulted the corresponding chiral (*2R,3R*) and (*2S,3S*) C3-arylated-THF scaffolds having *cis* stereochemistry with excellent regio- and diastereoselectivities and very good *ee*. Overall, this protocol has led to the production of a wide range of *cis* 2,3-disubstituted- THF-norlignan and benzodioxane-neolignan scaffolds with very high regio- and stereoselectivities.

EXPERIMENTAL SECTION

General. Melting points are uncorrected. FT-IR spectra of compounds were recorded as thin films or KBr pellets. ^1H and ^{13}C NMR spectra of all compounds were recorded on 400 MHz and 100 MHz spectrometers respectively (using TMS as an internal standard). HRMS measurements reported in this work were obtained from TOF mass analyzer using electrospray ionization (ESI). Column chromatography was carried out using silica gel 100-200 mesh. HPLC analyses were performed using OD-H (0.46 cm IDR, 25 cm length) as a chiral column (eluent, flow rate, detection method are listed on the HPLC charts). Reactions were performed in anhydrous solvent under a nitrogen atmosphere. Solutions were dried using anhydrous Na_2SO_4 . Thin layer chromatography analyses were performed on silica gel plates and components were visualized by observation under iodine. Isolated yields of all the compounds were reported and yields were not optimized. In all the reactions, purification of the crude reaction mixture by the column chromatography gave only the major diastereomer (as single compound) in pure form and we did not isolate any other compound in considerable quantity suitable for characterization.

Procedure for the synthesis of the carboxamides 1a-1i, 1bA-1bC, 1dA, 1eA and 1fA.

The corresponding carboxylic acid (1.5 mmol) was dissolved in SOCl_2 (4 mmol) and stirred for 24 h at rt under a nitrogen atmosphere. After this period, the reaction mixture was concentrated in vacuum and diluted with anhydrous DCM (3 mL) under a nitrogen atmosphere. Then, the corresponding acid chloride in DCM was added to a separate RB flask containing amine (1 mmol) and Et_3N (1.1 mmol) in anhydrous DCM (2 mL) under a nitrogen atmosphere. The reaction mixture was stirred at rt for 10 min and then, the reaction mixture was refluxed for 12 h under a nitrogen atmosphere. After this period, the reaction mixture was diluted with DCM (5 mL) and washed with water followed by saturated aqueous NaHCO_3 solution. The combined organic layers were dried over anhydrous Na_2SO_4 , concentrated in vacuum and purification of the resulting reaction mixture by column chromatography ($\text{EtOAc}/\text{hexanes} = 30:70$) furnished the corresponding cyclic ether carboxamides **1a-1i**, **1bA-1bC**, **1dA**, **1eA** and **1fA**.

General procedure for the Pd-catalyzed C-H arylation of the carboxamides 1a-1i, 1bA-1bC, 1dA, 1eA and 1fA and preparation of 3a-3r, 4a-4q, 5a-5h and 6a-6h. A mixture of the corresponding cyclic ether carboxamide **1** (0.25 mmol, 1 equiv), $\text{Pd}(\text{OAc})_2$ (5.6 mg, 10 mol%), ArI (1.0 mmol, 4 equiv) and AgOAc (91.8 mg, 0.55 mmol, 2.2 equiv) in anhydrous toluene (3 mL) was heated at 110 °C for 24-48 h under a nitrogen atmosphere. After the reaction period, the reaction mixture was diluted with EtOAc and concentrated in vacuum and purification of the resulting reaction mixture by silica gel column chromatography furnished the corresponding C-H arylated cyclic ether carboxamides **3a-3r/4a-4q/5a-5h/6a-6h** (see Tables/Schemes for specific examples).

Procedure for the hydrolysis of the amides 3b and 4a. To a RB flask (capacity 25 mL) molded with a Liebig condenser (length = 15 cm) sealed at the top and having a J Young air inlet valve at the side of the RB flask was sequentially added the corresponding carboxamide **3b** or **4a** (0.25

mmol) dissolved in a mixture of toluene (3 mL) and water (0.5 mL) and CF₃SO₃H (0.5 mL) using syringes. The air inlet was closed and the reaction mixture was heated at 100 °C and chilled water was circulated in the outer glass tube of the condenser. After 12 h, the reaction mixture was transferred from the RB flask into a separating funnel using a syringe, diluted with EtOAc and extracted with saturated aqueous Na₂CO₃ solution (20 mL x 2). Then, the combined aqueous layers were acidified with 1 N HCl (15 mL x 2) to get pH~2. Then, the aqueous layers were extracted using EtOAc (10 mL x 2), drying of the combined organic layers over anhydrous Na₂SO₄ and evaporation in vacuum gave the corresponding carboxylic acid **7** or **8**.

***N*-(Quinolin-8-yl)tetrahydrofuran-2-carboxamide (1a):** Following the general procedure, **1a** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as brown colour solid; Yield: 95% (230 mg); mp 85-87 °C; IR (KBr): 3441, 1653, 1554, 1260, 750 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 10.94 (br s, 1H), 8.88 (dd, 1H, *J*₁ = 4.2 Hz, *J*₂ = 1.7 Hz), 8.82 (dd, 1H, *J*₁ = 6.2 Hz, *J*₂ = 2.8 Hz), 8.17 (dd, 1H, *J*₁ = 8.3 Hz, *J*₂ = 1.7 Hz), 7.58-7.53 (m, 2H), 7.47 (dd, 1H, *J*₁ = 8.3 Hz, *J*₂ = 4.2 Hz), 4.64 (dd, 1H, *J*₁ = 8.4 Hz, *J*₂ = 5.6 Hz), 4.28-4.23 (m, 1H), 4.08 (dd, 1H, *J*₁ = 15.2 Hz, *J*₂ = 7.0 Hz), 2.48-2.39 (m, 1H), 2.32-2.25 (m, 1H), 2.04-1.98 (m, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 172.1, 148.6, 138.9, 136.2, 133.9, 128.0, 127.2, 121.9, 121.6, 116.5, 79.2, 69.8, 30.5, 25.6; HRMS (ESI): *m/z* [M + H]⁺ calcd for C₁₄H₁₅N₂O₂: 243.1134; found 243.1154.

***N*-(Quinolin-8-yl)tetrahydrofuran-3-carboxamide (1bA):** Following the general procedure, **1bA** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as red colour solid; Yield: 90% (218 mg); mp 80-82 °C; IR (KBr): 3440, 1676, 1527, 1385, 791 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 9.91 (br s, 1H), 8.72 (d, 1H, *J*₁ = 1.7 Hz), 8.71 (dd, 1H, *J*₁ = 3.1 Hz, *J*₂ = 1.7 Hz), 8.03 (dd, 1H, *J*₁ = 8.3 Hz, *J*₂ = 1.6 Hz), 7.45-7.38 (m, 2H), 7.34

(dd, 1H, $J_1 = 8.3$ Hz, $J_2 = 4.2$ Hz), 4.06 (d, 2H, $J = 6.9$ Hz), 4.02-3.97 (m, 1H), 3.87-3.81 (m, 1H), 3.27-3.19 (m, 1H), 2.34-2.20 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 172.0, 148.2, 138.2, 136.3, 134.3, 127.8, 127.2, 121.7, 121.6, 116.5, 71.0, 68.4, 46.9, 30.7; HRMS (ESI): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{14}\text{H}_{15}\text{N}_2\text{O}_2$: 243.1134; found 243.1158.

***N*-(Quinolin-8-yl)tetrahydro-2H-pyran-4-carboxamide (1bB):** Following the general procedure, **1bB** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 40:60) as brown colour solid. Yield: 88% (225 mg); mp 141-143°C; IR (KBr): 3352, 1682, 1528, 1280, 792 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 9.98 (br s, 1H), 8.82 (dd, 1H, $J_1 = 4.2$ Hz, $J_2 = 1.6$ Hz), 8.80 (dd, 1H, $J_1 = 7.1$ Hz, $J_2 = 1.8$ Hz), 8.19 (d, 1H, $J = 8.3$ Hz), 7.58-7.51 (m, 2H), 7.49 (dd, 1H, $J_1 = 8.3$ Hz, $J_2 = 4.2$ Hz), 4.14 (t, 1H, $J = 3.0$ Hz), 4.11 (t, 1H, $J = 3.0$ Hz), 3.55 (dt, 2H, $J_1 = 11.0$ Hz, $J_2 = 3.5$ Hz), 2.80-2.72 (m, 1H), 2.09-1.96 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3): δ 172.9, 148.2, 138.4, 136.5, 134.3, 128.0, 127.4, 121.7, 121.6, 116.5, 67.3, 43.6, 29.3; HRMS (ESI): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{15}\text{H}_{17}\text{N}_2\text{O}_2$: 257.1290; found 257.1290.

***N*-(Quinolin-8-yl)chroman-3-carboxamide (1bC):** Following the general procedure, **1bC** was obtained after purification by column chromatography on neutral alumina (EtOAc:Hexanes = 30:70) as yellow colour liquid. Yield: 85% (258 mg); IR (DCM): 3343, 1682, 1528, 1228, 1068, 752 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 10.17 (br s, 1H), 8.82-8.79 (m, 2H), 8.19 (d, 1H, $J = 8.2$ Hz), 7.59-7.54 (m, 2H), 7.48 (dd, 1H, $J_1 = 8.2$ Hz, $J_2 = 4.2$ Hz), 7.17 (t, 2H, $J = 8.0$ Hz), 6.93 (dd, 2H, $J_1 = 12.2$ Hz, $J_2 = 8.0$ Hz), 4.66-4.62 (m, 1H), 4.30 (t, 1H, $J = 10.4$ Hz), 3.37 (dd, 1H, $J_1 = 15.3$ Hz, $J_2 = 10.0$ Hz), 3.27-3.15 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 170.5, 154.0, 148.3, 138.4, 136.4, 134.1, 129.9, 127.9, 127.6, 127.4, 121.9, 121.7, 120.8, 120.5, 116.8, 116.7, 67.4, 41.3, 28.6; HRMS (ESI): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{19}\text{H}_{17}\text{N}_2\text{O}_2$: 305.1290; found 305.1286.

***N*-(2-(Dimethylamino)ethyl)tetrahydrofuran-2-carboxamide (1c):** Following the general procedure, **1c** was obtained after purification by column chromatography on silica gel (MeOH: EtOAc = 10:90) as dark brown colour liquid; Yield: 40% (75 mg); IR (DCM): 3433, 1637, 1528, 1260, 749 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 7.07 (br s, 1H), 4.36 (dd, 1H, $J_1 = 8.3$ Hz, $J_2 = 5.8$ Hz), 3.99-3.86 (m, 2H), 3.41-3.29 (m, 2H), 2.41 (dt, 2H, $J_1 = 6.3$ Hz, $J_2 = 1.5$ Hz), 2.33-2.26 (m, 1H), 2.24 (s, 6H), 2.10-2.02 (m, 1H), 1.95-1.83 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 173.3, 78.5, 69.4, 58.1, 45.3, 36.4, 30.2, 25.5; HRMS (ESI): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_9\text{H}_{19}\text{N}_2\text{O}_2$: 187.1447; found 187.1459.

***N*-(Pyridin-2-ylmethyl)tetrahydrofuran-2-carboxamide (1d):** Following the general procedure, **1d** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 60:40) as dark brown colour liquid; Yield: 71% (146 mg); IR (DCM): 3396, 1650, 1530, 1075, 758 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 8.46 (d, 1H, $J = 4.5$ Hz), 7.68 (br s, 1H), 7.58 (t, 1H, $J = 7.6$ Hz), 7.18 (d, 1H, $J = 7.6$ Hz), 7.12 (t, 1H, $J = 5.9$ Hz), 4.56-4.40 (m, 2H), 4.35 (dd, 1H, $J_1 = 8.3$ Hz, $J_2 = 6.1$ Hz), 3.95-3.90 (m, 1H), 3.85-3.79 (m, 1H), 2.27-2.18 (m, 1H), 2.06-1.96 (m, 1H), 1.88-1.78 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 173.4, 156.7, 149.1, 136.7, 122.3, 121.8, 78.5, 69.4, 43.9, 30.2, 25.4; HRMS (ESI): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{11}\text{H}_{15}\text{N}_2\text{O}_2$: 207.1133; found 207.1132.

***N*-((Tetrahydrofuran-2-yl)methyl)picolinamide (1dA):** Following the general procedure, **1dA** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 40:60) as dark brown colour liquid; Yield: 80% (165 mg); IR (DCM): 3480, 1668, 1590, 1077, 751 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 8.57-8.55 (m, 1H), 8.36 (br s, 1H), 8.19 (d, 1H, $J = 7.8$ Hz), 7.84 (dt, 1H, $J_1 = 7.7$ Hz, $J_2 = 1.7$ Hz), 7.44-7.40 (m, 1H), 4.13-4.07 (m, 1H), 3.95-3.90 (m, 1H), 3.82-3.71 (m, 2H), 3.47-3.41 (m, 1H), 2.07-1.99 (m, 1H), 1.95-1.87 (m, 2H), 1.68-1.59 (m,

1H); ^{13}C NMR (100 MHz, CDCl_3): δ 164.4, 149.8, 148.1, 137.3, 126.1, 122.2, 77.8, 68.3, 43.2, 28.8, 25.9; HRMS (ESI): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{11}\text{H}_{15}\text{N}_2\text{O}_2$: 207.1134; found 207.1157.

***N*-(2-(Methylthio)phenyl)tetrahydrofuran-2-carboxamide (1e):** Following the general procedure, **1e** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as yellow colour liquid; Yield: 81% (192 mg); IR (DCM): 3441, 1685, 1523, 1275, 750 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 9.57 (br s, 1H), 8.36 (dd, 1H, $J_1 = 8.2$ Hz, $J_2 = 1.3$ Hz), 7.47 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.3$ Hz), 7.32-7.28 (m, 1H), 7.09 (dt, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.3$ Hz), 4.54 (dd, 1H, $J_1 = 8.5$ Hz, $J_2 = 5.4$ Hz), 4.17-4.12 (m, 1H), 4.01 (dd, 1H, $J_1 = 15.2$ Hz, $J_2 = 7.0$ Hz), 2.41 (s, 3H), 2.39-2.33 (m, 1H), 2.26-2.18 (m, 1H), 2.02-1.93 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 171.7, 137.5, 132.4, 128.6, 126.0, 124.5, 120.3, 79.0, 69.8, 30.4, 25.6, 18.5; HRMS (ESI): m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{12}\text{H}_{15}\text{NNaO}_2\text{S}$: 260.0721; found 260.0734.

***N*-(2-(Methylthio)phenyl)tetrahydrofuran-3-carboxamide (1eA):** Following the general procedure, **1eA** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 40:60) as colourless solid. Yield: 70% (65 mg); mp 64-66 $^\circ\text{C}$; IR (KBr): 3437, 1661, 1471, 1554, 1261, 750 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 8.49 (br s, 1H), 8.26 (d, 1H, $J = 8.2$ Hz), 7.46 (d, 1H, $J = 7.2$ Hz), 7.28 (t, 1H, $J = 8.2$ Hz), 7.08 (t, 1H, $J = 7.2$ Hz), 4.09-3.97 (m, 3H), 3.87 (dd, 1H, $J_1 = 15.4$ Hz, $J_2 = 7.5$ Hz), 3.17-3.11 (m, 1H), 2.39 (s, 3H), 2.29 (dd, 2H, $J_1 = 14.0$ Hz, $J_2 = 7.0$ Hz); ^{13}C NMR (100 MHz, CDCl_3): δ 172.0, 137.9, 132.4, 128.6, 125.8, 124.6, 121.0, 70.9, 68.2, 46.8, 30.5, 18.7; HRMS (ESI): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{12}\text{H}_{16}\text{NO}_2\text{S}$: 238.0902; found 238.0908.

***N*-(2-Methylquinolin-8-yl)tetrahydrofuran-2-carboxamide (1f):** Following the general procedure, **1f** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as brown colour solid; Yield: 85% (217 mg); mp 83-85 $^\circ\text{C}$; IR (KBr):

3440, 1603, 1573, 1260, 757 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 10.99 (br s, 1H), 8.76 (dd, 1H, $J_1 = 5.5$ Hz, $J_2 = 3.4$ Hz), 8.03 (d, 1H, $J = 8.4$ Hz), 7.48-7.47 (m, 2H), 7.32 (d, 1H, $J = 8.4$ Hz), 4.64 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 5.3$ Hz), 4.29-4.24 (m, 1H), 4.12-4.07 (m, 1H), 2.77 (s, 3H), 2.44-2.37 (m, 1H), 2.33-2.25 (m, 1H), 2.04-1.97 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 172.1, 157.4, 138.3, 136.2, 133.3, 126.2, 126.1, 122.4, 121.7, 116.4, 79.2, 69.7, 30.5, 25.5, 25.4; HRMS (ESI): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{15}\text{H}_{17}\text{N}_2\text{O}_2$: 257.1290; found 257.1298.

***N*-(2-Methylquinolin-8-yl)tetrahydrofuran-3-carboxamide (1fA):** Following the general procedure, **1fA** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 40:60) as brown colour liquid. Yield: 90% (230 mg); IR (DCM): 3342, 1683, 1530, 1384, 763 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 10.05 (br s, 1H), 8.75-8.71 (m, 1H), 8.01 (d, 1H, $J = 8.4$ Hz), 7.45 (d, 2H, $J = 4.2$ Hz), 7.31 (d, 1H, $J = 8.4$ Hz), 4.17-4.05 (m, 3H), 3.93 (dd, 1H, $J_1 = 15.2$ Hz, $J_2 = 7.7$ Hz), 3.41-3.27 (m, 1H), 2.75 (s, 3H), 2.43-2.27 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 171.9, 157.3, 137.7, 136.4, 133.7, 126.3, 126.0, 122.5, 121.5, 116.5, 71.1, 68.5, 47.0, 30.7, 25.3; HRMS (ESI): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{15}\text{H}_{17}\text{N}_2\text{O}_2$: 257.1290; found 257.1281.

***N*-(Quinolin-8-yl)-2,3-dihydrobenzo[*b*][1,4]dioxine-2-carboxamide (1g):** Following the general procedure, **1g** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as brown colour solid; Yield: 84% (257 mg); mp 121-123 $^\circ\text{C}$; IR (KBr): 3440, 1682, 1491, 1274, 750 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 10.98 (br s, 1H), 8.84 (dd, 1H, $J_1 = 4.2$ Hz, $J_2 = 1.6$ Hz), 8.81 (t, 1H, $J = 4.4$ Hz), 8.17 (dd, 1H, $J_1 = 8.3$ Hz, $J_2 = 1.6$ Hz), 7.57 (d, 2H, $J = 4.3$ Hz), 7.47 (dd, 1H, $J_1 = 8.3$ Hz, $J_2 = 4.2$ Hz), 7.27-7.24 (m, 1H), 7.01-6.92 (m, 3H), 4.97 (dd, 1H, $J_1 = 7.0$ Hz, $J_2 = 2.7$ Hz), 4.69 (dd, 1H, $J_1 = 11.4$ Hz, $J_2 = 2.7$ Hz), 4.44 (dd, 1H, $J_1 = 11.4$ Hz, $J_2 = 7.0$ Hz); ^{13}C NMR (100 MHz, CDCl_3): δ 165.7, 148.7, 143.4, 141.8, 138.7,

136.2, 133.5, 127.9, 127.1, 122.5, 122.5, 122.0, 121.8, 117.7, 117.7, 116.9, 73.8, 65.3 ; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{18}H_{15}N_2O_3$: 307.1083; found 307.1094.

(R)-N-(Quinolin-8-yl)tetrahydrofuran-2-carboxamide (1h): Following the general procedure, **1h** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as dark brown colour liquid; Yield: 90% (218 mg); *ee* 99%; ($[\alpha]^{25}_D = -101.1$ (*c* 0.05, DCM); IR (DCM): 3377, 2964, 1276, 1263, 847 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 10.93 (br s, 1H), 8.86 (dd, 1H, $J_1 = 4.2$ Hz, $J_2 = 1.7$ Hz), 8.81 (dd, 1H, $J_1 = 6.6$ Hz, $J_2 = 2.3$ Hz), 8.14 (dd, 1H, $J_1 = 8.3$ Hz, $J_2 = 1.7$ Hz), 7.56-7.50 (m, 2H), 7.44 (dd, 1H, $J_1 = 8.3$ Hz, $J_2 = 4.2$ Hz), 4.63 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 5.6$ Hz), 4.26-4.21 (m, 1H), 4.06 (dd, 1H, $J_1 = 15.2$ Hz, $J_2 = 7.0$ Hz), 2.44-2.37 (m, 1H), 2.31-2.23 (m, 1H), 2.02-1.94 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 172.1, 148.6, 138.9, 136.2, 133.9, 128.0, 127.2, 121.9, 121.6, 116.5, 79.2, 69.8, 30.5, 25.6; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{14}H_{15}N_2O_2$: 243.1134; found 243.1138.

(S)-N-(Quinolin-8-yl)tetrahydrofuran-2-carboxamide (1i): Following the general procedure, **1i** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as dark brown colour liquid; Yield: 88% (213 mg); *ee* 99%; ($[\alpha]^{25}_D = +111.1$ (*c* 0.05, DCM); IR (DCM): 3334, 1683, 1578, 1530, 1067, 750 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 10.93 (br s, 1H), 8.87 (dd, 1H, $J_1 = 4.2$ Hz, $J_2 = 1.7$ Hz), 8.81 (dd, 1H, $J_1 = 6.3$ Hz, $J_2 = 2.7$ Hz), 8.16 (dd, 1H, $J_1 = 8.3$ Hz, $J_2 = 1.7$ Hz), 7.58-7.53 (m, 2H), 7.46 (dd, 1H, $J_1 = 8.3$ Hz, $J_2 = 4.2$ Hz), 4.64 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 5.6$ Hz), 4.28-4.22 (m, 1H), 4.08 (dd, 1H, $J_1 = 15.2$ Hz, $J_2 = 7.0$ Hz), 2.48-2.38 (m, 1H), 2.32-2.24 (m, 1H), 2.04-1.97 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 172.1, 148.6, 138.9, 136.2, 133.9, 128.0, 127.2, 122.0, 121.6, 116.5, 79.2, 69.8, 30.5, 25.6; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{14}H_{15}N_2O_2$: 243.1134; found 243.1130.

(2*R,3*R**)-3-(4-Methoxyphenyl)-*N*-(quinolin-8-yl)tetrahydrofuran-2-carboxamide (3a):**

Following the general procedure, **3a** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 40:60) as brown colour viscous liquid; Yield: 81% (71 mg); IR (DCM): 3341, 1683, 1489, 1326, 791 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 10.59 (br s, 1H), 8.87 (dd, 1H, $J_1 = 4.2$ Hz, $J_2 = 1.7$ Hz), 8.48 (dd, 1H, $J_1 = 7.2$ Hz, $J_2 = 1.7$ Hz), 8.12 (dd, 1H, $J_1 = 8.3$ Hz, $J_2 = 1.7$ Hz), 7.47-7.40 (m, 3H), 7.21 (d, 2H, $J = 8.8$ Hz), 6.68 (d, 2H, $J = 8.8$ Hz), 4.74 (d, 1H, $J = 7.0$ Hz), 4.63-4.57 (m, 1H), 4.21-4.15 (m, 1H), 3.90-3.85 (m, 1H), 3.62 (s, 3H), 2.58-2.53 (m, 1H), 2.31-2.26 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 168.6, 158.2, 148.5, 138.8, 136.1, 133.6, 132.5, 128.9, 127.9, 127.1, 121.7, 121.5, 116.6, 113.6, 83.9, 68.7, 55.0, 47.2, 33.7; HRMS (ESI): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{21}\text{H}_{21}\text{N}_2\text{O}_3$: 349.1552; found 349.1563.

(2*R,3*R**)-3-Phenyl-*N*-(quinolin-8-yl)tetrahydrofuran-2-carboxamide (3b):** Following the general procedure, **3b** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 40:60) as brown colour solid; Yield: 73% (58 mg); mp 102-104 $^\circ\text{C}$; IR (DCM): 3441, 1642, 1527, 1275, 750 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 10.60 (br s, 1H), 8.88 (dd, 1H, $J_1 = 4.2$ Hz, $J_2 = 1.7$ Hz), 8.45 (dd, 1H, $J_1 = 7.4$ Hz, $J_2 = 1.7$ Hz), 8.12 (dd, 1H, $J_1 = 8.3$ Hz, $J_2 = 1.7$ Hz), 7.47-7.39 (m, 3H), 7.31-7.29 (m, 2H), 7.15 (t, 2H, $J = 7.3$ Hz), 7.05 (t, 1H, $J = 7.3$ Hz), 4.78 (d, 1H, $J = 7.0$ Hz), 4.65-4.59 (m, 1H), 4.24-4.18 (m, 1H), 3.94-3.89 (m, 1H), 2.64-2.55 (m, 1H), 2.37-2.29 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 168.4, 148.5, 140.5, 138.8, 136.1, 133.6, 128.2, 127.9, 127.9, 127.1, 126.7, 121.7, 121.5, 116.6, 83.9, 68.7, 48.0, 33.7; HRMS (ESI): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{20}\text{H}_{19}\text{N}_2\text{O}_2$: 319.1447; found 319.1460.

(2*R,3*R**)-3-(4-Acetylphenyl)-*N*-(quinolin-8-yl)tetrahydrofuran-2-carboxamide (3c):**

Following the general procedure, **3c** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 50:50) as yellow colour solid; Yield: 72% (65 mg); mp 117-119

°C; IR (KBr): 3424, 1678, 1528, 1274, 749 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 10.62 (br s, 1H), 8.88 (dd, 1H, $J_1 = 4.2$ Hz, $J_2 = 1.6$ Hz), 8.42 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.6$ Hz), 8.12 (dd, 1H, $J_1 = 8.3$ Hz, $J_2 = 1.6$ Hz), 7.73 (d, 2H, $J = 8.3$ Hz), 7.47-7.39 (m, 3H), 7.38 (d, 2H, $J = 8.3$ Hz), 4.79 (d, 1H, $J = 7.0$ Hz), 4.65-4.59 (m, 1H), 4.24-4.18 (m, 1H), 3.99-3.94 (m, 1H), 2.65-2.57 (m, 1H), 2.42 (s, 3H), 2.34-2.25 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 197.7, 168.0, 148.6, 146.4, 138.7, 136.2, 135.5, 133.4, 128.4, 128.2, 127.9, 127.1, 122.0, 121.6, 116.6, 83.8, 68.7, 47.8, 33.6, 26.5; HRMS (ESI): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{22}\text{H}_{21}\text{N}_2\text{O}_3$: 361.1552; found 361.1568.

(2*R,3*R**)-3-(4-Chlorophenyl)-*N*-(quinolin-8-yl)tetrahydrofuran-2-carboxamide (3d):**

Following the general procedure, **3d** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as colourless solid; Yield: 62% (55 mg); mp 143-145 °C; IR (DCM): 3339, 1682, 1528, 1057, 757 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 10.61 (br s, 1H), 8.88 (dd, 1H, $J_1 = 4.2$ Hz, $J_2 = 1.7$ Hz), 8.47 (dd, 1H, $J_1 = 7.3$ Hz, $J_2 = 1.7$ Hz), 8.13 (dd, 1H, $J_1 = 8.3$ Hz, $J_2 = 1.7$ Hz), 7.49-7.41 (m, 3H), 7.22 (d, 2H, $J = 8.6$ Hz), 7.11 (d, 2H, $J = 8.6$ Hz), 4.75 (d, 1H, $J = 7.0$ Hz), 4.61-4.55 (m, 1H), 4.22-4.16 (m, 1H), 3.91-3.86 (m, 1H), 2.62-2.53 (m, 1H), 2.29-2.21 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 168.1, 148.5, 139.2, 138.8, 136.2, 133.5, 132.5, 129.3, 128.4, 127.9, 127.1, 121.9, 121.5, 116.2, 83.7, 68.6, 47.3, 33.7; HRMS (ESI): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{20}\text{H}_{18}\text{ClN}_2\text{O}_2$: 353.1057; found 353.1070.

(2*R,3*R**)-3-(4-Cyanophenyl)-*N*-(quinolin-8-yl)tetrahydrofuran-2-carboxamide (3e):**

Following the general procedure, **3e** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 50:50) as colourless solid; Yield: 76% (65 mg); mp 200-202 °C; IR (KBr): 3431, 1636, 1531, 1275, 749 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 10.60 (br s, 1H), 8.88 (dd, 1H, $J_1 = 4.2$ Hz, $J_2 = 1.7$ Hz), 8.41 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.7$ Hz), 8.16 (dd, 1H, $J_1 = 8.3$ Hz, $J_2 = 1.7$ Hz), 7.52-7.49 (m, 1H), 7.46 (dd, 1H, $J_1 = 8.3$ Hz, $J_2 = 4.0$ Hz), 7.44-7.38 (m,

5H), 4.78 (d, 1H, $J = 7.0$ Hz), 4.64-4.58 (m, 1H), 4.25-4.19 (m, 1H), 3.97-3.92 (m, 1H), 2.68-2.59 (m, 1H), 2.32-2.23 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 167.6, 148.6, 146.4, 138.7, 136.3, 133.2, 132.0, 128.8, 127.9, 127.1, 122.2, 121.6, 118.8, 116.6, 110.5, 83.7, 68.6, 47.8, 33.4; HRMS (ESI): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{21}\text{H}_{18}\text{N}_3\text{O}_2$: 344.1399; found 344.1408.

(2*R,3*R**)-3-(4-Nitrophenyl)-*N*-(quinolin-8-yl)tetrahydrofuran-2-carboxamide (3f):**

Following the general procedure, **3f** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 50:50) as brown colour solid; Yield: 56% (51 mg); mp 160-162 °C; IR (KBr): 3396, 1664, 1596, 1076, 750 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 10.64 (br s, 1H), 8.88 (dd, 1H, $J_1 = 4.2$ Hz, $J_2 = 1.7$ Hz), 8.41 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.7$ Hz), 8.13 (dd, 1H, $J_1 = 8.3$ Hz, $J_2 = 1.7$ Hz), 8.00 (d, 2H, $J = 8.8$ Hz), 7.49-7.39 (m, 5H), 4.80 (d, 1H, $J = 7.0$ Hz), 4.65-4.60 (m, 1H), 4.25-4.19 (m, 1H), 4.03-3.98 (m, 1H), 2.69-2.60 (m, 1H), 2.32-2.24 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 167.6, 148.6, 146.7, 138.7, 136.3, 133.2, 128.8, 127.9, 127.1, 123.5, 122.2, 121.7, 116.6, 83.7, 68.6, 47.6, 33.5; HRMS (ESI): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{20}\text{H}_{18}\text{N}_3\text{O}_4$: 364.1297; found 364.1309.

(2*R,3*R**)-3-(3-Nitrophenyl)-*N*-(quinolin-8-yl)tetrahydrofuran-2-carboxamide (3g):**

Following the general procedure, **3g** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 50:50) as brown colour solid; Yield: 75% (68 mg); mp 109-111 °C; IR (KBr): 3441, 1684, 1528, 1259, 791 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 10.57 (br s, 1H), 8.84 (dd, 1H, $J_1 = 4.2$ Hz, $J_2 = 1.7$ Hz), 8.37 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.7$ Hz), 8.17 (t, 1H, $J = 1.7$ Hz), 8.11 (dd, 1H, $J_1 = 8.3$ Hz, $J_2 = 1.7$ Hz), 7.87-7.84 (m, 1H), 7.60 (d, 1H, $J = 7.7$ Hz), 7.47-7.42 (m, 2H), 7.38 (t, 1H, $J = 8.0$ Hz), 7.26 (t, 1H, $J = 8.0$ Hz), 4.78 (d, 1H, $J = 6.8$ Hz), 4.70-4.64 (m, 1H), 4.26-4.20 (m, 1H), 4.03-3.98 (m, 1H), 2.70-2.61 (m, 1H), 2.36-2.28 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 167.6, 148.7, 148.0, 142.8, 138.6, 136.1, 134.4, 133.2, 129.0,

127.8, 126.9, 122.7, 122.1, 121.9, 121.7, 116.5, 83.7, 68.6, 47.5, 33.3; HRMS (ESI): m/z [M + H]⁺ calcd for C₂₀H₁₈N₃O₄: 364.1297; found 364.1310.

(2*R,3*R**)-3-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)-*N*-(quinolin-8-yl)tetrahydrofuran-2-**

carboxamide (3h): Following the general procedure, **3h** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 40:60) as colourless liquid; Yield: 53% (50 mg); IR (DCM): 3440, 1677, 1528, 1282, 749 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 10.55 (br s, 1H), 8.88 (dd, 1H, $J_1 = 4.2$ Hz, $J_2 = 1.7$ Hz), 8.52 (dd, 1H, $J_1 = 6.9$ Hz, $J_2 = 1.7$ Hz), 8.11 (dd, 1H, $J_1 = 8.2$ Hz, $J_2 = 1.7$ Hz), 7.46-7.42 (m, 3H), 6.80 (d, 1H, $J = 2.0$ Hz), 6.75 (dd, 1H, $J_1 = 8.3$ Hz, $J_2 = 2.0$ Hz), 6.60 (d, 1H, $J = 8.3$ Hz), 4.71 (d, 1H, $J = 6.8$ Hz), 4.60-4.55 (m, 1H), 4.20-4.14 (m, 1H), 4.09-3.94 (m, 4H), 3.82-3.78 (m, 1H), 2.58-2.49 (m, 1H), 2.30-2.22 (m, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 168.6, 148.5, 143.0, 142.2, 138.8, 136.0, 133.7, 127.9, 127.1, 121.6, 121.4, 120.9, 116.9, 116.8, 116.6, 83.8, 68.6, 64.1, 47.3, 33.6; HRMS (ESI): m/z [M + H]⁺ calcd for C₂₂H₂₁N₂O₄: 377.1501; found 377.1508.

(2*R,3*R**)-3-(Benzo[*d*][1,3]dioxol-5-yl)-*N*-(quinolin-8-yl)tetrahydrofuran-2-carboxamide**

(3i): Following the general procedure, **3i** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 40:60) as brown colour liquid; Yield: 46% (42 mg); IR (DCM): 3432, 1637, 1528, 1269, 749 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 10.57 (br s, 1H), 8.88 (dd, 1H, $J_1 = 4.2$ Hz, $J_2 = 1.7$ Hz), 8.51 (dd, 1H, $J_1 = 7.1$ Hz, $J_2 = 1.7$ Hz), 8.13 (dd, 1H, $J_1 = 8.3$ Hz, $J_2 = 1.7$ Hz), 7.47-7.42 (m, 3H), 6.79 (d, 1H, $J = 1.7$ Hz), 6.75 (dd, 1H, $J_1 = 8.0$ Hz, $J_2 = 1.7$ Hz), 6.57 (d, 1H, $J = 8.0$ Hz), 5.76 (d, 1H, $J = 1.5$ Hz), 5.66 (d, 1H, $J = 1.5$ Hz), 4.71 (d, 1H, $J = 6.8$ Hz), 4.61-4.55 (m, 1H), 4.21-4.15 (m, 1H), 3.86-3.81 (m, 1H), 2.60-2.51 (m, 1H), 2.30-2.22 (m, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 168.4, 148.5, 147.4, 146.1, 138.8, 136.1,

134.3, 133.6, 127.9, 127.1, 121.7, 121.5, 121.1, 116.6, 108.4, 108.0, 100.7, 83.8, 68.5, 47.7, 33.7; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{21}H_{19}N_2O_4$: 363.1345; found 363.1352.

(2*R,3*R**)-3-(4-Bromo-3-fluorophenyl)-*N*-(quinolin-8-yl)tetrahydrofuran-2-carboxamide**

(3j): Following the general procedure, **3j** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 40:60) as brown colour solid; Yield: 58% (60 mg); mp 99-101 °C; IR (KBr): 3339, 1686, 1530, 1325, 751 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$): δ 10.58 (br s, 1H), 8.88 (dd, 1H, $J_1 = 4.2$ Hz, $J_2 = 1.7$ Hz), 8.47 (dd, 1H, $J_1 = 7.4$ Hz, $J_2 = 1.7$ Hz), 8.13 (dd, 1H, $J_1 = 8.3$ Hz, $J_2 = 1.7$ Hz), 7.50-7.42 (m, 3H), 7.30-7.26 (m, 1H), 7.08 (dd, 1H, $J_1 = 9.8$ Hz, $J_2 = 2.1$ Hz), 6.95 (dd, 1H, $J_1 = 8.3$ Hz, $J_2 = 2.1$ Hz), 4.74 (d, 1H, $J = 6.8$ Hz), 4.60-4.54 (m, 1H), 4.22-4.15 (m, 1H), 3.88-3.84 (m, 1H), 2.63-2.54 (m, 1H), 2.27-2.18 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.8, 158.7 (d, $J_{C-F} = 245.6$ Hz), 148.6, 142.6 (d, $J_{C-F} = 6.4$ Hz), 138.7, 136.2, 133.3, 133.1, 127.9, 127.1, 125.0 (d, $J_{C-F} = 3.0$ Hz), 122.1, 121.6, 116.7, 116.0 (d, $J_{C-F} = 22.2$ Hz), 107.0 (d, $J_{C-F} = 20.7$ Hz), 83.6, 68.4, 47.2, 33.5; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{20}H_{17}BrFN_2O_2$: 415.0457; found 415.0465.

(2*R,3*R**)-*N*-(Quinolin-8-yl)-3-(3,4,5-trimethoxyphenyl)tetrahydrofuran-2-carboxamide**

(3k): Following the general procedure, **3k** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 60:40) as brown colour solid; Yield: 54% (55 mg); mp 89-91 °C; IR (DCM): 3441, 1681, 1590, 1127, 750 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$): δ 10.53 (br s, 1H), 8.82 (dd, 1H, $J_1 = 4.2$ Hz, $J_2 = 1.5$ Hz), 8.55 (dd, 1H, $J_1 = 6.8$ Hz, $J_2 = 2.2$ Hz), 8.11 (dd, 1H, $J_1 = 8.3$ Hz, $J_2 = 1.5$ Hz), 7.47-7.40 (m, 3H), 6.49 (s, 2H), 4.73 (d, 1H, $J = 6.6$ Hz), 4.61-4.55 (m, 1H), 4.22-4.16 (m, 1H), 3.85-3.81 (m, 1H), 3.63 (s, 6H), 3.44 (s, 3H), 2.62-2.53 (m, 1H), 2.32-2.24 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.4, 152.8, 148.3, 138.6, 136.5,

136.4, 136.2, 133.6, 127.9, 127.2, 121.7, 121.5, 116.4, 104.8, 84.0, 68.6, 60.4, 55.7, 48.2, 33.8;

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{23}H_{25}N_2O_5$: 409.1763; found 409.1768.

(2*R,3*R**)-3-(2,4-Dimethoxyphenyl)-*N*-(quinolin-8-yl)tetrahydrofuran-2-carboxamide (3l):**

Following the general procedure, **3l** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 40:60) as brown colour solid; Yield: 40% (38 mg); mp 105-107 °C; IR (KBr): 3424, 1614, 1529, 1260, 750 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$): δ 10.52 (br s, 1H), 8.87 (dd, 1H, $J_1 = 4.2$ Hz, $J_2 = 1.7$ Hz), 8.53 (dd, 1H, $J_1 = 7.2$ Hz, $J_2 = 1.7$ Hz), 8.14 (dd, 1H, $J_1 = 8.3$ Hz, $J_2 = 1.7$ Hz), 7.48-7.41 (m, 3H), 7.07 (d, 1H, $J = 8.4$ Hz), 6.39 (d, 1H, $J = 2.4$ Hz), 6.26 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 2.5$ Hz), 4.91 (d, 1H, $J = 8.2$ Hz), 4.62-4.57 (m, 1H), 4.20-4.12 (m, 2H), 3.85 (s, 3H), 3.67 (s, 3H), 2.47-2.29 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.5, 159.5, 158.3, 148.3, 138.7, 136.1, 134.0, 127.9, 127.9, 127.2, 121.5, 121.4, 119.8, 116.4, 103.9, 98.4, 81.8, 68.7, 55.5, 55.1, 41.5, 30.9; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{22}H_{23}N_2O_4$: 379.1658; found 379.1672.

(2*R,3*R**)-3-(6-Fluoropyridin-3-yl)-*N*-(quinolin-8-yl)tetrahydrofuran-2-carboxamide (3m):**

Following the general procedure, **3m** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 70:30) as yellow colour solid; Yield: 71% (60 mg); mp 117-119 °C; IR (KBr): 3441, 1679, 1528, 1259, 750 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$): δ 10.63 (br s, 1H), 8.86 (dd, 1H, $J_1 = 4.2$ Hz, $J_2 = 1.6$ Hz), 8.44 (dd, 1H, $J_1 = 7.5$ Hz, $J_2 = 1.6$ Hz), 8.14-8.11 (m, 2H), 7.70 (dt, 1H, $J_1 = 8.0$ Hz, $J_2 = 2.6$ Hz), 7.49-7.40 (m, 3H), 6.68 (dd, 1H, $J_1 = 8.5$ Hz, $J_2 = 3.0$ Hz), 4.74 (d, 1H, $J = 6.8$ Hz), 4.61-4.55 (m, 1H), 4.23-4.17 (m, 1H), 3.94-3.89 (m, 1H), 2.65-2.56 (m, 1H), 2.27-2.17 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.6, 162.6 (d, $J_{C-F} = 236.5$ Hz), 148.6, 146.8 (d, $J_{C-F} = 14.6$ Hz), 140.6 (d, $J_{C-F} = 7.8$ Hz), 138.7, 136.2, 133.9 (d, $J_{C-F} = 4.6$

Hz), 133.2, 127.9, 127.1, 122.2, 121.6, 116.6, 108.9 (d, J_{C-F} = 37.4 Hz), 83.4, 68.5, 44.5, 33.4;

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{19}H_{17}FN_3O_2$: 338.1305; found 338.1315.

(2*R,3*R**)-3-(6-Chloropyridin-3-yl)-*N*-(quinolin-8-yl)tetrahydrofuran-2-carboxamide (3n):**

Following the general procedure, **3n** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 80:20) as colourless solid; Yield: 56% (50 mg); mp 127-129 °C;

IR (DCM): 3435, 1579, 1459, 1325, 792 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$): δ 10.66 (br s, 1H),

8.86 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.45 (dd, 1H, J_1 = 7.5 Hz, J_2 = 1.7 Hz), 8.32 (d, 1H, J =

2.5 Hz), 8.13 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.56 (dd, 1H, J_1 = 8.3 Hz, J_2 = 2.6 Hz), 7.50-7.41

(m, 3H), 7.08 (d, 1H, J = 8.3 Hz), 4.76 (d, 1H, J = 6.9 Hz), 4.60-4.54 (m, 1H), 4.23-4.17 (m,

1H), 3.92-3.87 (m, 1H), 2.66-2.57 (m, 1H), 2.25-2.17 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ

167.6, 149.8, 149.1, 148.7, 138.7, 138.2, 136.2, 135.3, 133.2, 127.9, 127.1, 123.8, 122.2, 121.6,

116.7, 83.3, 68.5, 44.6, 33.4; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{19}H_{17}ClN_3O_2$: 354.1009;

found 354.1023.

(2*R,3*R**)-3-(5-Bromopyridin-2-yl)-*N*-(quinolin-8-yl)tetrahydrofuran-2-carboxamide (3o):**

Following the general procedure, **3o** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 80:20) as brown colour liquid; Yield: 31% (31 mg); IR (DCM):

3436, 1638, 1530, 1275, 749 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$): δ 10.66 (br s, 1H), 8.88 (dd, 1H,

J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.45 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.7 Hz), 8.40-8.39 (m, 1H), 8.15 (dd, 1H,

J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.60 (dd, 1H, J_1 = 8.3 Hz, J_2 = 2.4 Hz), 7.51-7.43 (m, 3H), 7.17 (dd, 1H,

J_1 = 8.3 Hz, J_2 = 0.4 Hz), 4.87 (d, 1H, J = 7.6 Hz), 4.70 (dd, 1H, J_1 = 14.9 Hz, J_2 = 6.9 Hz), 4.21

(dd, 1H, J_1 = 14.9 Hz, J_2 = 6.9 Hz), 4.04 (dd, 1H, J_1 = 13.9 Hz, J_2 = 6.9 Hz), 2.49 (dd, 2H, J_1 =

13.9 Hz, J_2 = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.8, 158.5, 150.1, 148.6, 138.8, 138.5,

136.1, 133.6, 127.9, 127.1, 124.7, 121.8, 121.5, 118.7, 116.5, 83.3, 69.5, 48.9, 32.4; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{19}H_{17}BrN_3O_2$: 398.0504; found 398.0512.

(2*R,3*R**)-3-(2-Chloropyridin-4-yl)-*N*-(quinolin-8-yl)tetrahydrofuran-2-carboxamide (3p):**

Following the general procedure, **3p** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 80:20) as brown colour solid; Yield: 51% (45 mg); mp 98-100 °C; IR (DCM): 3441, 1684, 1527, 1275, 750 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$): δ 10.61 (br s, 1H), 8.88 (dd, 1H, $J_1 = 4.2$ Hz, $J_2 = 1.7$ Hz), 8.43 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.7$ Hz), 8.14 (dd, 1H, $J_1 = 8.3$ Hz, $J_2 = 1.7$ Hz), 8.11 (d, 1H, $J = 5.2$ Hz), 7.51-7.41 (m, 3H), 7.26 (d, 1H, $J = 1.4$ Hz), 7.13 (dd, 1H, $J_1 = 5.2$ Hz, $J_2 = 1.6$ Hz), 4.77 (d, 1H, $J = 6.7$ Hz), 4.61-4.55 (m, 1H), 4.24-4.18 (m, 1H), 3.87-3.83 (m, 1H), 2.66-2.57 (m, 1H), 2.27-2.18 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.2, 153.3, 151.5, 149.4, 148.7, 138.7, 136.2, 133.0, 127.9, 127.1, 123.7, 122.3, 122.0, 121.6, 116.8, 83.4, 68.5, 46.9, 33.1; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{19}H_{17}ClN_3O_2$: 354.1009; found 354.1025.

(2*R,3*S**)-*N*-(Quinolin-8-yl)-3-(thiophen-2-yl)tetrahydrofuran-2-carboxamide (3q):**

Following the general procedure, **3q** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as brown colour solid; Yield: 87% (71 mg); mp 134-136 °C; IR (DCM): 3424, 1643, 1275, 1094, 750 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$): δ 10.63 (br s, 1H), 8.88 (dd, 1H, $J_1 = 4.2$ Hz, $J_2 = 1.7$ Hz), 8.56 (dd, 1H, $J_1 = 6.9$ Hz, $J_2 = 1.7$ Hz), 8.13 (dd, 1H, $J_1 = 8.2$ Hz, $J_2 = 1.7$ Hz), 7.49-7.43 (m, 3H), 7.00 (dd, 1H, $J_1 = 5.1$ Hz, $J_2 = 1.0$ Hz), 6.96 (dd, 1H, $J_1 = 3.5$ Hz, $J_2 = 1.0$ Hz), 6.79 (dd, 1H, $J_1 = 5.1$ Hz, $J_2 = 3.5$ Hz), 4.74 (d, 1H, $J = 6.3$ Hz), 4.62 (dd, 1H, $J_1 = 16.1$ Hz, $J_2 = 7.5$ Hz), 4.28-4.22 (m, 2H), 2.66-2.57 (m, 1H), 2.37-2.30 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.1, 148.5, 142.4, 138.8, 136.1, 133.7, 127.9, 127.1, 126.5, 125.5,

123.9, 121.8, 121.5, 116.6, 83.6, 68.4, 43.3, 34.6; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{18}H_{17}N_2O_2S$: 325.1011; found 325.1029.

(2*R,3*R**)-3-(1*H*-Indol-5-yl)-*N*-(quinolin-8-yl)tetrahydrofuran-2-carboxamide (3*r*):**

Following the general procedure, **3r** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 80:20) as dark brown colour liquid; Yield: 20% (18 mg); IR (DCM): 3339, 1731, 1672, 1325, 764 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$): δ 10.63 (br s, 1H), 8.86 (dd, 1H, $J_1 = 4.2$ Hz, $J_2 = 1.7$ Hz), 8.40 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.7$ Hz), 8.09 (dd, 1H, $J_1 = 8.3$ Hz, $J_2 = 1.7$ Hz), 8.03 (br s, 1H), 7.55 (s, 1H), 7.45-7.39 (m, 2H), 7.33 (t, 1H, $J = 8.0$ Hz), 7.11-7.05 (m, 2H), 7.00 (t, 1H, $J = 3.0$ Hz), 6.32 (t, 1H, $J = 2.2$ Hz), 4.81 (d, 1H, $J = 7.2$ Hz), 4.69-4.64 (m, 1H), 4.24-4.18 (m, 1H), 4.04-3.99 (m, 1H), 2.64-2.55 (m, 1H), 2.42-2.34 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.0, 148.4, 138.8, 136.0, 134.8, 133.7, 131.5, 127.8, 127.1, 124.1, 122.3, 121.5, 121.4, 119.7, 116.6, 110.8, 102.4, 84.1, 68.8, 48.3, 34.2; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{22}H_{20}N_3O_2$: 358.1556; found 358.1565.

(2*R,3*R**)-3-Phenyl-*N*-(quinolin-8-yl)-2,3-dihydrobenzo[*b*][1,4]dioxine-2-carboxamide (4*a*):**

Following the general procedure, **4a** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as colourless solid; Yield: 65% (62 mg); mp 168-170 $^{\circ}C$; IR (KBr): 3423, 1643, 1533, 1260, 750 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$): δ 10.64 (br s, 1H), 8.79 (dd, 1H, $J_1 = 4.2$ Hz, $J_2 = 1.7$ Hz), 8.73 (t, 1H, $J = 4.2$ Hz), 8.12 (dd, 1H, $J_1 = 8.3$ Hz, $J_2 = 1.7$ Hz), 7.53-7.52 (m, 2H), 7.43 (dd, 1H, $J_1 = 8.3$ Hz, $J_2 = 4.2$ Hz), 7.38 (d, 2H, $J = 7.1$ Hz), 7.28-7.26 (m, 1H), 7.22-7.00 (m, 6H), 5.95 (d, 1H, $J = 3.1$ Hz), 5.14 (d, 1H, $J = 3.1$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.9, 148.6, 143.3, 142.1, 138.7, 136.1, 135.8, 133.4, 128.4, 127.9, 127.1, 123.3, 122.4, 121.7, 121.5, 117.8, 117.4, 116.9, 76.4, 76.0; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{24}H_{19}N_2O_3$: 383.1396; found 383.1413.

(2*R,3*R**)-3-(4-Methoxyphenyl)-*N*-(quinolin-8-yl)-2,3-dihydrobenzo[*b*][1,4]dioxine-2-**

carboxamide (4b): Following the general procedure, **4b** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as colourless solid; Yield: 81% (84 mg); mp 119-121 °C; IR (KBr): 3431, 1634, 1531, 1259, 749 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 10.66 (br s, 1H), 8.81 (dd, 1H, *J*₁ = 4.2 Hz, *J*₂ = 1.6 Hz), 8.72 (dd, 1H, *J*₁ = 5.9 Hz, *J*₂ = 3.0 Hz), 8.14 (dd, 1H, *J*₁ = 8.2 Hz, *J*₂ = 1.6 Hz), 7.53-7.52 (m, 2H), 7.44 (dd, 1H, *J*₁ = 8.2 Hz, *J*₂ = 4.2 Hz), 7.30 (d, 2H, *J* = 8.8 Hz), 7.28-7.26 (m, 1H), 7.08-6.99 (m, 3H), 6.71 (d, 2H, *J* = 8.8 Hz), 5.88 (d, 1H, *J* = 3.1 Hz), 5.12 (d, 1H, *J* = 3.1 Hz), 3.62 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 165.0, 159.5, 148.6, 143.2, 142.0, 138.7, 136.1, 133.4, 128.5, 128.0, 127.9, 127.1, 123.3, 122.4, 121.7, 121.4, 117.7, 117.5, 116.9, 113.8, 76.4, 75.6, 55.0; HRMS (ESI): *m/z* [M + H]⁺ calcd for C₂₅H₂₁N₂O₄: 413.1501; found 413.1515.

(2*R,3*R**)-*N*-(Quinolin-8-yl)-3-(*p*-tolyl)-2,3-dihydrobenzo[*b*][1,4]dioxine-2-carboxamide**

(4c): Following the general procedure, **4c** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as brown colour liquid; Yield: 66% (65 mg); IR (DCM): 3431, 1636, 1534, 1363, 749 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 10.66 (br s, 1H), 8.80 (dd, 1H, *J*₁ = 4.2 Hz, *J*₂ = 1.7 Hz), 8.74 (t, 1H, *J* = 4.6 Hz), 8.13 (dd, 1H, *J*₁ = 8.3 Hz, *J*₂ = 1.7 Hz), 7.53-7.52 (m, 2H), 7.43 (dd, 1H, *J*₁ = 8.3 Hz, *J*₂ = 4.2 Hz), 7.28-7.26 (m, 3H), 7.10-6.98 (m, 5H), 5.91 (d, 1H, *J* = 3.0 Hz), 5.13 (d, 1H, *J* = 3.0 Hz), 2.16 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 165.0, 148.5, 143.3, 142.1, 138.7, 138.1, 136.1, 133.4, 132.8, 129.1, 127.9, 127.1, 127.0, 123.2, 122.4, 121.7, 121.4, 117.7, 117.4, 116.9, 76.5, 75.8, 21.1; HRMS (ESI): *m/z* [M + H]⁺ calcd for C₂₅H₂₁N₂O₃: 397.1552; found 397.1562.

(2*R,3*R**)-3-(4-Ethylphenyl)-*N*-(quinolin-8-yl)-2,3-dihydrobenzo[*b*][1,4]dioxine-2-**

carboxamide (4d): Following the general procedure, **4d** was obtained after purification by

column chromatography on silica gel (EtOAc:Hexanes = 30:70) as colourless solid; Yield: 40% (41 mg); mp 95-97 °C; IR (DCM): 3333, 1687, 1533, 1255, 825 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 10.62 (br s, 1H), 8.80 (dd, 1H, *J*₁ = 4.2 Hz, *J*₂ = 1.7 Hz), 8.73 (dd, 1H, *J*₁ = 5.5 Hz, *J*₂ = 3.5 Hz), 8.14 (dd, 1H, *J*₁ = 8.2 Hz, *J*₂ = 1.7 Hz), 7.54-7.53 (m, 2H), 7.44 (dd, 1H, *J*₁ = 8.2 Hz, *J*₂ = 4.2 Hz), 7.28-7.25 (m, 3H), 7.09-7.02 (m, 3H), 7.00 (d, 2H, *J* = 8.0 Hz), 5.91 (d, 1H, *J* = 3.1 Hz), 5.12 (d, 1H, *J* = 3.1 Hz), 2.45 (q, 2H, *J* = 7.6 Hz), 1.01 (t, 3H, *J* = 7.6 Hz); ¹³C NMR (100 MHz, CDCl₃): δ 165.0, 148.5, 144.3, 143.3, 142.1, 138.7, 136.1, 133.4, 133.0, 127.9, 127.8, 127.1, 127.0, 123.2, 122.3, 121.6, 121.4, 117.7, 117.4, 116.9, 76.5, 75.8, 28.4, 15.2; HRMS (ESI): *m/z* [M + H]⁺ calcd for C₂₆H₂₃N₂O₃: 411.1708; found 411.1697.

(2*R,3*R**)-3-(4-Fluorophenyl)-*N*-(quinolin-8-yl)-2,3-dihydrobenzo[*b*][1,4]dioxine-2-**

carboxamide (4e): Following the general procedure, **4e** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 40:60) as colourless solid; Yield: 40% (40 mg); mp 96-98 °C; IR (DCM): 3433, 1637, 1275, 1260, 764 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 10.64 (br s, 1H), 8.82 (dd, 1H, *J*₁ = 4.2 Hz, *J*₂ = 1.7 Hz), 8.70 (dd, 1H, *J*₁ = 6.8 Hz, *J*₂ = 2.1 Hz), 8.15 (dd, 1H, *J*₁ = 8.3 Hz, *J*₂ = 1.7 Hz), 7.57-7.51 (m, 2H), 7.46 (dd, 1H, *J*₁ = 8.3 Hz, *J*₂ = 4.2 Hz), 7.35 (dd, 2H, *J*₁ = 8.7 Hz, *J*₂ = 5.3 Hz), 7.28-7.26 (m, 1H), 7.10-7.00 (m, 3H), 6.87 (t, 2H, *J* = 8.7 Hz), 5.91 (d, 1H, *J* = 3.1 Hz), 5.11 (d, 1H, *J* = 3.1 Hz); ¹³C NMR (100 MHz, CDCl₃): δ 164.8, 162.6 (d, *J*_{C-F} = 245.7 Hz), 148.6, 143.0, 141.9, 138.7, 136.2, 133.2, 131.7 (d, *J*_{C-F} = 3.1 Hz), 129.0 (d, *J*_{C-F} = 8.4 Hz), 127.9, 127.1, 123.4, 122.6, 121.7, 121.6, 117.8, 117.4, 116.9, 115.4 (d, *J*_{C-F} = 21.2 Hz), 76.2, 75.4; HRMS (ESI): *m/z* [M + H]⁺ calcd for C₂₄H₁₈FN₂O₃: 401.1301; found 401.1314.

(2*R,3*R**)-3-(4-Bromophenyl)-*N*-(quinolin-8-yl)-2,3-dihydrobenzo[*b*][1,4]dioxine-2-**

carboxamide (4f): Following the general procedure, **4f** was obtained after purification by

column chromatography on silica gel (EtOAc:Hexanes = 30:70) as brown colour solid; Yield: 83% (96 mg); mp 146-148 °C; IR (KBr): 3424, 1684, 1490, 1257, 751 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 10.64 (br s, 1H), 8.81 (dd, 1H, *J*₁ = 4.2 Hz, *J*₂ = 1.7 Hz), 8.71 (dd, 1H, *J*₁ = 6.8 Hz, *J*₂ = 1.7 Hz), 8.15 (dd, 1H, *J*₁ = 8.3 Hz, *J*₂ = 1.7 Hz), 7.58-7.51 (m, 2H), 7.46 (dd, 1H, *J*₁ = 8.3 Hz, *J*₂ = 4.2 Hz), 7.33-7.22 (m, 5H), 7.10-7.00 (m, 3H), 5.90 (d, 1H, *J* = 3.0 Hz), 5.12 (d, 1H, *J* = 3.0 Hz); ¹³C NMR (100 MHz, CDCl₃): δ 164.7, 148.7, 143.0, 141.9, 138.7, 136.1, 134.9, 133.2, 131.5, 128.8, 127.9, 127.1, 123.5, 122.6, 122.6, 121.8, 121.7, 117.8, 117.4, 116.9, 76.2, 75.4; HRMS (ESI): *m/z* [M + H]⁺ calcd for C₂₄H₁₈BrN₂O₃: 461.0501; found 461.0506.

(2*R,3*R**)-3-(4-Chlorophenyl)-*N*-(quinolin-8-yl)-2,3-dihydrobenzo[*b*][1,4]dioxine-2-**

carboxamide (4g): Following the general procedure, **4g** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as colourless solid; Yield: 57% (59 mg); mp 148-149 °C; IR (KBr): 3431, 1785, 1635, 1533, 749 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 10.65 (br s, 1H), 8.81 (dd, 1H, *J*₁ = 4.2 Hz, *J*₂ = 1.7 Hz), 8.71 (dd, 1H, *J*₁ = 6.5 Hz, *J*₂ = 2.4 Hz), 8.15 (dd, 1H, *J*₁ = 8.3 Hz, *J*₂ = 1.7 Hz), 7.57-7.51 (m, 2H), 7.45 (dd, 1H, *J*₁ = 8.3 Hz, *J*₂ = 4.2 Hz), 7.30 (d, 2H, *J* = 8.6 Hz), 7.28-7.26 (m, 1H), 7.15 (d, 2H, *J* = 8.6 Hz), 7.11-7.01 (m, 3H), 5.92 (d, 1H, *J* = 3.0 Hz), 5.12 (d, 1H, *J* = 3.0 Hz); ¹³C NMR (100 MHz, CDCl₃): δ 164.7, 148.7, 143.0, 141.9, 138.7, 136.2, 134.4, 134.3, 133.2, 128.6, 128.5, 127.9, 127.1, 123.5, 122.6, 121.8, 121.7, 117.8, 117.4, 116.9, 76.2, 75.4; HRMS (ESI): *m/z* [M + H]⁺ calcd for C₂₄H₁₈ClN₂O₃: 417.1006; found 417.0993.

(2*R,3*R**)-3-(4-Nitrophenyl)-*N*-(quinolin-8-yl)-2,3-dihydrobenzo[*b*][1,4]dioxine-2-**

carboxamide (4h): Following the general procedure, **4h** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 40:60) as red colour solid; Yield: 56% (60 mg); mp 153-155 °C; IR (KBr): 3424, 1637, 1528, 1290, 750 cm⁻¹; ¹H NMR (400 MHz,

CDCl₃): δ 10.64 (br s, 1H), 8.76 (dd, 1H, $J_1 = 4.2$ Hz, $J_2 = 1.6$ Hz), 8.69 (dd, 1H, $J_1 = 7.0$ Hz, $J_2 = 1.6$ Hz), 8.15 (dd, 1H, $J_1 = 8.3$ Hz, $J_2 = 1.6$ Hz), 8.04 (d, 2H, $J = 8.6$ Hz), 7.58-7.52 (m, 4H), 7.45 (dd, 1H, $J_1 = 8.3$ Hz, $J_2 = 4.2$ Hz), 7.29-7.27 (m, 1H), 7.14-7.04 (m, 3H), 6.03 (d, 1H, $J = 3.0$ Hz), 5.17 (d, 1H, $J = 3.0$ Hz); ¹³C NMR (100 MHz, CDCl₃): δ 164.3, 148.7, 147.7, 143.1, 142.8, 141.8, 138.6, 136.2, 133.0, 128.0, 127.9, 127.0, 123.8, 123.5, 122.9, 122.1, 121.8, 118.0, 117.4, 116.9, 76.1, 75.3; HRMS (ESI): m/z [M + H]⁺ calcd for C₂₄H₁₈N₃O₅: 428.1246; found 428.1241.

(2*R,3*R**)-3-(4-Bromo-3-fluorophenyl)-*N*-(quinolin-8-yl)-2,3-dihydrobenzo[*b*][1,4]dioxine-2-carboxamide (4i):** Following the general procedure, **4i** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 40:60) as brown colour solid; Yield: 66% (79 mg); mp 117-119 °C; IR (KBr): 3329, 1685, 1490, 1256, 871 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 10.66 (br s, 1H), 8.82 (dd, 1H, $J_1 = 4.2$ Hz, $J_2 = 1.7$ Hz), 8.70 (dd, 1H, $J_1 = 6.9$ Hz, $J_2 = 1.7$ Hz), 8.16 (dd, 1H, $J_1 = 8.3$ Hz, $J_2 = 1.7$ Hz), 7.59-7.52 (m, 2H), 7.47 (dd, 1H, $J_1 = 8.3$ Hz, $J_2 = 4.2$ Hz), 7.34 (dd, 1H, $J_1 = 8.3$ Hz, $J_2 = 7.1$ Hz), 7.28-7.26 (m, 1H), 7.15 (dd, 1H, $J_1 = 9.7$ Hz, $J_2 = 2.0$ Hz), 7.11-7.03 (m, 4H), 5.90 (d, 1H, $J = 3.0$ Hz), 5.12 (d, 1H, $J = 3.0$ Hz); ¹³C NMR (100 MHz, CDCl₃): δ 164.5, 158.9 (d, $J_{C-F} = 246.0$ Hz), 148.7, 142.7, 141.8, 138.7, 137.6 (d, $J_{C-F} = 6.5$ Hz), 136.2, 133.4, 133.1, 127.9, 127.1, 124.0 (d, $J_{C-F} = 3.5$ Hz), 123.6, 122.7, 121.9, 121.8, 117.9, 117.4, 117.0, 115.4 (d, $J_{C-F} = 23.4$ Hz), 109.1 (d, $J_{C-F} = 20.6$ Hz), 76.0, 74.9 (d, $J_{C-F} = 1.2$ Hz); HRMS (ESI): m/z [M + H]⁺ calcd for C₂₄H₁₇BrFN₂O₃: 479.0407; found 479.0403.

(2*R,3*R**)-3-(3,4-Dichlorophenyl)-*N*-(quinolin-8-yl)-2,3-dihydrobenzo[*b*][1,4]dioxine-2-carboxamide (4j):** Following the general procedure, **4j** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 25:75) as colourless solid; Yield: 45% (51 mg); mp 170-172 °C; IR (KBr): 3328, 1597, 1491, 1254, 1031, 751 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 10.62 (br s, 1H), 8.81 (dd, 1H, $J_1 = 4.2$ Hz, $J_2 = 1.7$ Hz), 8.70 (dd, 1H, $J_1 = 6.9$

Hz, $J_2 = 1.7$ Hz), 8.17 (dd, 1H, $J_1 = 8.3$ Hz, $J_2 = 1.7$ Hz), 7.58-7.52 (m, 2H), 7.49-7.45 (m, 2H), 7.28-7.18 (m, 3H), 7.10-7.01 (m, 3H), 5.87 (d, 1H, $J = 3.0$ Hz), 5.11 (d, 1H, $J = 3.0$ Hz); ^{13}C NMR (100 MHz, CDCl_3): δ 164.5, 148.7, 142.7, 141.8, 138.7, 136.2, 136.1, 133.1, 132.6, 132.5, 130.4, 129.2, 127.9, 127.0, 126.4, 123.6, 122.7, 121.9, 121.8, 117.9, 117.4, 117.0, 76.1, 74.9; HRMS (ESI): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{24}\text{H}_{17}\text{Cl}_2\text{N}_2\text{O}_3$: 451.0616; found 451.0599.

(2*R,3*R**)-3-(3,5-Dichlorophenyl)-*N*-(quinolin-8-yl)-2,3-dihydrobenzo[*b*][1,4]dioxine-2-**

carboxamide (4k): Following the general procedure, **4k** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 25:75) as colourless solid; Yield: 52% (59 mg); mp 213-215 °C; IR (KBr): 3393, 1597, 1393, 1194, 1064 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 10.62 (br s, 1H), 8.82 (dd, 1H, $J_1 = 4.2$ Hz, $J_2 = 1.7$ Hz), 8.70 (dd, 1H, $J_1 = 6.6$ Hz, $J_2 = 2.3$ Hz), 8.16 (dd, 1H, $J_1 = 8.3$ Hz, $J_2 = 1.7$ Hz), 7.58-7.53 (m, 2H), 7.48 (dd, 1H, $J_1 = 8.3$ Hz, $J_2 = 4.2$ Hz), 7.29-7.26 (m, 1H), 7.25 (dd, 2H, $J_1 = 1.8$ Hz, $J_2 = 0.5$ Hz), 7.13 (t, 1H, $J = 1.9$ Hz), 7.11- 7.08 (m, 1H), 7.07-7.04 (m, 2H), 5.84 (d, 1H, $J = 3.0$ Hz), 5.11 (d, 1H, $J = 3.0$ Hz); ^{13}C NMR (100 MHz, CDCl_3): δ 164.4, 148.7, 142.7, 141.7, 139.2, 138.7, 136.2, 134.9, 133.0, 128.6, 127.9, 127.1, 125.6, 123.7, 122.7, 122.0, 121.8, 118.0, 117.4, 117.1, 76.0, 75.0; HRMS (ESI): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{24}\text{H}_{17}\text{Cl}_2\text{N}_2\text{O}_3$: 451.0616; found 451.0600.

(2*R,3*R**)-3-(3-Nitrophenyl)-*N*-(quinolin-8-yl)-2,3-dihydrobenzo[*b*][1,4]dioxine-2-**

carboxamide (4l): Following the general procedure, **4l** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 40:60) as brown colour solid; Yield: 50% (54 mg); mp 205-207 °C; IR (KBr): 3417, 1683, 1531, 1256, 750 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 10.67 (br s, 1H), 8.78 (dd, 1H, $J_1 = 4.2$ Hz, $J_2 = 1.7$ Hz), 8.69 (dd, 1H, $J_1 = 6.9$ Hz, $J_2 = 2.1$ Hz), 8.27 (t, 1H, $J = 2.1$ Hz), 8.15 (dd, 1H, $J_1 = 8.3$ Hz, $J_2 = 1.7$ Hz), 8.02 (dd, 1H, $J_1 = 7.8$ Hz, $J_2 = 1.3$ Hz), 7.71 (d, 1H, $J = 7.7$ Hz), 7.58-7.51 (m, 2H), 7.45 (dd, 1H, $J_1 = 8.3$ Hz, $J_2 = 4.2$

Hz), 7.38 (t, 1H, $J = 8.0$ Hz), 7.30-7.28 (m, 1H), 7.14-7.04 (m, 3H), 6.02 (d, 1H, $J = 3.0$ Hz), 5.19 (d, 1H, $J = 3.0$ Hz); ^{13}C NMR (100 MHz, CDCl_3): δ 164.4, 148.7, 148.1, 142.7, 141.7, 138.6, 138.0, 136.2, 133.1, 133.0, 129.4, 127.9, 127.1, 123.8, 123.3, 122.8, 122.3, 122.1, 121.8, 118.0, 117.5, 117.0, 76.1, 75.1; HRMS (ESI): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{24}\text{H}_{18}\text{N}_3\text{O}_5$: 428.1246; found 428.1257.

(2*R,3*R**)-3-(3-Bromophenyl)-*N*-(quinolin-8-yl)-2,3-dihydrobenzo[*b*][1,4]dioxine-2-**

carboxamide (4m): Following the general procedure, **4m** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as brown colour liquid; Yield: 50% (58 mg); IR (DCM): 3440, 1682, 1531, 1255, 825 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 10.61 (br s, 1H), 8.81 (dd, 1H, $J_1 = 4.2$ Hz, $J_2 = 1.7$ Hz), 8.71 (dd, 1H, $J_1 = 6.0$ Hz, $J_2 = 2.9$ Hz), 8.14 (dd, 1H, $J_1 = 8.3$ Hz, $J_2 = 1.7$ Hz), 7.55-7.51 (m, 3H), 7.45 (dd, 1H, $J_1 = 8.3$ Hz, $J_2 = 4.2$ Hz), 7.31-7.25 (m, 3H), 7.10-7.06 (m, 4H), 5.89 (d, 1H, $J = 3.0$ Hz), 5.13 (d, 1H, $J = 3.0$ Hz); ^{13}C NMR (100 MHz, CDCl_3): δ 164.6, 148.6, 143.0, 141.9, 138.7, 138.1, 136.1, 133.2, 131.5, 130.2, 129.9, 127.9, 127.1, 125.6, 123.5, 122.6, 122.5, 121.8, 121.7, 117.9, 117.4, 117.0, 76.2, 75.3; HRMS (ESI): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{24}\text{H}_{18}\text{BrN}_2\text{O}_3$: 461.0501; found 461.0503.

(2*R,3*R**)-3-(3,4-Dimethylphenyl)-*N*-(quinolin-8-yl)-2,3-dihydrobenzo[*b*][1,4]dioxine-2-**

carboxamide (4n): Following the general procedure, **4n** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as colourless liquid; Yield: 82% (84 mg); IR (DCM): 3440, 1641, 1533, 1275, 764 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 10.60 (br s, 1H), 8.79 (dd, 1H, $J_1 = 4.2$ Hz, $J_2 = 1.7$ Hz), 8.73 (t, 1H, $J = 4.2$ Hz), 8.13 (dd, 1H, $J_1 = 8.3$ Hz, $J_2 = 1.7$ Hz), 7.53-7.52 (m, 2H), 7.44 (dd, 1H, $J_1 = 8.3$ Hz, $J_2 = 4.2$ Hz), 7.27-7.25 (m, 1H), 7.13-6.98 (m, 5H), 6.93 (d, 1H, $J = 7.8$ Hz), 5.86 (d, 1H, $J = 3.1$ Hz), 5.13 (d, 1H, $J = 3.1$ Hz), 2.04 (s, 3H), 2.02 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 165.1, 148.5, 143.3, 142.1, 138.7, 136.8,

136.5, 136.1, 133.5, 133.1, 129.7, 128.5, 127.8, 127.1, 124.3, 123.2, 122.3, 121.6, 121.4, 117.7, 117.5, 116.9, 76.6, 75.8, 19.7, 19.4; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{26}H_{23}N_2O_3$: 411.1709; found 411.1694.

(2*R,3*R**)-*N*-(Quinolin-8-yl)-2,2',3,3'-tetrahydro-[2,6'-bibenzo[*b*][1,4]dioxine]-3-**

carboxamide (4o): Following the general procedure, **4o** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 40:60) as colourless liquid; Yield: 82% (90 mg); IR (DCM): 3334, 1595, 1533, 1253, 750 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$): δ 10.65 (br s, 1H), 8.83 (dd, 1H, $J_1 = 4.2$ Hz, $J_2 = 1.6$ Hz), 8.73 (dd, 1H, $J_1 = 5.5$ Hz, $J_2 = 3.4$ Hz), 8.14 (dd, 1H, $J_1 = 8.3$ Hz, $J_2 = 1.6$ Hz), 7.54-7.52 (m, 2H), 7.45 (dd, 1H, $J_1 = 8.2$ Hz, $J_2 = 4.2$ Hz), 7.27-7.24 (m, 1H), 7.07-6.97 (m, 3H), 6.90-6.86 (m, 2H), 6.67 (d, 1H, $J = 8.2$ Hz), 5.82 (d, 1H, $J = 3.1$ Hz), 5.09 (d, 1H, $J = 3.1$ Hz), 4.07 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.9, 148.6, 143.6, 143.2, 143.1, 142.0, 138.7, 136.1, 133.4, 129.1, 127.9, 127.1, 123.3, 122.3, 121.7, 121.4, 120.5, 117.8, 117.4, 117.1, 116.9, 116.3, 76.4, 75.4, 64.2, 64.1; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{26}H_{21}N_2O_5$: 441.1450; found 441.1467.

(2*R,3*S**)-*N*-(Quinolin-8-yl)-3-(thiophen-2-yl)-2,3-dihydrobenzo[*b*][1,4]dioxine-2-**

carboxamide (4p): Following the general procedure, **4p** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as colourless solid; Yield: 49% (48 mg); mp 184-186 °C; IR (DCM): 3439, 1682, 1533, 1490, 750 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$): δ 10.91 (br s, 1H), 8.90 (dd, 1H, $J_1 = 4.2$ Hz, $J_2 = 1.7$ Hz), 8.74 (dd, 1H, $J_1 = 6.9$ Hz, $J_2 = 2.1$ Hz), 8.17 (dd, 1H, $J_1 = 8.3$ Hz, $J_2 = 1.7$ Hz), 7.59-7.54 (m, 2H), 7.49 (dd, 1H, $J_1 = 8.3$ Hz, $J_2 = 4.2$ Hz), 7.33-7.29 (m, 1H), 7.16-7.15 (m, 1H), 7.12 (dd, 1H, $J_1 = 5.1$ Hz, $J_2 = 1.2$ Hz), 7.05-7.02 (m, 3H), 6.82 (dd, 1H, $J_1 = 5.1$ Hz, $J_2 = 3.6$ Hz), 6.24 (d, 1H, $J = 2.8$ Hz), 5.15 (d, 1H, $J = 2.8$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.6, 148.8, 141.7, 141.7, 138.8, 136.2, 136.2, 133.4,

127.9, 127.7, 127.1, 126.6, 126.4, 123.4, 122.5, 121.9, 121.8, 118.1, 117.7, 116.9, 75.7, 71.7;

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{22}H_{17}N_2O_3$ S: 389.0960; found 389.0970.

(2*R,3*R**)-3-(2-Chloropyridin-4-yl)-*N*-(quinolin-8-yl)-2,3-dihydrobenzo[*b*][1,4]dioxine-2-**

carboxamide (4q): Following the general procedure, **4q** was obtained after purification by

column chromatography on silica gel (EtOAc:Hexanes = 50:50) as colourless liquid; Yield: 49%

(51 mg); IR (DCM): 3416, 1667, 1531, 1325, 792 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$): δ 10.69 (br

s, 1H), 8.82 (dd, 1H, $J_1 = 4.2$ Hz, $J_2 = 1.7$ Hz), 8.71 (dd, 1H, $J_1 = 7.1$ Hz, $J_2 = 1.7$ Hz), 8.20-8.16

(m, 2H), 7.60-7.54 (m, 2H), 7.48 (dd, 1H, $J_1 = 8.3$ Hz, $J_2 = 4.2$ Hz), 7.30-7.26 (m, 2H), 7.19 (dd,

1H, $J_1 = 5.3$ Hz, $J_2 = 1.1$ Hz), 7.14-7.05 (m, 3H), 5.92 (d, 1H, $J = 3.0$ Hz), 5.15 (d, 1H, $J = 3.0$

Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.1, 151.8, 149.7, 148.8, 148.0, 142.5, 141.7, 138.7,

136.2, 132.9, 127.9, 127.0, 123.8, 122.9, 122.5, 122.3, 121.9, 120.4, 118.1, 117.3, 117.1, 75.7,

74.4; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{23}H_{17}ClN_3O_3$: 418.0958; found 418.0957.

(2*R*,3*R*)-3-(4-Methoxyphenyl)-*N*-(quinolin-8-yl)tetrahydrofuran-2-carboxamide (5a):

Following the general procedure, **5a** was obtained after purification by column chromatography

on silica gel (EtOAc:Hexanes = 40:60) as brown colour solid; Yield: 71% (60 mg); *ee* 95%;

($[\alpha]^{25}_D = -243.5$ (c 0.10, DCM); mp 90-92 $^{\circ}C$; IR (DCM): 3340, 1682, 1530, 1255, 750 cm^{-1} ; 1H

NMR (400 MHz, $CDCl_3$): δ 10.59 (br s, 1H), 8.88 (dd, 1H, $J_1 = 4.2$ Hz, $J_2 = 1.7$ Hz), 8.48 (dd,

1H, $J_1 = 7.3$ Hz, $J_2 = 1.7$ Hz), 8.13 (dd, 1H, $J_1 = 8.3$ Hz, $J_2 = 1.7$ Hz), 7.48-7.41 (m, 3H), 7.21 (d,

2H, $J = 8.8$ Hz), 6.68 (d, 2H, $J = 8.8$ Hz), 4.74 (d, 1H, $J = 7.0$ Hz), 4.63-4.58 (m, 1H), 4.22-4.16

(m, 1H), 3.90-3.85 (m, 1H), 3.62 (s, 3H), 2.60-2.52 (m, 1H), 2.33-2.24 (m, 1H); ^{13}C NMR (100

MHz, $CDCl_3$): δ 168.6, 158.2, 148.5, 138.8, 136.1, 133.6, 132.5, 128.9, 127.9, 127.1, 121.7,

121.5, 116.6, 113.6, 83.9, 68.7, 55.0, 47.2, 33.8; HRMS (ESI): m/z $[M + H]^+$ calcd for

$C_{21}H_{21}N_2O_3$: 349.1552; found 349.1553.

(2*R*,3*R*)-3-(4-Chlorophenyl)-*N*-(quinolin-8-yl)tetrahydrofuran-2-carboxamide (5b):

Following the general procedure, **5b** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 60:40) as colourless solid; Yield: 85% (75 mg); *ee* 88%; ($[\alpha]^{25}_D = -216.8$ (*c* 0.10, DCM); mp 130-132 °C; IR (KBr): 3336, 1682, 1528, 1325, 826 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 10.61 (br s, 1H), 8.88 (dd, 1H, *J*₁ = 4.2 Hz, *J*₂ = 1.7 Hz), 8.47 (dd, 1H, *J*₁ = 7.4 Hz, *J*₂ = 1.7 Hz), 8.13 (dd, 1H, *J*₁ = 8.3 Hz, *J*₂ = 1.7 Hz), 7.49-7.41 (m, 3H), 7.22 (d, 2H, *J* = 8.6 Hz), 7.11 (d, 2H, *J* = 8.6 Hz), 4.75 (d, 1H, *J* = 7.0 Hz), 4.61-4.56 (m, 1H), 4.22-4.16 (m, 1H), 3.91-3.86 (m, 1H), 2.62-2.53 (m, 1H), 2.29-2.21 (m, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 168.1, 148.5, 139.2, 138.8, 136.2, 133.5, 132.5, 129.3, 128.4, 127.9, 127.1, 121.9, 121.5, 116.6, 83.7, 68.6, 47.3, 33.7; HRMS (ESI): *m/z* [M + H]⁺ calcd for C₂₀H₁₈ClN₂O₂: 353.1057; found 353.1051.

(2*R*,3*R*)-3-(4-Acetylphenyl)-*N*-(quinolin-8-yl)tetrahydrofuran-2-carboxamide (5c):

Following the general procedure, **5c** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 70:30) as yellow colour solid; Yield: 81% (73 mg); *ee* 97%; ($[\alpha]^{25}_D = -239.6$ (*c* 0.10, DCM); mp 148-150 °C; IR (KBr): 3441, 1607, 1528, 1267, 792 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 10.63 (br s, 1H), 8.88 (dd, 1H, *J*₁ = 4.2 Hz, *J*₂ = 1.7 Hz), 8.42 (dd, 1H, *J*₁ = 7.6 Hz, *J*₂ = 1.7 Hz), 8.12 (dd, 1H, *J*₁ = 8.3 Hz, *J*₂ = 1.7 Hz), 7.73 (d, 2H, *J* = 8.4 Hz), 7.47-7.39 (m, 3H), 7.37 (d, 2H, *J* = 8.4 Hz), 4.79 (d, 1H, *J* = 7.0 Hz), 4.65-4.59 (m, 1H), 4.24-4.18 (m, 1H), 3.99-3.94 (m, 1H), 2.63-2.58 (m, 1H), 2.42 (s, 3H), 2.32-2.28 (m, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 197.8, 168.0, 148.6, 146.4, 138.7, 136.2, 135.5, 133.4, 128.4, 128.2, 127.9, 127.1, 122.0, 121.6, 116.6, 83.8, 68.7, 47.8, 33.6, 26.5; HRMS (ESI): *m/z* [M + H]⁺ calcd for C₂₂H₂₁N₂O₃: 361.1552; found 361.1545.

(2R,3R)-3-(4-Nitrophenyl)-N-(quinolin-8-yl)tetrahydrofuran-2-carboxamide (5d):

Following the general procedure, **5d** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 50:50) as red colour solid; Yield: 72% (65 mg); *ee* 84%; ($[\alpha]^{25}_D = -229.2$ (*c* 0.10, DCM); mp 139-141 °C; IR (KBr): 3439, 1682, 1523, 1344, 750 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 10.63 (br s, 1H), 8.88 (dd, 1H, $J_1 = 4.2$ Hz, $J_2 = 1.7$ Hz), 8.41 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.7$ Hz), 8.14 (dd, 1H, $J_1 = 8.3$ Hz, $J_2 = 1.7$ Hz), 8.00 (d, 2H, $J = 8.8$ Hz), 7.50-7.39 (m, 5H), 4.80 (d, 1H, $J = 7.0$ Hz), 4.66-4.61 (m, 1H), 4.26-4.20 (m, 1H), 4.03-3.99 (m, 1H), 2.70-2.61 (m, 1H), 2.33-2.25 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 167.6, 148.6, 146.7, 138.7, 136.3, 133.2, 128.8, 127.9, 127.1, 123.5, 122.2, 121.7, 116.6, 83.7, 68.6, 47.6, 33.5; HRMS (ESI): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{20}\text{H}_{18}\text{N}_3\text{O}_4$: 364.1297; found 364.1298.

(2R,3R)-3-(4-Cyanophenyl)-N-(quinolin-8-yl)tetrahydrofuran-2-carboxamide (5e):

Following the general procedure, **5e** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 50:50) as colourless solid; Yield: 78% (67 mg); *ee* 93%; ($[\alpha]^{25}_D = -223.4$ (*c* 0.10, DCM); mp 182-184 °C; IR (KBr): 3424, 1677, 1528, 1260, 764 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 10.60 (br s, 1H), 8.88 (dd, 1H, $J_1 = 4.2$ Hz, $J_2 = 1.7$ Hz), 8.40 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.7$ Hz), 8.14 (dd, 1H, $J_1 = 8.3$ Hz, $J_2 = 1.7$ Hz), 7.51-7.48 (m, 1H), 7.46 (dd, 1H, $J_1 = 8.3$ Hz, $J_2 = 4.0$ Hz), 7.42-7.37 (m, 5H), 4.77 (d, 1H, $J = 7.0$ Hz), 4.63-4.57 (m, 1H), 4.23-4.17 (m, 1H), 3.96-3.92 (m, 1H), 2.67-2.58 (m, 1H), 2.30-2.22 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 167.6, 148.6, 146.4, 138.7, 136.3, 133.2, 132.0, 128.8, 127.9, 127.1, 122.2, 121.7, 118.8, 116.6, 110.5, 83.7, 68.6, 47.8, 33.4; HRMS (ESI): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{21}\text{H}_{18}\text{N}_3\text{O}_2$: 344.1399; found 344.1395.

(2R,3R)-3-(3-Nitrophenyl)-N-(quinolin-8-yl)tetrahydrofuran-2-carboxamide (5f): Following the general procedure, **5f** was obtained after purification by column chromatography on silica gel

(EtOAc:Hexanes = 50:50) as brown colour solid; Yield: 70% (64 mg); *ee* 83%; ($[\alpha]^{25}_D = -219.2$ (*c* 0.10, DCM); mp 103-105 °C; IR (DCM): 3441, 1637, 1260, 1093, 764 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 10.57 (br s, 1H), 8.85 (dd, 1H, $J_1 = 4.2$ Hz, $J_2 = 1.7$ Hz), 8.37 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.7$ Hz), 8.17 (t, 1H, $J = 2.0$ Hz), 8.12 (dd, 1H, $J_1 = 8.3$ Hz, $J_2 = 1.7$ Hz), 7.87-7.85 (m, 1H), 7.62-7.59 (m, 1H), 7.47-7.43 (m, 2H), 7.39 (t, 1H, $J = 8.0$ Hz), 7.27 (t, 1H, $J = 8.0$ Hz), 4.78 (d, 1H, $J = 6.8$ Hz), 4.71-4.65 (m, 1H), 4.27-4.21 (m, 1H), 4.04-3.99 (m, 1H), 2.71-2.62 (m, 1H), 2.37-2.29 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 167.6, 148.7, 148.0, 142.8, 138.6, 136.1, 134.5, 133.1, 129.0, 127.8, 127.0, 122.7, 122.1, 121.9, 121.7, 116.5, 83.7, 68.6, 47.5, 33.3; HRMS (ESI): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{20}\text{H}_{18}\text{N}_3\text{O}_4$: 364.1297; found 364.1290.

(2*R*,3*R*)-3-(4-Bromo-3-fluorophenyl)-*N*-(quinolin-8-yl)tetrahydrofuran-2-carboxamide

(5g): Following the general procedure, **5g** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 50:50) as brown colour solid; Yield: 65% (68 mg); *ee* 81%; ($[\alpha]^{25}_D = -153.6$ (*c* 0.10, DCM); mp 100-102 °C; IR (KBr): 3425, 1682, 1485, 1530, 1092, 750 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 10.58 (br s, 1H), 8.88 (dd, 1H, $J_1 = 4.2$ Hz, $J_2 = 1.7$ Hz), 8.47 (dd, 1H, $J_1 = 7.4$ Hz, $J_2 = 1.7$ Hz), 8.14 (dd, 1H, $J_1 = 8.3$ Hz, $J_2 = 1.7$ Hz), 7.51-7.43 (m, 3H), 7.30-7.26 (m, 1H), 7.08 (dd, 1H, $J_1 = 9.8$ Hz, $J_2 = 2.0$ Hz), 6.95 (dd, 1H, $J_1 = 8.2$ Hz, $J_2 = 2.0$ Hz), 4.74 (d, 1H, $J = 6.8$ Hz), 4.61-4.55 (m, 1H), 4.22-4.16 (m, 1H), 3.89-3.84 (m, 1H), 2.64-2.55 (m, 1H), 2.27-2.18 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 167.8, 158.7 (d, $J_{\text{C-F}} = 245.3$ Hz), 148.6, 142.6 (d, $J_{\text{C-F}} = 6.5$ Hz), 138.7, 136.2, 133.3, 133.1, 127.9, 127.1, 125.0 (d, $J_{\text{C-F}} = 3.2$ Hz), 122.1, 121.6, 116.7, 116.0 (d, $J_{\text{C-F}} = 22.3$ Hz), 107.1 (d, $J_{\text{C-F}} = 20.0$ Hz), 83.6, 68.4, 47.2, 33.5; HRMS (ESI): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{20}\text{H}_{17}\text{BrFN}_2\text{O}_2$: 415.0457; found 415.0434.

(2*R*,3*S*)-*N*-(Quinolin-8-yl)-3-(thiophen-2-yl)tetrahydrofuran-2-carboxamide (5h): Following the general procedure, **5h** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 40:60) as brown colour solid; Yield: 81% (66 mg); *ee* 99%; ($[\alpha]^{25}_D = -134.2$ (*c* 0.10, DCM); mp 100-102 °C; IR (DCM): 3436, 1637, 1557, 1275, 749 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 10.63 (br s, 1H), 8.88 (dd, 1H, *J*₁ = 4.2 Hz, *J*₂ = 1.7 Hz), 8.56 (dd, 1H, *J*₁ = 7.0 Hz, *J*₂ = 2.0 Hz), 8.13 (dd, 1H, *J*₁ = 8.3 Hz, *J*₂ = 1.7 Hz), 7.50-7.43 (m, 3H), 7.00 (dd, 1H, *J*₁ = 5.1 Hz, *J*₂ = 1.0 Hz), 6.96 (dd, 1H, *J*₁ = 3.5 Hz, *J*₂ = 1.0 Hz), 6.79 (dd, 1H, *J*₁ = 5.1 Hz, *J*₂ = 3.5 Hz), 4.74 (d, 1H, *J* = 6.3 Hz), 4.61 (dd, 1H, *J*₁ = 16.0 Hz, *J*₂ = 7.5 Hz), 4.28-4.22 (m, 2H), 2.66-2.57 (m, 1H), 2.37-2.30 (m, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 168.1, 148.6, 142.4, 138.8, 136.1, 133.7, 127.9, 127.1, 126.5, 125.5, 123.9, 121.8, 121.5, 116.6, 83.6, 68.4, 43.3, 34.6; HRMS (ESI): *m/z* [M + H]⁺ calcd for C₁₈H₁₇N₂O₂S: 325.1011; found 325.1003.

(2*S*,3*S*)-3-(4-Methoxyphenyl)-*N*-(quinolin-8-yl)tetrahydrofuran-2-carboxamide (6a): Following the general procedure, **6a** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 40:60) as brown colour solid; Yield: 82% (71 mg); *ee* 93%; ($[\alpha]^{25}_D = +218.4$ (*c* 0.10, DCM); mp 100-102 °C; IR (KBr): 3432, 1636, 1528, 1260, 764 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 10.60 (br s, 1H), 8.88 (dd, 1H, *J*₁ = 4.2 Hz, *J*₂ = 1.7 Hz), 8.49 (dd, 1H, *J*₁ = 7.2 Hz, *J*₂ = 1.7 Hz), 8.11 (dd, 1H, *J*₁ = 8.3 Hz, *J*₂ = 1.7 Hz), 7.47-7.40 (m, 3H), 7.21 (d, 2H, *J* = 8.8 Hz), 6.68 (d, 2H, *J* = 8.8 Hz), 4.74 (d, 1H, *J* = 7.0 Hz), 4.63-4.57 (m, 1H), 4.21-4.15 (m, 1H), 3.90-3.85 (m, 1H), 3.61 (s, 3H), 2.58-2.51 (m, 1H), 2.32-2.24 (m, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 168.6, 158.2, 148.5, 138.8, 136.1, 133.6, 132.5, 128.9, 127.9, 127.1, 121.7, 121.5, 116.6, 113.6, 83.9, 68.7, 55.0, 47.2, 33.8; HRMS (ESI): *m/z* [M + H]⁺ calcd for C₂₁H₂₁N₂O₃: 349.1552; found 349.1566.

(2*S*,3*S*)-3-(4-Chlorophenyl)-*N*-(quinolin-8-yl)tetrahydrofuran-2-carboxamide (6b):

Following the general procedure, **6b** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 50:50) as colourless solid; Yield: 77% (68 mg); *ee* 83%; ($[\alpha]^{25}_D$ = +147.6 (*c* 0.10, DCM); mp 138-140 °C; IR (DCM): 3437, 1637, 1486, 1252, 750 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 10.61 (br s, 1H), 8.88 (dd, 1H, *J*₁ = 4.2 Hz, *J*₂ = 1.7 Hz), 8.47 (dd, 1H, *J*₁ = 7.4 Hz, *J*₂ = 1.7 Hz), 8.14 (dd, 1H, *J*₁ = 8.3 Hz, *J*₂ = 1.7 Hz), 7.50-7.42 (m, 3H), 7.22 (d, 2H, *J* = 8.6 Hz), 7.11 (d, 2H, *J* = 8.6 Hz), 4.75 (d, 1H, *J* = 7.0 Hz), 4.62-4.56 (m, 1H), 4.22-4.16 (m, 1H), 3.91-3.86 (m, 1H), 2.63-2.54 (m, 1H), 2.29-2.19 (m, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 168.1, 148.6, 139.2, 138.8, 136.2, 133.4, 132.5, 129.3, 128.4, 127.9, 127.1, 121.9, 121.6, 116.6, 83.7, 68.6, 47.3, 33.7; HRMS (ESI): *m/z* [M + H]⁺ calcd for C₂₀H₁₈ClN₂O₂: 353.1057; found 353.1039.

(2*S*,3*S*)-3-(4-Acetylphenyl)-*N*-(quinolin-8-yl)tetrahydrofuran-2-carboxamide (6c):

Following the general procedure, **6c** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 70:30) as yellow colour solid; Yield: 80% (72 mg); *ee* 85%; ($[\alpha]^{25}_D$ = +264.3 (*c* 0.10, DCM); mp 142-144 °C; IR (KBr): 3437, 1638, 1528, 1092, 749 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 10.63 (br s, 1H), 8.88 (dd, 1H, *J*₁ = 4.2 Hz, *J*₂ = 1.7 Hz), 8.42 (dd, 1H, *J*₁ = 7.6 Hz, *J*₂ = 1.7 Hz), 8.12 (dd, 1H, *J*₁ = 8.3 Hz, *J*₂ = 1.7 Hz), 7.73 (d, 2H, *J* = 8.4 Hz), 7.47-7.39 (m, 3H), 7.38 (d, 2H, *J* = 8.4 Hz), 4.79 (d, 1H, *J* = 7.0 Hz), 4.65-4.59 (m, 1H), 4.24-4.18 (m, 1H), 3.99-3.94 (m, 1H), 2.66-2.57 (m, 1H), 2.42 (s, 3H), 2.34-2.26 (m, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 197.8, 168.0, 148.6, 146.4, 138.7, 136.2, 135.5, 133.4, 128.4, 128.2, 127.9, 127.1, 122.0, 121.6, 116.6, 83.8, 68.7, 47.8, 33.6, 26.5; HRMS (ESI): *m/z* [M + H]⁺ calcd for C₂₂H₂₁N₂O₃: 361.1552; found 361.1544.

(2*S*,3*S*)-3-(4-Nitrophenyl)-*N*-(quinolin-8-yl)tetrahydrofuran-2-carboxamide (6d): Following the general procedure, **6d** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 50:50) as brown colour solid; Yield: 86% (78 mg); *ee* 87%; ($[\alpha]^{25}_D = +280.3$ (*c* 0.10, DCM); mp 134-136 °C; IR (DCM): 3336, 1598, 1486, 1344, 751 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 10.63 (br s, 1H), 8.88 (dd, 1H, *J*₁ = 4.2 Hz, *J*₂ = 1.7 Hz), 8.41 (dd, 1H, *J*₁ = 7.6 Hz, *J*₂ = 1.7 Hz), 8.13 (dd, 1H, *J*₁ = 8.3 Hz, *J*₂ = 1.7 Hz), 8.00 (d, 2H, *J* = 8.8 Hz), 7.49-7.38 (m, 5H), 4.80 (d, 1H, *J* = 7.0 Hz), 4.65-4.59 (m, 1H), 4.25-4.19 (m, 1H), 4.02-3.98 (m, 1H), 2.67-2.60 (m, 1H), 2.32-2.24 (m, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 167.6, 148.6, 146.7, 138.7, 136.3, 133.2, 128.8, 127.9, 127.1, 123.5, 122.2, 121.7, 116.6, 83.7, 68.6, 47.6, 33.5; HRMS (ESI): *m/z* [M + H]⁺ calcd for C₂₀H₁₈N₃O₄: 364.1297; found 364.1281.

(2*S*,3*S*)-3-(4-Cyanophenyl)-*N*-(quinolin-8-yl)tetrahydrofuran-2-carboxamide (6e): Following the general procedure, **6e** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 50:50) as colourless solid; Yield: 72% (62 mg); *ee* 94%; ($[\alpha]^{25}_D = +218.8$ (*c* 0.10, DCM); mp 176-178 °C; IR (KBr): 3425, 1712, 1530, 1266, 747 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 10.60 (br s, 1H), 8.88 (dd, 1H, *J*₁ = 4.2 Hz, *J*₂ = 1.7 Hz), 8.41 (dd, 1H, *J*₁ = 7.6 Hz, *J*₂ = 1.7 Hz), 8.15 (dd, 1H, *J*₁ = 8.3 Hz, *J*₂ = 1.7 Hz), 7.52-7.49 (m, 1H), 7.46 (dd, 1H, *J*₁ = 8.3 Hz, *J*₂ = 4.0 Hz), 7.44-7.38 (m, 5H), 4.78 (d, 1H, *J* = 6.9 Hz), 4.63-4.58 (m, 1H), 4.24-4.18 (m, 1H), 3.97-3.92 (m, 1H), 2.67-2.58 (m, 1H), 2.31-2.23 (m, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 167.6, 148.6, 146.4, 138.7, 136.3, 133.2, 132.0, 128.8, 127.9, 127.1, 122.2, 121.7, 118.8, 116.6, 110.5, 83.7, 68.6, 47.8, 34.4; HRMS (ESI): *m/z* [M + H]⁺ calcd for C₂₁H₁₈N₃O₂: 344.1399; found 344.1412.

(2*S*,3*S*)-3-(3-Nitrophenyl)-*N*-(quinolin-8-yl)tetrahydrofuran-2-carboxamide (6f): Following the general procedure, **6f** was obtained after purification by column chromatography on silica gel

(EtOAc:Hexanes = 50:50) as brown colour solid; Yield: 77% (70 mg); *ee* 89%; ($[\alpha]^{25}_D = +235.9$ (*c* 0.10, DCM); mp 114-116 °C; IR (DCM): 3335, 1683, 1528, 125, 792 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 10.57 (br s, 1H), 8.84 (dd, 1H, $J_1 = 4.2$ Hz, $J_2 = 1.6$ Hz), 8.37 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.6$ Hz), 8.16 (t, 1H, $J = 2.0$ Hz), 8.10 (dd, 1H, $J_1 = 8.3$ Hz, $J_2 = 1.6$ Hz), 7.86-7.83 (m, 1H), 7.61-7.59 (m, 1H), 7.46-7.42 (m, 2H), 7.38 (t, 1H, $J = 8.0$ Hz), 7.26 (t, 1H, $J = 8.0$ Hz), 4.78 (d, 1H, $J = 6.8$ Hz), 4.70-4.64 (m, 1H), 4.26-4.19 (m, 1H), 4.03-3.98 (m, 1H), 2.70-2.61 (m, 1H), 2.37-2.28 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 167.6, 148.7, 148.0, 142.8, 138.6, 136.1, 134.4, 133.2, 129.0, 127.8, 126.9, 122.7, 122.1, 121.9, 121.7, 116.5, 83.6, 68.6, 47.5, 33.3; HRMS (ESI): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{20}\text{H}_{18}\text{N}_3\text{O}_4$: 364.1297; found 364.1304.

(2*S*,3*S*)-3-(4-Bromo-3-fluorophenyl)-*N*-(quinolin-8-yl)tetrahydrofuran-2-carboxamide (6g):

Following the general procedure, **6g** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 60:70) as brown colour solid; Yield: 66% (69 mg); *ee* 89%; ($[\alpha]^{25}_D = +149.8$ (*c* 0.10, DCM); mp 110-112 °C; IR (KBr): 3440, 1638, 1530, 1275, 750 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 10.58 (br s, 1H), 8.88 (dd, 1H, $J_1 = 4.2$ Hz, $J_2 = 1.7$ Hz), 8.47 (dd, 1H, $J_1 = 7.4$ Hz, $J_2 = 1.7$ Hz), 8.14 (dd, 1H, $J_1 = 8.3$ Hz, $J_2 = 1.7$ Hz), 7.51-7.43 (m, 3H), 7.30-7.26 (m, 1H), 7.08 (dd, 1H, $J_1 = 9.8$ Hz, $J_2 = 2.0$ Hz), 6.96 (dd, 1H, $J_1 = 8.2$ Hz, $J_2 = 2.0$ Hz), 4.74 (d, 1H, $J = 6.8$ Hz), 4.61-4.55 (m, 1H), 4.22-4.16 (m, 1H), 3.89-3.84 (m, 1H), 2.64-2.55 (m, 1H), 2.27-2.18 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 167.8, 158.7 (d, $J_{\text{C-F}} = 245.4$ Hz), 148.6, 142.6 (d, $J_{\text{C-F}} = 6.5$ Hz), 138.7, 136.2, 133.3, 133.1, 127.9, 127.1, 125.0 (d, $J_{\text{C-F}} = 3.2$ Hz), 122.1, 121.6, 116.7, 116.0 (d, $J_{\text{C-F}} = 22.3$ Hz), 107.1 (d, $J_{\text{C-F}} = 20.0$ Hz), 83.6, 68.4, 47.2, 33.5; HRMS (ESI): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{20}\text{H}_{17}\text{BrFN}_2\text{O}_2$: 415.0457; found 415.0443

(2*S*,3*R*)-*N*-(Quinolin-8-yl)-3-(thiophen-2-yl)tetrahydrofuran-2-carboxamide (6h): Following the general procedure, **6h** was obtained after purification by column chromatography on silica

gel (EtOAc:Hexanes = 40:60) as brown colour solid; Yield: 90% (73 mg); *ee* 99%; ($[\alpha]^{25}_D = +169.4$ (*c* 0.10, DCM); mp 98-100 °C; IR (KBr): 3436, 1680, 1531, 1325, 750 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 10.64 (br s, 1H), 8.88 (dd, 1H, $J_1 = 4.2$ Hz, $J_2 = 1.7$ Hz), 8.58 (dd, 1H, $J_1 = 6.6$ Hz, $J_2 = 2.4$ Hz), 8.11 (dd, 1H, $J_1 = 8.2$ Hz, $J_2 = 1.7$ Hz), 7.48-7.41 (m, 3H), 7.00 (dd, 1H, $J_1 = 5.1$ Hz, $J_2 = 1.0$ Hz), 6.96 (dd, 1H, $J_1 = 3.5$ Hz, $J_2 = 1.0$ Hz), 6.79 (dd, 1H, $J_1 = 5.1$ Hz, $J_2 = 3.5$ Hz), 4.74 (d, 1H, $J = 6.3$ Hz), 4.61 (dd, 1H, $J_1 = 16.0$ Hz, $J_2 = 7.5$ Hz), 4.28-4.21 (m, 2H), 2.65-2.56 (m, 1H), 2.36-2.29 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 168.1, 148.5, 142.4, 138.8, 136.1, 133.7, 127.9, 127.1, 126.5, 125.5, 123.9, 121.8, 121.5, 116.6, 83.6, 68.3, 43.3, 34.6; HRMS (ESI): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{18}\text{H}_{17}\text{N}_2\text{O}_2\text{S}$: 325.1011; found 325.0998.

(2*R,3*R**)-3-Phenyltetrahydrofuran-2-carboxylic acid (7):**^{17b} Following the general procedure, **7** was obtained after concentrated in vacuum gave as brown colour solid (crude material was almost pure); Yield: 95% (46 mg); mp 216-218 °C; IR (KBr): 3432, 1637, 1275, 1260, 764, 750 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 7.33-7.19 (m, 5H), 5.03 (br s, 1H), 4.65 (d, 1H, $J = 7.7$ Hz), 4.43-4.37 (m, 1H), 4.06 (dd, 1H, $J_1 = 15.0$ Hz, $J_2 = 7.5$ Hz), 3.76 (dd, 1H, $J_1 = 15.0$ Hz, $J_2 = 7.5$ Hz), 2.48-2.29 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 174.3, 138.6, 128.5, 127.8, 127.3, 81.4, 68.9, 48.0, 32.2; HRMS (ESI): m/z $[\text{M} - \text{H}]^-$ calcd for $\text{C}_{11}\text{H}_{11}\text{O}_3$: 191.0708; found 191.0700. The stereochemistry of this compound **7** has been assigned based on the stereochemistry of the parent compound **3b**.

(2*R,3*R**)-3-Phenyl-2,3-dihydrobenzo[*b*][1,4]dioxine-2-carboxylic acid (8):**^{18a} Following the general procedure, **8** was obtained after concentrated in vacuum gave solid material as brown colour liquid (crude material was almost pure). Yield: 95% (59 mg); IR (DCM): 3456, 1723, 1598, 1257, 1032 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 7.42-7.35 (m, 5H), 7.08-6.95 (m, 4H), 6.43 (br s, 1H), 5.51 (d, 1H, $J = 3.2$ Hz), 5.04 (d, 1H, $J = 3.2$ Hz); ^{13}C NMR (100 MHz, CDCl_3):

δ 171.6, 143.0, 141.8, 134.8, 128.9, 128.6, 126.5, 122.5, 122.2, 117.4, 117.2, 75.1, 75.0; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{15}H_{13}O_4$: 257.0814; found 257.0821. The stereochemistry of this compound **8** has been assigned based on the stereochemistry of the parent compound **4a**.

ASSOCIATED CONTENT

Supporting Information

X-ray structures and CIF files, copies of 1H , ^{13}C and NOESY NMR charts and HPLC analysis charts. This material is available free of charge via the Internet at <http://pubs.acs.org/>.

Notes

The authors declare no competing financial interest.

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REFERENCES

- (1) (a) Lorente, A.; Lamariano-Merketegi, J. Albericio, F.; Álvarez, M. *Chem. Rev.* **2013**, *113*, 4567. (b) Bermejo, A.; Figadère, B.; Zafra-Polo, M.-C.; Barrachina, I.; Estornell, E.; Cortes, D. *Nat. Prod. Rep.* **2005**, *22*, 269. (c) Kang, E. J.; Lee, E. *Chem. Rev.* **2005**, *105*, 4348. (d) Faul, M. M.; Huff, B. E. *Chem. Rev.* **2000**, *100*, 2407. (e) Dutton, C. J.; Banks, B. J.; Cooper, C. B. *Nat. Prod. Rep.* **1995**, *12*, 165. (f) Fernández, J. J.; Souto, M. L.; Norte, M. *Nat. Prod. Rep.* **2000**, *17*, 235. (g) Sefkow, M. *Synthesis* **2003**, 2595. (h) Ward, R. S. *Nat. Prod. Rep.* **1999**, *16*, 75. (i)

Saleem, M.; Kim, H. J.; Ali, M. S.; Lee, Y. S. *Nat. Prod. Rep.* **2005**, *22*, 696. (j) Pan, J.-Y.; Chen, S.-L.; Yang, M.-H.; Wu, J.; Sinkkonen, J.; Zou, K. *Nat. Prod. Rep.* **2009**, *26*, 1251. (k) Nguyen, P.-H.; Yang, J.-L.; Uddin, M. N.; Park, S.-L.; Lim, S.-I.; Jung, D.-W.; Williams, D. R.; Oh, W.-K. *J. Nat. Prod.* **2013**, *76*, 2080. (l) Pilkington, L. I.; Barker, D. *J. Org. Chem.* **2012**, *77*, 8156. (m) Birch, A. M.; Bradley, P. A.; Gill, J. C.; Kerrigan, F.; Needham, P. L. *J. Med. Chem.* **1999**, *42*, 3342.

(2) (a) Dong, L.-B.; He, J.; Wang, Y.-Y.; Wu, X.-D.; Deng, X.; Pan, Z.-H.; Xu, G.; Peng, L.-Y.; Zhao, Y.; Li, Y.; Gong, X.; Zhao, Q.-S. *J. Nat. Prod.* **2011**, *74*, 234. (b) Zeng, Q.; Cheng, X.-R.; Qin, J.-J.; Guan, B.; Chang, R. J.; Yan, S. K.; Jin, H.-Z.; Zhang, W.-D. *Helvetica Chim. Acta* **2012**, *95*, 606. (c) Wang, P.-S.; Zhou, X.-L.; Gong, L.-Z. *Org. Lett.* **2014**, *16*, 976. (d) Fukuyama, Y.; Hasegawa, T.; Toda, M.; Kodama, M.; Okazaki, H. *Chem. Pharm. Bull.* **1992**, *40*, 252. (e) Fukuyama, Y.; Otsu, Y.; Kodama, M.; Hasegawa, T.; Okazaki, H.; Nagasawa, M. *Tetrahedron. Lett.* **1989**, *30*, 5907.

(3) For selected reviews, see: (a) Wolfe, J. P.; Hay, M. B. *Tetrahedron* **2007**, *63*, 261. (b) Jalce, G.; Franck, X.; Figadère, B. *Tetrahedron: Asymmetry* **2009**, *20*, 2537. (c) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199. (d) Wolfe, J. P. *Synlett* **2008**, 2913. (e) Miura, K.; Hosomi, A. *Synlett* **2003**, 143. (f) Bellur, E.; Feist, H.; Langer, P. *Tetrahedron* **2007**, *63*, 10865.

(4) For selected articles, see: (a) Mansueto, R.; Mallardo, V.; Perna, F. M.; Salomone, A.; Capriati, V. *Chem. Commun.* **2013**, *49*, 10160. (b) Kubo, O.; Yahata, K.; Maegawa, T.; Fujioka, H. *Chem. Commun.* **2011**, *47*, 9197. (c) Urabe, F.; Miyamoto, S.; Takahashi, K.; Ishihara, J.; Hatakeyama, S. *Org. Lett.* **2014**, *16*, 1004. (d) Campbell, M. J.; Johnson, J. S.; Parsons, A. T.; Pohlhaus, P. D.; Sanders, S. D. *J. Org. Chem.* **2010**, *75*, 6317. (e) Spivey, A. C.; Laraia, L.; Bayly, A. R.; Rzepa, H. S.; White, A. J. P. *Org. Lett.* **2010**, *12*, 900. (f) Kim, H.; Wooten, C. M.;

1
2
3 Park, Y.; Hong, J. *Org. Lett.* **2007**, *9*, 3965. (g) Jahn, U.; Rudakov, D. *Org. Lett.* **2006**, *8*, 4481.
4
5 (h) Evans, M. A.; Morken, J. P. *Org. Lett.* **2005**, *7*, 3367. (i) Arthuis, M.; Beaud, R.; Gandon, V.;
6
7 Roulland, E. *Angew. Chem. Int. Ed.* **2012**, *51*, 10510. (j) Fries, P.; Halter, D.; Kleinschek, A.;
8
9 Hartung, J. *J. Am. Chem. Soc.* **2011**, *133*, 3906. (k) McConville, M.; Ruan, J.; Blacker, J.; Xiao,
10
11 J. *Org. Biomol. Chem.* **2010**, *8*, 5614. (l) Ward, A. F.; Wolfe, J. P. *Org. Lett.* **2010**, *12*, 1268. (m)
12
13 Pandey, G.; Luckorse, S.; Budakoti, A.; Puranik, V. G. *Tetrahedron Lett.* **2010**, *51*, 2975. (n)
14
15 Gogoi, P.; Das V. K.; Saikia, A. K. *J. Org. Chem.* **2014**, *79*, 8592.
16
17

18
19 (5) For selected papers on α -C-H functionalization of THF systems, see: (a) Liu, D.; Liu, C.;
20
21 Li, H.; Lei, A. *Angew. Chem. Int. Ed.* **2013**, *52*, 4453. (b) Davies, H. M. L.; Hansen, T.;
22
23 Churchill, M. R. *J. Am. Chem. Soc.* **2000**, *122*, 3063. (c) Wei, W.-T.; Song, R.-J.; Li, J.-H. *Adv.*
24
25 *Synth. Catal.* **2014**, *356*, 1703. (d) Singh, P. P.; Gudup, S.; Ambala, S.; Singh, U.; Dadhwal, S.;
26
27 Singh, B.; Sawant, S. D.; Vishwakarma, R. A. *Chem. Commun.* **2011**, *47*, 5852 and references
28
29 cited therein. (e) Singh, P. P.; Gudup, S.; Aruri, H.; Singh, U.; Ambala, S.; Yadav, M.; Sawant, S.
30
31 D.; Vishwakarma, R. A. *Org. Biomol. Chem.* **2012**, *10*, 1587 and references cited therein. (f)
32
33 Pandit, R. P.; Lee, Y. R. *Adv. Synth. Catal.* **2014**, *356*, 3171 and references cited therein.
34
35
36
37

38
39 (6) For selected reviews on C-H functionalization, see: (a) Chen, X.; Engle, K. M.; Wang, D.-
40
41 H.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2009**, *48*, 5094. (b) Rouquet, G.; Chatani, N. *Angew. Chem.,*
42
43 *Int. Ed.* **2013**, *52*, 11726. (c) Corbet, M.; De Campo, F. *Angew. Chem., Int. Ed.* **2013**, *52*, 9896.
44
45 (d) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (e) White, C. M. *Science* **2012**,
46
47 *335*, 807. (f) Li, B.-J.; Shi, Z. -J. *Chem. Soc. Rev.* **2012**, *41*, 5588. (g) Baudoin, O. *Chem. Soc.*
48
49 *Rev.* **2011**, *40*, 4902. (h) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem. Int. Ed.*
50
51 **2012**, *51*, 8960. (i) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315.
52
53
54
55
56
57
58
59
60

(7) For selected reviews on C-H functionalization, see; (a) Kakiuchi, F.; Murai, S. *Acc. Chem. Res.*, **2002**, 35, 826. (b) Chen, D. Y. -K.; Youn, S. W. *Chem. Eur. J.* **2012**, 18, 9452. (c) Jazzar, R.; Hitce, H.; Renaudat, A.; Sofack-Kreutzer, J.; Baudoin, O. *Chem. Eur. J.* **2010**, 16, 2654. (d) Arockiam. P. B. Bruneau, C.; Dixneuf, P. H. *Chem. Rev.* **2012**, 112, 5879. (e) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, 110, 624. (f) Dastbaravardeh, N.; Christakakou, M.; Haider, M.; Schnürch, M. *Synthesis* **2014**, 46, 1421. (g) Zhang, Q.; Chen, K.; Shi, B.-F. *Synlett* **2014**, 25, 1941. (h) Topczewski, J. T.; Sanford, M. S. *Chem. Sci.* **2015**, 6, 70.

(8) For selected reviews on C-H functionalization, see: (a) Giri, R.; Shi, B.-F.; Engle, K. M.; Maugel, N.; Yu, J.-Q. *Chem. Soc. Rev.* **2009**, 38, 3242. (b) Wasa, M.; Engle, K. M.; Yu, J.-Q. *Isr. J. Chem.* **2010**, 50, 605. (c) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Rev.* **2011**, 111, 1293. (d) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem. Int. Ed.* **2009**, 48, 9792. (e) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, 111, 1215. (f) Liu, C.; Zhang, H.; Shi, W.; Lei, A. *Chem. Rev.* **2011**, 111, 1780. (g) Wencel- Delord, J.; Droge, T.; Liu, F.; Glorius, F. *Chem. Soc. Rev.* **2011**, 40, 4740. (h) Culkin, D. A.; Hartwig, J. F. *Acc. Chem. Res.* **2003**, 36, 234. (i) Hartwig, J. F. *Acc. Chem. Res.* **2012**, 45, 864. (j) Shilov, A. E.; Shul'pin, G. B. *Chem. Rev.* **1997**, 97, 2879.

(9) (a) For a themed issue on C-H activation reactions, see: C-H Functionalisation in organic synthesis; *Chem. Soc. Rev.* **2011**, 40, 1845. (b) Davies, H M. L.; Du Bois, J.; Yu, J.-Q. *Chem. Soc. Rev.* **2011**, 40, 1855. (c) McMurray, L.; O'Hara, F.; Gaunt, M. J. *Chem. Soc. Rev.* **2011**, 40, 1885. (d) Daugulis, O.; Do, H.-Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, 42, 1074. (e) Xu, L.-M.; Li, B.-J.; Yang, Z.; Shi, Z.-J. *Chem. Soc. Rev.* **2010**, 39, 712. (f) Li, B.; Dixneuf, P. H. *Chem. Soc. Rev.* **2013**, 42, 5744. (g) Wencel-Delord, J.; Glorius, F. *Nature Chem.* **2013**, 5, 369. (h) Gao, K.; Yoshikai, N. *Acc. Chem. Res.* **2014**, 47, 1208.

(10) For selected articles on C-H functionalization, see: (a) Wasa, M.; Engle, K. M.; Lin, D. W.; Yoo, E. J.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 19598. (b) Chen, X.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 12634. (c) Nadres, E. T.; Daugulis, O. *J. Am. Chem. Soc.* **2012**, *134*, 7. (d) Tran, L. D.; Popov, I.; Daugulis, O. *J. Am. Chem. Soc.* **2012**, *134*, 18237. (e) Tran, L. D.; Daugulis, O. *Angew. Chem. Int. Ed.* **2012**, *51*, 5188. (f) Tran, L. D.; Roane, J.; Daugulis, O. *Angew. Chem. Int. Ed.* **2013**, *52*, 6043. (g) Reddy, B. V. S.; Reddy, L. R.; Corey, E. *J. Org. Lett.* **2006**, *8*, 3391. (h) He, G.; Chen, G. *Angew. Chem., Int. Ed.* **2011**, *50*, 5192. (i) He, G.; Zhao, Y.; Zhang, S.; Lu, C.; Chen, G. *J. Am. Chem. Soc.* **2012**, *134*, 3.

(11) For selected articles on C-H functionalization, see: (a) Dyker, G. *Angew. Chem., Int. Ed.* **1992**, *31*, 1023. (b) Chaumontet, M.; Piccardi, R.; Audic, N.; Hitce, J.; Peglion, J.-L. Clot, E.; Baudoin, O. *J. Am. Chem. Soc.* **2008**, *130*, 15157. (c) Saget, T.; Cramer, N. *Angew. Chem., Int. Ed.* **2012**, *51*, 12842. (d) Baudoin, O.; Herrbach, A.; Guéritte, F. *Angew. Chem. Int. Ed.* **2003**, *42*, 5736. (e) Pan, F.; Shen, P.-X.; Zhang, L.-S.; Wang, X.; Shi, Z.-J. *Org. Lett.* **2013**, *15*, 4758. (f) Dick, A. R.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 2300.

(12) For selected articles on C-H functionalization, see: (a) Harvey, M. E.; Musaev, D. G.; Bois, J. D. *J. Am. Chem. Soc.* **2011**, *133*, 17207. (b) Shang, R.; Ilies, L.; Matsumoto, A.; Nakamura, E. *J. Am. Chem. Soc.* **2013**, *135*, 6030. (c) Allen, A. E.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2011**, *133*, 4260. (d) Desai, V. L.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 9542. (e) Rit, R. K.; Yadav, M. R.; Sahoo, A. K. *Org. Lett.* **2012**, *14*, 3724. (f) Nishino, M.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem. Int. Ed.* **2013**, *52*, 4457.

(13) For selected recent articles on C-H functionalization, see: (a) Gutekunst, W. R.; Baran, P. S. *J. Org. Chem.* **2014**, *79*, 2430. (b) Tang, H.; Zhou, B.; Huang, X.-R.; Wang, C.; Yao, J.; Chen, H. *ACS Catal.* **2014**, *4*, 649. (c) Murakami, R.; Tsunoda, K.; Iwai, T.; Sawamura, M. *Chem. Eur*

J. **2014**, *20*, 13127. (d) Odani, R.; Nishino, M.; Hirano, K.; Satoh, T.; Miura, M. *Heterocycles* **2014**, *88*, 595. (e) Wei, Y.; Tang, H.; Cong, X.; Rao, B.; Wu, C.; Zeng, X. *Org. Lett.* **2014**, *16*, 2248. (f) Li, M.; Dong, J.; Huang, X.; Li, K.; Wu, Q.; Song, F.; You, J. *Chem. Commun.* **2014**, *50*, 3944. (g) Paradine, S. M.; White, M. C. *J. Am. Chem. Soc.* **2012**, *134*, 2036. (h) Wu, X.; Zhao, Y.; Ge, H. *Chem. Eur. J.* **2014**, *20*, 9530. (i) Iyanaga, M.; Aihara, Y.; Chatani, N. *J. Org. Chem.* **2014**, *79*, 11933 and references cited therein.

(14) For selected articles on C-H functionalization of cyclopropane, cyclobutane, medium-sized rings, norbornane framework and acyclic amino acid derivatives, see: (a) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 13154. (b) Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2010**, *132*, 3965. (c) Gutekunst, W. R.; Baran, P. S. *J. Am. Chem. Soc.* **2011**, *133*, 19076. (d) Roman, D. S.; Charette, A. B. *Org. Lett.* **2013**, *15*, 4394. (e) Chen, K.; Hu, F.; Zhang, S.-Q.; Shi, B.-F. *Chem. Sci.* **2013**, *4*, 3906. (f) Fan, M.; Ma, D. *Angew. Chem., Int. Ed.* **2013**, *52*, 12152. (g) Rodríguez, N.; Romero-Revilla, J. A.; Fernández-Ibáñez, M. Á.; Carretero, J. C. *Chem. Sci.* **2013**, *4*, 175. (h) Gutekunst, W. R.; Baran, P. S. *Angew. Chem. Int. Ed.* **2012**, *51*, 7507. (i) Parella, R.; Gopalakrishnan, B.; Babu, S. A. *Org. Lett.* **2013**, *15*, 3238. (j) Parella, R.; Gopalakrishnan, B.; Babu, S. A. *J. Org. Chem.* **2013**, *78*, 11911. (k) Parella, R.; Babu, S. A. *Synlett.* **2014**, *25*, 1395.

(15) For selected articles on C-H functionalization of cyclopropane, cyclobutane, medium-sized rings, norbornane framework and acyclic amino acid derivatives, see: (a) Wasa, M.; Chan, K. S. L.; Zhang, X.-G.; He, J.; Miura, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2012**, *134*, 18570. (b) He, J.; Wasa, M.; Chan, K. S. L.; Yu, J.-Q. *J. Am. Chem. Soc.* **2013**, *135*, 3387. (c) Affron, D. P.; Davis, O. A.; Bull, J. A. *Org. Lett.* **2014**, *16*, 4956. (d) Sun, W.-W.; Cao, P.; Mei, R.-Q.; Li, Y.; Ma, Y.-L.; Wu, B. *Org. Lett.* **2014**, *16*, 480. (e) Zhang, S.-Y.; Li, Q.; He, G.; Nack, W. A.; Chen,

G. *J. Am. Chem. Soc.* **2013**, *135*, 12135. (f) Aihara, Y.; Chatani, N. *J. Am. Chem. Soc.* **2014**, *136*, 898. (g) Wu, X.; Zhao, Y.; Ge, H. *J. Am. Chem. Soc.* **2014**, *136*, 1789. (h) Wang, B.; Nack, W. A.; He, G.; Zhang, S.-Y.; Chen, G. *Chem. Sci.* **2014**, *5*, 3952. (i) Rousseaux, S.; Liégault, B.; Fagnou, K. *Chem. Sci.* **2012**, *3*, 244. (j) Hoshiya, N.; Kobayashi, T.; Arisawa, M.; Shuto, S. *Org. Lett.* **2013**, *15*, 6202. For a recent paper on C-H arylation of proline derivative, see: (k) Feng, R.; Wang, B.; Liu, Y.; Liu, Z.; Zhang, Y. *Eur. J. Org. Chem.* **2015**, 142.

(16) Crystallographic data of the X-ray structures of **3b** (CCDC 1041214), **3e** (CCDC 1029716), **4p** (CCDC 1029717) and **7** (CCDC 1041215) reported in this work have been deposited at the Cambridge Crystallographic Data Centre.

(17) (a) Lo, M. M.-C.; Fu, G. C. *Tetrahedron* **2001**, *57*, 2621, in this paper, the coupling constant (J) of the doublet peak of the OC(2)-H moiety present in *trans* 3-aryl tetrahydrofuran-2-carboxylates reported to be in the range of 5.8-6.4 Hz not exceeding 6.4 Hz. Further, the coupling constant (J) of the doublet peak of the OC(2)-H moiety present in *cis* 3-aryl tetrahydrofuran-2-carboxylates reported to be in the range of 7.3-7.6 Hz. Analogously, in addition to the unambiguous assignment of the stereochemistry of 3-aryl/heteroaryl tetrahydrofuran-2-carboxamides **3a-r** based on the X-ray structures of **3b** and **3e**, the coupling constants (J) of the doublet peak of the C2 proton of all the compounds **3a-r** were found to be in the range of 6.6-8.2 Hz (except the compound **3q** having a thiophene moiety at the C3-position, C2H, doublet, J = 6.3 Hz). (b) Nozaki, H.; Takaya, H.; Noyori, R. *Tetrahedron* **1966**, *22*, 3393.

(18) (a) The coupling constant (J) of the doublet peak of the OC-H moiety present in 2,3-disubstituted benzodioxane system having *cis* or *trans* stereochemistry has been reported to be 2.51 and 7-11 Hz, respectively, see: Quaglia, W.; Pignini, M.; Giannella, M.; Melchiorre, C. *J. Med. Chem.* **1990**, *33*, 2946 and references cited therein. (b) The coupling constant (J) of the

doublet peak of OC-H moiety in a typical 2,3-disubstituted benzodioxane compound having *trans* stereochemistry has been reported to be 9 Hz, see; Ganesh, T.; Sharma, K. K.; Krupadanam, G. L. D. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 2397.