# Synthesis of 6 or 7 membered nonplanar heterocycles presenting a $\mathrm{N}-\mathrm{O}$ bond <br> Shuang-Qi Tang 

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# ÉCOLE DOCTORALE DES SCIENCES CHIMIQUES <br> UMR7200 - Laboratoire d'Innovation Thérapeutique 

# THÈSE présentée par: Shuang-Qi TANG 

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## Synthèse d'hétérocycles non planaires à 6 ou 7 chaînons présentant une liaison N -

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## RESUME

# Synthèse d'hétérocycles non planaires à 6 ou 7 chaînons présentant une liaison $\mathrm{N}-\mathrm{O}$ 

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## 1. Introduction

Les hétérocycles présentant 2 atomes d'azote adjacents sont très populaires en chimie médicinale. Ainsi, le cycle à 5 de type pyrazole, ainsi que les cycles à 6 de type pyridazine et $1,2,4-$ triazine ont été intensivement étudiés en drug design. En effet, la présence des atomes d'azote permet à ces systèmes hétérocycliques aromatiques de présenter 2 à 3 sites potentiels d'interactions de type accepteur de liaison hydrogène avec une cible protéique. De plus, la présence d'atomes d'azote permet de diminuer la lipophilie de ces systèmes aromatiques en comparaison avec le benzène. Toutefois, le caractère aromatique de ces hétérocycles leur confère une géométrie planaire, ce qui constitue une limitation importante dans la recherche de structures moléculaires complexes. En 2009, Franck Lovering de Wyeth a proposé le concept "Escape from flatland", dans lequel il présente l'intérêt d'éviter les structures aromatiques pour privilégier des cycles saturés présentant des carbones $\mathrm{sp}^{3}$. Le rationnel de cette approche repose sur le fait que ces molécules non aromatiques sont plus proches des produits naturels, et que leur géométrie non-planaire permet une plus grande exploration de l'espace chimique tridimensionnel, tout en améliorant les propriétés d'ADME (solubilité, sélectivité, lipophilie, etc.).

Dans ce projet de thèse, nous proposons de développer de nouveaux hétérocycles non aromatiques et non planaires présentant une liaison N-O. Si les cycles à 5 (isoxazole ou isoxazole) sont bien connus, les cycles à 6 ou 7 chaînons présentant un motif $\mathrm{N}-\mathrm{O}$ sont particulièrement rares ou inexistants dans la littérature. Outre l'intérêt géométrique de ces hétérocycles, la présence de l'oxygène en alpha de l'azote permet de fortement diminuer la basicité de ce dernier, conférant à l'hétérocycle des propriétés physico-chimiques particulières. Par ailleurs, les oximes éthers (=N-O-) présentent une bonne résistance à la protonation, ce qui leur confère une stabilité intrinsèque à l'hydrolyse bien meilleure que celle observée avec les hydrazones ou les imines. Enfin, plusieurs
alkoxyamides sont actuellement en essai clinique. Durant cette thèse, nous avons focalisé nos travaux sur la synthèse de 3-amino-1,2,4-oxadiazine et benzo-2,3-oxazepin-4-one (Figure 1).


3-amino-1,2,4-oxadiazine


Aryl/Hétéroaryloxazépine

Figure 1 : Nouveaux châssis moléculaires

## 2. Résultats et discussions

### 2.1 Synthèse de 3-amino-1,2,4-oxadiazine

Les fonctions guanidines ont été extrêmement utilisées dans le développement d'outils pharmacologiques, tels que les antagonistes des récepteurs du NPFF, les inhibiteurs de FXa, de NOS ou encore d'urokinase. Toutefois, à cause de la basicité importante de la guanidine ( $\mathrm{pKa} \approx 13$ ), ainsi que sa capacité à former de nombreuses liaisons hydrogène, il est difficile de développer des molécules présentant un bon profil pharmacocinétique, notamment en termes d'absorption orale, de distribution dans le CNS, ou encore de durée d'action. Le système iminoguanidine constitue un moyen intéressant de diminuer la basicité de la guanidine, comme le montre le développement thérapeutique du guanabenz (Wytensin ${ }^{@}$ ) contre l'hypertension. Néanmoins, cette molécule est entièrement plane et présente une certaine sensibilité à l'hydrolyse. Dans un précédent programme, l'équipe du Dr Bihel a développé une forme cyclique du guanabenz qui présente un effet inhibiteur sur le développement des prions, tout en étant moins sensible à l'hydrolyse

Nous proposons de développer la synthèse de 3-amino-1,2,4-oxadiazines comme biomimétiques des fonctions guanidines et iminoguanidines. Alors que la synthèse des cycles à 6 chaînons 1,2-oxadiazines a été largement développée grâce à la réaction de cyclisation [4+2] de type nitroso-Diels Alder, les systèmes de type 3-amino-1,2,4-oxadiazines sont quasiment inconnus dans la littérature en termes de synthèse.

En partant de la Boc-Glycine, nous avons mis au point une synthèse multi-étape permettant d'accéder rapidement et avec d'excellents rendements au cycle 3 -amino-1,2,4-oxadiazine sans contrôle du centre chiral en position 6 (Schéma 1). En utilisant la L-Proline, nous avons été capables de développer une synthèse énantiosélective permettant d'obtenir le cycle 4-amino ou 4-hydroxypyrrolo-[1,2-d]-1,2-4-oxadiazine avec un parfait contrôle des centres chiraux. La structure et la géométrie de ces nouveaux cycles ont été vérifiées par cristallographie aux rayons X . La mesure des pKa a permis de confirmer une baisse importante de la basicité de ces alkoxyguanidines avec un $\mathrm{pKa} \approx 8$ à comparer avec les $\approx 10$ de l'iminoguanidine et $\approx 13$ pour une guanidine.



Schéma 1: Synthèse de 3-hydroxy- et 3-amino-1,2,4-oxadiazine

A ce jour, le seul produit naturel présentant un noyau 3-amino-1,2,4-oxadiazine est l'alchornédine, une molécule présentant des propriétés anti-parasitaires et extraites des feuilles d'alchornea glandulosa (Figure 2). Néanmoins, ce composé n'a jamais été synthétisé, et sa structure a été déduites d'analyses RMN. Nous avons mis au point une voie de synthèse permettant de synthétiser pour la première fois cet alcaloïde, et nous avons ainsi montré que la structure du produit décrit dans la littérature et nommé alchornédine était erronée. En effet, le cycle 3-amino-1,2,4oxadiazine n'est pas présent, et nous pensons que l'alchornédine présente plutôt un cycle à 5 chaînons de type 2 -amino-N-hydroxy-imidazole (Figure 2).


Figure 2: Structure publiée de l'alchornédine et notre contre-proposition

Au cours de ces travaux de synthèse, nous avons utilisé plusieurs voies de synthèse conduisant à l'insertion du motif N-O. L'une d'entre elles a consisté à insérer par réaction radicalaire en milieu
aqueux le motif N -hydroxyphtalimide en position béta de dérivés de styrène, suivi d'une oxydation de la position alpha (Schéma 2). La mise au point de cette réaction a nécessité l'utilisation de tensioactifs de type Triton X-100 permettant de réaliser la réaction en milieu micellaire. Cette méthodologie permet un meilleur respect des principes de la chimie verte, et a fait l'objet d'un article dans Tetrahedron Letters (Tang, S. Q.; Wang, A. P.; Schmitt, M.; Bihel, F. Dioxygenation of Styrenes with Molecular Oxygen in Water. Tetrahedron Lett. 2018. https://doi.org/10.1016/j.tetlet.2018.03.009).


Schéma 2: Dioxygénation de styrènes avec de l'oxygène moléculaire dans l'eau

### 2.2 Synthèse de benzo-2,3-oxazepin-4-one

Dans notre approche de développer et caractériser de nouveaux châssis moléculaires innovants présentant une fonction $\mathrm{N}-\mathrm{O}$, nous avons choisi de construire le châssis benzo-2,3-oxazepin-4-one (Figure 1), en tant que bioisostère de 2,3-benzodiazépin-4-one. En effet, les benzodiazépines sont connues depuis les années 60 , et près de 20 molécules sont actuellement utilisées en thérapie humaine comme anxiolytiques, myorelaxants et/ou hypnotiques. La majorité de ces médicaments sont des 1,4-benzodiazépines, à l'exception du Tofizopam qui présente un châssis de 1,2benzodiazepine. Ce dernier est utilisé en Europe comme anxiolytique atypique, ainsi que pour le traitement de l'alcoolisme. Le cycle à 7 chaînons des benzodiazépines est particulièrement intéressant car cela confère à ces molécules des géométries tridimensionnelles tout à fait particulières.

La synthèse de benzo-2,3-oxazepin-4-one s'est révélée particulièrement difficile, et de très nombreuses voies de synthèse ont été testées. Néanmoins, nous avons réussi à développer une voie de synthèse efficace et reproductible (Schéma 3). La structure finale de ce premier exemple de benzo-2,3-oxazepin-4-one a été confirmée par cristallographie au rayon X. Nous travaillons actuellement à tester sa réactivité chimique et sa capacité à être fonctionnalisé.



Schéma 3: Synthèse de la benzo-2,3-oxazepin-4-one

Durant la mise au point de cette synthèse, nous avons notamment travaillé sur la formation de la phénylacétophénone $\mathbf{4 a}$ (Tableau 1) via une réaction de Fukuyama pallado-catalysée. La présence du groupement ester à proximité rend cette synthèse particulièrement difficile à réaliser à cause d'une réaction de cyclisation intramoléculaire. Après analyse des mécanismes en jeu, nous avons émis l'hypothèse qu'une accélération de la réaction de couplage devrait permettre d'éviter la cyclisation de Dieckman. L’utilisation de précatalyseurs commerciaux (PEPPSI-IPr ou XPhos-PdG4), mis au point pour la réaction de Negishi, n'a pas permis d'améliorer la réaction (Tableau 1, entrées 9 et 10). Nous avons par conséquent développé un nouveau précatalyseur que nous avons nommé POxAP pour « Post-Oxydative Addition Precatalyst » (Tableau 1, entrée 11).

Tableau 1. Réaction de Fukuyama appliquée au thioester 3a

 $(0.26 \mathrm{~mL}), \mathrm{rt} .{ }^{b}$ Isolated yield. ${ }^{c} 1.4 \mathrm{~mol} \% \mathrm{P}(\mathrm{Fu})_{3} .{ }^{d} 2 \mathrm{~mol} \% \mathrm{PCy}_{3}$ and 1 equiv $\mathrm{ZnCl}_{2}$ were used. ${ }^{e} 10 \mathrm{~mol} \% \mathrm{Ni}(\mathrm{acac})_{2}$. ${ }^{f} 0.1 \mathrm{~mol} \%$

Grâce à ce précatalyseur de formule générique $\operatorname{PdX}(\mathrm{Ar})\left(\mathrm{PPh}_{3}\right)_{2}, 0.001 \mathrm{~mol} \%$ de catalyseur sont suffisants pour réaliser le couplage de Fukuyama avec d'excellent rendements, ouvrant l'accès à une très large variété de cétones (Tableau 2).

Tableau 2: Scope de la réaction de Fukuyama en utilisant le précatalyseur $\mathrm{PdCl}(\mathrm{Ph})(\mathrm{PPh} 3) 2$



4b, 98\%


4h, $95 \%$


4m, 82\%


4s, 86\%


4c, 98\%

$4 i, 65 \%$


4n, 95\%


4t, 87\%


4d, 97\%


4j, 95\%


40, 93\%

$4 u, 89 \%$


4e, 99\%


4a, $95 \%$


4p, 77\%


4v, 84\%


4f, $95 \%$


4k, 82\%


4q, 88\%


4w, 88\%
${ }^{a}$ Reaction conditions: Thioester $3(1 \mathrm{mmol}), \mathrm{PdCl}(\mathrm{Ph})\left(\mathrm{PPh}_{3}\right)_{2}(0.1 \mathrm{~mol} \%), \mathrm{R}^{2} \mathrm{ZnBr} 6(1.5 \mathrm{mmol}$ in THF$)$, toluene $(2.5 \mathrm{~mL}), \mathrm{rt}, 1-$ 3 h .

Ce nouveau précatalyseur POxAP nous a ainsi permis de synthétiser des analogues de la benzo-2,3-oxazepin-4-one, mais nous avons également valorisé ce nouveau réactif en réalisant la synthèse d'un précurseur de l'isoprekinamycine (IPK), un produit naturel connu pour ses propriétés antiparasitaires et anticancéreuses. Alors que la synthèse de ce précurseur de l'IPK avait été décrit dans la littérature en 16 étapes et $3 \%$ de rendement global, notre précatalyseur POxAP nous a permis de développer une stratégie alternative de synthèse conduisant au précurseur attendu en seulement 11 étapes et $29 \%$ de rendement global (Schéma 4). Ce travail a fait l'objet d’une publication dans Organic Letters (Tang, S. Q.; Bricard, J.; Schmitt, M.; Bihel, F. Fukuyama Cross-Coupling Approach to Isoprekinamycin: Discovery of the Highly Active and Bench-Stable Palladium Precatalyst POxAP. Org. Lett. 2019, 21 (3), 844-848. https://doi.org/10.1021/acs.orglett.9b00031.). Par ailleurs, nous avons montré également que POxAP est également efficace dans d'autres réactions telles que la réaction de Negishi, et ce travail est en cours de rédaction pour publication en 2019





Schéma 4: Synthèse du précurseur de l'isoprékinamycine en 11 étapes et $29 \%$ de rendement global

## 3. Conclusion générale

Au cours de ce travail de thèse, j'ai pu remplir mes 2 objectifs principaux, à savoir la synthèse de nouveaux châssis moléculaires hétérocycliques et non aromatiques présentant une liaison N-O. Un important travail d'optimisation de voies de synthèse a été accompli, incluant la mise au point de nouvelles méthodologies ( 2 articles publiés en $1^{\text {er }}$ auteur). Grâce à la cristallographie, nous avons pu par ailleurs démontrer la géométrie non planaire de ces molécules, et les mesures de pKa ont montré également l'effet alpha de l'oxygène sur la basicité de l'azote. La suite de ce travail consistera à évaluer les possibilités de fonctionnalisation de ces châssis moléculaires, mais également évaluer leur pertinence en chimie médicinale. Ainsi, les propriétés d'ADME (stabilités métaboliques et plasmatiques, perméabilité, solubilité, etc.) seront mesurées, et des dérivés spécifiques seront synthétisés pour être testés sur des cibles biologiques spécifiques. A titre d'exemple, les 3-amino-1,2,4-oxadiazines seront testées pour leur capacité à moduler le système PFAR dans des tests anti-prions.

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## LIST OF ABBREVIATIONS

| ADME | absorption, distribution, metabolism and excretion |
| :--- | :--- |
| Boc | $t$-butyloxycarbonyl |
| BOP | (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium |
|  | hexafluorophosphate |
| CCR | cross-coupling reaction |
| CDI | 1,1'-carbonyldiimidazole |
| COSY | homonuclear chemical shift correlation spectroscopy |
| cpd | compound |
| CYP450 | cytochrome P450 |
| DBE | dibromoethane |
| DBU | dichloromethane |
| DCM | diethyl azodicarboxylate |
| DEAD | diisopropyl azodicarboxylate |
| DIAD | diisobutyl aluminium hydride |
| DIBAL-H | 4-dimethylaminopyridine |
| DMAP | 2,4-dimethoxybenzyl |
| DMB | di-2-methoxyethyl azodicarboxylate |
| DMEAD | heteronuclear multiple bond correlation |
| DMF | 1-hydroxybenzotriazole |
| EDCI | 1-ethyl-3-(3-dimethyorenylmethoxycarbonyl |
| FDA | fraction of saturated carbons |
| Fmoc | type A $\gamma$-aminobutyric acid receptor |
| Fsp | H-bond acceptor |
| GABA | receptor |
| HBA | HOBt |


| HSAB | hard and soft acids and bases |
| :--- | :--- |
| HSQC | heteronuclear single quantum correlation |
| log D | distribution coefficient |
| MsCl | methanesulfonyl chloride |
| NHPI | N-hydroxyphthalimide |
| NOESY | nuclear overhauser effect spectroscopy |
| NPFFR | neuropeptide FF receptors |
| N-N heterocycles | heterocycles including two adjacent nitrogen atoms |
| N-O heterocycles | heterocycles including adjacent nitrogen and oxygen atoms |
| PDE4 | phosphodiesterase4 |
| pK $K_{\text {a }}$ | ionization constant |
| PMP | para-methoxyphenyl |
| POxAP | post-oxidative-addition precatalyst |
| rt | room temperature |
| SPhos | 2 -dicyclohexylphosphino-2',6'-dimethoxybiphenyl |
| S-CDI | 1,1'-thiocarbonyldiimidazole |
| TEA | triethylamine |
| TMSCl | trimethyl chlorosilane |

[^0](S)-3,3-diphenyl-1-methylpyrrolidino[1,2-c]-1,3,2-oxazaborole

## I. Introduction

## I. Introduction

## IA. Heterocycles in medicinal chemistry

For more than a century, heterocycles have constituted one of the largest areas of research in organic chemistry and been on the forefront of attention because of their numerous uses in pharmaceutical applications such as antimicrobial, anti-inflammatory, anticancer, antiviral, anticonvulsant and antidepressant (Figure 1.1). ${ }^{1-6}$


Tavaborole antimicrobial


Haworforbin C anti-inflammatory


Bortezomib anticancer


Scopolamine antidepressant

Figure 1.1. Heterocycles in pharmaceutical applications.

In particular, nitrogen- and oxygen-containing heterocycles are the two most common type of heterocycles that appear as structural components of U.S. Food and Drug Administration (FDA) approved pharmaceuticals. The analysis of the nitrogen or oxygen heterocyclic composition of U.S. FDA approved unique small-molecule pharmaceuticals shows that $59 \%$ of small-molecule drugs contain nitrogen heterocycle(s) and $27 \%$ contain oxygen heterocycle(s). ${ }^{7,8}$

Figure 1.2 displays the structures of the 20 most frequent nitrogen heterocycles
from 640 FDA approved unique nitrogen heterocycle-containing small molecule drugs (excluding pharmaceuticals with different international nonproprietary names) in order of decreasing frequency, which highlights the various ring system classes. Piperidine, pyridine and piperazine are the top three most common nitrogen heterocycles, appearing in 72,62 and 59 unique small-molecule drugs, respectively. Significantly behind the top three is cephem, a $\beta$-lactam core found in 41 approved drugs followed by pyrrolidine accounting for 37 drugs. Two more five-membered nitrogen heterocycles, thiazole and imidazole, are sixth and seventh most prevalent nitrogen heterocycles followed by penam. Rounding off the top 10 , with approximately equal representation, are indole, tetrazole, phenothiazine, and pyrimidine. It is interesting to note that 4 of the 10 most commonly used nitrogen heterocycles also contain a sulfur atom (cephem, thiazole, penam, and phenothiazine). Despite the similarity in frequency of the remaining top 20 nitrogen heterocycles, remarkable diversity in structures could be observed, ranging from simple five-membered rings (benzimidazole and imidazolidine) to complex natural motifs (morphinan, tropane and ergoline).


Figure 1.2. Top 20 most frequent nitrogen heterocycles in U.S. FDA approved drugs in order of decreasing frequency represented by a drawn to scale solid colored bar.
(adapted from Njardarson, J. T. et al ${ }^{7}$ )

Figure 1.3. displays the 20 most frequent oxygen heterocycles from 311 FDA approved unique oxygen heterocycle-containing drugs in order of decreasing frequency. The two most frequently used oxygen heterocycles are originated from carbohydrate-based drugs, where pyranoses are number 1 with 62 appearances followed by furanoses in a distant second place with 34 appearance. Macrolactones, morpholines, and dioxolanes account for the remaining top five with 26,26 and 24 appearance, respectively. When compared the frequency of the top two oxygen heterocycles or nitrogen heterocycles, a $45 \%$ decrease in frequency is observed between pyranose and furanose, while for nitrogen heterocycles, the decrease in frequency is $14 \%$ between piperidine and pyridine, suggesting the oxygen heterocycles are far more top heavy.


Figure 1.3. Top 20 most frequent oxygen heterocycles in U.S. FDA approved drugs, in order of decreasing frequency represented by a drawn to scale solid colored bar. (adapted from Njardarson, J. T. et al ${ }^{8}$ )

A closer look at these FDA approved pharmaceuticals containing nitrogen or oxygen heterocycles revealed that the majority are non-aromatic heterocycles (Figure 1.4). Although the rigidity of the non-aromatic heterocycles is decreased compared with the corresponding aromatic ones, the intercalation between molecules will be impaired and a better solubility will be obtained. Moreover, the non-aromatic scaffolds usually imply the presence of stereogenic elements, which increase the selectivity for targets and decrease the side effects. All these aspects lead to good drugggability of the non-aromatic heterocycles.


Figure 1.4. Structural classes and relative distribution of nitrogen (A) or oxygen (B) heterocycles in FDA approved drugs. (adapted from Njardarson, J. T. et al ${ }^{7,8}$ )

## IB. Nitrogen or oxygen heterocycles as privileged structures

The concept of privileged structures is the idea that certain structural features produce biological effects more often than others. More formally, privileged structures have been defined in the context of a minimal substructure capable of binding several types of receptors. ${ }^{9}$ As frequently appeared in drugs, nitrogen and oxygen heterocycles are always regarded as privileged structures in medicinal chemistry. Table 1.1 showed several examples of privileged structures containing nitrogen or oxygen heterocycles. Various biological activities of these heterocycles have been discovered, such as antibacterial, antiviral, anti-inflammatory, anticancer, antioxidant, antiplasmodial, antiglycation, anticonvulsant, antitubercular, antipsychotic, herbicidal, etc.

Table 1.1. Privileged structure containing nitrogen or oxygen heterocycles.

| Heterocyclic Privileged Structures |  |  | Biological Activities |
| :---: | :---: | :---: | :---: |
| Five-membered heterocycles | hydantoin ${ }^{10}$ |  | anticancer, anti-inflammatory, antidiabetic, antimicrobial, adrenoceptor modulating, anticonvulsant, antiplatelet, anti-HIV |
|  | 1,2,4-Oxadiazole ${ }^{11}$ | $\begin{aligned} & \pi \mathrm{O}_{1} \\ & \mathrm{~N}=\mathrm{N} \end{aligned}$ | anti-inflammatory, analgesic |
|  | isoxazolidine ${ }^{12}$ | $\Sigma^{\mathrm{O}} \mathrm{NH}$ | Anticancer, antifungal, <br> antimicrobial, anti-inflammatory, <br> antiglycation |
| Fused <br> five-membered | benzimidazole ${ }^{13}$ |  | anti-HIV, anti-HCV, anti-HBV, anti-HCMV, anti-RSV and anti-rhino/enteroviruses |
| heterocycles | benzoxazole ${ }^{14,15}$ |  | antimicrobial, antiglycation, <br> anticonvulsant, antitubercular, |



|  |  |  | anxiolytic, antimalarial, antifungal |
| :---: | :---: | :---: | :---: |
|  | imidazo[1,2-a]pyrimidine ${ }^{27}$ |  | anticancer, antiviral, antimicrobial, antibacterial, antifungal, anti-inflammatory, local anaesthetic |
|  | pyrrolo[2,1-f][1,2,4]triazine ${ }^{28}$ |  | Inhibitor of anaplastic lymphoma kinase (ALK), Janus kinase 2 <br> (JAK2), VEGFR-2, EGFR, <br> HER2, Met kinase, p38 $\alpha$ <br> mitogenactivated protein (MAP) <br> kinase and insulin-like growth <br> factor receptor (IGF-1R) kinase |
|  | 2,3-Dihydroquinazolin-4(1H)-one ${ }^{29}$ |  | Antihypertensive, diuretic, neurotransmitter, thermogenic, <br> stimulant, sedative, <br> muscle-relaxant, hypnotic, <br> antineoplastic, anti-inflammatory, <br> antifungal |
|  | chromene ${ }^{30}$ |  | antitumor, antihepatotoxic, antioxidant, anti-inflammatory, <br> diuretic, anticoagulant, antispasmolytic, estrogenic, antiviral, antifungal, antimicrobial, anti-helminthic, hypothermal, vasodilatory, antitubercular, herbicidal, anticonvulsant, analgesic |


|  | Xanthene ${ }^{31}$ |  | antibacterial, antiviral, anti-inflammatory, antitumor, antioxidant, antiplasmodial |
| :---: | :---: | :---: | :---: |
|  | coumarin ${ }^{\text {23,34 }}$ |  | antibacterial, antitubercular, antifungal, antiviral, antimutagenic, antioxidant, anti-inflammatory, antithrombotic, anticancer, anticoagulant, cyclooxygenase inhibitory, lipoxygenase inhibitory, cholinesterase inhibitory, monoamine oxidase inhibitory, CNS stimulant, vasodilator, and cytotoxic |
|  | chromone ${ }^{5,35,36}$ |  | Anticancer, anti-inflammatory, antidyslipidemic, estrogenic, immunosuppressant, antioxidant, antimicrobial |
|  | bispidine ${ }^{37}$ |  | Antiviral, antibacterial, antifungal, antidote, anticancer |
| Seven-membered heterocycles | 1,4-diazepine ${ }^{38}$ |  | anticonvulsant, sedative, and anxiolytic, anticancer, anti-inflammatory |

## IC. Molecular complexity in drug discovery

Since many drugs are derived from complex natural products (Figure 1.5), ${ }^{39}$ the medicinal chemistry community has become increasingly aware of the requirement to creating drug-like compounds containing a high degree of structural diversity and architectural complexity, ${ }^{40-44}$ to increase the chance to find bioactive compounds. Molecular complexity has been associated with major aspects in the drug development process such as success in progressing into clinical development, target selectivity and compound safety. ${ }^{45}$ However, like molecular similarity and chemical space, molecular complexity is an intuitive and subjective concept that is not easy to quantify in a unique and "best" manner.
natural product (source)

(-)-cytisine (plant)




varenicline (nicotine dependence)

morphine (plant)


methylnaltrexone (opioid-induced constipation)

thienamycin
(actino)


tebipenem pivoxi
(antibacterial)


fingolimod
(multiple sclerosis)

zucapsaicin (pain)

Figure 1.5. Nature product derived drugs.

Although routinely used in absorption, distribution, metabolism and excretion (ADME) prediction models and scrutinized as compounds progress from hit-to-lead, physicochemical indicators such as Lipinski's "rule of five" (H-bond donors or Log P $<5$, molecular weight $<500, \mathrm{H}$-bond acceptors $<10$ ), ${ }^{46}$ topological polar surface area $\left(\leq 140 \AA^{2}\right)$ and rotatable bonds $(\leq 10)^{47}$ did not describe the complexity of the molecules, but help to determine the potential or the risk factors of a compound in drug development. As a result, several approaches describing molecular complexity have been reported. Based on the concepts of graph theory and information theory, Bertz proposed a mathematical approach for evaluating the complexity of chemical structures, ${ }^{48}$ while Whitlock proposed an intuitive (metric) approach for molecular complexity, ${ }^{49}$ which was then ameliorated by Barone with a more empirical approach. ${ }^{50}$ After that, Allu proposed a new metric based on relative atomic electronegativities and bond parameters that evaluate both synthetic and molecular complexity starting from chemical structures. ${ }^{51}$ However, it reduced the correlation of complexity to molecular weight. More recently, Lovering proposed the descriptor of molecular complexity by using the fraction of saturated carbons $\left(\mathrm{Fsp}^{3}=\right.$ number of $\mathrm{sp}^{3}$ hybridized carbons/ total carbon count) and carbon chirality within a molecule. ${ }^{52}$ More importantly, he indicated that both complexity (as measured by $\mathrm{Fsp}^{3}$ ) and the presence of chiral centers correlate with success as compounds transition from discovery, through clinical testing, to drugs. Without increasing molecular weight significantly, saturation and chirality allow the preparation of architecturally more complex molecules, resulting in the exploration of more diverse chemical space. As a result, it increases opportunity to design in out-of-plane substituents and to adjust molecular shape, increasing receptor/ligand complementarity. This might also allow the engineering of additional protein-ligand interactions not accessible to a flat aromatic ring, and thus improve potency and selectivity to a given target while mitigating off-target effects. Although aromatic features can provide an opportunity to develop $\pi-\pi$ interactions or $\pi$-cation interactions, ${ }^{53,54}$ an overall level of saturation may provide the molecule with an opportunity to better place these types of moieties.

Furthermore, increasing $\mathrm{sp}^{3}$ character may improve several molecular attributes that contribute to clinical success. For instance, saturation increased solubility and decreased melting point, two experimental physical properties important to success in the drug discovery setting, as any compound with an intravenous mode of delivery should necessarily be very water soluble and a melting point above $250{ }^{\circ} \mathrm{C}$ will negatively impact oral bioavailability. ${ }^{55}$ Increasing complexity (measured by $\mathrm{Fsp}^{3}$ and chiral carbon count) also reduces promiscuity and cytochromeP450 (CYP450) inhibition, which were linked to toxicity. ${ }^{56}$

## ID. Increase complexity: from N-N heterocycles to N-O heterocycles

It is widely accepted that heterocycles including two adjacent nitrogen atoms (N-N heterocycles) are excellent drug candidates. More particularly, the five-membered ring pyrazole, as well as both six-membered rings pyridazine and 1,2,4-triazine, were extensively used in drug design (Figure 1.0). ${ }^{57-59}$ Indeed, thanks to the nitrogen atoms, these three aromatic scaffolds exhibit 2 to 3 H -bond acceptors, capable to interact with target proteins. Moreover, these nitrogen atoms allow to decrease the lipophilicity of these heterocycles in comparison with benzene. However, due to their aromatic character, these 3 scaffolds have still a planar geometry, partly contributing to the fact that they are widely used in developing pharmacological tools, but poorly represented in FDA-approved drugs.


Figure 1.6. N - N heterocycles, $\mathrm{N}-\mathrm{O}$ heterocycles and acyclic $\mathrm{N}-\mathrm{O}$ functions.
$1,2,4$-triazine ring is widely described as scaffold of many biological active compounds, natural or synthetic, with a great variety of pharmacological effects,
especially active as anti-inflammatory, antiproliferative, neuroprotective, antibacterial and antitumor agents (Figure 1.7). ${ }^{60-64}$


Figure 1.7. Bioactive 1,2,4-triazines.

Compound (cpd) $\mathbf{1}$ is an $\mathrm{N}-\mathrm{N}$ heterocycle containing 1,2,4-Triazine nucleus previously developed in our group as a neuropeptide FF receptors (NPFFR) antagonist (Figure 1.8). When we increased the complexity of cpd1 by saturated one of the $\mathrm{C}=\mathrm{N}$ double bond in the 1,2,4-triazine scaffold, cpd 2 (acid dissociation constant $\left(\mathrm{p} K_{\mathrm{a}}\right) \approx 9.3$ ) was obtained with a higher activity. Then, the cyclic iminoguanidine scaffold 2 was replaced by the conjugated cyclic guanidine $\mathbf{3}$ ( $\mathrm{p} K_{\mathrm{a}} \approx$ 10.6) according to isosterism concept. Cpd 3 appeared to be a potent selective $\mathrm{NPFF}_{1} \mathrm{R}$ antagonist, which could significantly reduce the long lasting fentanyl-induced hyperalgesia in rodents. ${ }^{65}$ However, removing the conjugation between the guanidine and phenyl moiety in $\mathbf{3}$ by saturating the $\mathrm{C}=\mathrm{C}$ double bond in-between increased $\mathrm{p} K_{\mathrm{a}}(\approx 13)$ and impaired the biological activity, indicating the importance of a proper basicity to activity.


Figure 1.8. Previous research on six-membered $N$-N heterocycle 1,2,4-triazine.

Besides 1,2,4-triazine, the seven-membered N-N heterocycle, 2,3-benzodiazepin -4-one also has attracted huge interest because of their diverse pharmacological activities, including neuroprotective, anticonvulsant, and antitumor effect (Figure 1.9). ${ }^{66-68}$


AMPA receptor antagonist neuroprotective, anticonvulsant


PARP-1 inhibitor antitumor

gama-secretase inhibitor neuroprotective

Figure 1.9. Bioactive 2,3-benzodiazepin-4-ones.

By pharmacophoric comparison between papaverine 5 (ring expansion) and tofisopam 6 (bioisosterism), cpd 7 was developed by our group as a novel class of phosphodiesterase4 (PDE4) inhibitor, which appears as a potential target for the development of new anti-asthmatic and anti-inflammatory drugs (Figure 1.10). ${ }^{69}$ As a result of the insertion of a saturated carbon into 5 and saturation one of the $\mathrm{C}=\mathrm{N}$ double bond in 6, the 2,3-benzodiazepin-4-one nucleus in 7 shown a non-planar boat-shaped conformation, ${ }^{70}$ which might be crucial to the target cognization.


Figure 1.10. Previous research on seven-membered $N$ - $N$ heterocycle

> 2,3-benzodiazepin-4-one.

As shown in Figure 1.9 and 1.10, increasing the complexity through the concept of "escape the flatland" (saturating carbon bonds and introducing chiral $\mathrm{sp}^{3}$ carbon atoms) enhanced the biological activity and target selectivity. Thus, in this project, we will continue to increase the complexity of two scaffolds, 4,5-dihydro-1,2,4-triazine 2 and 2,3-benzodiazepin-4-one 7, by developing non-planar heterocycles including adjacent nitrogen and oxygen atoms ( $\mathrm{N}-\mathrm{O}$ heterocycles), as bioisosteres of the corresponding N-N heterocycles. By transposing one of the two adjacent nitrogen atoms in cpd 2 and 7 by an oxygen atom, we will obtain two new scaffolds 1,2,4-oxadiazine $\mathbf{8}$ and 2,3-benzoxazepin-4-one $\mathbf{9}$ exhibiting an intracyclic N-O bond (Figure 1.11). As the oxygen atom is a H -bond acceptor (HBA), these scaffolds can be considered as biomimetic structures of the corresponding N-N heterocycles. However, thanks to the bivalent character of oxygen atom, these N-O hetercycles cannot be aromatic, and so show an interesting non-planar geometry. Moreover, a supplementary complexity can be obtained by introducing chirality on saturated carbon atoms.


8

escape the flatland


Figure 1.11. Developing $N-O$ heterocycles from $N-N$ heterocycles.

Drug-likeness rules consider N-O single bonds as "structural alerts" which should not be present in a perspective drug candidate (Figure 1.0), in particular $N$-alkoxyamines such as TEMPO. In most cases this concern is correct, since the
general weakness of the $O$-alkyl bond in the $N$-alkoxyamine moities, these compounds can undergo a C-ON bond homolysis to release a persistent nitroxyl radical NO particularly useful in controlled radical polymerization but triggering serious side effects in drugs. ${ }^{71,72}$ Thus, $N$-alkoxyamine cannot be used as a scaffold of interest for biological applications. However, the same type of metabolic behavior of $N$-alkoxyamine should not be expected when the nitrogen atom is "conjugated", either with an aromatic ring or with a chemical function including a double bond such as amide, amidine, etc...

In contrast to acyclic $N$-alkoxyamine, oxime ethers (Figure 1.0) are not sensitive to homolysis and are widely used in medicinal chemistry. Indeed, thanks to its resistance to protonation, oxime ethers possess greater intrinsic hydrolytic stability than hydrazones $(>\mathrm{N}-\mathrm{N}=<$ ) or imines $(-\mathrm{N}=<)$. This stability to hydrolysis allowed several acyclic oxime ethers to be pushed in clinical trials. Today, more than 15 are marketed in various indications including multiple sclerosis, bacterial infections or depression (Figure 1.12). This stability to hydrolysis is also true for the non-aromatic cyclic oxime ethers.


Fluvoxamine antidepressant


Cefotaxime
antibiotic


Siponimod
multiple sclerosis

Figure 1.12. Marketed drugs presenting acyclic oxime ether moiety.

Whereas the five-membered cyclic oxime ethers (Figure 1.6, isoxazole, isoxazoline) were used in organic and medicinal chemistry as early as the 60 s, with several marketed drugs (Figure 1.13), the synthetic and/or biologic potential of the six and seven-membered cyclic oxime ethers, also called 1,2-oxazines and 1,2-oxazepines (Figure 1.0), remained poorly explored because of the absence of convenient methods for the synthesis of these scaffolds. This is actually quite understandable if one
considers the preconceived idea that saturated N-O heterocycles are more difficult to prepare and the knowledge on their physicochemical properties are limited.


Sulfamethoxazole antibacterial


Topramezone
immunonutrition


Isocarboxazid antidepressant


Nivocasan
nonalcoholic steatohepatitis

Figure 1.13. Examples of marketed drugs presenting isoxazole or isooxazoline moiety.

As oxime ethers, alkoxyamides are not sensitive to homolysis and were widely used in organic chemistry, especially with the famous Weinreb amide. However, alkoxyamides have recently raised a growing interest in medicinal chemistry, 9 drugs are currently marketed or under clinical trials, including two cyclic alkoxyamide (Table 1.2).

Table 1.2. Alkoxyamides drugs marketed or under clinical trials.

| Alkoxyamide | Disease | State |
| :--- | :--- | :--- |
| $\mathrm{NH}^{-\mathrm{O}}$ | infection | Marketed (2019-01-18) |
| Cycloserine |  |  |



Binimetinib

diabetes

Reglitazar


Terizidone

colorectal cancer neoplasms
neoplasms


GDC-0623
tuberculosis

HIV
Phase IV

Phase I

Phase I


AZD-8330

neoplasms
Phase I

RO-4987655

infection
Phase I

Nacubactam

Based on the foremetioned stability of oxime ethers and alkoxyamides, we proposed the 1,2,4-oxadiazine and 2,3-benzoxazepin-4-one scaffolds described in Figure 1.11 should be stable in biological media and constitute promising building blocks for drug design.

## IE. Common synthetic strategies to $\mathrm{N}-\mathrm{O}$ heterocycles

Despite the importance of N-O heterocycles, limited synthetic strategies were reported on these scaffolds, which could be mainly divided into two types: (1) cycloaddition, and (2) acylation. Here the general equations and presentative examples are listed.

1. Cycloaddition:
(1) with nitrones


## Ref.












79

80

81
(2) with hydroxylamine analogs


Ref.


83


84

(3) with nitrosos

2. Acylation:







# II. Synthetic strategies and applications 

## II. Synthetic strategies and applications

New drugs with better efficacy and low toxicity are continually required to combat the unmet medical needs across diverse therapeutic areas and pharmaceutical industries are facing immense pressure to supply these drugs to the market. For the delivery of new drugs, molecular complexity is becoming a crucial concept in drug discovery due to its close association with target selectivity and success in progressing into clinical development ${ }^{96}$. One way to reach this complexity introduced in Chapter IC is to avoid aromatics, in favor of saturated carbon bonds ( $\mathrm{Fsp}^{3}$ ) and chiral $\mathrm{sp}^{3}$ carbon atoms, a concept that Franck Lovering called "Escape from Flatland". The rational of this approach is that these non-planar molecules will be more natural product-like, and more amenable to explore additional areas of chemical space. Moreover, significant gains are expected in terms of ADME properties (solubility, biological selectivity, lipophilicity, etc). ${ }^{56,97, ~ 98}$

Based on the "Escape from Flatland" theory, 1,2,4-oxadiazine 8 and 2,3-benzoxazepin-4-one 9 exhibiting an intracyclic N-O bond were designed to learn the geometries and physicochemical properties ( $\mathrm{p} K_{\mathrm{a}}$ and distribution coefficient (log D)) from their corresponding $\mathrm{N}-\mathrm{N}$ heterocycles 2 and 7, two biologically active compounds previously developed in our group (Figure 1.11)

2

7
escape the flatland


Figure 1.11. Developing N-O heterocycles from N-N heterocycles.

Although the cycloaddition reaction of nitrone, nitroso or hydroxylamine analogs with olefins or alkynes shown in Chapter IE opened an efficient synthetic pathway to N-O heterocycles, these reactions cannot be applied to the synthesis of 1,2,4-oxadiazine and 2,3-benzoxazepin-4-one scaffolds due to the presence of the second nitrogen atom and the carbonyl group, respectively. "Acylation" of alkoxyamine seems to be a better approach for the following reasons: (1) alkoxyamines are more stable than nitroso or nitrone, (2) the chirality of the carbon adjacent to the oxygen atom can be easily controlled when introduction the $\mathrm{C}-\mathrm{ON}$ moiety by the classical Mitsunobu reaction of a secondary alcohol with $N$-hydroxyphthalimide (NHPI) (Scheme 2.1).



Scheme 2.1. Generate N-O heterocycles by "Acylation" of alkoxyamine.

In this project, the first choice we proposed to construct the C-ON bond is using Mitsunobu reaction of chiral alcohol with NHPI, as this approach generally inversed the chirality of alcohol (Scheme 2.2). However, the limitation of this approach is that the Mitsunobu reaction does not work with bulky alcohols in some cases. As a result, nucleophilic substitution of NHPI with alkyl halides is proposed as an alternative approach. Despite the chirality of the reaction center might be difficult to control ( $\mathrm{S}_{\mathrm{N}} 1$ vs $\mathrm{S}_{\mathrm{N}} 2$ depending of the hydroxy substituents), the nucleophilic substitution is less vulnerable by the steric hinderance compared with the Mitsunobu reaction.

Approach 1:



Approach 2:


Scheme 2.2. Two approaches to construct C-ON bond

Applying the synthetic method towards 8, the structure of the natural product alchornedine, previously proposed based on the NMRs and mass spectra, will be verified by total synthesis (Figure 2.1).


8

alchornedine (Barrosa et al. 2014)

proposed structure for alchornedine based on total synthesis

Figure 2.1. Published structure for alchornedine and our proposition.

As the environment impact of the chemical industry has become a major issue and around $80 \%$ of the chemical waste in a reaction originated from the usage of organic solvent. A radical reaction of styrenes and NHPI under oxygen in water will also be developed to construct the C-ON bond, which could be easily transformed into 1,2,4-oxadiazine scaffolds (Scheme 2.3).


Scheme 2.3. Construction the C-ON bond in water.

Exploring the synthetic method of 2,3-benzoxazepin-4-one scaffold 9 led to the discovery of a new precatalyst named post-oxidative-addition precatalyst (POxAP),
which will be applied in Fukuyama CCR to investigate the catalytic activity and compatibility with different functional groups (Figure 2.2).



Synthesis of isoprekinamycin key-precursor

Figure 2.2. POxAP catalyzed Fukuyama cross-coupling reaction.

# III. Synthesis of 3-amino-1,2,4-oxadiazines and their physicochemical properties 

## III. Synthesis of 3-amino-1,2,4-oxadiazines and their physicochemical properties

1,2,4-triazine nucleus is a prominent structural core system present in numerous pharmacologically active compounds. Till date, various 1,2,4-triazine analogs, possessing a wide range of potent pharmacological activities, have been reported. ${ }^{59}$ Among them, four drugs are already marketed, including one 3 -amino-1,2,4-triazine Lamotrigine (Figure 3.1).


Lamotrigine antiepileptic


Vardenafil erectile dysfunction


Ceftriaxone
antibiotic


Capmatinib
anticancer

Figure 3.1. Marketed drugs presenting 1,2,4-triazine nucleus.

In our recent study, a NPFFRs antagonist $\mathbf{2}$ was obtained when we reduced one of the $\mathrm{C}=\mathrm{N}$ double bond of 3-amino-1,2,4-triazine $\mathbf{1}$. The biological evaluations showed that $\mathbf{2}$ exhibits two-digit nanomolar affinity for both NPFFRs leading to a significant reduction of the long lasting fentanyl-induced hyperalgesia in rodents. ${ }^{65}$ These results prompt us to further increase the complexity of 2 by transposing one of the two adjacent nitrogen atoms by an oxygen atom, leading to a non-planar N-O heterocycle 3-amino-1,2,4-oxadiazine 10a, as an unsaturated bioisostere of $\mathbf{1}$ and $\mathbf{2}$ (Figure 3.2).


Figure 3.2. Development of 3-amino-1,2,4-oxadiazine 10a.

To synthesize 10a, 3-amino-1,2,4-oxadiazine scaffold was searched as substructure in SciFinder and only one patent was founded, ${ }^{99}$ which used 11 as a precursor (Scheme 3.1). The N-O bond was introduced into $\mathbf{1 1}$ by a Mitsunobu reaction with NHPI. Then, para-methoxyphenyl (PMP) ether was cleaved by ceric ammonium nitrate, followed by the deprotection of alkoxyamine with methylamine. The Boc-protected alkoxyguanidine moiety was formed using $N$, $N^{\prime}$-bis-Boc-1-guanylpyrazole. Finally, the 3-amino-1,2,4-oxadiazine scaffold was cyclized after an intra-molecular Mitsunobu reaction.



Scheme 3.1. The exclusive reported method to synthesize 3-amino-1,2,4-oxadiazine scaffold.

Although the patented synthetic pathway in Scheme 3.1 provided a possibility to synthesize the achiral 3 -amino-1,2,4-oxadiazine 10a, the method is not adapted to introduce stereogenic centers at positions 5 and 6 , which would constitute an interesting perspective in terms of molecular complexity.

Herein, an approach is proposed, starting from amino acid (Scheme 3.2). The key intermediate $\mathbf{1 2}$ could be synthesized through the preparation of Weinreb amide, (stereo-selective) reduction and Mitsunobu reaction. After deprotection and cyclized with bromocyanide, 1,2,4-oxadiazine scaffold with one or two chiral centers at position 5 or 6 will be obtained. Compared with the approach in Scheme 3.1, $N$-protected amino acids are readily available and most of them already bear a chiral center at the $\alpha$ position.


Scheme 3.2. Proposed synthetic approach of 3-amino-1,2,4-oxadiazine from amino acid.

## IIIA. Synthesis of 6-(3,4-dichlorophenyl)-5,6-dihydro-4H-1,2,4-

## oxadiazin-3-amine 10a

To verify the feasibility of the synthetic approach of 3 -amino-1,2,4-oxadiazine scaffold proposed in Scheme 3.2, cpd 10a was synthesized from $N$-Boc or $N$-Fmoc glycine (Scheme 3.3). The advantage of N -Fmoc glycine is that the deprotection of Fmoc and phthalimide could be realized in one pot. ${ }^{100-102}$ While for $N$-Boc glycine, both deprotections will have to be done in a sequential manner. However, Boc group can be easily removed under acidic condition without requiring any purification step. ${ }^{103,} 104$


Scheme 3.3. Synthesis of 10a from N-Boc or N-Fmoc glycine.

## IIIA1. Synthesis of Weinreb amide from $N$-Boc or $N$-Fmoc glycine

$N$-Boc or $N$-Fmoc glycines was used to synthesize the corresponding Weinreb amides as precursors of ketones (Scheme 3.4).


Scheme 3.4. Synthesis of Weinreb amides 13 and $14 a$.

Although 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI) and 1-hydroxy-benzotriazole ( HOBt ) are two most commonly used coupling reagents for
the synthesis of Weinreb amide from carboxylic acid, here 1,1'-carbonyldiimidazole (CDI) was used. ${ }^{105-108}$ Acylimidazoles of corresponding $N$-Boc or $N$-Fmoc glycine formed as the intermediates by the addition of CDI. The advantage of this method is that the work up is much easier, as resulting side product imidazole can be easily removed by liquid-liquid extraction. Weinreb amide $\mathbf{1 3}$ and $\mathbf{1 4 a}$ were obtained in $81 \%$ (Fmoc) and 99\% (Boc) yields, respectively.

## IIIA2. Synthesis of ketone from Weinreb amide

Grignard reagent 15 was prepared from 1-bromo-3,4-dichlorobenzene (Scheme 3.5). A catalytical amount of dibromoethane (DBE) was added to remove the oxidized magnesium at the surface of the metal (giving $\mathrm{MgBr}_{2}$ and ethylene gas), leading to the formation of Grignard reagent 17 in $69 \%$ yield (determined by titration with a solution of menthol and 1,10-phenanthroline in THF). ${ }^{109}$


## Scheme 3.5. Synthesis of Grignard reagent 15.

The reaction of Weinreb amides $\mathbf{1 3}$ or $\mathbf{1 4 a}$ with excess amount of Grignard reagent 15 gave ketones 16 and 17a in $88 \%$ (Fmoc) and $86 \%$ (Boc) yields, respectively (Scheme 3.6).


Scheme 3.6. Synthesis of ketones 16 and 17a.

The successful acylation by excess Grignard reagent $\mathbf{1 5}$ is due to the putative and
stable tetrahedral intermediate $\mathbf{1 8}$ formed upon addition of the first equivalent of $\mathbf{1 7}$ (Scheme 3.8). This stability precludes the collapse of $\mathbf{1 8}$ to a ketone under the reaction conditions and thus prevents any additional reaction of $\mathbf{1 5}$ on the resulting ketone to form a tertiary alcohol. The aqueous workup not only facilitates the collapse of tetrahedral intermediate $\mathbf{1 8}$ to furnish the respective ketone, but also ensures simultaneous quenching of $\mathbf{1 5}$ in excess, thereby explaining why no over-addition product was formed despite the use of excess Grignard reagent. ${ }^{110-113}$



18


Scheme 3.7. Mechanism of the reaction between Weinreb amide and Grignard reagent.

## IIIA3. Reduction of ketone into alcohol

In consideration of the difficulty to identify enantiomers and current primary objective was to verify the feasibility of the synthetic approach of 10a proposed in Scheme 3.3, the chiral reduction for ketone $\mathbf{1 6}$ or $\mathbf{1 7 a}$ was not took into account here. Instead, the two ketones were directly reduced by $\mathrm{NaBH}_{4}$, giving alcohol 19 and 20a in quantitative yields (Scheme 3.8).


Scheme 3.8. Reduction of ketone 18 and 19a.

## IIIA4. Introduction of N-O moiety by Mitsunobu reation

One of the key steps to synthesize 1,2,4-oxadiazine was the building of the C-ON bond. Mitsunobu reaction between alcohol and NHPI seemed to be an ideal method using mild reaction conditions. More importantly, the reaction is supposed to be stereospecific, which will be favorable in controlling the stereogenic centers when a chiral alcohol will be used. ${ }^{114-118}$ The Mitsunobu reaction of $\mathbf{1 9}$ or 20a with NHPI was easily managed, producing the key intermediate 21 and 22a in 98\% (Fmoc) and 94\% (Boc) yields, respectively (Scheme 3.9).


Scheme 3.9. Mitsunobu reaction with alcohols 19 and 20a.

## IIIA5. Deprotection of the key intermediates 21 and 22a

Hydrazine hydrate, followed by piperidine was used to deprotect the phthalimide and Fmoc moieties of 21 in a one-pot reaction (Scheme 3.10). Although HPLC analysis of the crude reaction shown a high conversion, $\mathbf{2 3}$ could not be isolated due to its instability during purification steps whether in normal phase or in reverse phase chromatography

As 2,3-dihydrophthalazine-1,4-dione, formed from the deprotection of phthalimide with hydrazine, could be easily removed by precipitation from EtOH, we tried to prepare $\mathbf{2 4}$ by using piperidine, before deprotecting the phthalimide moiety with hydrazine hydrate and removing 2,3-dihydrophthalazine-1,4-dione by precipitation in EtOH (Scheme 3.10). This process would avoid any final purification of $\mathbf{2 3}$ on silica gel. However, based on the characteristic UV absorption of phthalimide moiety at 220 nm , traces of $\mathbf{2 4}$ were detected by HPLC. This is likely due to the nucleophilic amine of $\mathbf{2 4}$ which can intra- or inter-molecularly attack the carbonyl of the phthalimide moiety, leading to the formation of stable amides (Scheme 3.10).


21



intra-molecular
(hypothesized)


Scheme 3.10. Deprotection of Fmoc and phthalimide moiety.

In consideration of the instability of $\mathbf{2 3}$ on silica gel and spontaneous nucleophilic reaction between amine and phthalimide in 24, Boc protected 22a seemed to be a more suitable precursor for the preparation of the deprotected amino alkoxyamine 26a. The phthalimide moiety in 22a was first deprotected by hydrazine hydrate and the resulting 25a was obtained in $94 \%$ yield. Then, Boc was removed by HCl in dioxane
without additional purification, affording hygroscopic hydrochloride 26a in 96\% yield (Scheme 3.11).


Scheme 3.11. Deprotection of phthalimide moiety and Boc.

## IIIA6. Cyclization of amino alkoxyamine 26a

Amino alkoxyamine 26a was cyclized using BrCN . The reaction was run under diluted concentration ( 0.04 M of 26a in MeCN ) at $0^{\circ} \mathrm{C}$ to avoid: (1) disubstitution of CN group on 26a, (2) inter-molecular nucleophilic reaction of amino group and (3) excessive substitution of CN group on $\mathbf{1 0 a}$ (Scheme 3.12).


Scheme 3.12. Desired and possible side reactions during cyclization of $26 \boldsymbol{a}$.

Two products were isolated from the cyclization reaction of 26a with BrCN . Several possible structures were proposed based on ${ }^{1} \mathrm{H}$ and ${ }^{13} \mathrm{C}$ NMRs in DMSO- $d^{6}$ (Figure 3.3 and 3.4). The chemical shifts and integrations in ${ }^{1} \mathrm{H}$ NMR spectra shown that both compounds had an AB spin system for $-\mathrm{CH}_{2}-\mathrm{N}$ moiety in a cyclized structure, excluding the products of disubstitution and inter-molecular reaction shown in Scheme 3.12. The main difference of the two ${ }^{1} \mathrm{H}$ NMR spectra was that one compound contained a $-\mathrm{NH}-$ peak at 6.17 ppm and a $-\mathrm{NH}_{2}$ peak at 4.47 ppm , suggesting that the structure of this compound was 10a, since $\mathbf{2 8}$ should show three -NH peaks, while 27 should show a -NH-O- peak at a lower field due to its acidity. ${ }^{13} \mathrm{C}$ NMR spectrum was also in agreement with 10a.

The second isolated product shown only one active proton peak, $-\mathrm{NH}_{2}$ at 5.79 ppm , suggesting the formation of excessive substitution products $\mathbf{3 0}$ or $\mathbf{3 1}$ ( 29 should show two -NH peaks). ${ }^{13} \mathrm{C}$ NMR spectrum confirmed this hypothesis with an obvious -CN peak at 110.14 ppm .


Figure 3.3. ${ }^{1} H$ NMR (DMSO-d ${ }^{6}$ ) and proposed structures of the two products isolated from cyclization reaction of alkoxyamine 26a.




Figure 3.4. ${ }^{13} C$ NMR (DMSO- $\left.d^{6}\right)$ and proposed structures of the two products isolated from cyclization reaction of alkoxyamine 26a.

To clearly associate NMR spectra to $\mathbf{3 0}$ or 31, a 2 D HMBC NMR experiment was performed (Figure 3.5). Obvious correlation was observed between protons in $-\mathrm{CH}_{2}-\mathrm{N}$ moiety ( 3.98 and 4.11 ppm ) and the carbon in -CN group ( 110.14 ppm ), indicating the structure of the side product was $\mathbf{3 0}$ as this kind of correlation would not be observed in 31.


Figure 3.5. HMBC (DMSO- $\left.d^{6}\right)$ of $\mathbf{3 0}$.

In summary, 26a could be cyclized in MeCN using BrCN at $0^{\circ} \mathrm{C}$, affording 10a and $\mathbf{3 0}$ in $81 \%$ and $17 \%$ yields, respectively (Scheme 3.13). The appearance of $\mathbf{3 0}$ also indicated that the secondary nitrogen atom $\left(-\mathrm{HN}^{-} \mathrm{CH}_{2}-\right)$ of $\mathbf{1 0 a}$ was more nucleophilic than the primary and tertiary ones ( $-\mathrm{NH}_{2}$ and $>\mathrm{C}=\mathrm{N}-\mathrm{O}-$ ) towards BrCN .


Scheme 3.13. Cyclization of amino alkoxyamine 26a.

To further confirm the correctness of the synthesis and geometry of 10a, it was recrystallized by slow evaporation from MeCN solution. Single-crystal X-ray diffraction analysis shown that the crystal structure of 10a belongs to 3-amino-1,2,4-oxadiazine (Figure 3.6). The $\mathrm{C}=\mathrm{N}$ double bond located between N 2
and C 3 , rather than C 3 and N 4 . This is comprehensible since the $\mathrm{p}-\pi$ conjugative effect between oxygen atom and $\mathrm{C}=\mathrm{N}$ double bond in 10a is more stable than the $\sigma-\pi$ hyperconjugative effect between $\mathrm{C}-\mathrm{H}$ bond on C 5 and $\mathrm{C}=\mathrm{N}$ double bond in 27. Due to the bivalent character of the oxygen atom, the 1,2,4-oxadiazine scaffold shown a non-planar geometry in which C 6 is located far out of the plane constituted by $\mathrm{N}=\mathrm{C}-\mathrm{NH}$ moiety. Moreover, the $\mathrm{N}-\mathrm{O}$ bond and $\mathrm{NH}-\mathrm{CH}_{2}$ bond is unparallel due to the different bond angels between N-O-C and N-C-C. It also could be observed that the oxadiazine ring is approximately vertical to the phenyl ring since this orthogonal conformation decreased the steric hinderance. The details of the crystallographic data and structure refinement parameters were summarized in Appendix I.


Figure 3.6. X-ray crystallography of 10a displayed with front view, right view and top view.

In conclusion, 10a was synthesized from $N$-Boc glycine in 7 steps in $58 \%$ overall yield. The structures of the products were identified by NMR spectra and the geometry of 10a was confirmed by X-ray crystallography. The unsaturation of the 1,2,4-oxadiazine ring and the bivalent character of oxygen atom result in a non-planar geometry of 10a.

## IIIB. Synthesis of (1R,8aS)-1-phenyl-6,7,8,8a-tetrahydro-1H-pyrrolo

## [1,2- $d][1,2,4]$ oxadiazin-4-amine 10b

Now that the method to synthesize racemic 3-amino-1,2,4-oxadiazine scaffold from $N$-Boc glycine has been established (Section IIIA), we focused our interest on producing chiral 3 -amino-1,2,4-oxadiazine scaffolds. L-proline was selected as starting material for the synthesis of chiral 3 -amino-1,2,4-oxadiazine scaffolds exhibiting two stereogenic centers. Compared with glycine, L-proline already bears a stereogenic center at the $\alpha$ position of carboxyl group. After reduction of the targeted ketone 32, up to two diastereomers would be obtained (Scheme 3.14). It will facilitate isolation and characterization of the stereoisomers, since diastereomers have different chromatographic and NMR properties under commonly used achiral silica gel and deuterated solvent. ${ }^{19-121}$


Scheme 3.14. Synthesis of chiral 3-amino-1,2,4-oxadiazine scaffold.

## IIIB1. Synthesis of ketone 17b from L-proline

Ketone 17b was synthesized from L-proline by similar methods described in Section IIIA (Scheme 3.15). First, the amino group in L-proline was protected by $\mathrm{Boc}_{2} \mathrm{O}$ under basic condition in dioxane $/ \mathrm{H}_{2} \mathrm{O},{ }^{122}$ affording $N$-Boc L-proline $\mathbf{3 3}$ in $97 \%$
yield. After activation by CDI and substitution with $N, O$-dimethylhydroxylamine, ${ }^{123}$ 33 was transformed into Weinreb amide 14b in $94 \%$ yield. The addition-elimination reaction between Weinreb amide 14b and phenyl magnesium bromide furnished ketone 17b in $88 \%$ yield. ${ }^{124}$




Scheme 3.15. Synthesis of ketone 17b from L-proline.

## IIIB2. Stereoselective reduction of ketone 17b

A non-stereoselective reduction of ketone $\mathbf{1 7 b}$ would lead to a mixture $1: 1$ of two diastereoisomers. However, our goal was to find stereoselective conditions allowing to favor one diastereoisomer over the other. Several conditions were then tried to reduce ketone 17b (Table 3.1) and the structures of some complex reductants were presented in Figure 3.7. The two reduced diastereomeric alcohols could be distinguished by comparing their ${ }^{1} \mathrm{H}$ NMR spectra with the ones reported in literature, and obtained with a different strategy. ${ }^{125}$


L-selectride

(S)-2-Me-CBS


DIBAL-H

Figure 3.7. Structures of several complex reductants.

Chiral reductant L-selectride led to a poor enantioselective reduction, producing 20b $(S / R)$ and $\mathbf{3 4}(S / S)$ in $57 \%$ and $43 \%$ yields, respectively, while almost no reaction happened with (S)-3,3-diphenyl-1-methylpyrrolidino[1,2-c]-1,3,2-oxazaborole ((S)-2-Me-CBS). Surprisingly, reduction of $\mathbf{1 7 b}$ by $\mathrm{NaBH}_{4}$ appeared more enantioselective with the formation of both diastereomers $\mathbf{2 0 b}(S / R)$ and $34(S / S)$ in $24 \%$ and $72 \%$ yields, respectively. The weaker reductant $\mathrm{NaBH}_{3}(\mathrm{CN})$ failed to reduce ketone 17b. Aluminum-type reductants were tested, and while $\mathrm{LiAlH}_{4}$ appeared poorly enantioselective, producing $\mathbf{2 0 b}$ and $\mathbf{3 4}$ in $45 \%$ and $55 \%$ yields, respectively, the bulky reductant diisobutyl aluminium hydride (DIBAL-H) enantioselectively reduced ketone 17b into the diastereoisomer 20b in quantitative yield and $\mathbf{3 4}$ was not detected.

Table 3.1. Reduction of ketone $\mathbf{1 7 b}$.


| Entry | Conditions | $\mathbf{2 0 b}(S / R)(\%)$ | $\mathbf{3 4}(S / S)(\%)$ |
| :--- | :--- | :--- | :--- |
| 1 | L-selectride, THF, $0^{\circ} \mathrm{C}$ | 57 | 43 |
| 2 | $(S)-2-\mathrm{Me}-\mathrm{CBS}, \mathrm{BH} 3, \mathrm{THF}, 0^{\circ} \mathrm{C} / \mathrm{rt}$ | trace | 0 |
| 3 | $\mathrm{NaBH}_{4}, \mathrm{MeOH},-20^{\circ} \mathrm{C}$ | 24 | 72 |
| 4 | $\mathrm{NaBH}_{3}(\mathrm{CN}), \mathrm{THF}, \mathrm{rt}$ | 0 | 0 |
| 5 | $\mathrm{LiAlH}_{4}, \mathrm{THF}, \mathrm{rt}$ | 45 | 55 |
| 6 | DIBAL-H, THF, $\mathbf{0}^{\circ} \mathrm{C}$ | $\mathbf{1 0 0}$ | $\mathbf{0}$ |

The Newman projection formula of $\mathbf{1 7 b}$ explains the selectivity of DIBAL-H reduction originated from two effects in intermediate 35 (Scheme 3.16): (1) the complexation between aluminum atom of DIBAL-H and the oxygen atom of ketone $\mathbf{1 7 b}$, (2) the steric hinderance between isobutyls of DIBAL-H and Boc of $\mathbf{1 7 b}$. These
two effects orientated the attack of DIBAL-H on ketone 17b, favoring the formation of intermediate $\mathbf{3 5}$ and producing alcohol 20b after hydrolysis under acidic condition. The two effects also explained why other reductants in Table 3.1 were less selective: (1) attenuation of the complexation between the boron atom of borane-type reductants and the oxygen atom of ketone $\mathbf{1 7 b}$ (2) disappearance of the steric hinderance between $\mathrm{LiAlH}_{4}$ and 17b. At this stage, we did not find conditions to stereoselectively reduce ketone 17b into the diastereoisomer 34.


Scheme 3.16. Mechanism of selective reduction of ketone 17b by DIBAL-H.

## IIIB3. Introduction of N-O moiety by Mitsunobu reation

Starting with 20b $(S / R)$, Mitsunobu reaction with NHPI led to 22b in 94\% yield. Due to the inversion of configuration related to Mitsunobu mechanism, 22b was expected to show a $S / S$ configuration. However, when we performed X-ray crystallography of the final oxadiazine resulting from 22b, we were surprised to observe that the Mitsunobu reaction did not led to an inversion of configuration, but to a retention (See Figure 3.9). It is not a frequent case, but this kind of retention of configuration has already been reported when the Mitsunobu reaction is performed on
sterically hindered substrate. ${ }^{126}$ Using alcohol and NHPI as substrates, Scheme 3.17 shown two commonly accepted mechanisms of Mitsunobu reaction with configuration inversion or retention.


Unbulky alcohol:


Bulky alcohol:


Scheme3.17. Mechanism of Mitsunobu reaction with configuration inversion or retention.

We were also surprised to observe that the same condition of Mitsunobu reaction failed to transform diastereisomer $\mathbf{3 4}$ into $\mathbf{3 6}$ and the starting material was recovered quantitatively (Scheme 3.18).



34
$22 b$


36

Scheme 3.18. Configuration retained Mitsunobu reaction between $20 b$ or 34 and NHPI.

The difference reactivity of diastereomers 20b $(S / R)$ and $\mathbf{3 4}(S / S)$ in Mitsunobu reaction might originate from the hinderance between Boc and $\mathrm{PPh}_{3}{ }^{+}$moiety, which interfere attack of alcohol (Scheme 3.19). To surmount this hinderance, the Mitsunobu reaction between 34 and NHPI was tried at rt. Disappointedly, raising the reaction temperature resulted into a complex reaction mixture and no desired product was observed (based on the characteristic absorption of phthalimide moiety at 220 nm ).



Scheme 3.19. Hinderance of Boc in 34 prohibited Mitsunobu reaction.

## IIIB4. Deprotection of the key intermediate 22b

The phthalimide moiety in 22b was deprotected by hydrazine hydrate, producing 25b in $97 \%$ yield. Then, Boc was removed by HCl in dioxane without additional purification, affording highly hygroscopic 26b in 96\% yield (Scheme 3.20).


Scheme 3.20. Deprotection of the key intermediate 22b.

## IIIB5. Cyclization of amino alkoxyamine 26b

In a similar way to synthesize 10a, 26b was cyclized in MeCN with BrCN , affording chiral 3-amino-1,2,4-oxadiazine 10b in 94\% yield (Scheme 3.21).



Scheme 3.21. Synthesis of chiral 3-amino 1,2,4-oxadiazine scaffolds 10b.

It is noteworthy that intermediate $\mathbf{3 7}$ could be isolated if ceasing reaction after 30 minutes (Scheme 3.21). In ${ }^{1} \mathrm{H}$ NMR spectrum of intermediate 37 (Figure 3.8), one $-\mathrm{NH}_{2}$ peak rather than two -NH peaks were observed, indicating the cyano group is linked to pyrrolidine moiety, which means the secondary amine of $\mathbf{2 6 b}$ is more nucleophilic than the alkoxyamine towards BrCN . Despite the similarity in ${ }^{1} \mathrm{H} N \mathrm{NR}$, intermediate $\mathbf{3 7}$ and desired product $\mathbf{1 0 b}$ could be easily distinguished by ${ }^{13} \mathrm{C}$ NMR, since $\mathbf{3 7}$ shown a -CN peak at 117.48 ppm , while $\mathbf{1 0 b}$ shown a $-\mathrm{C}=\mathrm{N}$ - at 155.84 ppm (Figure 3.8).


Figure 3.8. ${ }^{1} \mathrm{H}$ and ${ }^{13} \mathrm{C} \mathrm{NMR} \mathrm{of} \mathbf{3 7}$ and $\mathbf{1 0 b}$ in DMSO- $d^{6}$.

To further confirm the structure and geometry of expected oxadiazine, $\mathbf{1 0 b}$ was recrystallized by slow evaporation from MeCN solution. Single-crystal X-ray diffraction analysis shown that the crystal structure of $\mathbf{1 0 b}$ belongs to ( $5 S$, $6 R$ )-3-amino-1,2,4-oxadiazine (Figure 3.9), highlighting the configuration retention of 22b during the Mitsunobu reaction (Scheme 3.18). Compared with 10a (Figure 3.0), the presence of the pyrrolidine ring in 10b decreases the mutual perpendicularity between oxadiazine and phenyl rings. The details of the crystallographic data and structure refinement parameters were summarized in Appendix II.


Figure 3.9. $X$-ray crystallography of $\mathbf{1 0 b}$ displayed with front view, right view and top view.

In conclusion, starting from L-proline, chiral 3-amino-1,2,4-oxadiazine 10b could be stereoselectively synthesized through DIBAL-H reduction and Mitsunobu reaction. The bulkiness of Boc plays a crucial role in the stereoselective reduction of ketone and consequent Mitsunobu reaction. Both stereogenic centers in 10b increases the spatial geometric complexity of the 1,2,4-oxadiazine scaffold.

## IIIC. Synthesis of (5S,6R)-5-isopropyl-6-phenyl-5,6-dihydro-4H-

## 1,2,4-oxadiazin-3-amine 10c

The results in Section IIIB shown that the stereoselectivity of DIBAL-H reduction and the reactivity of Mitsunobu reaction were originated from the bulkiness of Boc. However, the effect of the rigidity of pyrrolidine ring in these two reactions were not discussed. Here, $N$-Boc L-valine was used as the starting material to learn whether the stereoselectivity of DIBAL-H reduction and the reactivity of Mitsunobu reaction remained if the rigidity was impaired (Figure 3.10).


Figure 3.10. Removal of the rigidity in ketone.

In the same way, $N$-Boc L-valine was activated by CDI and substituted with $\mathrm{N}, \mathrm{O}$-dimethylhydroxylamine, producing Weinreb amide $\mathbf{1 4 c}$ in $94 \%$ yield. It was then reacted with PhMgBr , affording ketone $\mathbf{1 7 c}$ in $88 \%$ yield. Similar to the reduction of 17b, DIBAL-H could stereoselectively reduce ketone $17 \mathbf{c}$ into the only diastereomer 20c in $97 \%$ yield, while $\mathrm{NaBH}_{4}$ reduction produced both diastereomers 20c and $\mathbf{3 8}$ in $82 \%$ and $18 \%$ yields, respectively (Scheme 3.22). The structures of both diastereomers could be identified by comparing their ${ }^{1} \mathrm{H}$ NMR spectra with the ones reported in literature. ${ }^{127,128}$ The similarity of these results as those described in Section IIIB2 indicates that the stereoselective reduction of DIBAL-H is originated from the bulkiness of Boc, rather than the rigid frame between the nitrogen and $\alpha$ carbon atoms of ketone.



Scheme 3.22. Reduction of ketone 17c synthesized from N-Boc L-valine.

The N-O moiety was introduced into diastereomer 20c $(S / R)$ by Mitsunobu reaction with NHPI at $0{ }^{\circ} \mathrm{C}$ and key intermediate 22c $(S / R)$ was obtained in $81 \%$ yield. However, as observed before, the same Mitsunobu conditions failed to transform diastereomer $38(S / S)$ into key intermediate $39(S / S)$ and the starting material was recovered quantitatively (Scheme 3.23). Again, the similarity of these results as those described in Section IIIB3 indicates that the different reactivity of the two diastereomers 20c $(S / R)$ and $38(S / S)$ in Mitsunobu reaction is independent of the rigid frame between the nitrogen and $\alpha$ carbon atoms of alcohol.


Scheme 3.23. Mitsunobu reaction of diastereomer 20c or $\mathbf{3 8}$ with NHPI.

The phthalimide moiety in 22c was deprotect by hydrazine hydrate, producing 25c in $96 \%$ yield. Then, Boc was removed by HCl in dioxane without additional purification, affording highly hygroscopic amino alkoxyamine 26c in 94\% yield. Finally, 26c was cyclized in diluted MeCN solution by BrCN , affording chiral 3 -amino-1,2,4-oxadiazine 10c in 73\% yield (Scheme 3.24).



Scheme 3.24. Synthesis of $\mathbf{1 0 c}$ from key intermediate $\mathbf{2 2 c}$.

In conclusion, chiral 3-amino-1,2,4-oxadiazine 10c could be stereoselectively synthesized as 10b, indicating the absence of rigid frame between the nitrogen and $\alpha$ carbon atoms of amino acids did not influence the stereoselective reduction of DIBAL-H and the reactivity of Mitsunobu reaction. These results also revealed the versatility of DIBAL-H reduction and Mitsunobu reaction in synthesizing chiral 1,2,4-oxadiazine scaffold from Boc amino acids.

## IIID. Physicochemical studies of 3-amino 1,2,4-oxadiazines

Modern drug-discovery chemistry is based on a multidimensional optimization approach, in which the optimization of physicochemical properties, aspects of ADME and safety of a lead compound are considered at an equal level together with potency and selectivity. ${ }^{129}$ A large fraction of the drugs currently on the market or in development contain one or more basic nitrogen atoms. Whether or not basic nitrogen atoms are protonated in the biological environment may be critical not only for the variability of the biopharmaceutical characteristics of drugs but also parameters such as $\log \mathrm{D}$ and solubility. ${ }^{130,131}$ Therefore, it is important to know $\mathrm{p} K_{\mathrm{a}}$ and modulate its basicity in a rational, structure-based fashion.

In previous sections, three 3 -amino-1,2,4-oxadizines were synthesized as biomimetic compounds of cyclic amino guanidine. To investigate the influence of oxygen atom on the physicochemical properties of neighboring guanidine moiety, $\mathrm{p} K_{\mathrm{a}}$ and $\log \mathrm{D}$ of 3 -amino-1,2,4-oxadiazines (10a, 10b and 10c) will be measured by pH -metric and HPLC methods, respectively. ${ }^{132} \mathrm{p} K_{\mathrm{a}}$ and $\log \mathrm{D}$ of acyclic alkoxyl guanidine (42) and cyclic/acyclic (imino)guanidine (2, 3, 40 and 41) were also measured as reference points (Table 3.2).

Table 3.2. $\mathrm{p} K_{\mathrm{a}}$ and $\log \mathrm{D}_{7.4}$.

| Compound | $\mathrm{p} K_{\mathrm{a}} \mathrm{MeOH60} \mathrm{\%}{ }^{\text {a }}{ }^{\text {a] }}$ | $\mathrm{p} K_{\mathrm{a}}{ }^{\text {aq }}{ }^{[\mathrm{b}]}$ | $\log \mathrm{D}_{7.4}{ }^{[\mathrm{cc]}}$ |
| :---: | :---: | :---: | :---: |
|  <br> 40 | > 11 | > 11 | $-0.64 \pm 0.06$ |
|  <br> 3 | $10.6 \pm 0.1$ | 11.4 | $1.90 \pm 0.04$ |
|  | $9.29 \pm 0.05$ | 10.0 | $1.70 \pm 0.03$ |



41


42




10c



$8.50 \pm 0.05$
$7.29 \pm 0.05$
under progress
under progress
under progress
[a] $\mathrm{p} K_{\mathrm{a}}$ МеОН $60 \%$ was determined based on $\mathrm{pH}-\mathrm{V}_{\mathrm{NaOH}}$ titration curve (ionic strength 0.1 M , temperature $25^{\circ} \mathrm{C}$ ) and calculated by HYPERQUAD program.
$[\mathrm{b}] \mathrm{p} K_{\mathrm{a} \text { aq }}=\left(\mathrm{p} K_{\mathrm{a}}\right.$ МеОН $\left.60 \%+0.43\right) / 0.97$.
[c] Average of two individual samples (aqueous phase from tested compounds in the mixture PBS ( pH 7.4 ) and octanol at $20^{\circ} \mathrm{C}$ ) measured by HPLC at 280 nm .
 measured under the titration condition and $\mathrm{p} K_{\mathrm{a}}$ aq of $\mathbf{4 0}$ is estimated $>11$ as $\mathrm{p} K_{\mathrm{a}}$ меон60\%. Log $\mathrm{D}_{7.4}$ of $\mathbf{4 0}$ is negative $-0.64 \pm 0.06$, which means it is hydrophilic and unfavorable for membrane permeability by passive diffusion. Introducing one double bond and two chlorine atoms in 40 resulted in cpd $\mathbf{3}$, which is prepared in form of TFA salt. The presence of $-\mathrm{C}=\mathrm{C}$ - and chlorine atoms decreases $\mathrm{p} K_{\mathrm{a}}$ aq to 11.4 and increases $\log \mathrm{D}_{7.4}$ to $1.90 \pm 0.04$, indicating cpd $\mathbf{3}$ is approximately 100 times more soluble in octanol than in PBS. This kind of hydrophobicity is not only due to the decrease of $\mathrm{p} K_{\mathrm{a}}$ but also partially due to the presence of $\mathrm{CF} 3 \mathrm{COO}^{-}$which formed an ion pair with the protonated compound. Replacing one carbon atom in cpd $\mathbf{3}$ by a
nitrogen atom led to cyclic iminoguanidine 2 (TFA form) with $\mathrm{p} K_{\mathrm{a} \text { aq }}=10$ and $\log \mathrm{D}_{7.4}$ $=1.70 \pm 0.03$, which means it's approximately 50 times more soluble in octanol than in PBS. As cpd 3, the hydrophobicity of protonated cpd $\mathbf{2}$ is partially due to ion pair formed with $\mathrm{CF} 3 \mathrm{COO}^{-}$. Replacing 3,4-dichlorophenyl by 2-chlorophenyl and breaking the iminoguanidine ring in cpd 2 by removing a carbon atom gave cpd 41 with $\mathrm{p} K_{\mathrm{a} \text { aq }}=9.2$ and $\log \mathrm{D}_{7.4}=1.50 \pm 0.09$, a weak but sufficient hydrophobicity for crossing biological membrane. Acyclic alkoxyguanidine 42 was obtained by transposing the $\alpha$ nitrogen atom in acyclic iminoguanidine 41 by an oxygen atom, decreasing $\mathrm{p} K_{\mathrm{a} \text { aq }}$ to 8 and $\log \mathrm{D}_{7.4}$ to $1.07 \pm 0.03$. The order of magnitude of $\log \mathrm{D}_{7.4}$ is 1 , which means it's approximately 10 times more soluble in octanol than in PBS, sufficient for crossing biological membrane.

Comparing with the original cyclic guanidine 40, acyclic alkoxyguanidine $\mathbf{4 2}$ is three orders of magnitude less basic $\left(\Delta \mathrm{p} K_{\mathrm{a} \mathrm{aq}}<-3\right)$ and more favorable for membrane permeability $\left(\Delta \log \mathrm{D}_{7.4}=1.71 \pm 0.03\right)$ (Table 3.2). The electron-withdrawing nature of oxygen atom seems to be responsible for the reduction in basicity of the adjacent nitrogen atom in guanidine moiety. Due to 3 -amino-1,2,4-oxidazines, a kind of cyclic alkoxyguanidine is more structural complex relative to acyclic 42, better target selectivity is expected besides good physicochemical properties. As a result, several 3 -amino-1,2,4-oxadiazines (10a, 10b and 10c) have been synthesized and the measurements of their $\mathrm{p} K_{\mathrm{a}}$ and $\log \mathrm{D}_{7.4}$ are current under progress.

## IIIE. Conclusion

In this chapter, racemic 6-(3,4-dichlorophenyl)-5,6-dihydro-4H-1,2,4-oxadiazin-3amine 10a was synthesized in 7 steps in $58 \%$ overall yield from $N$-Boc glycine to verify the feasibility of the synthetic approach (Scheme 3.25). The X-ray crystallography of $\mathbf{1 0 a}$ shown a non-planar geometry of the 3 -amino- $1,2,4$-oxadiazine scaffold which was perpendicular with the phenyl ring.


Scheme 3.25. Synthesis of 10a from N-Boc glycine.

By chiral reduction of alcohol with DIBAL-H, ( $1 R, 8 \mathrm{a} S$ )-1-phenyl-6,7,8,8a-tetrahydro- $1 H$-pyrrolo[1,2- $d][1,2,4]$ oxadiazin-4-amine 10b could be synthesized from L-proline based on the established methods (Scheme 3.26). Due to the steric hinderance of alcohol, Mitsunobu reaction works only with diastereomer 20b and the configuration is retained. X-ray crystallography of $\mathbf{1 0 b}$ shown the presence of pyrrolidine ring decreased the mutual perpendicularity between the oxadiazine and
phenyl rings.


Scheme 3.26. Synthesis of $\mathbf{1 0 b}$ from L-proline.

To know whether the stereoselectivity of DIBAL-H reduction and the reactivity of Mitsubobu reaction would change if the rigidity of the pyrrolidine ring in 19b was removed, N -Boc L-valine was used as the starting material. (5S,6R)-5-isopropyl-6-phenyl-5,6-dihydro-4H-1,2,4-oxadiazin-3-amine 10c still could be stereoselectively synthesized by applying DIBAL-H reduction and Mitsubobu reaction as key steps, indicating the versatility of the established methods in synthesis chiral 3-amino-1,2,4-oxadiazine scaffold from Boc amino acid (Scheme 3.27).






Scheme 3.27. Synthesis of $\mathbf{1 0 c}$ from N-Boc L-valine.

To fully conclude about the effects of Boc vs amino acid side chain hindrance on the stereoselectivity of the DIBAL-H reduction or the Mitsunobu reaction, an 1,2,4-oxadiazin-3-amine will be synthesized starting from Boc-alanine, bearing a simple methyl group at the alpha position.

In preliminary results of physicochemical studies, significant decrease in $\mathrm{p} K a$ and improvement in $\log \mathrm{D}$ were observed in acyclic alkoxyl guanidine compared with cyclic/acyclic guanidine. To have a better comprehension of the influence of oxygen atom on the physicochemical properties of neighboring guanidine moiety, the measurements of pKa and $\log \mathrm{D}_{7.4}$ of 3-amino-1,2,4-oxadazines are currently under progress.
IV. Total synthesis of alchornedine

## IV. Total synthesis of alchornedine

In 2014, Barrosa et al isolated a new natural guanidine alkaloid with 3-amino-1,2,4oxadiazine scaffold, named alchornedine, from the leaves of Alchornea glandulosa, which is effective against both clinical forms of Trypanosoma cruzi and could be used as a scaffold for future drug designed against American trypanosomiasis (Figure 4.1). ${ }^{133}$ As the total synthesis of alchornedine has never been described, the structure was proposed by the authors based on the NMR spectra in MeOD- $d^{4}$, rather than DMSO- $d^{6}$ or X-ray crystallography. In fact, it's not a reliable way to confirm the exact structure of alchornedine because a hydrogen-deuterium exchange of NH proton signals is occurring in MeOD- $d^{4}$. In this chapter, the aim of our work was to propose the total synthesis of $\mathbf{4 3}$ and its NMR spectra would be compared with the literature to confirm the correctness of Barrosa's proposed structure for alchornedine ${ }^{133}$


43
Figure 4.1. Barrosa's proposed structure of alchornedine.

## IVA. Total synthesis of 40 from $\boldsymbol{N}$-Boc glycine

Based on the established method to synthesize 3-amino-1,2,4-oxadiazine scaffold in Chapter III, 43 was synthesized using $N$-Boc glycine as the starting material. Weinreb amide 14a was prepared quantitatively from $N$-Boc glycine using CDI as activating group and then reacted with isopropenyl magnesium bromide, furnishing $\alpha$, $\beta$-unsaturated ketone $\mathbf{1 7 d}$ in $99 \%$ yield. It is noteworthy that $\mathbf{1 7 d}$ was sensitive to temperature as the product degraded when it was concentrated in EtOAc/Heptane solution at $40^{\circ} \mathrm{C}$. Due to the alternant polarization of $\alpha, \beta$-unsaturated ketone $\mathbf{1 7 d}$, 1,4-reduction happened when $\mathrm{NaBH}_{4}$ was used without carbonyl activation agents, giving access to the $\alpha, \beta$-saturated ketone, tert-butyl (3-methyl-2-oxobutyl)carbamate. To realize 1,2 -reduction, $\mathrm{CeCl}_{3}$ was used as carbonyl activation agent before the addition of $\mathrm{NaBH}_{4}$, furnishing $\alpha, \beta$-unsaturated alcohol 20d in $83 \%$ yield. The N-O moiety was introduced by Mitsunobu reaction of 20d with NHPI, providing 22d in 95\% yield. The phthalimide moiety in 22d was then deprotected by hydrazine hydrate, followed by the deprotection of Boc by HCl in dioxane, affording amino alkoxyamine 26d in 99\% yield (Scheme 4.1).




Scheme 4.1. Synthesis of amino alkoxyamine 26d from N-Boc glycine.

Amino alkoxyamine 26d was cyclized into 3-amino-1,2,4-oxadiazine using BrCN . Two isomers 10d and 44 were separated in 80 and $9 \%$ yield, respectively (Scheme 4.2).


Scheme 4.2. Cyclization of amino alkoxyamine 26d.

The structure of $\mathbf{1 0 d}$ and $\mathbf{4 4}$ were identified by NMR spectra (Figure 4.2). Although the two compounds are similar in ${ }^{13} \mathrm{C}$ NMR, the electron-withdrawing effect of oxygen atom makes the ${ }^{1} \mathrm{H}$ chemical shift of -NH - in 44 located at 8.83 ppm compared to the one in $\mathbf{1 0 d}$ at 6.07 ppm . Tautomeric transformation between $\mathbf{1 0 d}$ and 44 won't happen since the chemical shifts remained unchanged when the ${ }^{1} \mathrm{H}$ NMR was measured at $50^{\circ} \mathrm{C}$.






Figure 4.2. ${ }^{1} \mathrm{H}$ and ${ }^{13} \mathrm{C}$ NMR spectra of 10 d and 44 in DMSO- $d^{6}$.

To clearly identified $\mathbf{1 0 d}$ and $\mathbf{4 4}$, NOESY of both compounds were also measured (Figure 4.3 and 4.4). In NOESY of $\mathbf{1 0 d}$, -NH - moiety is correlated with both $-\mathrm{CH}_{2}-\mathrm{N}$ and $-\mathrm{NH}_{2}$ moieties. However, correlation between $-\mathrm{NH}-$ and $-\mathrm{CH}_{2}-\mathrm{N}$ moiety could not be observed in 44 and only $-\mathrm{NH}_{2}$ moiety is correlated with -NH - moiety.


Figure 4.3. NOESY of 10d in DMSO- $d^{6}$.


Figure 4.4. NOESY of 44 in DMSO-d ${ }^{6}$.

Direct alkylation of $\mathbf{1 0 d}$ by 3,3-dimethyl allylic bromide with TEA produced $\mathbf{4 5}$ in $74 \%$ yield. Consistent with the concept of hard and soft acids and bases (HSAB), alkylation of $\mathbf{1 0 d}$ in presence of excess of NaH and 3,3-dimethyl allylic bromide, led to a mixture of the dialkylated cpd 48 and the monoalkylated cpd 45 in $53 \%$ and $37 \%$ yields, respectively (Scheme 4.3). X-ray crystallography of $\mathbf{4 8}$ exhibited a $\mathrm{C}=\mathrm{N}$ bond out of the oxadiazine ring (Figure 4.5). The details of 2D NMRs, crystallographic data and structure refinement parameters of $\mathbf{4 8}$ were summarized in Appendix III and VI. As the synthesis of $\mathbf{4 3}$ from 10d by direct alkylation was challenging, cpd 10d was first protected by $(\mathrm{Boc})_{2} \mathrm{O}$. Although exocyclic $N$-Boc protection was expected according to HSBA theory, endocyclic $N$-Boc protected 46 was obtained in $91 \%$ yield, which was indicated by the presence of a $-\mathrm{NH}_{2}$ peak at 5.25 ppm in ${ }^{1} \mathrm{H}$ NMR with $\mathrm{CDCl}_{3}$. The amino group in 46 was then deprotonated by NaH and alkylated by 3,3-dimethyl allylic bromide in THF, producing 47 in $76 \%$ yield. Other bases such as $\mathrm{K}_{2} \mathrm{CO}_{3}$ or TEA in DMF failed to alkylate 46 into 47. After Boc deprotection, cpd 43 was obtained in 96\% yield (Scheme 4.3).

45




(2) $\rangle={\underset{-B r}{ }}^{\text {, } \mathrm{THF},} 0^{\circ} \mathrm{C} / \mathrm{rt}$

48

45

Scheme 4.3. Alkylation of $\mathbf{1 0 d}$.


48




Figure 4.5. X-ray crystallography of $\mathbf{4 8}$ displayed with front view, right view and top view.

Because NOESY and HMBC of $\mathbf{4 5}$ and $\mathbf{4 3}$ did not provide sufficient information (Appendix VII), as well as the difficulty in crystallization to obtain good crystals, 45 and 43 were distinguished from their isomers (Figure 4.6) by referring to ${ }^{1} \mathrm{H}$ NMR spectra of 10d, 44 and $\mathbf{4 8}$ in DMSO- $d^{6}$ (Figure 4.2 and Figure 4.7). By comparing the chemical shifts of $-\mathrm{CH}_{2}$ - in allylic moieties of $\mathbf{4 8}$ and 45 (Figure 4.7), we could distinguish 45 from isomer 49 (Figure 4.0), as the chemical shift of allylic $-\mathrm{CH}_{2}$ - will locate at a lower field if it links to the nitrogen atom adjacent to oxygen atom. ${ }^{1} \mathrm{H}$ NMR of $\mathbf{4 4}$ indicates that the chemical shift of -NH-O- moiety is located at around 9 ppm (Figure 4.2) and no such acidic proton signal is observed in ${ }^{1} \mathrm{H}$ NMR of 43 (Figure 4.7), thus, the three isomers of $\mathbf{4 3}$ bearing -NH-O- moiety could be excluded (Figure 4.6.). Cpd $\mathbf{4 3}$ and $\mathbf{5 0}$ could be distinguished based on the chemical shift of -CH-O- moiety. Referring to ${ }^{1} \mathrm{H}$ NMR of 48 (Figure 4.7), we could estimate that the chemical shift of -CH-O- moiety in $\mathbf{5 0}$ should locate around 4.56 ppm due to their similarity in scaffold. However, the chemical shift of -CH-O- moiety in $\mathbf{4 3}$ locates at 3.72 ppm (Figure 4.7), which is far from 4.56 ppm , while quite close to 10 d at 3.74 ppm (Figure 4.2), excluding the formation of isomer 50. At this point, $\mathbf{4 5}$ and $\mathbf{4 3}$ have been distinguished from all their isomers (Figure 4.0) based on their characteristic peaks in ${ }^{1} \mathrm{H}$ NMR.


Figure 4.6. Isomers of 45 and 43.


Figure 4.7. ${ }^{1} H$ NMR spectra of 48,45 and 43 in DMSO- $d^{6}$.

To know the correctness of the synthetic approach towards the proposed structure of alchornedine, ${ }^{1} \mathrm{H}$ NMR spectra of $\mathbf{4 5}$ and $\mathbf{4 3}$ were also measured in MeOD-d ${ }^{4}$ (Figure 4.8). However, neither of them was consistent with the ${ }^{1} \mathrm{H}$ NMR reported in literature (Figure 4.9). ${ }^{133}$


Figure 4.8. ${ }^{1} H$ NMR spectra of 45 and 43 in MeOD-d ${ }^{4}$.


Figure 4.9. ${ }^{1} H$ NMR spectra of alchornedine in MeOD-d ${ }^{4}$ reported in literature.

This fact suggested that the structure of alchornedine proposed in literature was not correct. Since the mass spectrum of alchornedine in literature shown a $\mathrm{M}+1-16$ peak, a dissociated hydroxy group might exist in the structure of alchornedine. The biogenetic formation of alchornedine proposed in literature showed the oxirane moiety in $\mathbf{5 1}$ was attacked by the oxygen atom and finally formed a six-membered ring 43, the proposed structure of alchornedine. However, this structure seemed not consistent with the aforementioned $\mathrm{M}+1-16$ peak in mass spectra. Thus, we proposed the oxirane moiety in $\mathbf{5 1}$ might be attacked the nitrogen atom and finally formed a five-membered ring 52, the corrected structure of alchornedine (Scheme 4.4). The rationality of this speculation is that $\mathbf{5 2}$ bears a hydroxy group, which is consistent with the $\mathrm{M}+1-16$ peak in mass spectrum of alchornedine provided in the literature, indicating the structure of alchornedine should be $\mathbf{5 2}$, not 43.


Scheme 4.4. Proposed structure of alchornedine by biogenetic formation.

## IVB. Other methods to synthesize 43

## IVB1. Starting from Boc amino alkoxyamine 25d

Due to the fact that endocyclic nitrogen in 3-amino-1,2,4-oxadiazine 10d is more nucleophilic than the exocyclic one towards 3,3-dimethyl allylic bromide, the use of appropriate $N$-2,4-dimethoxybenzyl (DMB) protected isothiocyanate derivative 53 could be a way to directly cyclize 25d into Boc protected 1,2,4-oxadiazines $\mathbf{5 4}$ or 55 . An iodine-mediated cyclodesulfurization was tried as it was reported in literature to synthesize cyclic guanidine from $N$-Boc amine and isothiocyanate. ${ }^{134}$ Despite HPLC of the reaction mixture shown a total consumption of the starting material 25d, the purification of the two reactions were difficult due to the complexity of the crude (Scheme 4.5).


Scheme 4.5. Synthesis of $\mathbf{4 7}$ from 25d with isothiocyanate derivatives.

Direct introduction of 3,3-dimethyl allylic amine moiety into 25d was also tried using carbothioamide 57, which was prepared from the reaction of $N$-DMB allylic amine 56 with 1,1'-thiocarbonyldiimidazole (S-CDI). Solvents such as $\mathrm{MeOH}, \mathrm{MeCN}$
and DMF with/without catalytic amount of 4-dimethylaminopyridine (DMAP) were tried. However, no reaction happened even heated at $150^{\circ} \mathrm{C}$ (Scheme 4.0).



Scheme 4.6. Synthesis of $\mathbf{5 8}$ from 25d with carbothioamide 57.

## IVB2. Starting from 26d

Another strategy to avoid the formation of $\mathbf{4 5}$ was to focus on umpollung reactions involving the introduction of allylic moiety on oxadiazine-3-ol 59 or its corresponding thiol 60 by nucleophilic substitution with the help of the $N$-DMB amine 56 (Scheme 4.7). Although 26d could be transformed into $\mathbf{5 9}$ and $\mathbf{6 0}$ easily in $89 \%$ and $96 \%$ yields, respectively, the synthesis of $\mathbf{6 1}$ was difficult. Three conditions were tried to transform 59 into the corresponding iminochloride with $\mathrm{POCl}_{3}$, while subsequent substitution with amine 56 gave a complex reaction mixture. Directly transformation of 59 into 61 with 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU) and (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (BOP) in THF was unsuccessful and starting material was recovered quantitatively. Introduction of the allylic moiety into $\mathbf{6 0}$ with amine $\mathbf{5 6}, \mathrm{HgCl}_{2}$ and TEA in DMF or MeCN also failed and gave a complex reaction mixture. Moreover, 3-mercapto-1,2,4-oxadiazine $\mathbf{6 0}$ is instable since degradation happened after it was stored at room temperature for several days.



Scheme 4.7. Synthesis of $\mathbf{6 1}$ from 26d via 3-hydroxy-1,2,4-oxadiazine 59 or
3-mercapto-1,2,4-oxadiazine $\mathbf{6 0}$.

## IVB3. Starting from 2-hydroxyacetic acid

In Scheme 3.1 (see Chapter III ), an exclusive reported method to synthesize 3-amino-1,2,4-oxadazine scaffold was described in which it introduced the guanidine moiety on alkoxyamine by $N, N^{\prime}$-bis-Boc-1-guanylpyrazole. ${ }^{99}$ Here, a similar method was tried using 2-hydroxyacetic acid as starting material. Hydroxyl group in 2-hydroxyacetic acid was first protected by tert-butyldiphenylsilyl group, obtaining 62 in $92 \%$ yield. The resulting product was then transformed into Weinreb amide 63 in $98 \%$ yield. The reaction of $\mathbf{6 3}$ with isopropenyl magnesium bromide furnished $\alpha$, $\beta$-unsaturated ketone 64 in $98 \%$ yield, which was then reduced into alcohol $\mathbf{6 5}$ by $\mathrm{NaBH}_{4}$ in the presence of $\mathrm{CeCl}_{3}$ as a carbonyl activating agent. The N-O moiety was introduced into $\mathbf{6 5}$ by Mitsunobu reaction with NHPI, followed by the deprotection of phthalimide moiety with hydrazine hydrate, affording alkoxyamine 67 in $99 \%$ yield (Scheme 4.7).




Scheme 4.7. Synthesis of alkoxyamine $\mathbf{6 7}$ from 2-hydroxyacetic acid.

To avoid the substitution of undesired nitrogen atom in final oxadiazine ring, we have previously introduced the allylic moiety on the starting reagents: $N$, $N^{\prime}$-bis-Boc-S-Methyl-thiourea or $N$-DMB-3-methylbut-2-en-1-amine (Scheme 4.8). The key step of this approach was introducing the guanidine moiety by the reaction of hydroxylamine 67 with the previous synthesized $S$-methyl-thiourea 68 or cyanamide 69, then transformed the resulting cpds 70 and 71 into 43 after a sequence of deprotection-Mitsunobu-deprotection reactions. Despite the synthesis of alkoxyamine 67 went smoothly from 2-hydroxyacetic acid, the reaction of 67 with $S$-methyl thiourea 68 gave a complex reaction mixture. In contrary, no reaction happened between 67 and cyanogen amide 69 even heated at $100^{\circ} \mathrm{C}$ (Scheme 4.8).








71
Scheme 4.8. Synthesis of 70 and 71 from alkoxyamine 67.

## IVC. Verification of the structure of alchornedine

In Section IVA, we apprehended the total synthesis of cpd $\mathbf{4 3}$ as it was previously proposed to be alchornedine, a new natural product isolated from the leaves of Alchornea glandulosa. However, the NMRs of $\mathbf{4 3}$ did not conform to those provided in literature, indicating the true structure of alchornedine was not 43. Based on the proposed biogenetic formation of alchornedine and $\mathrm{M}+1-16$ peak in mass spectrum, 2-amino-imidazol-1-ol 52 was proposed to be the right structure of alchornedine, rather than $\mathbf{4 3}$ (Scheme 4.4). In this section, $\mathbf{5 2}$ would be synthesized to confirm our proposition for the structure of alchornedine.

The synthesis 52 was started from a previously synthesized alcohol 20d (Scheme 4.9). Mitsunobu reaction of $\mathbf{2 0 d}$ with $N, O-d i B o c ~ h y d r o x y l a m i n e ~ f u r n i s h e d ~ t h e ~ k e y ~$ intermediate $\mathbf{7 3}$ in $97 \%$ yield. The deprotection of $\mathbf{7 3}$ by HCl in dioxane provided $N$-alkyl hydroxylamine 74 in $99 \%$ yield, which was then cyclized into $\mathbf{7 5}$ by BrCN in 81\% yield. 3,3-dimethyl allylic bromide and TEA in DMF failed to directly alkylated 75 into 52 even heated at $80^{\circ} \mathrm{C}$. When a stronger base NaH was used, 75 was N,O-dialkylated affording 77 in $76 \%$ yield. As shown in Figure $4.10,{ }^{1} \mathrm{H}$ NMR of 77 in MeOD- $d^{4}$ is quite similar to the one of alchornedine reported in literature (Figure 4.9), supporting our proposed structure of alchornedine. To block the nucleophilicity of the oxygen atom, TBDPSCl was used to protect the hydroxyl group in $\mathbf{7 4}$ or $\mathbf{7 5}$. However, 76 was obtained in a low yield and TBDPSCl failed to protect the hydroxyl group in 75 .


Scheme 4.9. Synthesis of $\mathbf{5 2}$ via direct alkylation of $\mathbf{7 5}$ or TBDPS pre-protection.


Figure 4.11. ${ }^{1} H$ NMR of 77 in MeOD- $d^{4}$.

Since it is difficult to protect the hydroxyl group in $\mathbf{7 4}$ or $\mathbf{7 5}$ by TBDPSCl, $\mathrm{Boc}_{2} \mathrm{O}$ was tried to protect 75 ( 2.1 eq. $\mathrm{Boc}_{2} \mathrm{O}$ was used, decrease the equivalent of $\mathrm{Boc}_{2} \mathrm{O}$ led to the remaining of 75). As expected, three products, 79a, 79b and 79c were separated by reverse phase chromatography in $35 \%, 15 \%$ and $22 \%$ yields, respectively. Their structures were identified by characteristic signals in ${ }^{1} \mathrm{H}$ NMR in DMSO- $d^{6}$ (Scheme 4.10). 3,3-dimethyl allylic moiety was then introduced into 79a after deprotonating the amino group with NaH , providing $\mathbf{8 0}$ in $66 \%$ yield. The structure of $\mathbf{8 0}$ was confirmed by ${ }^{1} \mathrm{H}$ NMR in DMSO- $d^{6}$ where a -NH - peak ( 7.5 ppm ), three $=\mathrm{C}^{-} \mathrm{CH}_{3}$ peaks ( $1.74 \mathrm{ppm}, 1.69 \mathrm{ppm}, 1.64 \mathrm{ppm}$ ) and a Boc peak ( 1.47 ppm ) were observed. The Boc deprotection of $\mathbf{8 0}$ with HCl in dioxane is currently under progress (Scheme 4.10). After $\mathbf{5 2}$ was obtained, ${ }^{1} \mathrm{H}$ NMR will be compared with the one in Figure 4.9 so that confirm our proposition for the corrected structure of alchornedine.


Scheme 4.10. Synthesis of $\mathbf{5 2}$ from $\mathbf{7 5}$ via Boc protection.

## IVD. Conclusion

In this chapter, we try to synthesized $\mathbf{4 3}$ as it was proposed to be natural product alchornedine. ${ }^{133}$ However, the inconsistence in ${ }^{1} \mathrm{H}$ NMRs indicated that $\mathbf{4 3}$ was not right structure of alchornedine (Figure 4.8 and 4.9). Based on mass spectrum and biogenetic formation (Scheme 4.4), we proposed the structure of alchornedine should be $\mathbf{5 2}$. To confirm the proposition, the synthesis of $\mathbf{5 2}$ is currently under progress and its NMR will be compare with the one in literature (Figure 4.9).

# V. Dioxygenation of styrenes with molecular oxygen in water, a green approach to introduce N - O moiety 

## V. Dioxygenation of styrenes with molecular oxygen in water, a green approach to introduce N - O moiety

Recently, green chemistry awareness attempts to address the environmental impact of both chemical products and the processes by which these are produced. Around $80 \%$ of the chemical waste from a reaction mixture corresponds to the organic solvent. ${ }^{135}$ Hence, the development of alternatives to organic solvents has emerged as a research topic of great interest. Water is commonly considered as a benign solvent in view of its environmentally safe and abundantly available in nature. Unfortunately, most organic reactants have poor solubility in water, leading to low yield and reaction rate. The development of organic synthesis in aqueous medium using surfactants appears as a promising ecofriendly strategy ${ }^{136}$. Indeed, thanks to their amphiphilic nature, surfactants in water undergo spontaneous self-assembly into micelles, which then act as nanoreactors, as their hydrophobic cores play the role of reaction vessels in which the organic transformation involving water-insoluble reagents can occur (Figure 5.1). ${ }^{137}$


Figure 5.1 Surfactant assisted organic reaction in water.

In Chapter III and IV, various 1,2,4-oxadiazines have been synthesized and the key step was the introduction of N-O moiety by Mitsunobu reaction in THF. In view of
the importance of this key step and its environment concerns, a radical reaction was established to introduce the N-O moiety by dioxygenation of styrenes with molecular oxygen in water. The products obtained could be easily transformed into compounds with 1,2,4-oxadiazine scaffolds (Scheme 5.1). This part of work has been published in Tetrahedron Letters (Tang et al, DOI: 10.1016/j.tetlet.2018.03.009) and the article has been inserted in Appendix VIII. ${ }^{138}$


Scheme 5.1. Dioxygenation of styrenes with molecular oxygen in water.

# VI. Synthesis of 2,3-benzoxazepin-4-one scaffold 

## VI. Synthesis of 2,3-benzoxazepin-4-one scaffold

Compounds containing diazepine moieties are of significant interest in medicinal and pharmaceutical research because of their important biological activities. Among them, seven-membered ring 1,4-benzodiazepine heterocycles have captured the imagination of medicinal and organic chemists for the past 60 years. ${ }^{139}$ Besides being the core unit of traditional anxiolytics such as diazepam, oxazepam, lorazepam, cloxazolam, and ketazolam (Figure 6.1), there are numerous 1,4-benzodiazepines under research (Figure 6.2), which exhibits biological activities such as anti-ulcer, ${ }^{140}$ anti-viral, ${ }^{141}$ anti-toxin,,${ }^{142}$ anti-inflammatory, ${ }^{143}$ anti-cancer, ${ }^{144}$ and anti-bacterial. ${ }^{145}$


1,4-benzodiazepine

lorazepam

diazepam

cloxazolam

oxazepam

ketazolam

Figure 6.1. Examples of drugs exhibiting a 1,4-benzodiazepine scaffold

pirenzepine anti-ulcer


AKOS002710276 anti-inflammatory


TIBO
anti-viral


anti-cancer


STK862172 anti-toxin

tomaymycin anti-bacterial

Figure 7.2. 1,4-benzodiazepines with different biological activities.

Changing the position of the nitrogen atoms in classical structure of 1,4benzodiazepines leads to 2,3-benzodiazepines, which exhibit extremely rich pharmacological activities. ${ }^{146}$ The first remarkable 2,3-benzodiazepine is tofisopam, a phosphodiesterases inhibitor which has been claimed to exert anxiolytic effects without sedation (Figure 6.3). ${ }^{147,148}$ Further modifications of the substituents on the pharmacophore of tofisopam led to the discovery of GYKI 52466 (Figure 6.3). Similar to tofisopam, GYKI 52466 is a 2,3-benzodiazepine pharmacologically different from conventional 1,4-benzodiazepines, such as diazepam, in that they do not bind to type A $\gamma$-aminobutyric acid receptor $\left(\mathrm{GABA}_{\mathrm{A}}\right.$ receptor), and lack sedative-hypnotic activity. In addition, GYKI 52466 also acts as a noncompetitive AMPA receptor antagonist with anticonvulsant and neuroprotective properties, which induced growing interest focused on 2,3-benzodiazepines. ${ }^{149}$ One major modification of the 2,3-benzodiazepine scaffold in GYKI 52466 is replacing the methyl by an oxygen or sulfur atom, leading to 1-aryl-2,3-benzodiazepine-4-one or 1-aryl-2,3-benzodiazepine-4-thione scaffold with higher anti-convulsant potency (Figure 6.3). ${ }^{149-159}$


tofisopam


GYKI 52466


1-aryl-2,3-benzodiazepin-4-ones


1-aryl-2,3-benzodiazepine-4-thiones

Figure 6.3. Tofisopam, GYKI 52466 and 1-aryl-2,3-benzodiazepine-4-(thi)ones.

Several 2,3-benzodiazepin-4-one derivatives were also developed as PDE-4 inhibitors in our group by pharmacophoric comparison between papaverine and tofisopam (Figure 1.10, Chapter I). Since most current researches of benzodiazepine focused on modifying the position of the two nitrogen atoms, the complexity of the scaffold is not significantly increased. In this chapter, one of the two adjacent nitrogen atoms in 2,3-benzodiazepine-4-one scaffold will be transposed by an oxygen atom to form 2,3-benzoxazepin-4-one scaffold (Figure 6.4). Due to the bivalent character of the oxygen atom, an additional stereogenic center will be obtained, making the geometry of 2,3-benzoxazepin-4-one more complex than the corresponding $\mathrm{N}-\mathrm{N}$ heterocycle.


Figure 6.4. Development of 2,3-benzoxazepin-4-one from 2,3-benzodiazepine-4-one.

## VIA. Synthesis of 1-phenyl-2,3-benzoxazepin-4-one scaffold

Contrary to benzodiazepine, little research has been done with benzoxazepine (49694 vs 842 references in Scifinder, using "benzodiazepine" or "benzoxazepine" as research topic). Only one reference was found when using 2,3-benzoxazepin-4-one as substructure in Scifinder (Figure 6.5). ${ }^{89}$ Although this reported scaffold can be easily obtained in 6 steps, the methoxyimino function at position 5 is indispensable since "Meerwein arylation" between diazonium chloride and methyl 2-hydroxyiminoacetate was used as the initial step (Scheme 6.1). ${ }^{89,}{ }^{160}$ Furthermore, most of these benzoxazepin-4-ones are achiral due to the unalterable methoxyimino function at position 5 and the limited substitution at position 1 .


| $\mathbf{R}_{\mathbf{1}}$ | $\mathbf{R}_{\mathbf{2}}$ | $\mathbf{R}_{\mathbf{1}}$ | $\mathbf{R}_{\mathbf{2}}$ |
| :--- | :--- | :--- | :--- |
| H | H | H | 4-Me-benzyl |
| H | Me | H | 4-CN-benzyl |
| H | Et | H | 4-NO |
| H | $n$-Pr | H | 2-Cl-benzyl |
| H | allyl | H | (6-Cl-3-pyridinyl)methyl |
| H | propargyl | H | (2-chloro-5-thiazolyl)methyl |
| H | $n$-butyl | allyl | allyl |
| H | $n$-pentyl | $n$-hexanyl | 2-Cl-benzyl |
| H | 2-Cl-benzyl |  |  |
| H | $n$-heptanyl |  |  |

Figure 6.5. Reported fungicidal 2,3-benzoxazepin-4-one.




Scheme 6.1. Reported method to synthesize 2,3-benzoxazepin-4-one scaffold.

As shown above, no synthetic approach has been reported so far to synthesize 1,5 positions modifiable 2,3-benzoxazepine-4-ones. Indeed, relative to five- or sixmembered N-O heterocycles, the seven-membered one is more difficult to synthesize. Here, a general approach to synthesize 1-phenyl-2,3-benzoxazepin-4-one scaffold was proposed (Scheme 6.2), which mainly relies on the formation of a benzolactone as key-intermediate.


Scheme 6.2. Retrosynthesis of 1-phenyl-2,3-benzoxazepin-4-one scaffold.

## VIA1. Synthesis of 2-(2-ethyloxy-2-oxoethyl)benzoic acid 82a

One concise way to synthesize 82a was the esterification of homophthalic acid with EtOH under the catalysis of concentrated $\mathrm{H}_{2} \mathrm{SO}_{4}$, furnishing 82a in $81 \%$ yield (Scheme 6.3). Another method to synthesize 82a involved the Hurtley reaction, a
copper-mediated acetylation of 2-halobenzoic acid with 1,3-dicarbonyl compounds. ${ }^{161}$ 2-bromobenzoic acid was coupled with ethyl acetoacetate in the presence of NaOEt and catalytic amount of CuBr in EtOH , which was then deacetylated in situ via retro-Claisen condensation to afford 2a in 98\% yield (Scheme 6.4). Although this method is relatively more complex than the one in Scheme 6.3, it has a better availability in starting materials with functionalized aryles.


Scheme 6.3. Synthesis of 82a by esterification of homophthalic acid.


Scheme 6.4. Synthesis of 82a by tandem Hurtley-retro-Claisen reaction (2-bromobenzoic acid:ethyl acetoacetate:NaOEt = 1:2:3).

Scheme 6.5 shows a proposed mechanism of the tandem Hurtley-retro-Claisen reaction. The copper (I) carboxylate $\mathbf{8 3}$ is the essential intermediate for Hurtley reaction in that the polarization of the $\mathrm{C}-\mathrm{Br}$ bond is augmented by intra-molecular coordination of the bromine atom to the copper (I) atom, facilitating the attack of ethyl acetoacetate carbanion and promoting the formation of the coupling product 84. ${ }^{162-164}$ As EtONa (3 eq.) is fully used to deprotonate 2-bromobenzoic acid (1 eq.) as well ethyl acetoacetate ( 2 eq ), the carbonyl of $\mathbf{8 4}$ is attacked by remaining ethyl acetoacetate carbanion and undergoes a retro-Claisen condensation by removing an ethyl diacetoacetate. Acidification of the reaction mixture finally gave the desired product 82a.


Scheme 6.5. Mechanism of Hurtley-retro-Claisen reactions.

It is noteworthy that the carboxylic group is indispensable since no reaction happened when replacing 2-bromobenzoic acid by 1-(2-bromophenyl)ethanol. Moreover, under microwave irradiation at $150{ }^{\circ} \mathrm{C}$, ethoxylation rather than Hurtley reaction happened (Scheme 6.6A). In the literature, $\mathrm{Cu}(\mathrm{II})$ catalysts were efficiently used in Hurtley reaction. ${ }^{165,166}$ Surprisingly, replacement of $\mathrm{Cu}(\mathrm{I}) \mathrm{Br}$ by $\mathrm{Cu}(\mathrm{II})(\mathrm{OAc})_{2}$ prevented Hurtley reaction (Scheme $6.6 B$ ).

(B)


Scheme 6.6. (A) Hurtley reaction in the absence of carboxylic group. (B) Hurtley reaction in the absence of CuBr .

The ratio of the reactants (2-halobenzoic acid:ethyl acetoacetate: $\mathrm{NaOEt}=1: 2: 3$ ) was also important to Hurtley-retro-Claisen reaction. An excess of NaOEt (2-halobenzoic acid:ethyl acetoacetate: $\mathrm{NaOEt}=1: 2: 4$ ) led to the formation of ethoxylated product $\mathbf{8 6}$ in $95 \%$ yield (Scheme 6.7).


Scheme 6.7. Ethoxylation, rather than Hurtley reaction in an excess NaOEt
(2-bromo-3-methoxybenzoic acid:ethyl acetoacetate:NaOEt = 1:2:4).

To explore the scope of the tandem Hurtley-retro-Claisen reaction, different 2-halobenzoic acids were used as starting material (Figure 6.6). The reactions worked well with 2-bromo or 2-iodobenzoic acids bearing electro-donating/withdrawing substituents (82b-82h, 82k). For 2-chlorobenzoic acids, the synthesis of $\mathbf{8 2 j}$ needed a
longer reaction time but led to a good $89 \%$ yield, while no reaction happened with 2,3-dichlorobenzoic acid (82i).


82

$\mathbf{X}=\mathbf{B r}$
82b, 93\%

$\mathbf{X}=\mathbf{B r}$ 82f, $93 \%$

$\mathbf{X}=\mathbf{C l}$ 82j, 89\%

$\mathbf{X}=\mathbf{B r}$
82c, 97\%

$\mathbf{X}=\mathbf{B r}$
82g, $98 \%$

$\mathbf{X}=\mathbf{I}$
82k, $91 \%$

Figure 6.6. CuBr catalyzed tandem Hurtley-retro-Claisen reaction.

## VIA2. Synthesis of ethyl 2-(2-benzoylphenyl)acetate 87

During the synthesis of 1,2,4-oxadiazine scaffolds, the ketone intermediates were synthesized through the reaction of Weinreb amide with Grignard reagent (Scheme 6.8A). However, this method was not suitable for the synthesis of ketone 87 because of the presence of ester function, which could be attacked by the organo-magnesium reagents (Scheme 6.8B). Since the organo-zinc reagents were less active relative to the corresponding organo-magnesium, the Fukuyama CCR between thioester and organo-zinc reagent was applied to form the diaryketone 87 (Scheme 6.8C).
(A)

(B)

(C)


Scheme 6.8. (A) Ketone synthesis through Weinreb amide and Grignard reagent. (B) Ester function incompatible with Grignard reagent. (C) Fukuyama cross-coupling reaction.

By using HOBt and EDCI as coupling reagents, 82a was thioesterified into $\mathbf{8 8}$ in $95 \%$ yield (Scheme 6.9). Organo-zinc reagent $\mathbf{8 9}$ was afforded in quantitative yield by adding PhMgBr into excess anhydrous $\mathrm{ZnCl}_{2} / \mathrm{THF}$ solution. $\mathrm{PdCl}_{2}\left(\mathrm{PPh}_{3}\right)_{2}$ successfully catalyzed the Fukuyama reaction between thioester $\mathbf{8 8}$ and organo-zinc reagent 89, giving diarylketone 87 in 95\% yield (Scheme 7.9).



Scheme 6.9. Synthesis of diarylketone 87 via Fukuyama cross-coupling reaction of thioester 88 and organo-zinc reagent 89.

## VIA3. Reduction of ethyl 2-(2-benzoylphenyl)acetate 87

As a prerequisite condition to introduce the $\mathrm{N}-\mathrm{O}$ bond, several methods were tried
to reduce diarylketone $\mathbf{8 7}$ into alcohol $\mathbf{9 0}$ (Table 6.1). However, both $\mathrm{Zn} / \mathrm{NaOH}$ at 100 ${ }^{\circ} \mathrm{C}$ or $\mathrm{NaBH}_{4}$ at rt reduced the ester group, leading to the formation of diol 91 in $100 \%$ and $94 \%$ yields, respectively. Reduction of ester group by $\mathrm{NaBH}_{4}$ was inevitable even when the temperature was decreased to $-70^{\circ} \mathrm{C}$, leading to a mixture of the desired product 90, diol 91 and lactone 92. Purification of the reaction mixture by normal phase chromatography resulted in total transformation of $\mathbf{9 0}$ into $\mathbf{9 2}$, lactone $\mathbf{9 2}$ and diol 91 were obtained in $51 \%$ and $47 \%$ yields, respectively. A weaker reductant, $\mathrm{Na}(\mathrm{CN}) \mathrm{BH}_{3}$ failed to reduce ketone 87 .

Table 6.1. Reduction of diarylketone 87.


| Conditions | $\mathbf{9 0}(\%)$ | $\mathbf{9 1}(\%)$ | $\mathbf{9 2}(\%)$ |
| :--- | :--- | :--- | :--- |
| $\mathrm{Zn}, \mathrm{NaOH}, \mathrm{H}_{2} \mathrm{O}, 100^{\circ} \mathrm{C}$ | - | 100 | - |
| $\mathrm{NaBH}_{4}, \mathrm{EtOH}, \mathrm{rt}$ | - | 94 | - |
| $\mathrm{NaBH}_{4}, \mathrm{EtOH},-70{ }^{\circ} \mathrm{C}$ | instable | 47 | 51 |
| $\mathrm{Na}(\mathrm{CN}) \mathrm{BH}_{3}, \mathrm{EtOH}, \mathrm{rt}$ |  | no reaction |  |

Generally, ester groups could not be reduced by $\mathrm{NaBH}_{4}$ at $-70{ }^{\circ} \mathrm{C}$. However, due to the benzophenone moiety at the $\alpha$-carbon of ester function in 87 , the enol tautomer 93 will be stabilized by the presence of a long conjugation system. As electron-withdrawing groups, the hydroxy and ethoxy groups in 93 enhance the polarity of the enol double bond, facilitating the attack of $\mathrm{NaBH}_{4}$ and leading to the formation of diol 91. In a different mechanism, lactone 92 is formed through two kinds of favored six-membered transition states 94 and $\mathbf{9 5}$ after the desired reduction of 87. (Scheme 6.11)


Scheme 6.11. Proposed mechanism for $\mathrm{NaBH}_{4}$ reduction of diarylketone 87.

To avoid the formation of diol 91, the ester group in diarylketone 87 was first hydrolyzed into carboxylic group as it is more tolerant towards $\mathrm{NaBH}_{4}$ reduction. Diarylketone 87 was hydrolyzed by LiOH , followed by $\mathrm{NaBH}_{4}$ reduction, leading to a mixture of intermediate 96 and lactone 92. However, further acidification of the reaction mixture produced lactone $\mathbf{9 2}$ in quantitative yield through an expected $\mathrm{S}_{\mathrm{N}} 1$ mechanism favoring the lactone formation (Scheme 7.12).


Scheme 6.12. Synthesis and mechanism of lactone 92 from diarylketone 87 in a tandem hydrolysis, reduction and acidification.

## VIA4. Introduction of the N-O moiety

During the synthesis of 1,2,4-oxadiazine scaffold, the N-O moiety was introduced by Mitsunobu reaction between alcohol and NHPI. However, as shown in Scheme 6.12, reduction of diarylketone $\mathbf{8 7}$ led to lactone $\mathbf{9 2}$, which means N-O moiety cannot be readily introduced by Mitsunobu reaction with NHPI anymore. As a result, two methods were proposed here to open the lactone ring, either by nucleophilic attack of the ester group with hydroxylamine, or by chlorination of the diphenylmethyl position followed by the introduction of NHPI (Scheme 6.13).


Scheme 6.13. Introduction of the N-O moiety in lactone.
$N$-benzylhydroxylamine 98, which was prepared from $\mathrm{Na}(\mathrm{CN}) \mathrm{BH}_{3}$ reduction of oxime 97 (Scheme 6.14), was first tried to insert the N-O moiety into 92. As shown in Table 6.2, coupling reagents DCC and DMAP in DCM led to a complex mixture, while no reaction happened between lactone 92 and $N$-benzylhydroxylamine 98 in MeOH with/without TEA. Strong bases such as KOH in MeOH or NaOEt in EtOH quantitatively oxidized 98 into oxime 97, along with the formation of carboxylate 100, which was easily cyclized into lactone $\mathbf{9 2}$ after acidification (mechanism discussed in Scheme 6.12.).


Scheme 6.14. Reduction of ( $E$ )-benzaldehyde oxime 97.

Table 6.2. Insertion $N-O$ moiety with $N$-benzylhydroxylamine 98.


Because of the instability of $\mathbf{9 8}$ under basic conditions, hydroxylamine in MeOH was used to insert N-O moiety into lactone 92, affording an instable hydroxamic acid 101 in 90\% yield (Scheme 6.15). Similar to carboxylate 100, hydroxamic acid 101 could be easily cyclized into lactone 92 under acidic condition. Even stored at $-20^{\circ} \mathrm{C}$, spontaneous cyclization of $\mathbf{1 0 1}$ was observed although in relatively slow rate.


Scheme 6.15. Synthesis of hydroxamic acid 101 and its instability.

In agreement with its poor stability, $\mathbf{1 0 1}$ was used immediately for next step. So far, no efficient method was found to cyclize hydroxamic acid 101 into benzoxazepinone 81 (Table 6.3). The first attempt we tried was to transform the benzylic hydroxyl group of 101 into a good leaving group such as mesylate or bromide, which would facilitate the cyclization. Unexpectedly, MsCl or $\mathrm{PBr}_{3}$ under basic conditions led to lactone $\mathbf{9 2}$ as major product. Intra-molecular Mitsunobu reaction of $\mathbf{1 0 1}$ produced oxime $\mathbf{1 0 2}$, carbamate $\mathbf{1 0 3}$ and lactone $\mathbf{9 2}$ in $18 \%, 41 \%$ and $34 \%$ yields, respectively. Similarly, application of CDI at room temperature led to the cyclization of hydroxamic acid 101 into oxime 102, carbamate 103 and lactone 92 in $56 \%, 27 \%$ and $11 \%$ yields, respectively. Finally, microwave irradiation of 101 with CDI at $120^{\circ} \mathrm{C}$ led to lactone $\mathbf{9 2}$ in quantitative yield.

Table 6.3. Cyclization of hydroxamic acid 101.

|  |  |  <br> 103 |  |  |
| :---: | :---: | :---: | :---: | :---: |
| Conditions | 81 (\%) | 102 | 103 | 92 (\%) |
|  |  | (\%) | (\%) |  |
| TEA, MsCl, DMAP, toluene, rt | 0 | trace | trace | 64 |
| TEA, MsCl, DMAP, THF, rt | 0 | trace | trace | 83 |
| pyridine, $\mathrm{PBr}_{3}, \mathrm{Et}_{2} \mathrm{O}, 0^{\circ} \mathrm{C}$ | 0 | trace | trace | 91 |
| DIAD, $\mathrm{PPh}_{3}$, THF, $0^{\circ} \mathrm{C} / \mathrm{rt}$ | 0 | 18 | 41 | 34 |
| CDI, THF, rt | 0 | 56 | 27 | 11 |
| CDI, THF, m.w., $120{ }^{\circ} \mathrm{C}$ | 0 | 0 | 0 | 100 |

Here we proposed a potential mechanism for the CDI-mediated formation of alkoxy oxime 102 and cyclic carbamate 103 (Scheme 6.16). Tautomerism of hydroxamic acid 101 into imino-diol and subsequent reaction with CDI led to the
formation of a dioxazolone ring, which was then opened by hydroxyl group nearby to form the cyclic oxime 102. ${ }^{167}$ Although NMR spectra (See Figure 6.8) as well as exact mass of $\mathbf{1 0 2}$ were in agreement with the initially expected $6 / 7$ fused bicycle benzoxazepinone 81, X-ray crystallography of single crystals recrystallized by slow evaporation from MeCN solution allowed us to formally identify the $6 / 6$ fused bicycle 102 (Figure 6.7). The details of the crystallographic data and structure refinement parameters are summarized in Appendix IV.





Figure 6.7. X-ray crystallography of oxime 102 displayed with front view, right view and top view.

Concomitantly with the formation of $\mathbf{1 0 2}$, direct nucleophilic attack of $\mathbf{1 0 1}$ towards CDI generated an amidoacetate, which underwent Lossen rearrangement and produced an isocyanate (Scheme 6.16). Intra-molecular nucleophilic addition of the benzylic hydroxyl group on isocyanate and subsequent tautomerism resulted into the formation of 103. Its structure was confirmed by comparison with litterature. ${ }^{168}$ Similar mechanism may be proposed under Mitsunobu conditions (DIAD/ $\mathrm{PPh}_{3}$ ).


Scheme 6.16. Mechanism for the formation of oxime 102 and carbamate 103.

As shown above, inserting N-O moiety on carbonyl group of $\mathbf{9 2}$ under basic conditions and subsequent cyclization by intra-molecular Mitsunobu reaction or CDI finally led to the formation of oxime $\mathbf{1 0 2}$ and carbamate $\mathbf{1 0 3}$, rather than the desired benzoxazepinone 81. Thus, a tandem approach was tried to first introduce N-O moiety at benzylic position (Scheme 6.17). $\mathrm{SOCl}_{2}$ with catalytic amount of $\mathrm{ZnCl}_{2}$ successfully transformed 92 into benzyl acyl dichloride 104, which was subsequently esterified by MeOH . The addition of NHPI under basic condition afforded the expected alkoxyamine 105 as well as the alkoxy ester 106 in $47 \%$ and $44 \%$ yields, respectively. Deprotection of $\mathbf{1 0 5}$ with methyl hydrazine directly led to the cyclized 2,3-benzoxazepin-4-one $\mathbf{8 1}$ in $84 \%$ yield (Scheme 6.17).


Scheme 6.17. Introduction of N-O moiety at benzylic position.

As isomers, the structure of oxime 102, carbamate $\mathbf{1 0 3}$ and benzoxazepinone $\mathbf{8 1}$ could be identified by NMRs (Figure 6.8 and 6.9). The main difference of oxime 102 from the other two is that it shown $\mathrm{a}=\mathrm{N}-\mathrm{OH}$ peak at 9.35 ppm in ${ }^{1} \mathrm{H} \mathrm{NMR}$, a $-\mathrm{CH}_{2}-$ peak at 30.1 ppm and a $-\mathrm{C}=\mathrm{N}$ - peak at 150.77 ppm in ${ }^{13} \mathrm{C}$ NMR. In ${ }^{1} \mathrm{H}$ NMR of carbamate $\mathbf{1 0 3}$, it shown a - NH- peak at 7.74 ppm and one of the two protons in $-\mathrm{CH}_{2}-$ shown a $d d$ peak at 4.06 ppm due to the presence of the adjacent -NH- group. Because of the electro-withdrawing effect of bilateral oxygen atom and carbonyl group, the -NH- peak of benzoxazepinone 1 locates at 11.01 ppm in ${ }^{1} \mathrm{H}$ NMR. Far different from the carbamate $>\mathrm{C}=\mathrm{O}$ peak of $\mathbf{1 0 3}$ at 154.59 ppm ., the hydroxamate $>\mathrm{C}=\mathrm{O}$ peak of benzoxazepinone $\mathbf{8 1}$ locates at 176.48 ppm in ${ }^{13} \mathrm{C}$ NMR.


Figure 6.8. ${ }^{1}$ H NMRs of oxime 102, carbamate 103 and benzoxazepinone 81.


103


81


Figure 6.9. ${ }^{13}$ C NMRs of oxime 102, carbamate 103 and benzoxazepinone 81.

To provide more evidence for the structures of 81, it was recrystallized by slow evaporation from MeCN solution. Single-crystal X-ray diffraction analysis showed that the crystal structure $\mathbf{8 1}$ belongs to 2,3-benzoxazepin-4-one scaffold (Figure 6.10). The details of the crystallographic data and structure refinement parameters are summarized in Appendix V.


Figure 6.10. X-ray crystallography of 1-phenyl-2,3-benzoxazepin-4-one 81 displayed with front view, right view and top view.

## VIB. Other methods to synthesize 1-phenyl-2,3-benzoxazepin-4-one scaffold

During the development of aforementioned method to synthesize 1-phenyl-2,3-benzoxazepin-4-one 81, other synthetic approaches were attempted in which 2-bromobenzaldehyde or 2-iodobenzoic acid was used as starting material. The general idea of these approaches was to couple the ester moiety on diaryl ketone or alkoxyamine (Scheme 6.18).



Scheme 6.18. Coupling the ester moiety on diaryl ketone or alkoxyamine.

## VIB1. Starting from 2-bromobenzaldehyde

To construct the diaryl scaffold, 2-bromobenzaldehyde was used as starting material (Scheme 6.19). By addition reaction between 2-bromobenzaldehyde and PhMgBr at $-30{ }^{\circ} \mathrm{C}$, diaryl alcohol $\mathbf{1 0 7}$ was obtained in $87 \%$ yield. Since direct substitution of alcohol 107 by NHPI did not work under the catalysis of tris(pentafluorophenyl)borane, alcohol 107 was brominated into 109 by $\mathrm{PBr}_{3}$ in $99 \%$ yield. Three reactants were tried to substitute bromide by a N-O moiety. While $N$-protected hydroxylamine $\mathbf{9 8}$ or $\mathbf{1 1 1}$ led to complex reaction mixtures, NHPI with

TEA in DMF at rt successfully transformed bromide 109 into $N$-alkoxyl phthalimide $\mathbf{1 0 8}$ in $98 \%$ yield. The attempt to directly introduce the ester moiety into $\mathbf{1 0 8}$ by tandem Hurtley-retro-Claisen reaction led to a complex reaction mixture. $\mathrm{PdCl}(\mathrm{Ph})\left(\mathrm{PPh}_{3}\right)_{2}$ (a precatalyst developed in our lab, see Appendix IX) catalyzed Negishi CCR between 108 and organo-zinc reagent also failed to furnish 114. Another method to obtain 114 was by first performing a Pd-catalyzed cyanation of $\mathbf{1 0 8}$ into 113, followed by hydrolysis of the cyano group into ester. ${ }^{169,}{ }^{170}$ Despite methyl cyanation of $\mathbf{1 0 8}$ by sodium cyanoacetate under the catalysis of allylpalladium chloride dimer and 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (S Phos) gave 33 in a modest $34 \%$ yield, the hydrolysis of the cyano group with trimethyl chlorosilane (TMSCl) in EtOH resulted in a complex reaction mixture. Because of the inability to introduce the ester moiety into bromide 108, it was deprotected into $\mathbf{1 1 5}$ by hydrazine in EtOH in 99\% yield (Scheme 6.20). Unfortunately, tandem Hurtley-retro-Claisen reaction on $\mathbf{1 1 5}$ led also to complex reaction mixture. To limit side-reactions, the amino group in 115 was first protected with Boc group(s) (mono-Boc 117 \& di-Boc 119) before applying a Negishi CCR. $\operatorname{PdCl}(\mathrm{Ph})\left(\mathrm{PPh}_{3}\right)_{2}$ catalyzed Negishi CCR between 117 and organo-zinc reagent at $100^{\circ} \mathrm{C}$ resulted in a complex reaction mixture, while the same reaction between 119 and organo-zinc reagent at $60{ }^{\circ} \mathrm{C}$ led to the loss of one Boc group and the formation of $\mathbf{1 1 7}$ in quantitative yield. Steric hindrance due to Boc protection is likely preventing the Negishi CCR.


Scheme 6.19. Synthesis of $\mathbf{1 0 8}$ from 2-bromobenzaldehyde.


Scheme 6.20. Introduction of ester moiety on O-diphenylmethylhydroxyamine.

## VIB2. Starting from 2-iodobenzoic acid

As iodine atom is a better leaving group than bromo, the synthetic approach using 2-iodobenzoic acid as starting material was also tried (Scheme 6.21). Friedel-Craft acylation of benzene worked well with 2-iodobenzoyl chloride under the catalysis of $\mathrm{AlCl}_{3}$, furnishing ketone 121 in $99 \%$ yield. As discussed in Section VI A1, carboxylic group at the $\alpha$ position of halogen is essential for Hurtley reaction, so an ethanol-assisted CuI-catalyzed coupling reaction was attempted, leading to complex reaction mixture. ${ }^{171}$ Reduction of ketone $\mathbf{1 2 1}$ with $\mathrm{NaBH}_{4}$ produced alcohol $\mathbf{1 2 2}$ in quantitative yield. Three methods were tried to substitute alcohol 122 by a $\mathrm{N}-\mathrm{O}$ moiety. Di-2-methoxyethyl azodicarboxylate (DMEAD) or diisopropyl azodicarboxylate (DIAD) mediated Mitsunobu reaction between 122 and NPHI gave the desired product 123 in $15 \%$ and $14 \%$ yields, respectively. No reaction happened
when PTSA was used to assist the substitution reaction between $\mathbf{1 2 2}$ and NHPI. ${ }^{172}$ As it was difficult to directly transform $\mathbf{1 2 2}$ into 123, alcohol $\mathbf{1 2 2}$ was first brominated with $\mathrm{PBr}_{3}$ in DCM , affording 124 in $94 \%$ yield. However, substitution of the resulting bromide $\mathbf{1 2 4}$ by BocNHOH in presence of TEA or DBU failed. In contrary, by using NHPI with TEA in DMF, compound $\mathbf{1 2 3}$ was obtained in $87 \%$ yield. Since the phthalimide moiety was incompatible with Negishi or Hurtley reaction conditions, 123 was deprotected by hydrazine and re-protected by diboc, affording 127 in $76 \%$ yield. To introduce the ester moiety in 127, an ethanol-assisted CuI-catalyzed coupling reaction with ethyl acetoacetate was applied, but led to mono boc protected alkoxyamine 125 (54\% yield) and unreacted starting material 127 (37\%), while no desired product 120 was obtained. Similarly, the $\operatorname{PdCl}(\mathrm{Ph})\left(\mathrm{PPh}_{3}\right)_{2}$ catalyzed Negishi CCR between 126 and organo-zinc reagent $\mathrm{BrZnCH}_{2} \mathrm{CO}_{2} \mathrm{Et}$ led to undesired compound $\mathbf{1 2 5}$ in quantitative yield.


Scheme 6.21. Synthetic approach starting from 2-iodobenzoic acid.

## VIC. Synthesis of 1-benzyl-2,3-benzoxazepin-4-one scaffold

In section VI A, we managed to synthesize the first 1-phenyl-2,3-benzoxazepin-4-one 81. The next challenge in terms of molecular diversity was to insert a benzyl group at position 1 instead of the benzene ring. Based on the established synthetic approach of 1-phenyl-2,3-benzoxazepin-4-one 81, we attempted here to synthesize 1-benzyl-2,3-benzoxazepin-4-one 128 (Scheme 6.22). Several classical catalysts for Fukuyama CCR were tried to synthesize ketone 130. However, the competition between Dieckman condensation and Fukuyama CCR led to naphthalenediol $\mathbf{1 2 9}$, rather than ketone $\mathbf{1 3 0}$ as the major product. To accelerate the Fukuyama CCR, $\operatorname{PdCl}(\mathrm{Ph})\left(\mathrm{PPh}_{3}\right)_{2}$, a post-oxidative-addition precatalyst (POxAP) was developed (For more details on POxAPs, see Appendix IX). Thanks to this novel precatalyst POxAP, Fukuyama CCR between thioester $\mathbf{8 8}$ and BnZnBr afforded the desired ketone 130 in $95 \%$ yield. In agreement with previous results described in Table 6.1, reduction of ketone $\mathbf{1 3 0}$ with $\mathrm{NaBH}_{4}$ at rt led to diol $\mathbf{1 3 1}$ in $82 \%$ yield. In contrary, reduction at $0^{\circ} \mathrm{C}$ followed by acidification afforded the expected lactone $\mathbf{1 3 2}$ in $94 \%$ yield. As expected, reaction between lactone $\mathbf{1 3 2}$ and BnNHOH or $\mathrm{NH}_{2} \mathrm{OH}$ under basic condition led to complex reaction mixtures. We will next investigate the synthetic strategy including a chlorination step with $\mathrm{SOCl}_{2} / \mathrm{ZnCl}_{2}$, followed by a substitution with NHPI and its deprotection with methylhydrazine to obtain the expected 1-benzyl-2,3-benzoxazepin-4-one $\mathbf{1 2 8}$.


Scheme 6.22. Synthesize 1-benzyl-2,3-benzoxazepin-4-one 128 through lactone 132.

## VID. Conclusion

In this chapter, the new scaffold 1-phenyl-2,3-benzoxazepin-4-one $\mathbf{8 1}$ was synthesized in 10 steps in $35 \%$ overall yield. The key step was introducing the $\mathrm{N}-\mathrm{O}$ moiety into lactone $\mathbf{9 2}$. Opening the lactone ring under acidic condition followed by NHPI substitution and cyclization gave the desired product $\mathbf{8 1}$. An overall view of the synthesis is shown in Scheme 6.23. The structure of benzoxazepinone $\mathbf{1}$ was identified by NMRs and X-ray crystallography (Figure 6.10).




Scheme 6.23. Synthesis of 1-phenyl-2,3-benzoxazepin-4-one 81.

Several attempts were also tried to synthesize 1-benzyl-2,3-benzoxazepin-4-one $\mathbf{1 2 8}$, an analog of $\mathbf{8 1}$. Although none of these synthetic approaches worked well till now, a novel catalyst, named POxAP, was developed during the synthesis of ketone 130 (Scheme 6.24). The application of POxAP in Fukuyama CCR provided a novel synthetic approach towards isoprekinamycin, a natural product with anti-cancer
activities. This part of my PhD work was recently published in Organic Letters (Tang et al, DOI: 10.1021/acs.orglett.9b00031) and this article has been inserted in Appendix IX. ${ }^{173}$


Scheme 6.24. Attempts to synthesize 1-benzyl-2,3-benzoxazepin-4-one 128 leading to the discovery of POxAP.

## VII. Summary

## VII. Summary

The guanidine moiety is widely used in the development of pharmalogical tools such as NPFF receptors antagonists, inhibitors of FXa, NOS, as well as urokinase. However, due to the significant basicity of guanidine ( $\mathrm{pKa} \approx 13$ ), as well as its capacity to form numerous hydrogen bonds, it's difficult to develop the molecules with good pharmacological profiles, especially in terms of oral absorption, distribution in center nervous system or duration of action. The iminoguanidine system is an interesting way to decrease the basicity of guanidine as shown by the development of the antihypertensive guanabenz (Wytensin®). Yet this molecule is entirely flat and shows a certain sensibility to hydrolysis. In a previous project, Dr Bihel's group has developed a cyclic guanabenz which shown an inhibitory effect on prions while less sensitive to hydrolysis.

In this project, we proposed to develop 3 -amino-1,2,4-oxadiazines as the biomimetic structure of guanidines et iminoguanidines. Although the synthesis of six-membered ring 1,2-oxadiazines were widely developed thanks to [4+2] nitroso-Diels Alder cyclization, the synthesis of 3-amino-1,2,4-oxadiazines system is nearly unknown in literature.

Starting from $N$-Boc glycine, a multi-step synthetic approach has been established without the control of chiral center at position 6 , providing a rapid access to cyclic 3-amino-1,2,4-oxadiazine with high yields (Scheme 3.25). When using L-proline or $N$-Boc L-valine, cyclic 4-amino or 4-hydroxypyrrolo-[1,2-d]-1,2-4-oxadiazine could be enantioselectively synthesized by stereoselective reduction of the ketone intermediate (Scheme 3.26 and 3.27). The structure and geometry of these new heterocycles were identified by X-ray crystallography (Figure 3.6 and 3.9). Preliminary results of pKa indicated a significant decrease in basicity of these alkoxyguanidines $(\mathrm{pKa} \approx 8)$ compared with iminoguanidines $(\mathrm{pKa} \approx 10)$ and guanidines $(\mathrm{pKa} \approx 13)$ (Table 3.2).

Up to now, the only one natural product presenting a 3 -amino- $1,2,4$-oxadiazine scaffold is alchornedine, a molecule with anti-parasite effects isolated from the leaves
of Alchornea glandulosa. Since alchornedine has never been synthesized and its structure was deducted by NMR analysis (Figure 4.9), we synthesized this alkaloid for the first time. However, the results shown that the structure named alchornedine described in the literature is not correct. We proposed alchornedine presented a five-membered 2 -amino- $N$-hydroxy-imidazole ring rather than six-membered 3-amino-1,2,4-oxadiazine ring (Scheme 4.4). The synthesis of this scaffold is currently under progress.

During the course of synthesizing 1,2,4-oxadiazine, several methods were tried to introduce the N-O moiety, one of which was inserting NHPI at the $\alpha$ position of styrene derivatives, followed by oxidation at $\beta$ postion (Appendix VIII). In presence of Triton X-100, the reaction could be run in water, meeting the principles of green chemistry. This method has been published in Tetrahedron Letters (Tang, S.-Q.; Wang, A.-P.; Schmitt, M.; Bihel, F. Dioxygenation of Styrenes with Molecular Oxygen in Water. Tetrahedron Lett. 2018. https://doi.org/10.1016/j.tetlet.2018.03.009).

Benzodiazepines have been known since 1960s and near 20 molecules are used in clinic as anxiolytics, muscle relaxants or hypnotics. Most of these benzodiazepines belong to 1,4- benzodiazepines except Tofizopam which presents a 1,2-benzodiazepine scaffold and is used for the treatments of atypical anxiety and alcoholism. The seven-membered ring in benzodiazepine is particularly interesting since it endowed the molecule a specific three-dimensional geometry. During the development and characterization of new N-O heterocycles, 2,3-benzoxazepin-4-one was also synthesized as a bioisostere of 2,3-benzodiazepin-4-one. Although the synthesis of 2,3-benzoxazepin-4-one is extremely difficult, an effective synthetic approach was established after numerous methods were tried (Scheme 6.23). The structure of this first 2,3-benzoxazepin-4-one was confirmed by X-ray crystallography (Figure 6.10) and the research on the physicochemical properties is under progress.

During the synthesis of 2,3-benzoxazepin-4-one, several attempts were also tried to synthesize 1-benzyl-2,3-benzoxazepin-4-one. Although none of these synthetic approaches worked well till now, a novel catalyst, named POxAP, was developed. The
application of POxAP in Fukuyama CCR provided a novel synthetic approach towards isoprekinamycin, a natural product with anti-cancer activities (Appendix IX). This method has been published in Tetrahedron Letters (Tang, S. Q.; Bricard, J.; Schmitt, M.; Bihel, F. Fukuyama Cross-Coupling Approach to Isoprekinamycin: Discovery of the Highly Active and Bench-Stable Palladium Precatalyst POxAP. Org. Lett. 2019, 21 (3), 844-848. https://doi.org/10.1021/acs.orglett.9b00031.).

# VIII. Experiment section and NMR spectra 

## VIII. Experiment section and NMR spectra

## VIIIA. General information

All commercial reagents were used without additional purification. Analytical TLC was performed using silica gel plates Merck $60 \mathrm{~F}_{254}$ and plates were visualized by exposure to ultraviolet light ( 254 nm ). Compounds were purified on silica gel Merck 60 (particle size $0.040-0.063 \mathrm{~nm}$ ).
${ }^{1} \mathrm{H}$ and ${ }^{13} \mathrm{C}$ NMR spectra were recorded on Bruker Avance Spectrometer operating at 400 or 500 MHz and 100 or 125 MHz , respectively. All chemical shift values $\delta$ and coupling constants $J$ are quoted in ppm and in Hz , respectively, multiplicity ( $\mathrm{s}=$ singulet, $\mathrm{d}=$ doublet, $\mathrm{t}=$ triplet, $\mathrm{q}=$ quartet, quin $=$ quintet, $\mathrm{sex}=$ sextet $\mathrm{m}=$ multiplet, br= broad).

Analytical RP-HPLC-MS was performed using a LC 1200 Agilent with quadrupole-time-of-flight (QTOF) (Agilent Accurate Mass QToF 6520) with a Zorbax Agilent C18-column (C18, $50 \mathrm{~mm} \times 2.1 \mathrm{~mm} ; 1.8 \mu \mathrm{~m}$ ) using the following parameters: 1) The solvent system: A $(0.05 \%$ of formic acid in acetonitrile) and $B(0.05 \%$ of formic acid in $\mathrm{H}_{2} \mathrm{O}$ ); 2) A linear gradient: $\mathrm{t}=0 \mathrm{~min}, 98 \% \mathrm{~B} ; \mathrm{t}=8 \mathrm{~min}, 0 \% \mathrm{~B} ; \mathrm{t}=12.5$ $\min , 0 \% \mathrm{~B} ; \mathrm{t}=12.6 \mathrm{~min}, 98 \% \mathrm{~B} ; \mathrm{t}=13 \mathrm{~min}, 98 \% \mathrm{~B} ; 3$ ) Flow rate of $0.5 \mathrm{~mL} / \mathrm{min} ; 4$ ) Column temperature: $35^{\circ} \mathrm{C}$; 5) DAD scan from 190 nm to 700 nm ; 6) Ionization mode : $\mathrm{ESI}^{+}$or ESI'.

HPLC were performed using a Dionex UltiMate 3000 using the following parameters: Flow rate of $0.5 \mathrm{~mL} / \mathrm{min}$, column temperature: $30^{\circ} \mathrm{C}$, solvent system: $\mathrm{A}(\mathrm{MeOH})$ and B $(0.05 \%$ of TFA in H2O), $t=0 \mathrm{~min}$ to $1 \mathrm{~min}: 50$ to $60 \%$ of B , then $\mathrm{t}=1 \mathrm{~min}$ to $\mathrm{t}=10$ $\min : 60$ to $100 \%$ of B and $\mathrm{t}=10 \mathrm{~min}$ to $\mathrm{t}=15 \mathrm{~min}: 100 \%$ of B .

The single-crystal structure analysis was performed using X-ray diffraction with a Thermo Fisher ESCALAB 250 diffractometer.

## VIIIB. Physicochemical studies of 1,2,4-oxadiazines

## VIIIB1. Measurement of $\mathbf{p} K_{\mathbf{a}}{ }^{132}$

m mg compound was dissolved in $\mathrm{v} \mathrm{mL} \mathrm{H}_{2} \mathrm{O}$ containing $60 \% \mathrm{MeOH}, 0.005 \mathrm{M} \mathrm{HCl}$ and NaCl in sufficient quantity to adjust the ionic strength to 0.1 M .1 mL forementioned solution was transfered by a micropipette into a 2 mL glass tube and titrated by the solution of $\mathrm{NaOH}(0.1 \mathrm{M})$ in $\mathrm{MeOH} / \mathrm{H}_{2} \mathrm{O}(60 \% / 40 \%)$. $\mathrm{p} K_{\mathrm{a}}$ in $60 \%$ $\mathrm{MeOH}\left(\mathrm{p} K_{\mathrm{a}}\right.$ меОН $60 \%$ ) was determined based on $\mathrm{pH}-\mathrm{V}_{\mathrm{NaOH}}$ titration curve and calculated by HYPERQUAD program. Aqueous $\mathrm{p} K_{\mathrm{a}}\left(\mathrm{p} K_{\mathrm{a}}\right.$ aq) is estimated by the following equation: $\mathrm{p} K_{\mathrm{a}}$ МеОН $60 \%=0.97 \times \mathrm{p} K_{\mathrm{a} \text { аq }}-0.43$.

## VIIIB2. Measurement of $\log D^{174}$

1. Preparation of stock, reference and tested solutions:
(1) PBS buffer: 150 mM NaCl and $100 \mathrm{mM} \mathrm{Na}_{2} \mathrm{HPO}_{4}$ in $\mathrm{H}_{2} \mathrm{O}$
(2) Stock solution $(10 \mathrm{mM})$ : tested compound was dissolved in DMSO and conserved at $4{ }^{\circ} \mathrm{C}$.
(3) Reference solution $(100 \mu \mathrm{M}): 10 \mu \mathrm{~L}$ stock solution diluted with $990 \mu \mathrm{~L}$ $\mathrm{MeCN} / \mathrm{H}_{2} \mathrm{O}$.
(4) Tested solution $(100 \mu \mathrm{M})$ : (1) $10 \mu \mathrm{~L}$ stock solution $+20 \mu \mathrm{~L}$ octanol $+970 \mu \mathrm{~L}$ PBS;
(2) $10 \mu \mathrm{~L}$ stock solution $+200 \mu \mathrm{~L}$ octanol $+790 \mu \mathrm{~L}$ PBS; (3) $10 \mu \mathrm{~L}$ stock solution + $660 \mu \mathrm{~L}$ octanol $+330 \mu \mathrm{~L}$ PBS. The three mixtures were mixed on a rotary agitator at $20^{\circ} \mathrm{C}$ for 1 h and centrifuged at $10,000 \mathrm{~g}$ for 5 min . The aqueous phase was collected for analysis.
2. The reference solution and aqueous phases of tested solutions were analyzed by HLPC equipped with a C18 column (kinetex $2.6 \mu \mathrm{C} 18$ 100A 50 x 4.6 mm ) an automatic injector and a diode array detector. The inject volume was $10 \mu \mathrm{~L}$ and column temperature was $30^{\circ} \mathrm{C}$. Detected wave lenghth was 280 nm . The solvent system: A $\left(0.05 \%\right.$ of TFA in $\left.\mathrm{H}_{2} \mathrm{O}\right)$ and $\mathrm{B}(\mathrm{MeCN})$, flow rate $2 \mathrm{~mL} / \mathrm{min}, \mathrm{t}=0 \mathrm{~min}$ to
$0.1 \mathrm{~min}: 5 \% \mathrm{~B}$, then $\mathrm{t}=2.6 \mathrm{~min}$ to $\mathrm{t}=3.1 \mathrm{~min}: 95 \% \mathrm{~B}$ and $\mathrm{t}=3.3 \mathrm{~min}$ to $\mathrm{t}=6 \mathrm{~min}: 5 \%$ of B. The measurements were first carried out in octanol/PBS with three different proportions. Then, the repeated measurement was carried out with best adapted octanol/PBS proportion. Log D was calculated by area under curve of the reference solution and tested solution.
3. Due to $\log \mathrm{D}$ of DMSO in octanol $/ \mathrm{H}_{2} \mathrm{O}$ is -1.35 and $10 \mu \mathrm{~L}$ DMSO was added in each tube, we assume $9.6 \mu \mathrm{~L}$ DMSO is in $\mathrm{H}_{2} \mathrm{O}$ and $0.4 \mu \mathrm{~L}$ is in octanol.
$\operatorname{LogD}$ of the tested compounds can be calculated with the following equation:
$\log \mathrm{D}=\log \left(\left(\mathrm{V}_{\text {ref }} \times \mathrm{A}_{\text {ref }}-\mathrm{V}_{\mathrm{aq}} \times \mathrm{A}_{\mathrm{aq}}\right) /\left(\mathrm{V}_{\text {oct }} \times \mathrm{A}_{\mathrm{aq}}\right)\right)$
$\mathrm{V}_{\text {ref: }}$ : volume of reference solution $=1 \mathrm{~mL}$
$\mathrm{A}_{\text {ref: }}$ area under curve of the reference solution
$\mathrm{V}_{\mathrm{aq}}$ : Volume of the aqueous phase ( $979.6 \mu \mathrm{~L} ; 799.6 \mu \mathrm{~L} ; 339.6 \mu \mathrm{~L}$ )
$\mathrm{A}_{\mathrm{aq}}$ : area under curve of the tested solution
$\mathrm{V}_{\text {oct: }}$ volume of the organic phase ( $20.4 \mu \mathrm{~L} ; 200.4 \mu \mathrm{~L} ; 660.4 \mu \mathrm{~L}$ )

## VIIIC. Synthetic procedures and analytic data

## VIIIC1 Typical procedures

1. Typical procedures 1 (TP1)


To a solution of $N$-Boc amino acid (1 eq.) in DCM was slowly added CDI (1.2 1.3 eq.) and stirred at rt for 30 minutes until $\mathrm{CO}_{2}$ evolution ceased. $N, O$-dimethylhydroxylamine hydrochloride ( $1.2 \sim 1.3$ eq.) was then added to the reaction mixture and stirred at rt for 16 h . The mixture was quenched with water and extrated with DCM thrice. The combined organic phases were washed brine, dried over anhydrous $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and filtered. The filtrate was concentrated in vacuo to afford the product.
2. Typical procedures 2 (TP2)


Grignard reagent ( $1.4 \sim 4$ eq.) in THF was added dropwise to a solution of Weinreb amide (1 eq.) in THF or $\mathrm{Et}_{2} \mathrm{O}$ at $-10^{\circ} \mathrm{C}$ under Ar. After stirred at $-10^{\circ} \mathrm{C}$ overnight, the reaction mixture was poured slowly into saturated $\mathrm{NH}_{4} \mathrm{Cl}$ aqueous solution at $0{ }^{\circ} \mathrm{C}$ under stirring. After 10min, the resulting mixture was extracted with EtOAc thrice. The combined organic phases were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and filtered. The filtrate was concentrated in vacuo and purified by silica gel chromatography to afford the product.
3. Typical procedures 3 (TP3)


To a solution of ketone (1 eq.) in THF or MeOH was slowly added $\mathrm{NaBH}_{4}$ (2 $\sim 4$ eq.) at $0^{\circ} \mathrm{C}$. The mixture was then stirred at rt for $1 \sim 3 \mathrm{~h}$. After completion, the reaction mixture was poured slowly into saturated $\mathrm{NH}_{4} \mathrm{Cl}$ aqueous solution at $0{ }^{\circ} \mathrm{C}$ under stirring. After 10 min , the resulting mixture was extracted with EtOAc thrice (if MeOH was used as solvent, removed under reduced pressure before extraction). The combined organic phases were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and filtered. The filtrate was concentrated in vacuo to afford the product.
4. Typical procedures 4 (TP4)


After degassed and back filled with Ar thrice, a solution of alcohol (1 eq.), NHPI (1.3 $\sim 1.5$ eq.) and $\mathrm{PPh}_{3}$ ( $1.3 \sim 1.8$ eq.) in THF was cooled to the given temperature. Then, DEAD ( $1.3 \sim 1.8$ eq.) was added dropwise to the solution and stirred at the given temperature overnight. The reaction mixture quenched by the addition of water and extracted with EtOAc thrice. The combined organic phases were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and filtered. The filtrate was concentrated and purified by silica gel chromatography to afford the product.
5. Typical procedures 5 (TP5)


Hydrazine hydrate (15 eq.) was added dropwise to a solution of $N$-alkoxyl phthalimide (1 eq.) in EtOH and stirred at rt for the given time. The reaction mixture was concentrated in vacuo, and purified by reverse chromatography $\left(\mathrm{MeOH} / \mathrm{H}_{2} \mathrm{O}\right)$ to
afford the product.
6. Typical procedures 6 (TP6)


A solution of Boc amino alkoxyamine (1 eq.) in $\mathrm{HCl} /$ dioxane ( 4 M ) was stirred at rt for 16 h . The reaction was concentrated in vacuo and dried under reduced pressure overnight to afford the product.
7. Typical procedures 7 (TP7)


TEA (4 eq.) was slowly added to a solution of amino alkoxyamine dihydrochloride (1 eq.) in MeCN at $0^{\circ} \mathrm{C}$ and stirred for 5 min . Then a solution of $\operatorname{BrCN}(1.1 \sim 1.2 \mathrm{eq}$.) in MeCN was slowly added at $0^{\circ} \mathrm{C}$. After stirring at $0^{\circ} \mathrm{C}$ for 30 min , the mixture was stirred at rt overnight. The crude was concentrated in vacuo and purified by reverse phase chromatography $\left(\mathrm{ACN} / \mathrm{H}_{2} \mathrm{O}\right)$ to afford the product.

## 8. Typical procedures 8 (TP8)



To an oven dried microwave tube prefilled with Ar was added NaOEt (3 or 4 eq.), anhydrous ethanol and sonicated until the suspension became clear. Ethyl acetoacetate (2 eq.) was then added and stirred at rt for 2 min . After the addition of $\mathrm{CuBr}(0.1 \mathrm{eq}$.) and 2-bromobenzoic acid (1 eq.), the reaction mixture was stirred under Ar at $80^{\circ} \mathrm{C}$ for the given time. The reaction was concentrated in vacuo and water was added. The
aqueous mixture was washed with EtOAc , acidfied by $\mathrm{HCl}_{\mathrm{aq}}(2 \mathrm{M})$ until $\mathrm{pH} \sim 3$ and extracted by EtOAc thrice, the organic phases were washed with brine, dried over anhydrous $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and filtered. The filterate was concentrated in vacuo to afford the product.

## VIIIC2 Preparation and and analytic data

Preparation of 6-(3,4-dichlorophenyl)-5,6-dihydro-4H-1,2,4-oxadiazin-3-amine (10a) and 3-amino-6-(3,4-dichlorophenyl)-5,6-dihydro-4H-1,2,4-oxadiazine-4carbonitrile (30)


10a


30

According to typical procedure TP7, the reaction was performed with 26a (1 eq., 20 $\mathrm{mg}, 0.068 \mathrm{mmol}$ ) in $\mathrm{MeCN}(1.43 \mathrm{~mL})$, TEA ( $4 \mathrm{eq} ., 0.0378 \mathrm{~mL}, 0.272 \mathrm{mmol}$ ) and a solution of $\mathrm{BrCN}(1.2$ eq., $8.65 \mathrm{mg}, 0.0816 \mathrm{mmol})$ in $\mathrm{MeCN}(0.286 \mathrm{~mL})$, affording $\mathbf{1 0 a}(13.6 \mathrm{mg}, 81 \%)$ and $\mathbf{3 0}$ as white solids ( $3.2 \mathrm{mg}, 17 \%$ ).
${ }^{1} \mathrm{H}$ NMR ( 400 MHz , DMSO- $d^{6}$ ) of 10a: $\delta 7.66-7.57(\mathrm{~m}, 2 \mathrm{H}), 7.35(\mathrm{dd}, J=8.3,2.0$ Hz, 1H), 6.16 (s, 1H), 4.46 (s, 2H), 4.42 (dd, $J=9.0,3.1 \mathrm{~Hz}, 1 \mathrm{H}$ ), 3.45 (dd, $J=11.4$, $3.2 \mathrm{~Hz}, 1 \mathrm{H}), 3.15(\mathrm{dd}, J=11.4,9.0 \mathrm{~Hz}, 1 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( 101 MHz, DMSO- $d^{6}$ ) of 10a: $\delta 154.08,140.44,130.89,130.44,130.25$, 128.70, 126.98, 71.97, 45.30.
${ }^{1} \mathrm{H}$ NMR ( 400 MHz, DMSO- $d^{6}$ ) of 30: $\delta 7.71-7.65(\mathrm{~m}, 2 \mathrm{H}), 7.42(\mathrm{dd}, J=8.4,2.0$ $\mathrm{Hz}, 1 \mathrm{H}), 5.78(\mathrm{~s}, 2 \mathrm{H}), 4.82(\mathrm{dd}, J=9.4,3.1 \mathrm{~Hz}, 1 \mathrm{H}), 4.10(\mathrm{dd}, J=11.0,3.2 \mathrm{~Hz}, 1 \mathrm{H})$, 3.97 (dd, $J=11.0,9.5 \mathrm{~Hz}, 1 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR (101 MHz, DMSO- $d^{6}$ ) of 30: $\delta 147.23,137.23,131.30,131.21,130.74$, 129.08, 127.30, 109.65, 72.06, 50.65.

## oxadiazin-4-amine (10b)



10b
According to typical procedure TP7, The reaction was performed with 26b (1 eq., 20 $\mathrm{mg}, 0.0754 \mathrm{mmol})$ in $\mathrm{MeCN}(1.5 \mathrm{~mL})$, TEA ( 4 eq., $0.0419 \mathrm{~mL}, 0.302 \mathrm{mmol}$ ) and a solution of BrCN ( 1.2 eq., $9.59 \mathrm{mg}, 0.0905 \mathrm{mmol}$ ) in $\mathrm{MeCN}(0.3 \mathrm{~mL})$, affording 10b as a white solid ( $15.4 \mathrm{mg}, 94 \%$ ).
${ }^{1} \mathrm{H}$ NMR (400 MHz, DMSO-d $\mathrm{d}^{6}$ ): $\delta 7.36-7.21(\mathrm{~m}, 5 \mathrm{H}), 4.99(\mathrm{~d}, J=4.4 \mathrm{~Hz}, 1 \mathrm{H}), 4.81$ (s, 2H), $3.67(\mathrm{dt}, J=9.6,5.0 \mathrm{~Hz}, 1 \mathrm{H}), 3.33-3.25(\mathrm{~m}, 2 \mathrm{H}), 1.69-1.49(\mathrm{~m}, 3 \mathrm{H}), 1.30$ - 1.15 (m, 1H).
${ }^{13} \mathrm{C}$ NMR ( 101 MHz, DMSO- $d^{6}$ ): $\delta 155.83,139.18,128.43,127.67,127.62,75.92$, 58.47, 47.87, 27.53, 23.00.

Preparation of (5R,6S)-5-isopropyl-6-phenyl-5,6-dihydro-4H-1,2,4-oxadiazin-3amine (10c)


10c
According to typical procedure TP7, the reaction was performed with a solution of 26c ( 1 eq., $40 \mathrm{mg}, 0.15 \mathrm{mmol}$ ) in $\mathrm{MeCN}(3.48 \mathrm{~mL}$ ), TEA (4 eq., $0.0832 \mathrm{~mL}, 0.599$ $\mathrm{mmol})$ and a solution of $\mathrm{BrCN}(1.1 \mathrm{eq} ., 17.4 \mathrm{mg}, 0.165 \mathrm{mmol})$ in $\mathrm{MeCN}(0.174 \mathrm{~mL})$, affording 10c as a white solid ( $24 \mathrm{mg}, 73 \%$ ).
${ }^{1} \mathrm{H}$ NMR ( 400 MHz, DMSO- $d^{6}$ ): $\delta 7.38-7.30(\mathrm{~m}, 5 \mathrm{H}), 5.86(\mathrm{~s}, 1 \mathrm{H}), 4.44(\mathrm{~s}, 2 \mathrm{H})$, $4.09(\mathrm{~d}, \mathrm{~J}=8.2 \mathrm{~Hz}, 1 \mathrm{H}), 3.34-3.31(\mathrm{~m}, 1 \mathrm{H}), 1.42(\mathrm{pd}, \mathrm{J}=6.9,2.7 \mathrm{~Hz}, 1 \mathrm{H}), 0.86(\mathrm{~d}, \mathrm{~J}$ $=7.1 \mathrm{~Hz}, 3 \mathrm{H}), 0.79(\mathrm{~d}, \mathrm{~J}=6.8 \mathrm{~Hz}, 3 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR (101 MHz, DMSO- $d^{6}$ ): $\delta 154.95,138.83,128.21,127.99,127.75,77.02$,

## Preparation of 6-(prop-1-en-2-yl)-5,6-dihydro-4H-1,2,4-oxadiazin-3-amine (10d)

 and 6-(prop-1-en-2-yl)-5,6-dihydro-2H-1,2,4-oxadiazin-3-amine (44)
10d

44

According to typical procedure TP7, The reaction was performed with a sloution of 26d ( 1 eq., $152 \mathrm{mg}, 0.804 \mathrm{mmol}$ ) in $\mathrm{MeCN}(18.5 \mathrm{~mL}$ ), TEA ( 4 eq., $0.447 \mathrm{~mL}, 3.22$ mmol ) and a solution of $\mathrm{BrCN}(1.1 \mathrm{eq} ., 93.7 \mathrm{mg}, 0.884 \mathrm{mmol})$ in $\mathrm{MeCN}(1 \mathrm{~mL})$, affording 10 d ( $91 \mathrm{mg}, 80 \%$ ) and 44 as white solids ( $10 \mathrm{mg}, 9 \%$ ).
${ }^{1} \mathrm{H}$ NMR ( 400 MHz, DMSO- $d^{6}$ ) of 10d: $\delta 6.07(\mathrm{~s}, 1 \mathrm{H}), 4.94(\mathrm{dt}, J=2.2,1.1 \mathrm{~Hz}, 1 \mathrm{H})$, $4.89(\mathrm{t}, J=1.9 \mathrm{~Hz}, 1 \mathrm{H}), 4.48(\mathrm{~s}, 2 \mathrm{H}), 3.74(\mathrm{dd}, J=9.4,3.0 \mathrm{~Hz}, 1 \mathrm{H}), 3.28(\mathrm{dd}, J=11.2$, $3.1 \mathrm{~Hz}, 1 \mathrm{H}), 3.02(\mathrm{dd}, J=11.2,9.5 \mathrm{~Hz}, 1 \mathrm{H}), 1.70(\mathrm{~s}, 3 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR (101 MHz, DMSO- $d^{6}$ ) of 10d: $\delta$ 154.08, 142.36, 111.95, 74.27, 19.01.
${ }^{1} \mathrm{H}$ NMR ( 400 MHz, DMSO- $\mathrm{d}^{6}$ ) of 44: $\delta 8.83(\mathrm{~s}, 1 \mathrm{H}), 7.38(\mathrm{~s}, 2 \mathrm{H}), 5.09-5.07(\mathrm{~m}$, $1 \mathrm{H}), 5.05(\mathrm{q}, J=1.2 \mathrm{~Hz}, 1 \mathrm{H}), 4.36(\mathrm{dd}, J=9.0,3.3 \mathrm{~Hz}, 1 \mathrm{H}), 3.50(\mathrm{dd}, J=12.6,3.5$ $\mathrm{Hz}, 1 \mathrm{H}), 3.31(\mathrm{dd}, J=12.6,9.1 \mathrm{~Hz}, 1 \mathrm{H}), 1.75(\mathrm{~s}, 3 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR (101 MHz, DMSO- $d^{6}$ ) of 44: $\delta 154.90,139.56,115.17,77.90,42.51,19.24$.

Preparation of (9H-fluoren-9-yl)methyl (2-(methoxy(methyl)amino)-2-oxoethyl) carbamate (13)


CDI ( 1.2 eq., $2.62 \mathrm{~g}, 16.1 \mathrm{mmol}$ ) was slowly added to a solution of $N$-Fmoc glycine ( 1 eq., $4 \mathrm{~g}, 13.5 \mathrm{mmol})$ in $\mathrm{DCM}(30 \mathrm{~mL})$ and the resulting mixture was stirred at rt for 30 minutes until $\mathrm{CO}_{2}$ evolution ceased. $\mathrm{N}, \mathrm{O}$-dimethylhydroxylamine hydrochloride (1.2
eq., $1.57 \mathrm{~g}, 16.1 \mathrm{mmol}$ ) was then added and stirred at rt for 16 h . The reaction mixture was concentrated in vacuo, diluted with water and extracted with EtOAc thrice. The combined organic phase was washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, and concentrated in vacuo. The crude was purified by silica gel chromatography (heptane:EtOAc $=2: 1$ to $1: 1$ ) to afford $\mathbf{1 3}$ as a colorless oil $(3.7 \mathrm{~g}, 81 \%)$.

Rf: 0.5 (EtOAc:heptane = 3:1).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.76$ (d, $J=7.5 \mathrm{~Hz}, 2 \mathrm{H}$ ), 7.62 (d, $J=7.4 \mathrm{~Hz}, 2 \mathrm{H}$ ), 7.40 (t, $J=7.3 \mathrm{~Hz}, 2 \mathrm{H}), 7.32(\mathrm{td}, J=7.4,1.1 \mathrm{~Hz}, 2 \mathrm{H}), 5.64(\mathrm{~s}, 1 \mathrm{H}), 4.39(\mathrm{~d}, J=7.2 \mathrm{~Hz}$, $2 \mathrm{H}), 4.25(\mathrm{t}, J=7.2 \mathrm{~Hz}, 1 \mathrm{H}), 4.17(\mathrm{~d}, J=4.4 \mathrm{~Hz}, 2 \mathrm{H}), 3.72(\mathrm{~s}, 3 \mathrm{H}), 3.22(\mathrm{~s}, 3 \mathrm{H})$. These data are consistent with the previously reported characterization. ${ }^{175}$

## Preparation of tert-butyl (2-(methoxy(methyl)amino)-2-oxoethyl)carbamate (14a)



The reaction was performed with $N$-Boc glycine ( $1 \mathrm{eq} ., 4 \mathrm{~g}, 22.8 \mathrm{mmol}$ ), CDI ( 1.2 eq ., $4.44 \mathrm{~g}, 27.4 \mathrm{mmol}$ ) and $\mathrm{N}, \mathrm{O}$-dimethylhydroxylamine hydrochloride ( $1.2 \mathrm{eq} ., 2.67 \mathrm{~g}$, $27.4 \mathrm{mmol})$ in DCM ( 45 mL ) according to typical procedure TP1, , affording 14a as a white solid ( $4.9 \mathrm{~g}, 99 \%$ ).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 5.26$ (s, 1H), 4.07 (d, $J=3.8 \mathrm{~Hz}, 2 \mathrm{H}$ ), $3.70(\mathrm{~s}, 3 \mathrm{H})$, 3.19 (s, 3H), 1.45 (s, 9H).

These data are consistent with the previously reported characterization. ${ }^{176}$

Preparation of (S)-tert-butyl 2-(methoxy(methyl)carbamoyl)pyrrolidine-1carboxylate (14b)


14b
The reaction was performed with 33 ( $1 \mathrm{eq} ., 3 \mathrm{~g}, 13.9 \mathrm{mmol}$ ), CDI ( $1.2 \mathrm{eq} ., 2.71 \mathrm{~g}$, 16.7 mmol ) and $N, O$-dimethylhydroxylamine hydrochloride ( 1.2 eq., $1.63 \mathrm{~g}, 16.7$ mmol ) in DCM ( 28 mL ) according to typical procedure TP1, affording $\mathbf{1 4 b}$ as a colorless oil ( $3.4 \mathrm{~g}, 94 \%$ ).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$, mixture of rotamers): $\delta 4.63(\mathrm{~m}, 1 \mathrm{H}), 3.76(\mathrm{~s}, 1.4 \mathrm{H}), 3.69$ $(\mathrm{s}, 1.6 \mathrm{H}), 3.60-3.34(\mathrm{~m}, 2 \mathrm{H}), 3.17(\mathrm{~s}, 3 \mathrm{H}), 2.25-2.07(\mathrm{~m}, 1 \mathrm{H}), 1.99-1.79(\mathrm{~m}, 3 \mathrm{H})$, $1.43(\mathrm{~s}, 4.7 \mathrm{H}), 1.39(\mathrm{~s}, 4.3 \mathrm{H})$.

These data are consistent with the previously reported characterization. ${ }^{124}$

## Preparation of (S)-tert-butyl (1-(methoxy(methyl)amino)-3-methyl-1-oxobutan-2-

 yl)carbamate (14c)

14 c
The reaction was performed with $N$-Boc L-valine ( $1 \mathrm{eq} ., 3 \mathrm{~g}, 13.8 \mathrm{mmol}$ ), CDI ( 1.2 eq., $2.69 \mathrm{~g}, 16.6 \mathrm{mmol}$ ) and $N, O$-dimethylhydroxylamine hydrochloride ( 1.2 eq., 1.62 $\mathrm{g}, 16.6 \mathrm{mmol})$ in DCM $(27.9 \mathrm{~mL})$ according to TP1, affording $\mathbf{1 4 c}$ as a colorless oil ( $3.37 \mathrm{~g}, 94 \%$ ).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 5.12(\mathrm{~d}, J=9.9 \mathrm{~Hz}, 1 \mathrm{H}), 4.55(\mathrm{t}, J=8.0 \mathrm{~Hz}, 1 \mathrm{H}), 3.74$ (s, 3H), $3.19(\mathrm{~s}, 3 \mathrm{H}), 1.96(\mathrm{dq}, J=13.4,6.7 \mathrm{~Hz}, 1 \mathrm{H}), 1.41(\mathrm{~s}, 9 \mathrm{H}), 0.93(\mathrm{~d}, J=6.8 \mathrm{~Hz}$, $3 \mathrm{H}), 0.88(\mathrm{~d}, J=6.8 \mathrm{~Hz}, 3 \mathrm{H})$.

These data are consistent with the previously reported characterization. ${ }^{177}$


15
To a flame-dried 25 mL round bottom flask was charged activated Mg ( 1.5 eq., 0.365 $\mathrm{g}, 15 \mathrm{mmol}$ ) and anhydrous THF ( 10 mL ). The suspension was then degassed and back filled with Ar thrice, followed by the additon of 1,2-dibromoethane (3 \%, 0.025 $\mathrm{mL}, 0.3 \mathrm{mmol}$ ). After 5 min , a solution of 1-bromo-3,4-dichlorobenzene ( $1 \mathrm{eq} ., 2.26 \mathrm{~g}$, 10 mmol ) in anhydrous THF ( 10 mL ) was slowly added to the suspension of Mg and stirred at rt for 3 h to afford a brown solution of $\mathbf{1 5}$ in 20 mL THF ( $0.34 \mathrm{M}, 6.85 \mathrm{mmol}$, 69\%).

The obtained Grignard reagent was titrated by the following method ${ }^{109}$ : A 20 mL microwave tube fitted with a magnetic stirring bar was charged with menthol (42.8 $\mathrm{mg}, 0.274 \mathrm{mmol}$ ) and $1,10-\mathrm{phenanthroline} \mathrm{( } 6 \mathrm{mg}, 0.03 \mathrm{mmol}$ ) before being capped with a rubber septum and flushed with dry Ar. Dry THF ( 3 mL ) was introduced, and the resulting solution was stirred at rt for 2 min . The Grignard solution was then added dropwise by the syringe until a distinct burgundy color persisted for longer than one minute. $[\mathrm{RMgX}]$ in $\mathrm{M}=\mathrm{mmol}$ of menthol/volume of RMgX in mL

In this reaction, 0.8 mL Grignard reagent was consumed for titration.

## Preparation of (9H-fluoren-9-yl)methyl (2-(3,4-dichlorophenyl)-2-oxoethyl) carbamate (16)



16
The reaction was performed with $\mathbf{1 3}$ ( $1 \mathrm{eq} ., 0.5 \mathrm{~g}, 1.47 \mathrm{mmol}$ ) in THF ( 8 mL ) and a THF solution of 15 ( 2 eq., $0.34 \mathrm{M}, 8.64 \mathrm{~mL}, 2.94 \mathrm{mmol}$ ) according to typical procedure TP2. The crude was purified by silica gel chromatography (heptane:EtOAc
$=5: 1$ to $4: 1$ ) to afford 16 as a white solid ( $0.55 \mathrm{~g}, 88 \%$ ).
Rf: 0.3 (heptane: $E t O A c=3: 1$ ).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 8.06(\mathrm{~d}, J=2.0 \mathrm{~Hz}, 1 \mathrm{H}), 7.81-7.75(\mathrm{~m}, 3 \mathrm{H}), 7.65-$ $7.59(\mathrm{~m}, 3 \mathrm{H}), 7.41(\mathrm{t}, J=7.3 \mathrm{~Hz}, 2 \mathrm{H}), 7.33(\mathrm{t}, J=7.3 \mathrm{~Hz}, 2 \mathrm{H}), 5.75(\mathrm{~s}, 1 \mathrm{H}), 4.69(\mathrm{~d}, J$ $=4.6 \mathrm{~Hz}, 2 \mathrm{H}), 4.44(\mathrm{~d}, J=7.1 \mathrm{~Hz}, 2 \mathrm{H}), 4.26(\mathrm{t}, J=7.0 \mathrm{~Hz}, 1 \mathrm{H})$.

These data are consistent with the previously reported characterization. ${ }^{173}$

Preparation of tert-butyl (2-(3,4-dichlorophenyl)-2-oxoethyl)carbamate (17a)


17a
The reaction was performed with $\mathbf{1 4 a}$ ( 1 eq., $0.4 \mathrm{~g}, 1.83 \mathrm{mmol}$ ) in THF ( 9 mL ) and a THF solution of $\mathbf{1 5}$ ( $2 \mathrm{eq} ., 0.5 \mathrm{M}, 7.33 \mathrm{~mL}, 3.67 \mathrm{mmol}$ ) according to typical procedure TP2. The crude was purified by silica gel chromatography (heptane:EtOAc $=5: 1$ ) to afford $17 \mathbf{a}$ as a white solid ( $0.48 \mathrm{~g}, 86 \%$ ).

Rf: 0.35 (heptane: $\operatorname{EtOAc}=3: 1$ ).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 8.04(\mathrm{~d}, J=1.9 \mathrm{~Hz}, 1 \mathrm{H}), 7.78-7.74(\mathrm{~m}, 1 \mathrm{H}), 7.58(\mathrm{~d}$, $J=8.4 \mathrm{~Hz}, 1 \mathrm{H}), 5.46(\mathrm{~s}, 1 \mathrm{H}), 4.60(\mathrm{~d}, J=4.6 \mathrm{~Hz}, 2 \mathrm{H}), 1.47(\mathrm{~s}, 9 \mathrm{H})$.

These data are consistent with the previously reported characterization. ${ }^{178}$

## Preparation of (S)-tert-butyl 2-benzoylpyrrolidine-1-carboxylate (17b)



The reaction was performed with $\mathbf{1 4 b}(1 \mathrm{eq} ., 1.5 \mathrm{~g}, 5.81 \mathrm{mmol})$ in $\mathrm{Et}_{2} \mathrm{O}(50 \mathrm{~mL})$ and a THF solution of $\mathrm{PhMgBr}(1.4 \mathrm{eq} ., 1 \mathrm{M}, 8.13 \mathrm{~mL}, 8.13 \mathrm{mmol})$ according to typical procedure TP2. The crude was purified by silica gel chromatography (heptane:EtOAc
$=20: 1$ to $5: 1$ ) to afford $\mathbf{1 7 b}$ as a white solid ( $1.4 \mathrm{~g}, 88 \%$ ).
${ }^{1} \mathrm{H}$ NMR (400 MHz, $\mathrm{CDCl}_{3}$, mixture of rotamers): $\delta 8.02-7.89(\mathrm{~m}, 2 \mathrm{H}), 7.62-7.50$ $(\mathrm{m}, 1 \mathrm{H}), 7.45(\mathrm{~m}, 2 \mathrm{H}), 5.32(\mathrm{dd}, J=9.3,2.9 \mathrm{~Hz}, 0.35 \mathrm{H}), 5.18(\mathrm{dd}, J=8.7,3.7$ $\mathrm{Hz}, 0.55 \mathrm{H}), 3.57(\mathrm{~m}, 2 \mathrm{H}), 2.31(\mathrm{~m}, 1 \mathrm{H}), 2.01-1.84(\mathrm{~m}, 3 \mathrm{H}), 1.45(\mathrm{~s}, 3.5 \mathrm{H}), 1.25(\mathrm{~s}$, $5.5 \mathrm{H})$.

Rf: 0.5 (heptane: $\mathrm{EtOAc}=2: 1$ ).
These data are consistent with the previously reported characterization. ${ }^{124}$

## Preparation of (S)-tert-butyl (3-methyl-1-oxo-1-phenylbutan-2-yl)carbamate

 (17c)

17c
The reaction was performed with $\mathbf{1 4 c}(1 \mathrm{eq} ., 2.6 \mathrm{~g}, 9.99 \mathrm{mmol})$ in $\mathrm{Et}_{2} \mathrm{O}(27.9 \mathrm{~mL})$ and a THF solution of PhMgBr ( 3 eq., $1 \mathrm{M}, 30 \mathrm{~mL}, 30 \mathrm{mmol}$ ) according to typical procedure TP2. The crude was purified by silica gel chromatography (heptane:EtOAc $=10: 1)$ to afford $\mathbf{1 7 c}$ as a colorless oil $(2.45 \mathrm{~g}, 88 \%)$.
${ }^{1} \mathrm{H}$ NMR $\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right): \delta 8.00-7.92(\mathrm{~m}, 2 \mathrm{H}), 7.63-7.55(\mathrm{~m}, 1 \mathrm{H}), 7.48(\mathrm{~m}$, $2 \mathrm{H}), 5.43(\mathrm{~d}, J=9.1 \mathrm{~Hz}, 1 \mathrm{H}), 5.23(\mathrm{dd}, J=9.1,4.1 \mathrm{~Hz}, 1 \mathrm{H}), 2.14(\mathrm{~m}, 1 \mathrm{H}), 1.45(\mathrm{~s}$, $9 \mathrm{H}), 1.03(\mathrm{~d}, J=6.8 \mathrm{~Hz}, 3 \mathrm{H}), 0.75(\mathrm{~d}, J=6.8 \mathrm{~Hz}, 3 \mathrm{H})$.

Rf: 0.4 (heptane: $\operatorname{EtOAc}=5: 1$ ).
These data are consistent with the previously reported characterization. ${ }^{179}$

## Preparation of tert-butyl (3-methyl-2-oxobut-3-en-1-yl)carbamate (17d)



17d

The reaction was performed with $\mathbf{1 4 a}(1 \mathrm{eq} ., 2 \mathrm{~g}, 9.16 \mathrm{mmol})$ in THF $(30 \mathrm{~mL})$ and a

THF solution of isopropenylmagnesium bromide ( 4 eq., $0.5 \mathrm{M}, 73.3 \mathrm{~mL}, 36.7 \mathrm{mmol}$ ) according to typical procedure TP2 without further purifucation to afford 17d as a yellow oil ( $1.8 \mathrm{~g}, 99$ \%).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 5.99(\mathrm{~s}, 1 \mathrm{H}), 5.83(\mathrm{q}, J=1.4 \mathrm{~Hz}, 1 \mathrm{H}), 5.36(\mathrm{~s}, 1 \mathrm{H})$, $4.35(\mathrm{~d}, J=4.5 \mathrm{~Hz}, 2 \mathrm{H}), 1.90(\mathrm{t}, J=1.2 \mathrm{~Hz}, 3 \mathrm{H}), 1.44(\mathrm{~s}, 9 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 196.11,155.88,142.47,125.54,79.89,46.74,28.49$, 17.54.

Rf: 0.8 (heptane:EtOAc = 1:1).

Preparation of (9H-fluoren-9-yl)methyl (2-(3,4-dichlorophenyl)-2-hydroxyethyl) carbamate (19)


19
The reaction was performed with $\mathbf{1 6}(1 \mathrm{eq} ., 500 \mathrm{mg}, 1.17 \mathrm{mmol})$ in THF $(10 \mathrm{~mL})$ with $\mathrm{NaBH}_{4}$ (4 eq., $177 \mathrm{mg}, 4.69 \mathrm{mmol}$ ) according to typical procedure $\mathbf{T P} 3$ in 1 h , affording 19 as a white solid ( $496 \mathrm{mg}, 99 \%$ ).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.80-7.74(\mathrm{~m}, 2 \mathrm{H}), 7.60-7.55(\mathrm{~m}, 2 \mathrm{H}), 7.49-7.29$ $(\mathrm{m}, 6 \mathrm{H}), 7.16(\mathrm{~d}, J=7.6 \mathrm{~Hz}, 1 \mathrm{H}), 5.15(\mathrm{~s}, 1 \mathrm{H}), 4.84-4.74(\mathrm{~m}, 1 \mathrm{H}), 4.51-4.40(\mathrm{~m}$, $2 \mathrm{H}), 4.21(\mathrm{t}, J=6.5 \mathrm{~Hz}, 1 \mathrm{H}), 3.57-3.18(\mathrm{~m}, 2 \mathrm{H}), 3.11(\mathrm{~s}, 1 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 155.56,144.46,143.88,141.53,133.16,131.97$, 130.66, 128.07, 127.92, 127.25, 125.36, 125.07, 120.18, 72.82, 67.08, 48.64, 47.40.

Rf: 0.4 (heptane: $\operatorname{EtOAc}=1: 1$ ).

Preparation of tert-butyl (2-(3,4-dichlorophenyl)-2-hydroxyethyl)carbamate (20a)

$20 a$
The reaction was performed with $\mathbf{1 7 a}$ ( $1 \mathrm{eq} ., 500 \mathrm{mg}, 1.64 \mathrm{mmol}$ ) in THF ( 15 mL ) with $\mathrm{NaBH}_{4}$ ( 4 eq., $177 \mathrm{mg}, 4.69 \mathrm{mmol}$ ) according to typical procedure TP3 in 1 h , affording 20a as a white solid ( $498 \mathrm{mg}, 99 \%$ ).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.46(\mathrm{~d}, J=1.9 \mathrm{~Hz}, 1 \mathrm{H}), 7.40(\mathrm{~d}, J=8.3 \mathrm{~Hz}, 1 \mathrm{H}), 7.17$ (dd, $J=8.4,1.8 \mathrm{~Hz}, 1 \mathrm{H}), 4.98(\mathrm{t}, J=5.6 \mathrm{~Hz}, 1 \mathrm{H}), 4.86-4.75(\mathrm{~m}, 1 \mathrm{H}), 3.78(\mathrm{~s}, 1 \mathrm{H})$, 3.49 - 3.13 (m, 2H), 1.43 (s, 9H).
${ }^{13} \mathrm{C}^{\mathrm{NMR}}\left(101 \mathrm{MHz}, \mathrm{CDCl}_{3}\right): \delta 157.44,142.30,132.76,131.71,130.54,128.12$, 125.37, 80.50, 73.17, 48.50, 28.45.

Rf: 0.5 (heptane:EtOAc = 1:1).

Preparation of (S)-tert-butyl 2-((R)-hydroxy(phenyl)methyl)pyrrolidine-1carboxylate (20b)


20b
A solution of DIBAL-H ( 2 eq., $1 \mathrm{M}, 0.145 \mathrm{~mL}, 0.145 \mathrm{mmol}$ ) in THF was added slowly to a solution of $\mathbf{1 7 b}$ in THF $(0.5 \mathrm{~mL})$ under Ar at $0^{\circ} \mathrm{C}$. The mixture was stirred at $0^{\circ} \mathrm{C}$ for 1 h and quenched with water and extracted with EtOAc thrice. The combined organic phases were washed with brine, dried over anhydrous $\mathrm{Na}_{2} \mathrm{SO}_{4}$, and filtered. The filtrate was concentrated in vacuo, then dissolved in 2 mL $\mathrm{EtOAc} / \mathrm{Heptane}$ (1:1) and filtered through a silica gel pad with EtOAc/Heptane (1:1), the filtrate was concentrtated in vacuo to afford $\mathbf{2 0 b}$ as a colorless oil ( 20.1 mg , 100 \%).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.41-7.24(\mathrm{~m}, 5 \mathrm{H}), 5.47(\mathrm{~s}, 0.68 \mathrm{H}), 5.17(\mathrm{~s}, 0.28 \mathrm{H})$,
$4.89(\mathrm{~s}, 0.64 \mathrm{H}), 4.33(\mathrm{~s}, 0.57 \mathrm{H}), 4.03(\mathrm{~s}, 0.34 \mathrm{H}), 3.57(\mathrm{~s}, 0.44 \mathrm{H}), 3.32(\mathrm{~s}, 1 \mathrm{H}), 2.84(\mathrm{~s}$, $0.66 \mathrm{H}), 2.30(\mathrm{~m}, 0.34 \mathrm{H}), 1.94(\mathrm{~m}, 1 \mathrm{H}), 1.79(\mathrm{~m}, 1 \mathrm{H}), 1.54(\mathrm{~s}, 9 \mathrm{H}), 1.25-1.09(\mathrm{~m}$, $1 \mathrm{H})$.

Rf: 0.55 (heptane: $E t O A c=2: 1$ ).
These data are consistent with the previously reported characterization. ${ }^{125}$

## Preparation of tert-butyl ( $(1 R, 2 S)$-1-hydroxy-3-methyl-1-phenylbutan-2-yl) carbamate (20c)



20c
A solution of DIBAL-H ( 3 eq., $1 \mathrm{M}, 0.541 \mathrm{~mL}, 0.541 \mathrm{mmol}$ ) in THF was slowly added to a solution of $\mathbf{1 7 c}(1 \mathrm{eq} ., 50 \mathrm{mg}, 0.18 \mathrm{mmol})$ in THF $(1 \mathrm{~mL})$ under $\operatorname{Ar}$ at $0^{\circ} \mathrm{C}$. After stirred at $0^{\circ} \mathrm{C}$ for 3 h , the mixture was quenched with water and extracted with EtOAc thrice. The combined organic phases were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, and concentrated in vacuo. The crude was purified by reverse phase chromatography $\left(\mathrm{MeOH} / \mathrm{H}_{2} \mathrm{O}\right)$ to afford 20 c as a white solid ( $49 \mathrm{mg}, 97 \%$ ).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.36-7.27(\mathrm{~m}, 5 \mathrm{H}), 4.87(\mathrm{t}, J=4.6 \mathrm{~Hz}, 1 \mathrm{H}), 4.35(\mathrm{~d}$, $J=9.8 \mathrm{~Hz}, 1 \mathrm{H}), 3.84-3.74(\mathrm{~m}, 1 \mathrm{H}), 1.76-1.66(\mathrm{~m}, 1 \mathrm{H}), 1.39(\mathrm{~s}, 9 \mathrm{H}), 1.29(\mathrm{~s}, 1 \mathrm{H})$, $1.04(\mathrm{~d}, J=6.7 \mathrm{~Hz}, 3 \mathrm{H}), 0.89(\mathrm{~d}, J=6.7 \mathrm{~Hz}, 3 \mathrm{H})$.

These data are consistent with the previously reported characterization. ${ }^{127}$

## Preparation of tert-butyl (2-hydroxy-3-methylbut-3-en-1-yl)carbamate (20d)



20d
Trichlorocerium heptahydrate ( $1.6 \mathrm{eq} ., 2.74 \mathrm{~g}, 7.35 \mathrm{mmol}$ ) was added to a solution of $\mathbf{1 7 d}$ ( $1 \mathrm{eq} ., 0.92 \mathrm{~g}, 4.59 \mathrm{mmol}$ ) in $\mathrm{MeOH}(20.8 \mathrm{~mL})$ and stirred at rt until the
suspension became clear. Then, the mixture was cooled to $-70^{\circ} \mathrm{C}$ and $\mathrm{NaBH}_{4}$ (1.3 eq., $225 \mathrm{mg}, 5.97 \mathrm{mmol}$ ) was added portionwise. The reaction was stirred at $-70^{\circ} \mathrm{C}$ for 20 min and quenched by the addition of $\mathrm{H}_{2} \mathrm{O}$ at $-20^{\circ} \mathrm{C}$. After MeOH was removed under reduced pressure, the aqueous suspension was extracted with EtOAc thrice. The combined organic phases were washed with brine, dried over anhydrous $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and concentrated in vacuo. The crude was purified by silica gel chromatography (heptane: $\mathrm{EtOAc}=2: 1$ ) to afford 20d as a colorless oil $(0.82 \mathrm{~g}, 89 \%)$.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 5.04(\mathrm{~s}, 1 \mathrm{H}), 4.92(\mathrm{~s}, 1 \mathrm{H}), 4.14(\mathrm{dt}, J=7.3,3.4 \mathrm{~Hz}$, $1 \mathrm{H}), 3.43-3.34(\mathrm{~m}, 1 \mathrm{H}), 3.17-3.07(\mathrm{~m}, 1 \mathrm{H}), 2.64(\mathrm{~s}, 1 \mathrm{H}), 1.74(\mathrm{~s}, 3 \mathrm{H}), 1.44(\mathrm{~s}, 9 \mathrm{H})$. ${ }^{13} \mathrm{C}$ NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 156.95,145.17,111.82,79.81,75.05,45.21,28.51$, 18.74.

Rf: 0.5 (heptane:EtOAc = 1:1).

## Preparation of (9H-fluoren-9-yl)methyl (2-(3,4-dichlorophenyl)-2-((1,3-

 dioxoisoindolin-2-yl)oxy)ethyl)carbamate (21)

21
According to typical procedure TP4, the reaction was performed by the addition of DEAD (1.3 eq., $71.4 \mu \mathrm{~L}, 0.455 \mathrm{mmol}$ ) into a solution of 19 ( 1 eq., $150 \mathrm{mg}, 0.35$ mmol ), NHPI ( $1.3 \mathrm{eq} ., 74.3 \mathrm{mg}, 0.455 \mathrm{mmol}$ ) and $\mathrm{PPh}_{3}(1.3 \mathrm{eq} ., 119 \mathrm{mg}, 0.455 \mathrm{mmol}$ ) in THF ( 4 mL ) under $\operatorname{Ar}$ at $0^{\circ} \mathrm{C}$ and stirred at $0^{\circ} \mathrm{C}$ overnight. The crude was purified by silica gel chromatography (heptane: $\mathrm{EtOAc}=5: 1$ ) to afford 21 as a white solid (196 $\mathrm{mg}, 98 \%)$.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.82$ (dd, $J=5.5,3.1 \mathrm{~Hz}, 2 \mathrm{H}$ ), 7.76 (dt, $J=5.1,3.4 \mathrm{~Hz}$, $4 \mathrm{H}), 7.65(\mathrm{~d}, J=6.5 \mathrm{~Hz}, 3 \mathrm{H}), 7.47-7.38(\mathrm{~m}, 4 \mathrm{H}), 7.33(\mathrm{t}, J=7.4 \mathrm{~Hz}, 2 \mathrm{H}), 5.97(\mathrm{t}, J$
$=6.2 \mathrm{~Hz}, 1 \mathrm{H}), 5.27(\mathrm{dd}, J=7.5,3.7 \mathrm{~Hz}, 1 \mathrm{H}), 4.38(\mathrm{dd}, J=7.5,2.3 \mathrm{~Hz}, 2 \mathrm{H}), 4.26(\mathrm{t}, J$ $=7.3 \mathrm{~Hz}, 1 \mathrm{H}), 3.80-3.64(\mathrm{~m}, 2 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 163.89,156.62,144.08,141.44,136.14,134.96$, 133.52, 132.90, 130.72, 129.62, 128.81, 127.83, 127.22, 126.77, 125.40, 123.96, 120.10, 87.81, 67.39, 47.33, 45.03.

Rf: 0.5 (heptane: $\mathrm{EtOAc}=1: 1$ ).

Preparation of tert-butyl (2-(3,4-dichlorophenyl)-2-((1,3-dioxoisoindolin-2-yl)oxy) ethyl)carbamate (22a)


22a
According to typical procedure TP4, the reaction was performed by the addition of DEAD ( 1.3 eq., $26.6 \mu \mathrm{~L}, 0.17 \mathrm{mmol}$ ) into a solution of $\mathbf{2 0 a}$ ( $1 \mathrm{eq} ., 40 \mathrm{mg}, 0.131$ $\mathrm{mmol})$, NHPI ( $1.3 \mathrm{eq} ., 27.7 \mathrm{mg}, 0.17 \mathrm{mmol}$ ) and $\mathrm{PPh}_{3}(1.3 \mathrm{eq} ., 44.5 \mathrm{mg}, 0.17 \mathrm{mmol})$ in THF ( 1.49 mL ) under $\operatorname{Ar}$ at $0^{\circ} \mathrm{C}$ and stirred at $0^{\circ} \mathrm{C}$ overnight. The crude was purified by silica gel chromatography (heptane:EtOAc $=5: 1$ to $4: 1$ ) to afford 22a as a white solid ( $55.4 \mathrm{mg}, 94 \%$ ).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.83-7.78(\mathrm{~m}, 2 \mathrm{H}), 7.77-7.72(\mathrm{~m}, 2 \mathrm{H}), 7.63(\mathrm{~s}, 1 \mathrm{H})$, $7.45(\mathrm{~d}, J=8.3 \mathrm{~Hz}, 1 \mathrm{H}), 7.38(\mathrm{dd}, J=8.3,2.1 \mathrm{~Hz}, 1 \mathrm{H}), 5.50(\mathrm{t}, J=6.2 \mathrm{~Hz}, 1 \mathrm{H}), 5.29$ $(\mathrm{t}, J=5.3 \mathrm{~Hz}, 1 \mathrm{H}), 3.61(\mathrm{t}, J=6.2 \mathrm{~Hz}, 2 \mathrm{H}), 1.43(\mathrm{~s}, 9 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 163.88,151.77,134.89,133.37,132.80,130.63$, 129.72, 128.87, 126.93, 124.42, 123.92, 87.23, 84.52, 44.34, 28.48.

Rf: 0.6 (heptane:EtOAc = 1:1).

Preparation of (S)-tert-butyl 2-((R)-((1,3-dioxoisoindolin-2-yl)oxy)(phenyl) methyl)pyrrolidine-1-carboxylate (22b)


22b
According to typical procedure TP4, the reaction was performed by the addition of DEAD ( 1.8 eq., $0.305 \mathrm{~mL}, 1.95 \mathrm{mmol}$ ) into a solution of $\mathbf{2 0 b}(1 \mathrm{eq} ., 300 \mathrm{mg}, 1.08$ mmol), NHPI ( $1.5 \mathrm{eq} ., 264 \mathrm{mg}, 1.62 \mathrm{mmol}$ ) and $\mathrm{PPh}_{3}(1.8 \mathrm{eq} ., 510 \mathrm{mg}, 1.95 \mathrm{mmol}$ ) in THF ( 12 mL ) under $\operatorname{Ar}$ at $0^{\circ} \mathrm{C}$ and stirred at $0^{\circ} \mathrm{C}$ overnight. The crude was purified by silica gel chromatography (heptane: $\mathrm{EtOAc}=4: 1$ ) to afford $\mathbf{2 2 b}$ as a white solid (429 $\mathrm{mg}, 94 \%$ ).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.72-7.38(\mathrm{~m}, 6 \mathrm{H}), 7.30-7.19(\mathrm{~m}, 3 \mathrm{H}), 5.88$ (s, $0.45 \mathrm{H}), 5.68(\mathrm{~s}, 0.55 \mathrm{H}), 4.03(\mathrm{~m}, 1 \mathrm{H}), 3.59-3.32(\mathrm{~m}, 2 \mathrm{H}), 2.50-2.19(\mathrm{~m}, 1 \mathrm{H}), 2.05$ $(\mathrm{m}, 1 \mathrm{H}), 1.75(\mathrm{~m}, 2 \mathrm{H}), 1.40(\mathrm{~s}, 4 \mathrm{H}), 1.36(\mathrm{~s}, 5 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 163.61,158.46,134.37,129.16,128.57,128.22$, $127.75,127.52,123.45,88.86,77.36,61.80,29.86,28.63,22.84,14.26$.

Rf: 0.49 (heptane: $\mathrm{EtOAc}=2: 1$ ).

## Preparation of tert-butyl ((1R,2S)-1-((1,3-dioxoisoindolin-2-yl)oxy)-3-methyl-1-

 phenylbutan-2-yl)carbamate (22c)

22c
According to typical procedure TP4, the reaction was performed by the addition of DEAD ( 1.8 eq., $0.526 \mathrm{~mL}, 3.35 \mathrm{mmol}$ ) into a solution of $\mathbf{2 0 c}(1 \mathrm{eq} ., 0.52 \mathrm{~g}, 1.86$ mmol), NHPI ( $1.5 \mathrm{eq} ., 0.455 \mathrm{~g}, 2.79 \mathrm{mmol}$ ) and $\mathrm{PPh}_{3}(1.8 \mathrm{eq} ., 0.879 \mathrm{~g}, 3.35 \mathrm{mmol}$ ) in

THF ( 13.5 mL ) under Ar at $0^{\circ} \mathrm{C}$ and stirred at $0^{\circ} \mathrm{C}$ overnight. The crude was purified by silica gel chromatography (heptane: $\mathrm{EtOAc}=4: 1$ to $3: 1$ ) to afford $\mathbf{2 2 c}$ as a white solid ( $0.64 \mathrm{~g}, 81 \%$ ).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.71-7.65(\mathrm{~m}, 4 \mathrm{H}), 7.51-7.47(\mathrm{~m}, 2 \mathrm{H}), 7.31-7.27$ (m, 3H), $5.52(\mathrm{~d}, J=4.7 \mathrm{~Hz}, 1 \mathrm{H}), 5.12(\mathrm{~d}, J=10.2 \mathrm{~Hz}, 1 \mathrm{H}), 3.84-3.77(\mathrm{~m}, 1 \mathrm{H}), 1.96$ - $1.87(\mathrm{~m}, 1 \mathrm{H}), 1.39(\mathrm{~s}, 9 \mathrm{H}), 1.16(\mathrm{~d}, J=6.7 \mathrm{~Hz}, 3 \mathrm{H}), 0.95(\mathrm{~d}, J=6.8 \mathrm{~Hz}, 3 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 163.74,156.09,136.51,134.46,128.99,128.94$, $128.31,128.14,123.48,88.21,79.20,60.00,30.56,28.54,20.30,18.47$.

Rf: 0.35 (heptane: $\mathrm{EtOAc}=3: 1$ ).

## Preparation of tert-butyl (2-((1,3-dioxoisoindolin-2-yl)oxy)-3-methylbut-3-en-1-

 yl)carbamate (22d)

22d
According to typical procedure TP4, the reaction was performed by the addition of DEAD ( 1.3 eq., $0.274 \mathrm{~mL}, 1.74 \mathrm{mmol}$ ) into a solution of $\mathbf{2 0 d}(1 \mathrm{eq} ., 270 \mathrm{mg}, 1.34$ mmol ), NHPI ( $1.3 \mathrm{eq} ., 284 \mathrm{mg}, 1.74 \mathrm{mmol}$ ) and $\mathrm{PPh}_{3}(1.3 \mathrm{eq} ., 457 \mathrm{mg}, 1.74 \mathrm{mmol})$ in THF ( 8 mL ) under Ar at $0^{\circ} \mathrm{C}$ and stirred at $0^{\circ} \mathrm{C}$ overnight. The crude was purified by silica gel chromatography (heptane:EtOAc $=5: 1$ to $3: 1$ ) to afford 22d as a colorless oil ( $440 \mathrm{mg}, 95 \%$ ).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.86-7.66(\mathrm{~m}, 4 \mathrm{H}), 5.42(\mathrm{~s}, 1 \mathrm{H}), 5.09-4.97(\mathrm{~m}, 2 \mathrm{H})$, $4.70-4.55(\mathrm{~m}, 1 \mathrm{H}), 3.55-3.38(\mathrm{~m}, 2 \mathrm{H}), 1.92(\mathrm{~s}, 3 \mathrm{H}), 1.46(\mathrm{~s}, 9 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 163.93,156.16,140.32,134.65,128.94,123.69$, 117.71, 90.65, 79.59, 42.00, 28.52, 17.91.

Rf: 0.6 (heptane:EtOAc = 1:1).

## Preparation of tert-butyl (2-(aminooxy)-2-(3,4-dichlorophenyl)ethyl)carbamate

 (25a)

25a
According to typical procedure TP5, the reaction was performed with 22a (1 eq., 400 $\mathrm{mg}, 0.886 \mathrm{mmol}$ ) and hydrazine hydrate ( 15 eq., $1.29 \mathrm{~mL}, 13.3 \mathrm{mmol}$ ) in EtOH ( 12 mL ) in 30 min , affording $\mathbf{2 5 a}$ as a white solid ( $267 \mathrm{mg}, 94 \%$ ).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl} 3$ ): $\delta 7.46-7.41$ (m, 2H), 7.16 (dd, $J=8.2,1.8 \mathrm{~Hz}, 1 \mathrm{H}$ ), $5.44(\mathrm{~s}, 2 \mathrm{H}), 4.86(\mathrm{~s}, 1 \mathrm{H}), 4.60(\mathrm{dd}, J=7.9,3.8 \mathrm{~Hz}, 1 \mathrm{H}), 3.56-3.44(\mathrm{~m}, 1 \mathrm{H}), 3.19$ (ddd, $J=14.4,7.9,4.8 \mathrm{~Hz}, 1 \mathrm{H}), 1.43$ (s, 9H).
${ }^{13} \mathrm{C}$ NMR (101 MHz, CDCl3): $\delta 155.94,139.87,132.95,132.19,130.74,128.78$, 126.18, 84.70, 79.79, 44.93, 28.50.

Preparation of $(S)$-tert-butyl 2-((R)-(aminooxy)(phenyl)methyl)pyrrolidine-1carboxylate (25b)


25b
According to typical procedure TP5, the reaction was performed with 22b (1 eq., 100 $\mathrm{mg}, 0.237 \mathrm{mmol}$ ) and hydrazine hydrate ( 15 eq., $0.344 \mathrm{~mL}, 3.55 \mathrm{mmol}$ ) in EtOH (3 mL ) in 16 h , affording $\mathbf{2 5 b}$ as a colorless oil ( $67 \mathrm{mg}, 97 \%$ ).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.42-7.27(\mathrm{~m}, 5 \mathrm{H}), 5.43(\mathrm{~s}, 2 \mathrm{H}), 5.01(\mathrm{~m}, 1 \mathrm{H}), 4.00$ $(\mathrm{m}, 1 \mathrm{H}), 3.61-3.26(\mathrm{~m}, 2 \mathrm{H}), 2.13-1.70(\mathrm{~m}, 3 \mathrm{H}), 1.63(\mathrm{~m}, 1 \mathrm{H}), 1.52-1.46(\mathrm{~m}, 9 \mathrm{H})$. ${ }^{13}{ }^{3}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 154.62,128.61,127.63,126.44,125.97,88.10,79.68$, 62.04, 47.04, 28.71, 25.79, 23.73.

## Preparation of tert-butyl ((1R,2S)-1-(aminooxy)-3-methyl-1-phenylbutan-2-yl)

 carbamate (25c)

25c
According to typical procedure TP5, the reaction was performed in 1 h using 22c (1 eq., $45 \mathrm{mg}, 0.106 \mathrm{mmol}$ ) and hydrazine hydrate ( $15 \mathrm{eq} ., 0.154 \mathrm{~mL}, 1.59 \mathrm{mmol}$ ) in EtOH ( 1.5 mL ) in 1 h , affording $\mathbf{2 5 c}$ as a white solid ( $30 \mathrm{mg}, 96 \%$ ).
${ }^{1} \mathrm{H}$ NMR (400 MHz, CDCl3): $\delta 7.31-7.25$ (m, 5H), 5.26 (s, 2H), 4.68 (d, $J=10.4 \mathrm{~Hz}$, $1 \mathrm{H}), 4.60(\mathrm{~d}, J=4.9 \mathrm{~Hz}, 1 \mathrm{H}), 3.59-3.49(\mathrm{~m}, 1 \mathrm{H}), 1.75-1.65(\mathrm{~m}, 1 \mathrm{H}), 1.31(\mathrm{~s}, 9 \mathrm{H})$, $0.96(\mathrm{~d}, J=6.7 \mathrm{~Hz}, 3 \mathrm{H}), 0.86(\mathrm{~d}, J=6.8 \mathrm{~Hz}, 3 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR (101 MHz, CDCl3): $\delta 156.05,139.67,128.57,127.88,127.04,86.77,78.95$, $60.04,30.12,28.48,20.32,18.33$.

Preparation of tert-butyl (2-(aminooxy)-3-methylbut-3-en-1-yl)carbamate (25d)


25d
According to typical procedure TP5, the reaction was performed with 22d (1 eq., 1.65 $\mathrm{g}, 4.76 \mathrm{mmol}$ ) and hydrazine hydrate ( $15 \mathrm{eq} ., 6.93 \mathrm{~mL}, 71.5 \mathrm{mmol}$ ) in EtOH ( 23.6 mL ) in 1 h . The reaction mixture was concentrated in vacuo directly and purified by silica gel chromatography (heptane: $\mathrm{EtOAc}=2: 1$ to $1: 1$ ) to afford $\mathbf{2 5 d}$ as a white solid ( 1.01 g, $98 \%)$.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 5.31(\mathrm{~s}, 2 \mathrm{H}), 5.04-4.99(\mathrm{~m}, 2 \mathrm{H}), 4.85(\mathrm{~s}, 1 \mathrm{H}), 3.96$ (dd, $J=7.7,3.9 \mathrm{~Hz}, 1 \mathrm{H}), 3.46-3.34(\mathrm{~m}, 1 \mathrm{H}), 3.14-3.01(\mathrm{~m}, 1 \mathrm{H}), 1.71(\mathrm{~s}, 3 \mathrm{H}), 1.43$ ( $\mathrm{s}, 9 \mathrm{H}$ ).
${ }^{13} \mathrm{C}$ NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 156.06,142.26,113.93,87.18,79.42,42.25,28.52$, 18.56.

Rf: 0.4 (heptane: $E t O A c=1: 1$ ).

Preparation of 2-(aminooxy)-2-(3,4-dichlorophenyl)ethanamine dihydrochloride (26a)


26a
The reaction was performed with $\mathbf{2 5 a}$ ( 1 eq., $91 \mathrm{mg}, 0.283 \mathrm{mmol}$ ) in $\mathrm{HCl} /$ dioxane ( 4 $\mathrm{M}, 2.73 \mathrm{~mL}$ ) according to typical procedure TP6, affording 26a as a white solid (80 $\mathrm{mg}, 96 \%)$.
${ }^{1} \mathrm{H}$ NMR ( 400 MHz, DMSO- $d^{6}$ ): $\delta 10.48$ (s, 3H), $8.42(\mathrm{~s}, 3 \mathrm{H}), 7.76-7.72(\mathrm{~m}, 2 \mathrm{H})$, $7.46(\mathrm{dd}, J=8.3,2.0 \mathrm{~Hz}, 1 \mathrm{H}), 5.43(\mathrm{dd}, J=8.6,4.0 \mathrm{~Hz}, 1 \mathrm{H}), 3.34-3.17(\mathrm{~m}, 2 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR (101 MHz, DMSO- $d^{6}$ ): $\delta 135.98,132.06,131.41,130.95,129.84,128.11$, 80.76, 41.66.

Preparation of $O-((R)$-phenyl $((S)$-pyrrolidin-2-yl)methyl)hydroxylamine dihydrochloride (26b)


26b
The reaction was performed with $\mathbf{2 5 b}$ ( $1 \mathrm{eq} ., 60 \mathrm{mg}, 0.205 \mathrm{mmol}$ ) in $\mathrm{HCl} /$ dioxane ( 4 $\mathrm{M}, 2 \mathrm{~mL}$ ) according to typical procedure TP6, affording 26b as a white solid (52.2 $\mathrm{mg}, 96 \%$ ).
${ }^{1} \mathrm{H}$ NMR ( 400 MHz, DMSO- $d^{6}$ ): $\delta 10.16(\mathrm{~s}, 5 \mathrm{H}), 7.62-7.31(\mathrm{~m}, 5 \mathrm{H}), 5.59(\mathrm{~d}, J=5.0$ $\mathrm{Hz}, 1 \mathrm{H}), 3.85(\mathrm{~m}, 1 \mathrm{H}), 3.24-3.06(\mathrm{~m}, 2 \mathrm{H}), 1.88(\mathrm{~m}, 4 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR (101 MHz, DMSO- $d^{6}$ ): $\delta 135.05,129.14,128.76,127.03,83.15,61.72$, 45.37, 24.56, 23.48.

## Preparation of (1R,2S)-1-(aminooxy)-3-methyl-1-phenylbutan-2-amine

 dihydrochloride (26c)

26c
The reaction was performed with $\mathbf{2 5 c}$ ( 1 eq., $285 \mathrm{mg}, 0.968 \mathrm{mmol}$ ) in $\mathrm{HCl} /$ dioxane ( 4 M, 5 mL ) according to typical procedure TP6, affording 26c as a white solid ( 244 mg , $94 \%$ ).
${ }^{1} \mathrm{H}$ NMR ( 400 MHz, DMSO- $d^{6}$ ): $\delta 9.02(\mathrm{~s}, 6 \mathrm{H}), 7.50-7.46(\mathrm{~m}, 5 \mathrm{H}), 5.25(\mathrm{~d}, \mathrm{~J}=9.9$ $\mathrm{Hz}, 1 \mathrm{H}), 3.44(\mathrm{dd}, \mathrm{J}=9.9,2.5 \mathrm{~Hz}, 1 \mathrm{H}), 1.48-1.36(\mathrm{~m}, 1 \mathrm{H}), 0.93(\mathrm{~d}, \mathrm{~J}=7.1 \mathrm{~Hz}, 3 \mathrm{H})$, $0.81(\mathrm{~d}, \mathrm{~J}=7.0 \mathrm{~Hz}, 3 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( 101 MHz, DMSO- $d^{6}$ ): $\delta 130.29,129.38,128.93,85.18,58.57,27.55$, 19.58, 15.61.

Preparation of 2-(aminooxy)-3-methylbut-3-en-1-amine dihydrochloride (26d)


26d
The reaction was performed with $\mathbf{2 5 d}$ ( 1 eq., $300 \mathrm{mg}, 1.39 \mathrm{mmol}$ ) in $\mathrm{HCl} /$ dioxane ( 4 M, 15 mL ) according to typical procedure TP6, affording 26d as a white solid (259 mg, 99 \%).
${ }^{1} \mathrm{H}$ NMR ( 400 MHz, DMSO- $d^{6}$ ): $\delta 10.90(\mathrm{~s}, 3 \mathrm{H}), 8.35(\mathrm{~s}, 3 \mathrm{H}), 5.24(\mathrm{~s}, 1 \mathrm{H}), 5.22-$ $5.19(\mathrm{~m}, 1 \mathrm{H}), 4.79(\mathrm{dd}, J=8.2,4.0 \mathrm{~Hz}, 1 \mathrm{H}), 3.09-2.98(\mathrm{~m}, 2 \mathrm{H}), 1.72(\mathrm{~s}, 3 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR (101 MHz, DMSO- $d^{6}$ ): $\delta 138.73,118.52,83.96,66.82,17.88$.

## Preparation of (S)-1-(tert-butoxycarbonyl)pyrrolidine-2-carboxylic acid (33)



33
$\mathrm{Boc}_{2} \mathrm{O}$ ( 1.2 eq., $11.4 \mathrm{~g}, 11.2 \mathrm{~mL}, 52.1 \mathrm{mmol}$ ) was added portionwise to a solution of proline ( 1 eq., $5 \mathrm{~g}, 3.7 \mathrm{~mL}, 43.4 \mathrm{mmol}$ ) in $\mathrm{NaOH}_{\text {aq }}$ ( 2 eq., $1 \mathrm{M}, 87 \mathrm{~mL}, 87 \mathrm{mmol}$ ) and dioxane ( 21.7 mL ) at $0{ }^{\circ} \mathrm{C}$ over 10 min . The resulting mixture was stirred at $0{ }^{\circ} \mathrm{C}$ for 30 min , then allowed to warm to rt and stirred overnight. The organic solvent was removed under reduced pressure. The remaining aqueous solution was acidified to pH $\sim 2$ with saturated aq. citric acid. The aqueous solution was extracted with DCM thrice. The combined organic layers were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, and concentrated in vacuo to afford 33 as a white solid ( $9.1 \mathrm{~g}, 97 \%$ ).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$, mixture of rotamers): $\delta 11.12(\mathrm{~s}, 1 \mathrm{H}), 4.28(\mathrm{~m}, 1 \mathrm{H}), 3.61$ $-3.28(\mathrm{~m}, 2 \mathrm{H}), 2.32-2.16(\mathrm{~m}, 1 \mathrm{H}), 2.15-1.99(\mathrm{~m}, 1 \mathrm{H}), 1.91(\mathrm{~m}, 2 \mathrm{H}), 1.46(\mathrm{~s}, 4.5 \mathrm{H})$, 1.41 ( $\mathrm{s}, 4.5 \mathrm{H}$ ).

Rf: 0.58 (EtOAc with $0.1 \% \mathrm{AcOH}$ ).
These data are consistent with the previously reported characterization. ${ }^{180}$

## Preparation of (S)-tert-butyl 2-((S)-hydroxy(phenyl)methyl)pyrrolidine-1-

 carboxylate (34)

34
The reaction was performed with $\mathbf{1 7 b}$ ( 1 eq., $400 \mathrm{mg}, 1.45 \mathrm{mmol}$ ) in $\mathrm{MeOH}(6 \mathrm{~mL}$ ) with $\mathrm{NaBH}_{4}$ (4 eq., $219 \mathrm{mg}, 5.81 \mathrm{mmol}$ ) according to typical procedure TP3 in 1 h . The crude was purified by reverse phase chromatography $\left(\mathrm{MeOH} / \mathrm{H}_{2} \mathrm{O}\right)$ to afford 34 as a colorless oil ( $290 \mathrm{mg}, 72 \%$ ).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.37-7.27(\mathrm{~m}, 5 \mathrm{H}), 5.94-5.74(\mathrm{~m}, 1 \mathrm{H}), 4.52(\mathrm{~d}, J=$
$8.9 \mathrm{~Hz}, 1 \mathrm{H}), 4.09(\mathrm{td}, J=8.3,3.8 \mathrm{~Hz}, 1 \mathrm{H}), 3.53-3.32(\mathrm{~m}, 2 \mathrm{H}), 1.71(\mathrm{~m}, 3 \mathrm{H}), 1.52(\mathrm{~s}$, 9H).

Rf: 0.55 (heptane:EtOAc = 2:1).
These data are consistent with the previously reported characterization. ${ }^{125}$

## Preparation of (S)-2-((R)-(aminooxy)(phenyl)methyl)pyrrolidine-1-carbonitrile

 (37)

37
TEA ( 3 eq., $17.2 \mathrm{mg}, 0.0236 \mathrm{~mL}, 0.17 \mathrm{mmol}$ ) was slowly added to a solution of $\mathbf{2 6 b}$ ( $1 \mathrm{eq} ., 15 \mathrm{mg}, 0.0566 \mathrm{mmol})$ in $\mathrm{MeCN}(1.25 \mathrm{~mL})$ at $0^{\circ} \mathrm{C}$ and stirred for 5 min . Then, a solution of $\mathrm{BrCN}(1.2$ eq., $7.19 \mathrm{mg}, 0.0679 \mathrm{mmol})$ in $\mathrm{MeCN}(0.25 \mathrm{~mL})$ was added dropwise at $0{ }^{\circ} \mathrm{C}$. The resulting mixture was stirred at $0{ }^{\circ} \mathrm{C}$ for 30 min and concentrated in vacuo. The crude was purified by reverse phase chromatography $\left(\mathrm{MeOH} / \mathrm{H}_{2} \mathrm{O}\right)$ to afford 37 as a white solid ( $8.4 \mathrm{mg}, 68 \%$ ).
${ }^{1} \mathrm{H}$ NMR ( 400 MHz, DMSO- $d^{6}$ ): $\delta 7.41-7.31$ (m, 5H), 6.05 (s, 2H), 4.54 (d, $J=4.1$ Hz, 1H), 3.92 (m, 1H), $3.34-3.08$ (m, 3H), $1.85-1.69$ (m, 2H), 1.37 (m, 1H).
${ }^{13} \mathrm{C}$ NMR (101 MHz, DMSO-d ${ }^{6}$ ): $\delta$ 138.66, 128.08, 127.64, 127.37, 117.01, 86.09, 64.24, 51.20, 26.23, 23.86.

## Preparation of tert-butyl ((1S,2S)-1-hydroxy-3-methyl-1-phenylbutan-2-yl)

 carbamate (38)

38
The reaction was performed with $\mathbf{1 7 c}(1$ eq., $1 \mathrm{~g}, 3.61 \mathrm{mmol})$ in $\mathrm{MeOH}(30 \mathrm{~mL})$ with
$\mathrm{NaBH}_{4}$ (2 eq., $0.273 \mathrm{~g}, 7.21 \mathrm{mmol}$ ) according to typical procedure $\mathbf{T P} 3$ in 2 h . The crude was purified by reverse phase chromatography $\left(\mathrm{MeOH} / \mathrm{H}_{2} \mathrm{O}\right)$ to afford 38 as a white solid ( $201 \mathrm{mg}, 20 \%$ ).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.35-7.33(\mathrm{~m}, 4 \mathrm{H}), 7.28-7.26(\mathrm{~m}, 1 \mathrm{H}), 4.83-4.75$ $(\mathrm{m}, 2 \mathrm{H}), 3.50-3.42(\mathrm{~m}, 1 \mathrm{H}), 1.89-1.79(\mathrm{~m}, 1 \mathrm{H}), 1.36(\mathrm{~s}, 9 \mathrm{H}), 1.19(\mathrm{~s}, 1 \mathrm{H}), 1.01(\mathrm{~d}$, $J=6.7 \mathrm{~Hz}, 3 \mathrm{H}), 0.94(\mathrm{~d}, J=6.8 \mathrm{~Hz}, 3 \mathrm{H})$.

These data are consistent with the previously reported characterization. ${ }^{128}$

## Preparation of $N$-(3-methylbut-2-en-1-yl)-6-(prop-1-en-2-yl)-5,6-dihydro-4H-

## 1,2,4-oxadiazin-3-amine (43)



43
47 ( 1 eq., $6.5 \mathrm{mg}, 0.021 \mathrm{mmol}$ ) was added to a solution of HCl in dioxane $(4 \mathrm{M}, 1 \mathrm{~mL})$ and stirred at rt for 25 h . The reaction mixture was concentrated in vacuo and basified by an aqueous solution of saturated $\mathrm{NaHCO}_{3}$ until $\mathrm{pH} \sim 8$. After concentrated under reduced pressure, the residue was purified by reverse phase chromatography ( $\mathrm{ACN} / \mathrm{H}_{2} \mathrm{O}$ ) to afford 43 as a white solid ( $4.2 \mathrm{mg}, 96 \%$ ).
${ }^{1} \mathrm{H}$ NMR ( 400 MHz, DMSO- $d^{6}$ ): $\delta 5.76(\mathrm{~s}, 1 \mathrm{H}), 5.20(\mathrm{t}, J=7.0 \mathrm{~Hz}, 1 \mathrm{H}), 4.95(\mathrm{~s}, 1 \mathrm{H})$, $4.89(\mathrm{~s}, 1 \mathrm{H}), 4.63-4.59(\mathrm{~m}, 1 \mathrm{H}), 3.72(\mathrm{dd}, J=9.5,3.0 \mathrm{~Hz}, 1 \mathrm{H}), 3.43-3.37(\mathrm{~m}, 2 \mathrm{H})$, $3.29-3.26(\mathrm{~m}, 1 \mathrm{H}), 3.05-2.99(\mathrm{~m}, 1 \mathrm{H}), 1.71(\mathrm{~s}, 3 \mathrm{H}), 1.67(\mathrm{~s}, 3 \mathrm{H}), 1.59(\mathrm{~s}, 3 \mathrm{H})$.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{MeOD}-d^{4}$ ): $\delta 5.28-5.22(\mathrm{~m}, 1 \mathrm{H}), 5.03-4.97(\mathrm{~m}, 2 \mathrm{H}), 3.97(\mathrm{dd}$, $J=9.6,3.3 \mathrm{~Hz}, 1 \mathrm{H}), 3.54(\mathrm{~d}, J=6.8 \mathrm{~Hz}, 2 \mathrm{H}), 3.40(\mathrm{dd}, J=11.2,3.3 \mathrm{~Hz}, 1 \mathrm{H}), 3.27-$ $3.21(\mathrm{~m}, 1 \mathrm{H}), 1.80-1.66(\mathrm{~m}, 9 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR (101 MHz, DMSO- $d^{6}$ ): $\delta$ 153.77, 142.46, 132.62, 122.75, 111.90, 74.47, 43.65, 38.81, 25.35, 19.04, 17.65.

## 1,2,4-oxadiazin-3-amine (45)



45
10d ( 1 eq., $10 \mathrm{mg}, 0.0708 \mathrm{mmol}$ ) was dissolved in $\mathrm{MeCN}(0.6 \mathrm{~mL})$, followed by the addition of 3,3 -dimethylallyl bromide ( $1 \mathrm{eq} ., 8.3 \mu \mathrm{~L}, 0.0708 \mathrm{mmol}$ ) and TEA ( 2 eq., $19.7 \mu \mathrm{~L}, 0.142 \mathrm{mmol})$. The resulting mixture was stirred at rt for 16 h , then, concentrated in vacuo and purified by reverse phase choromatography $\left(\mathrm{MeCN} / \mathrm{H}_{2} \mathrm{O}\right)$ to afford 45 as a white solid ( $11 \mathrm{mg}, 74 \%$ ).
${ }^{1} \mathrm{H}$ NMR ( 400 MHz, DMSO- $d^{6}$ ): $\delta 7.50(\mathrm{~s}, 2 \mathrm{H}), 5.32-5.23(\mathrm{~m}, 1 \mathrm{H}), 5.02-4.96(\mathrm{~m}$, $2 \mathrm{H}), 4.21$ (dd, $J=10.0,3.3 \mathrm{~Hz}, 1 \mathrm{H}), 4.13$ (dd, $J=15.8,7.1 \mathrm{~Hz}, 1 \mathrm{H}), 4.00(\mathrm{dd}, J=$ $15.7,7.0 \mathrm{~Hz}, 1 \mathrm{H}), 3.32-3.27(\mathrm{~m}, 1 \mathrm{H}), 3.20(\mathrm{dd}, J=13.7,10.1 \mathrm{~Hz}, 1 \mathrm{H}), 1.73-1.71$ (m, 6H), $1.66(\mathrm{~s}, 3 \mathrm{H})$.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{MeOD}-d^{4}$ ): $\delta 5.37-5.30(\mathrm{~m}, 1 \mathrm{H}), 5.14-5.12(\mathrm{~m}, 1 \mathrm{H}), 5.09(\mathrm{q}, J$ $=1.1 \mathrm{~Hz}, 1 \mathrm{H}), 4.48(\mathrm{dd}, J=10.0,3.5 \mathrm{~Hz}, 1 \mathrm{H}), 4.34(\mathrm{dd}, J=15.9,7.0 \mathrm{~Hz}, 1 \mathrm{H}), 4.21$ (dd, $J=15.9,7.5 \mathrm{~Hz}, 1 \mathrm{H}), 3.54(\mathrm{dd}, J=12.3,3.5 \mathrm{~Hz}, 1 \mathrm{H}), 3.42(\mathrm{dd}, J=12.4,10.1 \mathrm{~Hz}$, $1 \mathrm{H}), 1.82-1.79(\mathrm{~m}, 6 \mathrm{H}), 1.76(\mathrm{~s}, 3 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR (101 MHz, DMSO- $d^{6}$ ): $\delta 153.73,140.15,138.29,117.88,113.67,75.95$, 49.53, 44.57, 25.49, 18.87, 17.84.

Preparation of tert-butyl 3-amino-6-(prop-1-en-2-yl)-5,6-dihydro-4H-1,2,4-oxadiazine-4-carboxylate (46)


46
TEA ( 2 eq., $39.4 \mu \mathrm{~L}, 0.283 \mathrm{mmol}$ ) was added to a solution of $\mathbf{1 0 d}$ ( $1 \mathrm{eq} ., 20 \mathrm{mg}, 0.142$ $\mathrm{mmol})$ and $\mathrm{Boc}_{2} \mathrm{O}(1.1$ eq., $34 \mathrm{mg}, 0.156 \mathrm{mmol})$ in $\mathrm{DCM}(1 \mathrm{~mL})$. The mixture was stirred at rt for 16 h , then, concentrated in vacuo and purified by reverse phase
chromatography $\left(\mathrm{MeOH} / \mathrm{H}_{2} \mathrm{O}\right)$ to afford 46 as a white solid ( $31 \mathrm{mg}, 91 \%$ ).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 5.25(\mathrm{~s}, 2 \mathrm{H}), 5.07-5.05(\mathrm{~m}, 1 \mathrm{H}), 5.04-5.02(\mathrm{~m}, 1 \mathrm{H})$, $4.14(\mathrm{dd}, J=10.3,3.0 \mathrm{~Hz}, 1 \mathrm{H}), 3.84(\mathrm{dd}, J=12.0,3.1 \mathrm{~Hz}, 1 \mathrm{H}), 3.53(\mathrm{dd}, J=12.0$, $10.3 \mathrm{~Hz}, 1 \mathrm{H}), 1.81(\mathrm{~s}, 3 \mathrm{H}), 1.52(\mathrm{~s}, 9 \mathrm{H})$.
${ }^{13}{ }^{3}$ NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 151.81,150.68,140.65,114.18,84.06,76.58,48.39$, 28.23, 19.18.

Preparation of tert-butyl 3-((3-methylbut-2-en-1-yl)amino)-6-(prop-1-en-2-yl) -5,6-dihydro-4H-1,2,4-oxadiazine-4-carboxylate (47)


47
A solution of $\mathrm{NaH}(4 \mathrm{eq} ., 4.61 \mathrm{mg}, 0.182 \mathrm{mmol})$ in THF $(0.4 \mathrm{~mL})$ was slowly added to a solution of 46 ( 1 eq., $11 \mathrm{mg}, 0.0456 \mathrm{mmol}$ ) in THF ( 0.7 mL ) under Ar at rt. The mixture was stirred at $60^{\circ} \mathrm{C}$ for 1 h and then a solution of 3,3-dimethylallyl bromide (4 eq., $21.4 \mu \mathrm{~L}, 0.182 \mathrm{mmol}$ ) in THF ( 0.1 mL ) was added and stirred at $60^{\circ} \mathrm{C}$ for an additional 4 h . The reaction mixture was concentrated in vacuo and purified by reverse phase choromatography $\left(\mathrm{ACN} / \mathrm{H}_{2} \mathrm{O}\right)$ to afford 47 as a white solid ( $10.7 \mathrm{mg}, 76 \%$ ).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 6.65(\mathrm{~s}, 1 \mathrm{H}), 5.34-5.24(\mathrm{~m}, 1 \mathrm{H}), 5.07-4.93(\mathrm{~m}, 2 \mathrm{H})$, $4.11(\mathrm{~d}, J=10.6 \mathrm{~Hz}, 1 \mathrm{H}), 3.81(\mathrm{dd}, J=11.9,3.1 \mathrm{~Hz}, 1 \mathrm{H}), 3.70-3.60(\mathrm{~m}, 2 \mathrm{H}), 3.54(\mathrm{t}$, $J=11.3 \mathrm{~Hz}, 1 \mathrm{H}), 1.81(\mathrm{~s}, 3 \mathrm{H}), 1.72(\mathrm{~s}, 3 \mathrm{H}), 1.66(\mathrm{~s}, 3 \mathrm{H}), 1.51(\mathrm{~s}, 9 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 162.28,150.53,140.95,138.85,120.88,113.69$, 83.73, 76.54, 48.83, 39.86, 29.86, 28.25, 25.82, 19.19.

Preparation of $\mathrm{N}, 4-\mathrm{bis}(3-m e t h y l b u t-2-e n-1-\mathrm{yl})$-6-(prop-1-en-2-yl)-5,6-dihydro -4H-1,2,4-oxadiazin-3-amine hydrobromide (48)


A solution of $\mathrm{NaH}(1.5 \mathrm{eq} ., 5.1 \mathrm{mg}, 0.213 \mathrm{mmol})$ in THF $(0.2 \mathrm{~mL})$ was added to a solution of $\mathbf{1 0 d}(1 \mathrm{eq} ., 20 \mathrm{mg}, 0.142 \mathrm{mmol})$ in THF $(0.4 \mathrm{~mL})$ at $0^{\circ} \mathrm{C}$ under Ar. The mixture was stirred at $0{ }^{\circ} \mathrm{C}$ for 2 h , followed by the addition of 3,3-dimethylallyl bromide ( 1.5 eq., $24.9 \mu \mathrm{~L}, 0.213 \mathrm{mmol}$ ) at $0{ }^{\circ} \mathrm{C}$ and stirred at rt for 16 h . Two drops of water was added to quench the reaction. The mixture was concentrated in vacuo and purified by reverse phase chromatography $\left(\mathrm{ACN} / \mathrm{H}_{2} \mathrm{O}\right)$ to afford 48 as a white solid ( $21 \mathrm{mg}, 53 \%$ ).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{MeOD}-d^{4}$ ): $\delta 5.38-5.32(\mathrm{~m}, 1 \mathrm{H}), 5.29-5.23(\mathrm{~m}, 1 \mathrm{H}), 5.14-$ $5.12(\mathrm{~m}, 1 \mathrm{H}), 5.09(\mathrm{q}, J=1.1 \mathrm{~Hz}, 1 \mathrm{H}), 4.56-4.50(\mathrm{~m}, 1 \mathrm{H}), 4.41-4.21(\mathrm{~m}, 2 \mathrm{H}), 4.20$ $-4.01(\mathrm{~m}, 2 \mathrm{H}), 3.49-3.44(\mathrm{~m}, 2 \mathrm{H}), 1.82(\mathrm{~d}, J=1.3 \mathrm{~Hz}, 3 \mathrm{H}), 1.80(\mathrm{t}, J=1.2 \mathrm{~Hz}, 6 \mathrm{H})$, $1.78-1.76(\mathrm{~m}, 3 \mathrm{H}), 1.75(\mathrm{~d}, J=1.3 \mathrm{~Hz}, 3 \mathrm{H})$.
${ }^{1} \mathrm{H}$ NMR ( 400 MHz, DMSO- $d^{6}$ ): $\delta 8.07(\mathrm{~s}, 2 \mathrm{H}), 5.34-5.20(\mathrm{~m}, 2 \mathrm{H}), 5.10(\mathrm{~s}, 1 \mathrm{H})$, $5.04(\mathrm{~s}, 1 \mathrm{H}), 4.56(\mathrm{dd}, J=8.7,5.2 \mathrm{~Hz}, 1 \mathrm{H}), 4.42(\mathrm{dd}, J=15.7,7.5 \mathrm{~Hz}, 1 \mathrm{H}), 4.27-$ 4.14 (m, 2H), 3.98 (dd, $J=15.6,6.3 \mathrm{~Hz}, 1 \mathrm{H}), 3.46-3.40(\mathrm{~m}, 2 \mathrm{H}), 1.75(\mathrm{~s}, 3 \mathrm{H}), 1.73$ ( $\mathrm{s}, 6 \mathrm{H}$ ), $1.70(\mathrm{~s}, 3 \mathrm{H}), 1.67-1.65(\mathrm{~m}, 3 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR (101 MHz, DMSO- $d^{6}$ ): $\delta 153.59,138.58,138.56,138.44,116.91,116.48$, $115.25,77.52,50.21,48.15,47.38,25.45,18.63,17.87$.

## Preparation of 1-(isothiocyanatomethyl)-2,4-dimethoxybenzene (53)



53
A solution of 2,4-dimethoxybenzylamine ( $1 \mathrm{eq} ., 0.45 \mathrm{~mL}, 2.99 \mathrm{mmol}$ ) in anhydrous DCM ( 3 mL ) was added slowly to a solution of thiophosgene ( $3 \mathrm{eq} ., 1.03 \mathrm{~g}, 8.97$
$\mathrm{mmol})$ in anhydrous $\mathrm{DCM}(18 \mathrm{~mL})$ at $0{ }^{\circ} \mathrm{C}$ under Ar. $\mathrm{NaOH}(3 \mathrm{eq} ., 0.36 \mathrm{~g}, 8.97 \mathrm{mmol})$ was then added at $0^{\circ} \mathrm{C}$. After stirred at rt for 2 h , the reaction mixture was filtered through a silica gel pad with DCM. The filtrate was concentrated in vacuo to afford 53 as a yellow oil ( $0.62 \mathrm{~g}, 99 \%$ ).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.18(\mathrm{~d}, J=8.8 \mathrm{~Hz}, 1 \mathrm{H}), 6.50-6.45(\mathrm{~m}, 2 \mathrm{H}), 4.60(\mathrm{~s}$, 2 H ), 3.83 ( $\mathrm{s}, 3 \mathrm{H}$ ), 3.81 ( $\mathrm{s}, 3 \mathrm{H}$ ).
${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 161.40,158.01,131.71,129.53,115.22,104.34$, 98.73, 55.60, 55.54, 44.19.

## Preparation of $N$-(2,4-dimethoxybenzyl)-3-methylbut-2-en-1-amine (56)



A solution of 3,3-dimethylallyl bromide ( 1 eq., $0.472 \mathrm{~mL}, 4.03 \mathrm{mmol}$ ) in THF ( 2.4 mL ) was added dropwise to a solution of 2,4-dimethoxybenzylamine ( $1.5 \mathrm{eq} ., 0.91$ $\mathrm{mL}, 6.04 \mathrm{mmol}$ ) and TEA ( 2 eq., $814 \mathrm{mg}, 1.12 \mathrm{~mL}, 8.05 \mathrm{mmol}$ ) in THF ( 18 mL ). The mixture was stirred at rt for 3 h . The reaction was quenched by the addition of water and extracted with EtOAc thrice. The combined organic phases were concentrated in vacuo and purified by silica gel chromatography ( $\mathrm{DCM}: \mathrm{MeOH}=20: 1$, contain $0.5 \%$ ammonia) to afford 56 as a yellow oil ( $0.72 \mathrm{~g}, 76 \%$ ).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 9.31(\mathrm{~s}, 1 \mathrm{H}), 7.31(\mathrm{~d}, J=8.5 \mathrm{~Hz}, 1 \mathrm{H}), 6.44-6.39(\mathrm{~m}$, 2H), $5.42(\mathrm{~s}, 1 \mathrm{H}), 3.96(\mathrm{~s}, 2 \mathrm{H}), 3.86(\mathrm{~s}, 3 \mathrm{H}), 3.75-3.72(\mathrm{~m}, 3 \mathrm{H}), 3.39(\mathrm{~s}, 2 \mathrm{H}), 1.74(\mathrm{~s}$, $3 \mathrm{H}), 1.54(\mathrm{~s}, 3 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 162.11,159.21,141.36,132.87,114.72,111.36$, 104.65, 98.49, 55.79, 55.47, 44.15, 43.18, 25.92, 18.38.

Preparation of N -(2,4-dimethoxybenzyl)- N -(3-methylbut-2-en-1-yl)-1 H -imidazole -1-carbothioamide (57)


A solution of $\mathbf{5 6}(1 \mathrm{eq} ., 30 \mathrm{mg}, 0.127 \mathrm{mmol})$ in $\mathrm{MeCN}(0.47 \mathrm{~mL})$ was added dropwise to a solution of 1,1'-thiocarbonyldiimidazole ( 2 eq., $45.4 \mathrm{mg}, 0.255 \mathrm{mmol}$ ) in MeCN $(0.94 \mathrm{~mL})$ and stirred at rt for 2 h . The mixture was concentrated in vacuo and purified by reverse phase choromatography $\left(\mathrm{MeOH} / \mathrm{H}_{2} \mathrm{O}\right)$ to afford $\mathbf{5 7}$ as an orange solid (40 mg, 91 \%).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.86(\mathrm{~s}, 1 \mathrm{H}), 7.22(\mathrm{~s}, 1 \mathrm{H}), 7.10-6.98(\mathrm{~m}, 2 \mathrm{H}), 6.48-$ $6.42(\mathrm{~m}, 2 \mathrm{H}), 5.24(\mathrm{~s}, 1 \mathrm{H}), 4.74(\mathrm{~s}, 2 \mathrm{H}), 4.27(\mathrm{~s}, 2 \mathrm{H}), 3.79(\mathrm{~s}, 3 \mathrm{H}), 3.77(\mathrm{~s}, 3 \mathrm{H}), 1.73$ (s, 3H), 1.47 ( $\mathrm{s}, 3 \mathrm{H}$ ).
${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 179.75,161.21,158.68,138.55,137.36,129.94$, $129.58,119.47,117.49,115.04,104.37,98.80,55.52,55.46,51.48,50.84,25.81$, 18.16.

## Preparation of 6-(prop-1-en-2-yl)-5,6-dihydro-4H-1,2,4-oxadiazin-3-ol (59)



59
A mixture of $\mathbf{2 6 d}$ ( $1 \mathrm{eq} ., 15 \mathrm{mg}, 0.0793 \mathrm{mmol}$ ) and TEA ( 2 eq., $22.1 \mu \mathrm{~L}, 0.159 \mathrm{mmol}$ ) in DMF ( 1 mL ) was stirred at rt for 1 min . Then, CDI ( $1.05 \mathrm{eq} ., 13.5 \mathrm{mg}, 0.0833$ mmol ) was added to the mixture and stirred for another 2 h . After completion, the reaction, mixture was evaporated to dryness and the crude was purified by reverse phase chromatography $\left(\mathrm{ACN} / \mathrm{H}_{2} \mathrm{O}\right)$ to afford 59 as a white solid ( $10 \mathrm{mg}, 89 \%$ ).
${ }^{1} \mathrm{H}$ NMR ( 400 MHz, DMSO- $\mathrm{d}^{6}$ ): $\delta 9.30(\mathrm{~s}, 1 \mathrm{H}), 7.13(\mathrm{~s}, 1 \mathrm{H}), 5.05-4.90(\mathrm{~m}, 2 \mathrm{H})$, $4.20(\mathrm{dd}, J=9.6,3.6 \mathrm{~Hz}, 1 \mathrm{H}), 3.31-3.26(\mathrm{~m}, 1 \mathrm{H}), 3.20-3.13(\mathrm{~m}, 1 \mathrm{H}), 1.72(\mathrm{~s}, 3 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR (101 MHz, DMSO- $d^{6}$ ): $\delta 156.99,140.36,113.15,77.11,43.86,18.86$.

## Preparation of 6-(prop-1-en-2-yl)-5,6-dihydro-4H-1,2,4-oxadiazine-3-thiol (60)



A mixture of 26d ( 1 eq., $20 \mathrm{mg}, 0.106 \mathrm{mmol}$ ) and TEA ( $2.2 \mathrm{eq} ., 32.3 \mu \mathrm{~L}, 0.233 \mathrm{mmol}$ ) in $\mathrm{MeCN}(0.67 \mathrm{~mL})$ was stirred at rt for 1 min . Then, 1,1 '-thiocarbonyldiimidazole ( 1.1 eq., $21.8 \mathrm{mg}, 0.116 \mathrm{mmol}$ ) in $\mathrm{MeCN}(0.333 \mathrm{~mL})$ was added dropwise to the mixture at $0^{\circ} \mathrm{C}$ and stirred at rt for 30 min . The mixture was concentrated in vacuo at $30^{\circ} \mathrm{C}$ and purified by reverse phase chromatography $\left(\mathrm{MeCN} / \mathrm{H}_{2} \mathrm{O}\right)$ to afford $\mathbf{6 0}$ as a yellow solid ( $16 \mathrm{mg}, 96 \%$ ).
${ }^{1} \mathrm{H}$ NMR ( 400 MHz, DMSO-d ${ }^{6}$ ): $\delta 6.13$ (s, 1H), $4.97-4.94$ (m, 1H), $4.88-4.81$ (m, 2 H ), $3.72(\mathrm{dd}, J=12.0,9.4 \mathrm{~Hz}, 1 \mathrm{H}), 3.42-3.25(\mathrm{~m}, 2 \mathrm{H}), 1.65(\mathrm{~s}, 3 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR (101 MHz, DMSO- $d^{6}$ ): $\delta 160.09,143.70,111.17,81.11,56.56,16.52$.

## Preparation of 2-((tert-butyldiphenylsilyl)oxy)acetic acid (62)



62
DMAP ( $3 \%, 0.144 \mathrm{~g}, 1.18 \mathrm{mmol}$ ) and TEA ( 1.06 eq., $5.79 \mathrm{~mL}, 41.7 \mathrm{mmol}$ ) was added to a solution of glycolic acid ( 1 eq., $2.36 \mathrm{~mL}, 39.4 \mathrm{mmol}$ ) in THF ( 150 mL ) and stirred at $0{ }^{\circ} \mathrm{C}$ for five minutes. Then, chlorotrimethylsilane ( 1.05 eq ., $5.28 \mathrm{~mL}, 41.3$ mmol ) was added dropwise over 15 minutes. After stirred at $0{ }^{\circ} \mathrm{C}$ for 1 h and at rt for 2 h , a second portion of TEA ( 1.06 eq., $5.8 \mathrm{~mL}, 41.7 \mathrm{mmol}$ ) was added at rt followed by the addition of tert-butylchlorodiphenylsilane ( 1.05 eq., $10.7 \mathrm{~mL}, 41.3 \mathrm{mmol}$ ). The resulted mixture was stirred for at rt for 3 hours. Upon completion, the reaction was
quenched by the addition of an aqueous solution of $\mathrm{AcOH}\left(45 \mathrm{~mL}\right.$ in 100 mL of $\mathrm{H}_{2} \mathrm{O}$ ). After stirred at rt for 2 hour, the mixture was poured into water, and extracted with $\mathrm{Et}_{2} \mathrm{O}$ thrice. The combined organic phases were washed with brine, dried over anhydrous $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and filtered. The filtrate was concentrated in vacuo and purified by silical gel chromatography $\left(\mathrm{Et}_{2} \mathrm{O} /\right.$ heptane $=10: 1$ to $\left.1: 1\right)$ to afford $\mathbf{6 2}$ as a light yellow oil ( $11.4 \mathrm{~g}, 92 \%$ ).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 10.07(\mathrm{~s}, 1 \mathrm{H}), 7.70-7.67(\mathrm{~m}, 4 \mathrm{H}), 7.49-7.40(\mathrm{~m}$, $6 \mathrm{H}), 4.28$ ( $\mathrm{s}, 2 \mathrm{H}$ ), 1.12 ( $\mathrm{s}, 9 \mathrm{H}$ ).

These data are consistent with the previously reported characterization. ${ }^{181}$

## Preparation of 2-((tert-butyldiphenylsilyl)oxy)- N -methoxy- N -methylacetamide

 (63)

63
The reaction was performed with $62(1 \mathrm{eq} ., 1.7 \mathrm{~g}, 5.41 \mathrm{mmol})$, CDI ( $1.3 \mathrm{eq} ., 1.14 \mathrm{~g}$, 7.03 mmol ) and $\mathrm{N}, \mathrm{O}$-dimethylhydroxylamine hydrochloride ( $1.3 \mathrm{eq} ., 0.686 \mathrm{~g}, 7.03$ $\mathrm{mmol})$ in DCM ( 15 mL ) according to typical procedure TP1, affording 63 as a colorless oil ( $1.9 \mathrm{~g}, 98 \%$ ).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.75-7.72(\mathrm{~m}, 4 \mathrm{H}), 7.43-7.37(\mathrm{~m}, 6 \mathrm{H}), 4.43(\mathrm{~s}, 2 \mathrm{H})$, $3.44(\mathrm{~s}, 3 \mathrm{H}), 3.14$ ( $\mathrm{s}, 3 \mathrm{H}$ ), 1.11 ( $\mathrm{s}, 9 \mathrm{H})$.
${ }^{13} \mathrm{C}^{\mathrm{NMR}}\left(101 \mathrm{MHz}, \mathrm{CDCl}_{3}\right): \delta 171.90,135.82,133.35,129.89,127.86,62.17,61.32$, 32.59, 26.89, 19.49.

## Preparation of 1-((tert-butyldiphenylsilyl)oxy)-3-methylbut-3-en-2-one (64)



64
The reaction was performed with 63 ( 1 eq., $600 \mathrm{mg}, 1.68 \mathrm{mmol}$ ) in THF ( 5.5 mL ) and the THF solution of isopropenylmagnesium bromide ( 4 eq., $0.5 \mathrm{M}, 13.4 \mathrm{~mL}, 6.71$ mmol ) according to typical procedure TP2 without further purification to afford $\mathbf{6 4}$ as a yellow oil ( $557 \mathrm{mg}, 98 \%$ ).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.71$ - $7.66(\mathrm{~m}, 4 \mathrm{H}), 7.43-7.37(\mathrm{~m}, 6 \mathrm{H}), 5.74(\mathrm{~s}, 1 \mathrm{H})$, $5.66(\mathrm{~d}, J=1.6 \mathrm{~Hz}, 1 \mathrm{H}), 4.65(\mathrm{~s}, 2 \mathrm{H}), 1.84(\mathrm{dd}, J=1.5,0.9 \mathrm{~Hz}, 3 \mathrm{H}), 1.12-1.09(\mathrm{~m}$, 9 H ).
${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 198.23,142.47,135.74,133.20,129.96,127.89$, 124.09, 66.82, 26.88, 19.47, 17.86.

## Preparation of 1-((tert-butyldiphenylsilyl)oxy)-3-methylbut-3-en-2-ol (65)



Trichlorocerium heptahydrate ( 1.6 eq., $1041 \mathrm{mg}, 2.79 \mathrm{mmol}$ ) was added to a solution of $\mathbf{6 4}(1 \mathrm{eq} ., 591 \mathrm{mg}, 1.75 \mathrm{mmol})$ in $\mathrm{MeOH}(10 \mathrm{~mL})$ and stirred at rt until the solution became clear. Then, the mixture was cooled to $-70^{\circ} \mathrm{C}$ and $\mathrm{NaBH}_{4}(1.3 \mathrm{eq} ., 85.9 \mathrm{mg}$, 2.27 mmol ) was added portionwise. After stirred at $-70^{\circ} \mathrm{C}$ for 20 min , the reaction was quenched by the addition of $\mathrm{H}_{2} \mathrm{O}$ at $-20^{\circ} \mathrm{C}$ and stirred for 5 min . MeOH was removed under reduced pressure. The resulting suspension was extracted with EtOAc thrice. The combined organic phases were washed with brine, dried over anhydrous $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and filtered. The filtrate was concentrated in vacuo without further purification to
afford 65 as a colorless oil ( $571 \mathrm{mg}, 96 \%$ ).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.69-7.66(\mathrm{~m}, 4 \mathrm{H}), 7.45-7.38(\mathrm{~m}, 6 \mathrm{H}), 5.02(\mathrm{~s}, 1 \mathrm{H})$, $4.89(\mathrm{~s}, 1 \mathrm{H}), 4.20-4.14(\mathrm{~m}, 1 \mathrm{H}), 3.73(\mathrm{dd}, J=10.2,3.7 \mathrm{~Hz}, 1 \mathrm{H}), 3.59(\mathrm{dd}, J=10.2$, $7.7 \mathrm{~Hz}, 1 \mathrm{H}), 2.72(\mathrm{~s}, 1 \mathrm{H}), 1.64(\mathrm{~s}, 3 \mathrm{H}), 1.08(\mathrm{~s}, 9 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 143.84,135.71,133.31,130.00,127.93,112.08$, 75.49, 67.08, 27.01, 19.41, 18.89.

Rf: 0.8 (heptane: $E t O A c=2: 1$ ).

Preparation of 2-((1-((tert-butyldiphenylsilyl)oxy)-3-methylbut-3-en-2-yl)oxy) isoindoline-1,3-dione (66)


66
According to typical procedure TP4, the reaction was performed by the addition of DEAD ( 1.3 eq., $0.353 \mathrm{~mL}, 2.25 \mathrm{mmol}$ ) into a solution of $\mathbf{6 5}(1 \mathrm{eq} ., 590 \mathrm{mg}, 1.73$ mmol), NHPI ( 1.3 eq., $367 \mathrm{mg}, 2.25 \mathrm{mmol}$ ) and $\mathrm{PPh}_{3}(1.3$ eq., $590 \mathrm{mg}, 2.25 \mathrm{mmol}$ ) in THF ( 10 mL ) under Ar at $0^{\circ} \mathrm{C}$ and stirred at rt for 2 h . The crude was purified by silica gel chromatography (heptane: $\mathrm{EtOAc}=7: 1$ ) to afford $\mathbf{6 6}$ as a yellow oil $(723 \mathrm{mg}$, 86 \%).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.81(\mathrm{dd}, J=5.4,3.1 \mathrm{~Hz}, 2 \mathrm{H}), 7.72(\mathrm{dd}, J=5.5,3.0$ $\mathrm{Hz}, 2 \mathrm{H}$ ), $7.68-7.65$ (m, 4H), $7.41-7.35$ (m, 6H), $5.04-4.98$ (m, 2H), 4.83 (dd, $J=$ $6.6,5.0 \mathrm{~Hz}, 1 \mathrm{H}), 4.12(\mathrm{dd}, J=11.4,6.6 \mathrm{~Hz}, 1 \mathrm{H}), 3.83(\mathrm{dd}, J=11.4,5.0 \mathrm{~Hz}, 1 \mathrm{H}), 1.78$ (s, 3H), 1.00 ( $\mathrm{s}, 9 \mathrm{H}$ ).
${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 163.72,140.48,135.80,134.36,133.37,129.89$, $129.20,127.84,123.50,118.18,91.21,64.07,26.81,19.27,17.73$.

Rf: 0.7 (heptane:EtOAc = 2:1).

## Preparation of $\boldsymbol{O}$-(1-((tert-butyldiphenylsilyl)oxy)-3-methylbut-3-en-2-yl)

 hydroxylamine (67)

67
According to typical procedure TP5, the reaction was performed with 66 (1 eq., 250 $\mathrm{mg}, 0.515 \mathrm{mmol}$ ) and hydrazine hydrate ( 15 eq., $0.749 \mathrm{~mL}, 7.72 \mathrm{mmol}$ ) in EtOH ( 6.25 mL ) in 20 min . The reaction mixture was concentrated in vacuo and filtered through a silica gel pad with EtOAc. The filtrate was concentrated in vacuo to afford $\mathbf{6 7}$ as a colorless oil ( $181 \mathrm{mg}, 99 \%$ ).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.72-7.68(\mathrm{~m}, 4 \mathrm{H}), 7.42-7.37(\mathrm{~m}, 6 \mathrm{H}), 5.29(\mathrm{~s}, 2 \mathrm{H})$, 4.99 - 4.96 (m, 2H), 4.04 (dd, $J=6.8,4.5 \mathrm{~Hz}, 1 \mathrm{H}), 3.74(\mathrm{dd}, J=11.1,6.8 \mathrm{~Hz}, 1 \mathrm{H})$, $3.66(\mathrm{dd}, J=11.1,4.5 \mathrm{~Hz}, 1 \mathrm{H}), 1.64-1.62(\mathrm{~m}, 3 \mathrm{H}), 1.06(\mathrm{~s}, 9 \mathrm{H})$. ${ }^{13} \mathrm{C}$ NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 142.51,135.79,133.75,129.79,127.78,113.93$, 89.41, 64.82, 26.98, 19.40, 18.72.

## Preparation of tert-butyl $\boldsymbol{N}$-((1Z)-(((tert-butoxy)carbonyl)imino)(methylsulfanyl)

 methyl)- $N$-(3-methylbut-2-en-1-yl)carbamate (68)

68
A solution of $N, N^{\prime}$-bis-Boc-S-Methyl-thiourea ( $1 \mathrm{eq} ., 500 \mathrm{mg}, 1.72 \mathrm{mmol}$ ) in DCM $(8.14 \mathrm{~mL}) / \mathrm{MeCN}(0.429 \mathrm{~mL})$ was added dropwise to a stirred mixture of $\mathrm{KOH}(2.81$ eq., $271 \mathrm{mg}, 4.84 \mathrm{mmol}$ ) and TBAB ( $0.185 \mathrm{eq} ., 102 \mathrm{mg}, 0.319 \mathrm{mmol}$ ) in DCM ( 8.14 $\mathrm{mL}) / \mathrm{MeCN}(0.429 \mathrm{~mL})$ at rt . After the resulting solution was stirred for 10 min , a
solution of 3,3-dimethylallyl bromide ( 2.39 eq., $0.484 \mathrm{~mL}, 4.12 \mathrm{mmol}$ ) in DCM ( 13.6 $\mathrm{mL}) / \mathrm{MeCN}(0.714 \mathrm{~mL})$ was slowly added over 10 min and stirred at rt for 3 h . The reaction mixture was diluted with water, and extracted with DCM thrice. The combine organic phases were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and filtered. The filtrate was concentrated in vacuo to afford the residue, which was then filtered through a short silica gel pad with heptane/EtOAc (9:1). The filtrate was concentrated in vacuo to afford $\mathbf{6 8}$ as a colorless oil ( $592 \mathrm{mg}, 96 \%$ ).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 5.28-5.21(\mathrm{~m}, 1 \mathrm{H}), 4.11(\mathrm{~d}, J=6.8 \mathrm{~Hz}, 2 \mathrm{H}), 2.34(\mathrm{~s}$, 3 H ), $1.70(\mathrm{~s}, 3 \mathrm{H}), 1.65(\mathrm{~s}, 3 \mathrm{H}), 1.48(\mathrm{~s}, 9 \mathrm{H}), 1.44(\mathrm{~s}, 9 \mathrm{H})$.
${ }^{13}{ }^{3}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 163.34,158.12,152.02,136.02,119.79,82.31,81.81$, 46.95, 28.25, 28.16, 25.85, 18.16, 15.74.

Preparation of $N$-(2,4-dimethoxybenzyl)- $N$-(3-methylbut-2-en-1-yl)cyanamide (69)


69
$\operatorname{BrCN}(1.1$ eq., $32.7 \mathrm{mg}, 0.309 \mathrm{mmol})$ was added to a solution of $56(1 \mathrm{eq} ., 66 \mathrm{mg}$, 0.28 mmol ) and TEA ( 1.1 eq., $42.9 \mu \mathrm{~L}, 0.309 \mathrm{mmol}$ ) in THF ( 1 mL ) and stirred at rt for 20 min . The crude was washed with saturated $\mathrm{NaHCO}_{3}$ aqueous solution and extracted with EtOAc. The organic phase was separated and filtered through a silica gel pad. The filtrate was concentrated in vacuo to afford $\mathbf{6 9}$ as a colorless oil ( 73 mg , 100 \%).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.22-7.12(\mathrm{~m}, 1 \mathrm{H}), 6.54-6.42(\mathrm{~m}, 2 \mathrm{H}), 5.37-5.22$ (m, 1H), 4.09 (s, 2H), $3.90-3.78(\mathrm{~m}, 6 \mathrm{H}), 3.52(\mathrm{~d}, J=7.2 \mathrm{~Hz}, 2 \mathrm{H}), 1.76(\mathrm{~s}, 3 \mathrm{H}), 1.62$ (s, 3H).
${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 161.39,159.04,139.33,131.34,118.64,117.73$, $115.85,104.24,98.76,55.48,49.50,48.07,25.88,18.07$.

## Preparation of tert-butyl (tert-butoxycarbonyl)oxycarbamate (72)



72
A solution of $\mathrm{Boc}_{2} \mathrm{O}(2.1 \mathrm{eq} ., 27.9 \mathrm{~g}, 127 \mathrm{mmol})$ and TEA ( $2.1 \mathrm{eq} ., 17.8 \mathrm{~mL}, 127$ $\mathrm{mmol})$ in petroleum ether $(20 \mathrm{~mL}) /$ methyl tert-butyl ether $(7 \mathrm{~mL})$ was added dropwise over 45 minutes to a solution of hydroxylamine hydrochloride ( $1 \mathrm{eq} ., 4.23 \mathrm{~g}, 60.9$ $\mathrm{mmol})$ in $\mathrm{H}_{2} \mathrm{O}(40 \mathrm{~mL})$ at $0^{\circ} \mathrm{C}$. The resulting biphasic reaction mixture was stirred at $0{ }^{\circ} \mathrm{C}$ for 6 hours, and then at rt for 16 hours. The reaction mixture was extracted with ether thrice. The combined organic phases were washed with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and filtered. The filtrate was concentrated in vacuo and purified by silica gel chromatography (Heptane: $\mathrm{EtOAc}=20: 1$ to $10: 1$ ) to $\mathbf{7 2}$ as a colorless oil $(11.6 \mathrm{~g}$, 82 \%).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.58$ (s, 1H), 1.51 (s, 9H), 1.48 (s, 9H).
Rf: 0.8 (heptane:EtOAc $=5: 1$ ).
These data are consistent with the previously reported characterization. ${ }^{182}$

## Preparation of tert-butyl (1-((tert-butoxycarbonyl)amino)-3-methylbut-3-en-2-yl)

 ((tert-butoxycarbonyl)oxy)carbamate (73)

73
To a solution of $\mathbf{2 0 d}$ ( $1 \mathrm{eq} ., 600 \mathrm{mg}, 2.98 \mathrm{mmol}$ ), $\mathrm{PPh}_{3}(1.4 \mathrm{eq} ., 1094 \mathrm{mg}, 4.17 \mathrm{mmol}$ ) and 72 ( 1.4 eq., $973 \mathrm{mg}, 4.17 \mathrm{mmol}$ ) in THF ( 18 mL ) was added dropwise DEAD (1.4 eq., $0.66 \mathrm{~mL}, 4.17 \mathrm{mmol}$ ) under Ar at $0^{\circ} \mathrm{C}$. The resulting mixture was stirred for an additionnal 1 h at $0^{\circ} \mathrm{C}$ then at rt for 16 h . The reaction was quenched with the addition of water and extracted with EtOAc thrice. The combined organic phases were washed
with brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and filtered. The filtrate was concentrated in vacuo and purified by silica gel chromatography (Heptane:EtOAc $=15: 1$ to $10: 1$ )to afford 73 as a colorless oil ( $1.2 \mathrm{~g}, 97 \%$ ).
${ }^{1} \mathrm{H}_{\mathrm{NMR}}\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right): \delta 5.47(\mathrm{~s}, 0.63 \mathrm{H}), 4.96(\mathrm{~s}, 1 \mathrm{H}), 4.88(\mathrm{~s}, 1 \mathrm{H}), 4.81(\mathrm{~s}$, 0.35 H ), $4.69-4.61(\mathrm{~m}, 1 \mathrm{H}), 3.79(\mathrm{t}, J=11.1 \mathrm{~Hz}, 0.66 \mathrm{H}), 3.58(\mathrm{~s}, 0.34 \mathrm{H}), 3.40(\mathrm{~s}$, $0.3 \mathrm{H}), 2.89(\mathrm{t}, J=12.0 \mathrm{~Hz}, 0.7 \mathrm{H}), 1.83(\mathrm{~s}, 1 \mathrm{H}), 1.75(\mathrm{~s}, 2 \mathrm{H}), 1.54-1.42(\mathrm{~m}, 27 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 159.12,156.18,154.80,140.70,114.00,85.42,82.88$, 79.41, 63.20, 39.39, 28.58, 28.27, 27.70, 21.15.

Rf: 0.55 (heptane: $\mathrm{EtOAc}=3: 1$ ).

## Preparation of 2-(hydroxyamino)-3-methylbut-3-en-1-amine dihydrochloride

 (74)

A solution of 73 ( $1 \mathrm{eq} ., 187 \mathrm{mg}, 0.449 \mathrm{mmol}$ ) in $\mathrm{HCl} /$ dioxane $(4 \mathrm{M}, 3 \mathrm{~mL})$ was stirred at rt for 3 h . The reaction was concentrated in vacuo and dried under reduced pressure overnight to afford 74 as a hygroscopic white solid ( $84 \mathrm{mg}, 99 \%$ ).
${ }^{1} \mathrm{H}$ NMR ( 400 MHz, DMSO- $d^{6}$ ): $\delta 11.86$ ( $\mathrm{s}, 2 \mathrm{H}$ ), 10.91 ( $\mathrm{s}, 1 \mathrm{H}$ ), 8.35 ( $\mathrm{s}, 3 \mathrm{H}$ ), 5.28 (s, $1 \mathrm{H}), 5.25(\mathrm{t}, J=1.5 \mathrm{~Hz}, 1 \mathrm{H}), 4.10(\mathrm{t}, J=6.6 \mathrm{~Hz}, 1 \mathrm{H}), 3.32-3.11(\mathrm{~m}, 2 \mathrm{H}), 1.82(\mathrm{~s}$, $3 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR (101 MHz, DMSO- $d^{6}$ ): $\delta 135.48,120.57,62.94,36.34,19.34$.

Preparation of 2-amino-5-(prop-1-en-2-yl)-4,5-dihydro-1H-imidazol-1-ol (75)


75
TEA (4 eq., $119 \mathrm{mg}, 0.165 \mathrm{~mL}, 1.18 \mathrm{mmol}$ ) was added dropwise to a solution of 74 ( 1
eq., $56 \mathrm{mg}, 0.296 \mathrm{mmol})$ in $\mathrm{MeCN}(12 \mathrm{~mL})$ under at $0{ }^{\circ} \mathrm{C}$ and stirred for additional 15 min . Then a solution of $\mathrm{BrCN}(1.1 \mathrm{eq} ., 34.5 \mathrm{mg}, 0.326 \mathrm{mmol})$ in $\mathrm{MeCN}(2 \mathrm{~mL})$ was added slowly at $0{ }^{\circ} \mathrm{C}$. After stirring at $0{ }^{\circ} \mathrm{C}$ for 4 h , the reaction mixture was concentrated in vacuo and purified by reverse phase chromatography $\left(100 \% \mathrm{H}_{2} \mathrm{O}\right)$ to afford 75 as a white solid ( $34 \mathrm{mg}, 81 \%$ ).
${ }^{1} \mathrm{H}$ NMR ( 400 MHz, DMSO- $d^{6}$ ): $\delta 10.29(\mathrm{~s}, 1 \mathrm{H}), 8.60(\mathrm{~s}, 2 \mathrm{H}), 5.13(\mathrm{~s}, 1 \mathrm{H}), 5.06(\mathrm{t}, J$ $=1.7 \mathrm{~Hz}, 1 \mathrm{H}), 4.31(\mathrm{t}, J=9.3 \mathrm{~Hz}, 1 \mathrm{H}), 3.64(\mathrm{t}, J=9.4 \mathrm{~Hz}, 1 \mathrm{H}), 3.25(\mathrm{t}, J=9.9 \mathrm{~Hz}$, 1H), 1.74 (s, 3H).
${ }^{13} \mathrm{C}$ NMR (101 MHz, DMSO- $d^{6}$ ): $\delta 161.96,139.50,116.68,68.26,43.84,17.14$.

## Preparation of 2-(((tert-butyldiphenylsilyl)oxy)amino)-3-methylbut-3-en-1-amine

 (76)

TEA ( 2 eq., $0.147 \mathrm{~mL}, 1.06 \mathrm{mmol}$ ) was slowly added to a suspension of 74 ( $1 \mathrm{eq} ., 100$ $\mathrm{mg}, 0.529 \mathrm{mmol})$ in dry DMF ( 3 mL ) at $0^{\circ} \mathrm{C}$ and stirred for 10 min . Then TBDMSCl ( 3 eq., $0.411 \mathrm{~mL}, 1.59 \mathrm{mmol}$ ) and imidazole ( $3.5 \mathrm{eq} ., 126 \mathrm{mg}, 1.85 \mathrm{mmol}$ ) was added and stirred at $60^{\circ} \mathrm{C}$ for 4 h . The crude was purified by reverse phase chromatography $\left(\mathrm{MeOH} / \mathrm{H}_{2} \mathrm{O}\right)$ to afford 76 was a white solid ( $26 \mathrm{mg}, 14 \%$ ).
${ }^{1} \mathrm{H}$ NMR (400 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 10.76$ (s, 2H), $7.72-7.67$ (m, 4H), $7.48-7.39(\mathrm{~m}$, $6 \mathrm{H}), 5.45(\mathrm{~d}, J=6.8 \mathrm{~Hz}, 1 \mathrm{H}), 5.01-4.93(\mathrm{~m}, 1 \mathrm{H}), 4.78(\mathrm{~s}, 1 \mathrm{H}), 3.69-3.59(\mathrm{~m}, 2 \mathrm{H})$, 3.38 (dd, $J=14.0,7.7 \mathrm{~Hz}, 1 \mathrm{H}), 1.79$ (s, 3H), 1.06 (s, 9H). ${ }^{13} \mathrm{C}$ NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 150.84,143.11,135.73,130.24,128.11,119.89$, 66.50, 37.42, 27.22, 20.44, 19.32.

## Preparation of $N$-(3-methylbut-2-en-1-yl)-1-((3-methylbut-2-en-1-yl)oxy)-5-

## (prop-1-en-2-yl)-4,5-dihydro-1H-imidazol-2-amine (77)



77
A solution of $\mathrm{NaH}(3 \mathrm{eq} ., 9.84 \mathrm{mg}, 0.41 \mathrm{mmol})$ in $\mathrm{THF}(0.4 \mathrm{~mL})$ was added slowly to a solution of 75 ( 1 eq., $19.3 \mathrm{mg}, 0.137 \mathrm{mmol}$ ) in THF $(0.2 \mathrm{~mL})$ at $0{ }^{\circ} \mathrm{C}$ under Ar. The mixture was stirred at $0{ }^{\circ} \mathrm{C}$ for 2 h followed by the addition of 3,3-dimethylallyl bromide ( 3 eq., $48.1 \mu \mathrm{~L}, 0.41 \mathrm{mmol}$ ) and then the resulting mixture was stirred at rt for additional 16 h . The reaction mixture was concentrated in vacuo and purified by reverse phase chromatography $\left(\mathrm{MeOH} / \mathrm{H}_{2} \mathrm{O}\right)$ to afford 77 as a white solid ( 29 mg , 76 \%).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{MeOD}-d^{4}$ ): $\delta 5.46-5.40(\mathrm{~m}, 1 \mathrm{H}), 5.24-5.17(\mathrm{~m}, 2 \mathrm{H}), 5.17-$ $5.14(\mathrm{~m}, 1 \mathrm{H}), 4.54(\mathrm{dd}, J=8.7,7.2 \mathrm{~Hz}, 1 \mathrm{H}), 4.51-4.40(\mathrm{~m}, 2 \mathrm{H}), 4.02(\mathrm{~d}, J=7.3 \mathrm{~Hz}$, $2 \mathrm{H}), 3.68$ (dd, $J=10.0,8.8 \mathrm{~Hz}, 1 \mathrm{H}), 3.40(\mathrm{dd}, J=10.0,7.2 \mathrm{~Hz}, 1 \mathrm{H}), 1.82-1.80(\mathrm{~m}$, $3 \mathrm{H}), 1.80-1.78(\mathrm{~m}, 6 \mathrm{H}), 1.77-1.75(\mathrm{~m}, 3 \mathrm{H}), 1.72-1.70(\mathrm{~m}, 3 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{MeOD}-d^{4}$ ): $\delta$ 161.57, 142.62, 142.23, 140.71, 119.69, 119.06, 116.07, 73.90, 68.46, 49.39, 44.00, 25.97, 25.81, 18.26, 18.05, 17.10.

Preparation of 2-amino-5-(prop-1-en-2-yl)-4,5-dihydro-1 $\boldsymbol{H}$-imidazol-1-yl tert-butyl carbonate (79a), tert-butyl(1-((tert-butoxycarbonyl)oxy)-5-(prop-1-en-2-yl)-4,5-dihydro-1H-imidaz ol-2-yl)carbamate (79b) and

2-(bis((tert-butoxy)carbonyl)amino)-5-(prop-1-en-2-yl)-4,5-dihydro-1H-imidazol-1-yl tert-butyl carbonate (79c)


79a


79b


79c

75 ( 1 eq., $25 \mathrm{mg}, 0.177 \mathrm{mmol}$ ) and TEA ( 2.1 eq., $51.7 \mu \mathrm{~L}, 0.372 \mathrm{mmol}$ ) were dissolved in THF ( 2.45 mL ), cooled to $0^{\circ} \mathrm{C}$, and then a solution of $\mathrm{Boc}_{2} \mathrm{O}(2.1 \mathrm{eq}$., $81.2 \mathrm{mg}, 0.372 \mathrm{mmol})$ in THF $(0.49 \mathrm{~mL})$ was added. The mixture was stirred at $0^{\circ} \mathrm{C}$ for an additional 12 h and concentrated in vacuo. The crude was purified by reverse phase chromatography $\left(\mathrm{ACN} / \mathrm{H}_{2} \mathrm{O}\right)$ to afford 79a ( $15 \mathrm{mg}, 35 \%$ ), 79b ( $9 \mathrm{mg}, 15 \%$ ) and 79c ( $17 \mathrm{mg}, 22 \%$ ) as white solids.
${ }^{1} \mathrm{H}$ NMR ( 400 MHz , DMSO- $d^{6}$ ) of 79a: $\delta 8.28(\mathrm{~s}, 2 \mathrm{H}), 5.05(\mathrm{~s}, 1 \mathrm{H}), 4.97(\mathrm{t}, J=1.7$ $\mathrm{Hz}, 1 \mathrm{H}), 3.90(\mathrm{t}, J=9.0 \mathrm{~Hz}, 1 \mathrm{H}), 3.75(\mathrm{dd}, J=10.0,8.4 \mathrm{~Hz}, 1 \mathrm{H}), 3.23(\mathrm{t}, J=9.8 \mathrm{~Hz}$, $1 \mathrm{H}), 1.70(\mathrm{~s}, 3 \mathrm{H}), 1.46(\mathrm{~s}, 9 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR (101 MHz, DMSO- $d^{6}$ ) of 79a: $\delta 155.73,151.39,141.28,114.93,82.15$, 63.79, 44.68, 27.67, 17.00.
${ }^{1} \mathrm{H}$ NMR ( 400 MHz, DMSO- $d^{6}$ ) of 79b: $\delta 9.53(\mathrm{~s}, 1 \mathrm{H}), 5.07(\mathrm{~s}, 1 \mathrm{H}), 5.01-4.99(\mathrm{~m}$, $1 \mathrm{H}), 4.07(\mathrm{t}, J=9.0 \mathrm{~Hz}, 1 \mathrm{H}), 3.83(\mathrm{dd}, J=10.1,8.8 \mathrm{~Hz}, 1 \mathrm{H}), 3.37-3.34(\mathrm{~m}, 1 \mathrm{H})$, $1.72(\mathrm{~s}, 3 \mathrm{H}), 1.44(\mathrm{~s}, 9 \mathrm{H}), 1.38(\mathrm{~s}, 9 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR (101 MHz, DMSO- $d^{6}$ ) of 79b: $\delta 158.18,149.83,148.90,140.55,115.88$, 81.72, 78.14, 64.79, 45.35, 27.83, 27.58, 16.74.
${ }^{1} \mathrm{H}$ NMR ( 400 MHz, DMSO- $d^{6}$ ) of 79c: $\delta 5.13(\mathrm{~s}, 1 \mathrm{H}), 5.06-5.03(\mathrm{~m}, 1 \mathrm{H}), 4.35(\mathrm{t}, J$ $=8.8 \mathrm{~Hz}, 1 \mathrm{H}), 3.94(\mathrm{dd}, J=10.2,8.7 \mathrm{~Hz}, 1 \mathrm{H}), 3.59(\mathrm{dd}, J=10.2,9.1 \mathrm{~Hz}, 1 \mathrm{H}), 1.77(\mathrm{~s}$, $3 \mathrm{H}), 1.45(\mathrm{~s}, 9 \mathrm{H}), 1.43(\mathrm{~s}, 9 \mathrm{H}), 1.39(\mathrm{~s}, 9 \mathrm{H})$.

Preparation of tert-butyl (2-((3-methylbut-2-en-1-yl)amino)-5-(prop-1-en-2-yl)

## -4,5-dihydro-1H-imidazol-1-yl) carbonate (80)



80

A suspension of $\mathrm{NaH}(1.2 \mathrm{eq} ., 1.55 \mathrm{mg}, 0.0647 \mathrm{mmol})$ in THF $(0.4 \mathrm{~mL})$ was added slowly to a solution of $\mathbf{7 9 a}$ ( 1 eq., $13 \mathrm{mg}, 0.0539 \mathrm{mmol}$ ) in THF $(1 \mathrm{~mL})$ at $0{ }^{\circ} \mathrm{C}$ under Ar and stirred for an additional 2 h at $0^{\circ} \mathrm{C}$. Then, 3,3-dimethylallyl bromide ( 1.2 eq., $7.6 \mu \mathrm{~L}, 0.0647 \mathrm{mmol}$ ) was added to the reaction mixture at $0^{\circ} \mathrm{C}$ and the resulting mixture was stirred at rt for 16 h . The reaction mixture was then concentrated in vacuo and purified by reverse phase chromatography $\left(\mathrm{ACN} / \mathrm{H}_{2} \mathrm{O}\right)$ to afford $\mathbf{8 0}$ as a white solid ( $11 \mathrm{mg}, 66 \%$ ).
${ }^{1} \mathrm{H}$ NMR ( 400 MHz, DMSO- $d^{6}$ ): $\delta 7.50(\mathrm{~s}, 1 \mathrm{H}), 5.30(\mathrm{t}, J=7.0 \mathrm{~Hz}, 1 \mathrm{H}), 5.11(\mathrm{~s}, 1 \mathrm{H})$, $5.05-5.01(\mathrm{~m}, 1 \mathrm{H}), 4.51(\mathrm{t}, J=9.0 \mathrm{~Hz}, 1 \mathrm{H}), 4.30(\mathrm{dd}, J=10.6,7.3 \mathrm{~Hz}, 1 \mathrm{H}), 3.95(\mathrm{t}$, $J=8.7 \mathrm{~Hz}, 1 \mathrm{H}), 3.69(\mathrm{dd}, J=10.2,8.3 \mathrm{~Hz}, 1 \mathrm{H}), 3.28(\mathrm{t}, J=9.8 \mathrm{~Hz}, 1 \mathrm{H}), 1.74(\mathrm{~s}, 3 \mathrm{H})$, $1.69(\mathrm{~s}, 3 \mathrm{H}), 1.65-1.62(\mathrm{~m}, 3 \mathrm{H}), 1.47(\mathrm{~s}, 9 \mathrm{H})$.
${ }^{13}$ C NMR (101 MHz, DMSO-d ${ }^{6}$ ): $\delta$ 166.32, 161.96, 140.73, 140.36, 119.31, 116.41, $70.45,65.15,63.28,44.25,27.65,25.39,17.93,16.86$.

## Preparation of 1-phenyl-3,5-dihydrobenzo[e][1,2]oxazepin-4(1H)-one (81)



81
TEA ( 2.2 eq., $8.32 \mathrm{mg}, 0.0114 \mathrm{~mL}, 0.0822 \mathrm{mmol}$ ) was added to solution of $\mathbf{1 0 5}$ ( 1 eq ., $15 \mathrm{mg}, 0.0374 \mathrm{mmol}$ ) and methylhydrazine sulphate ( $1.1 \mathrm{eq} ., 5.93 \mathrm{mg}, 0.0411 \mathrm{mmol}$ ) in EtOH ( 0.97 mL ). After stirred at $25^{\circ} \mathrm{C}$ for 4 h , the mixture was concentrated in vacuo and purified by reverse phase chromatography $\left(\mathrm{MeOH} / \mathrm{H}_{2} \mathrm{O}\right)$ to $\mathbf{8 1}$ as a white solid ( $7.5 \mathrm{mg}, 84 \%$ ).
${ }^{1} \mathrm{H}$ NMR ( 400 MHz, DMSO- $d^{6}$ ): $\delta 11.01(\mathrm{~s}, 1 \mathrm{H}), 7.38-7.34(\mathrm{~m}, 5 \mathrm{H}), 7.30-7.27(\mathrm{~m}$, $1 \mathrm{H}), 7.21-7.15(\mathrm{~m}, 2 \mathrm{H}), 6.90-6.85(\mathrm{~m}, 1 \mathrm{H}), 6.18(\mathrm{~s}, 1 \mathrm{H}), 4.63(\mathrm{~d}, \mathrm{~J}=13.5 \mathrm{~Hz}, 1 \mathrm{H})$, $3.64-3.63(\mathrm{~m}, 1 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR (101 MHz, DMSO- $d^{6}$ ): $\delta 176.48,140.14,137.99,130.74,130.53,128.78$, $128.60,128.58,128.52,127.12,127.06,87.82,41.60$.

## Preparation of 2-(2-ethoxy-2-oxoethyl)benzoic acid (82a)



82a
Method 1: $\mathrm{H}_{2} \mathrm{SO}_{4}(0.5$ eq., $0.71 \mathrm{~mL}, 13.3 \mathrm{mmol})$ was added to a solution of homophthalic acid ( 1 eq., $4.8 \mathrm{~g}, 26.6 \mathrm{mmol}$ ) in $\mathrm{EtOH}(12 \mathrm{~mL})$ and the resulting mixture was refluxed at $85^{\circ} \mathrm{C}$ for 2 h . After completion, the reaction mixture was concentrated in vacuo, water was added and basified by $\mathrm{Na}_{2} \mathrm{CO}_{3}$ to $\mathrm{pH} \sim 9$. The aqueous layer was washed with EtOAc, then acidified by $\mathrm{H}_{2} \mathrm{SO}_{4}$ (1M) to $\mathrm{pH} \sim 3$ and extracted with EtOAc thrice. The organic phases were washed with brine, dried over anhydrous $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and filtered. The filtrate was concentrated in vacuo to afford 82a as a white solid ( $4.5 \mathrm{~g}, 81 \%$ ).

Method 2: The reaction was performed with 2-bromobenzoic acid (1 eq., 500 mg , 2.49 mmol ), ethyl acetoacetate ( $2 \mathrm{eq} ., 0.629 \mathrm{~mL}, 4.97 \mathrm{mmol}$ ), NaOEt ( 3 eq., 507 mg , $7.46 \mathrm{mmol})$ and $\mathrm{CuBr}(0.1 \mathrm{eq} ., 35.7 \mathrm{mg}, 0.249 \mathrm{mmol})$ in anhydrous ethanol $(10 \mathrm{~mL})$ in 1.5 h according to typical procedure method TP8, affording 82a as a yellow solid ( $507 \mathrm{mg}, 98 \%$ ).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 8.13(\mathrm{~d}, \mathrm{~J}=7.8 \mathrm{~Hz}, 1 \mathrm{H}), 7.54(\mathrm{t}, \mathrm{J}=7.5 \mathrm{~Hz}, 1 \mathrm{H}), 7.40$ $(\mathrm{t}, \mathrm{J}=7.6 \mathrm{~Hz}, 1 \mathrm{H}), 7.28(\mathrm{~d}, \mathrm{~J}=7.6 \mathrm{~Hz}, 1 \mathrm{H}), 4.17(\mathrm{q}, \mathrm{J}=7.0 \mathrm{~Hz}, 2 \mathrm{H}), 4.05(\mathrm{~s}, 2 \mathrm{H})$, $1.26(\mathrm{t}, \mathrm{J}=7.0 \mathrm{~Hz}, 3 \mathrm{H})$.

Rf: 0.5 ( $\mathrm{DCM}: \mathrm{MeOH}=20: 1$, containing $0.5 \% \mathrm{AcOH}$ ).
These data are consistent with the previously reported characterization. ${ }^{183}$

## Preparation of 2-(2-ethoxy-2-oxoethyl)-3-methoxybenzoic acid (82b)



82b
The reaction was performed with 2-bromo-3-methoxybenzoic acid (1 eq., 50 mg , 0.216 mmol ), ethyl acetoacetate ( $2 \mathrm{eq} ., 0.0547 \mathrm{~mL}, 0.433 \mathrm{mmol}$ ), NaOEt ( $3 \mathrm{eq} ., 44.2$ $\mathrm{mg}, 0.649 \mathrm{mmol})$ and $\mathrm{CuBr}(0.1$ eq., $3.1 \mathrm{mg}, 0.0216 \mathrm{mmol}$ ) in anhydrous ethanol $(0.75 \mathrm{~mL})$ in 16 h according to typical procedure TP8, affording $\mathbf{8 2 b}$ as a white solid ( $48.5 \mathrm{mg}, 94 \%$ ).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.69(\mathrm{~d}, J=7.8 \mathrm{~Hz}, 1 \mathrm{H}), 7.34(\mathrm{t}, J=8.1 \mathrm{~Hz}, 1 \mathrm{H}), 7.11$ (d, $J=8.2 \mathrm{~Hz}, 1 \mathrm{H}), 4.21-4.12(\mathrm{~m}, 4 \mathrm{H}), 3.85(\mathrm{~s}, 3 \mathrm{H}), 1.26(\mathrm{t}, J=7.1 \mathrm{~Hz}, 3 \mathrm{H})$.

These data are consistent with the previously reported characterization. ${ }^{173}$

## Preparation of 4-bromo-2-(2-ethoxy-2-oxoethyl)benzoic acid (82c)



82c
The reaction was performed with 2,4-dibromobenzoic acid (1 eq., $1.4 \mathrm{~g}, 5 \mathrm{mmol}$ ), ethyl acetoacetate ( 2 eq., $1.26 \mathrm{~mL}, 10 \mathrm{mmol}$ ), NaOEt ( 3 eq., $1.02 \mathrm{~g}, 15 \mathrm{mmol}$ ) and $\mathrm{CuBr}(0.1 \mathrm{eq} ., 71.7 \mathrm{mg}, 0.5 \mathrm{mmol})$ in anhydrous ethanol $(16 \mathrm{~mL})$ in 3 h according to typical procedure TP8, affording 82c as a white solid ( $1.4 \mathrm{~g}, 97 \%$ ).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.98(\mathrm{~d}, J=8.4 \mathrm{~Hz}, 1 \mathrm{H}), 7.54(\mathrm{dd}, J=8.4,2.0 \mathrm{~Hz}, 1 \mathrm{H})$, 7.45 (d, $J=2.0 \mathrm{~Hz}, 1 \mathrm{H}), 4.17$ (q, $J=7.1 \mathrm{~Hz}, 2 \mathrm{H}), 4.00(\mathrm{~s}, 2 \mathrm{H}), 1.26(\mathrm{t}, J=7.1 \mathrm{~Hz}$, $3 \mathrm{H})$.
${ }^{13}{ }^{3}$ NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 171.81,170.99,138.97,135.54,133.42,130.95$, 128.29, 127.73, 61.18, 40.62, 14.29.


82d
The reaction was performed with 2-bromo-4-methoxybenzoic acid (1 eq., $600 \mathrm{mg}, 2.6$ mmol ), ethyl acetoacetate ( 2 eq., $0.656 \mathrm{~mL}, 5.19 \mathrm{mmol}$ ), NaOEt ( 3 eq., 530 mg 7.79 $\mathrm{mmol})$ and $\mathrm{CuBr}(0.1$ eq., 37.3 mg 0.26 mmol ) in anhydrous ethanol $(10 \mathrm{~mL})$ in 3 h according to typical procedure TP8, affording 82d as a white solid ( $602 \mathrm{mg}, 97 \%$ ).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 8.13$ (d, $\left.J=8.8 \mathrm{~Hz}, 1 \mathrm{H}\right), 6.87$ (dd, $J=8.8,2.6 \mathrm{~Hz}, 1 \mathrm{H}$ ), $6.77(\mathrm{~d}, J=2.6 \mathrm{~Hz}, 1 \mathrm{H}), 4.17(\mathrm{q}, J=7.1 \mathrm{~Hz}, 2 \mathrm{H}), 4.01(\mathrm{~s}, 2 \mathrm{H}), 3.86(\mathrm{~s}, 3 \mathrm{H}), 1.26(\mathrm{t}, J$ $=7.1 \mathrm{~Hz}, 3 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 172.08,171.50,163.39,139.71,134.46,120.85$, $118.32,112.44,60.88,55.58,41.33,14.32$.

## Preparation of 5-chloro-2-(2-ethoxy-2-oxoethyl)benzoic acid (82e)



82e
Method 1: The reaction was performed with 2-bromo-5-chlorobenzoic acid (1 eq., 1 g , 4.25 mmol ), ethyl acetoacetate ( $2 \mathrm{eq} ., 1.07 \mathrm{~mL}, 8.49 \mathrm{mmol}$ ), NaOEt ( $3 \mathrm{eq} ., 1.01 \mathrm{~g}$, $14.9 \mathrm{mmol})$ and CuBr ( $0.1 \mathrm{eq} ., 60.9 \mathrm{mg}, 0.425 \mathrm{mmol}$ ) in anhydrous ethanol ( 12 mL ) in 1 h according to typical procedure TP8, affording 82e as a white solid ( $1 \mathrm{~g}, 97 \%$ ).

Method 2: The reaction was performed with 5-chloro-2-iodobenzoic acid (1 eq., 1.4 g , 4.96 mmol ), ethyl acetoacetate ( $2 \mathrm{eq} ., 1.25 \mathrm{~mL}, 9.91 \mathrm{mmol}$ ), $\mathrm{NaOEt}(3 \mathrm{eq} ., 1.01 \mathrm{~g}$, $14.9 \mathrm{mmol})$ and $\mathrm{CuBr}(0.1 \mathrm{eq} ., 71.1 \mathrm{mg}, 0.496 \mathrm{mmol})$ in anhydrous ethanol ( 12 mL ) in 3 h according to typical procedure $\mathbf{T P 8}$, affording 82e as a white solid $(1.1 \mathrm{~g}$, $91 \%$ ).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 10.09(\mathrm{~s}, 1 \mathrm{H}), 8.10(\mathrm{~d}, J=2.4 \mathrm{~Hz}, 1 \mathrm{H}), 7.50(\mathrm{dd}, J=$ 8.2, 2.3 Hz, 1H), 7.23 (d, $J=8.2 \mathrm{~Hz}, 1 \mathrm{H}), 4.17(\mathrm{q}, J=7.1 \mathrm{~Hz}, 2 \mathrm{H}), 4.01(\mathrm{~s}, 2 \mathrm{H}), 1.26$ (t, $J=7.1 \mathrm{~Hz}, 3 \mathrm{H}$ ).
${ }^{13} \mathrm{C}$ NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 171.33,171.25,135.42,133.83,133.64,133.27$, $131.89,130.33,61.17,40.29,14.29$.

Preparation of 2-(2-ethoxy-2-oxoethyl)-5-nitrobenzoic acid (82f)


82f
The reaction was performed with 2-bromo-5-nitrobenzoic acid ( $1 \mathrm{eq} ., 1 \mathrm{~g}, 4.06 \mathrm{mmol}$ ), ethyl acetoacetate ( 2 eq., $1.03 \mathrm{~mL}, 8.13 \mathrm{mmol}$ ), NaOEt ( $3 \mathrm{eq} ., 0.83 \mathrm{~g}, 12.2 \mathrm{mmol}$ ) and $\mathrm{CuBr}(0.1$ eq., $58.3 \mathrm{mg}, 0.406 \mathrm{mmol}$ ) in anhydrous ethanol $(12 \mathrm{~mL})$ in 3 h according to typical procedure TP8, affording 82 f as a white solid ( $0.96 \mathrm{~g}, 93 \%$ ).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 8.96(\mathrm{~d}, J=2.5 \mathrm{~Hz}, 1 \mathrm{H}), 8.38(\mathrm{dd}, J=8.4,2.4 \mathrm{~Hz}, 1 \mathrm{H})$, $7.51(\mathrm{~d}, J=8.4 \mathrm{~Hz}, 1 \mathrm{H}), 4.23-4.15(\mathrm{~m}, 4 \mathrm{H}), 1.27(\mathrm{t}, J=7.1 \mathrm{~Hz}, 3 \mathrm{H})$.
These data are consistent with the previously reported characterization. ${ }^{183}$

## Preparation of 2-(2-ethoxy-2-oxoethyl)-5-(trifluoromethyl)benzoic acid (82g)



82g
The reaction was performed with 2-bromo-5-(trifluoromethyl)benzoic acid (1 eq., $1.35 \mathrm{~g}, 5 \mathrm{mmol}$ ), ethyl acetoacetate ( $2 \mathrm{eq} ., 1.26 \mathrm{~mL}, 10 \mathrm{mmol}$ ), $\mathrm{NaOEt}(3 \mathrm{eq} ., 1.02 \mathrm{~g}$, $15 \mathrm{mmol})$ and $\mathrm{CuBr}(0.1 \mathrm{eq} ., 71.7 \mathrm{mg}, 0.5 \mathrm{mmol})$ in anhydrous ethanol $(12 \mathrm{~mL})$ in 1 h according to typical procedure TP8, affording $\mathbf{8 2 g}$ as a white solid ( $1.35 \mathrm{~g}, 98 \%$ ).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 9.99(\mathrm{~s}, 1 \mathrm{H}), 8.39(\mathrm{~d}, J=2.0 \mathrm{~Hz}, 1 \mathrm{H}), 7.78(\mathrm{dd}, J=$ $8.1,2.0 \mathrm{~Hz}, 1 \mathrm{H}), 7.44(\mathrm{~d}, J=8.0 \mathrm{~Hz}, 1 \mathrm{H}), 4.18(\mathrm{q}, J=7.1 \mathrm{~Hz}, 2 \mathrm{H}), 4.12(\mathrm{~s}, 2 \mathrm{H}), 1.27$ ( $\mathrm{t}, J=7.1 \mathrm{~Hz}, 3 \mathrm{H}$ ).
${ }^{13} \mathrm{C}$ NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 171.27,170.91,140.83,133.25,130.83,130.50$, 130.17, 129.83, 129.79, 129.75, 129.65, 129.01, 128.97, 128.93, 128.90, 127.68, $124.98,122.27,119.57,61.36,40.76,14.25$.

## Preparation of 2-(2-ethoxy-2-oxoethyl)-4,5-dimethoxybenzoic acid (82h)



82h
The reaction was performed with 2-bromo-4,5-dimethoxybenzoic acid (1 eq., 0.922 g , 3.53 mmol ), ethyl acetoacetate ( $2 \mathrm{eq} ., 0.892 \mathrm{~mL}, 7.06 \mathrm{mmol}$ ), NaOEt ( $3 \mathrm{eq},. 0.721 \mathrm{~g}$, $10.6 \mathrm{mmol})$ and CuBr ( 0.1 eq., $50.7 \mathrm{mg}, 0.353 \mathrm{mmol}$ ) in anhydrous ethanol ( 15 mL ) in 3 h according to typical procedure TP8, affording $\mathbf{8 2 h}$ as a white solid $(0.94 \mathrm{~g}$, 99 \%).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.65(\mathrm{~s}, 1 \mathrm{H}), 6.73(\mathrm{~s}, 1 \mathrm{H}), 4.17(\mathrm{q}, J=7.1 \mathrm{~Hz}, 2 \mathrm{H})$, 3.99 (s, 2H), 3.94 (s, 3H), 3.93 (s, 3H), 1.26 (t, $J=7.0 \mathrm{~Hz}, 3 \mathrm{H})$.

## Preparation of 4-chloro-2-(ethoxycarbonyl)benzoic acid (82j)



82j
The reaction was performed with 2,4-dichlorobenzoic acid ( $1 \mathrm{eq} ., 0.96 \mathrm{~g}, 5.03 \mathrm{mmol}$ ), ethyl acetoacetate ( 2 eq., $1.27 \mathrm{~mL}, 10.1 \mathrm{mmol}$ ), NaOEt ( 3 eq., $1.03 \mathrm{~g}, 15.1 \mathrm{mmol}$ ) and $\mathrm{CuBr}(0.1 \mathrm{eq} ., 72.1 \mathrm{mg}, 0.503 \mathrm{mmol}$ ) in anhydrous ethanol ( 12 mL ) in 24 h according to typical procedure TP8, affording $\mathbf{8 2 j}$ as a white solid ( $1.08 \mathrm{~g}, 89 \%$ ).
${ }^{1}{ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 8.07(\mathrm{~d}, J=8.4 \mathrm{~Hz}, 1 \mathrm{H}), 7.41-7.35(\mathrm{~m}, 1 \mathrm{H}), 7.29(\mathrm{~d}$, $J=2.1 \mathrm{~Hz}, 1 \mathrm{H}), 4.17(\mathrm{q}, J=7.1 \mathrm{~Hz}, 2 \mathrm{H}), 4.01(\mathrm{~s}, 2 \mathrm{H}), 1.26(\mathrm{t}, J=7.1 \mathrm{~Hz}, 3 \mathrm{H})$. ${ }^{13} \mathrm{C}$ NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 171.00,139.61,139.00,133.56,133.48,132.67$, $127.95,61.17,40.70,14.29$.

## Preparation of 2-chloro-6-(2-ethoxy-2-oxoethyl)benzoic acid (82k)



82k
The reaction was performed with 2 -chloro-6-iodobenzoic acid (1 eq., $1.41 \mathrm{~g}, 4.99$ mmol ), ethyl acetoacetate ( 2 eq., $1.26 \mathrm{~mL}, 9.98 \mathrm{mmol}$ ), NaOEt ( $3 \mathrm{eq} ., 1.02 \mathrm{~g}, 15$ $\mathrm{mmol})$ and $\mathrm{CuBr}(0.1$ eq., $71.6 \mathrm{mg}, 0.499 \mathrm{mmol})$ in anhydrous ethanol $(12 \mathrm{~mL})$ in 48 h according to typical procedure TP8, affording 82k as a white solid ( $1.1 \mathrm{~g}, 91 \%$ ).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 9.59(\mathrm{~s}, 1 \mathrm{H}), 7.41-7.31(\mathrm{~m}, 2 \mathrm{H}), 7.24$ (dd, $J=7.4$, $1.2 \mathrm{~Hz}, 1 \mathrm{H}), 4.17(\mathrm{q}, J=7.1 \mathrm{~Hz}, 2 \mathrm{H}), 3.80(\mathrm{~s}, 2 \mathrm{H}), 1.25(\mathrm{t}, J=7.1 \mathrm{~Hz}, 3 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 171.12,133.99,131.97,131.13,129.40,129.13$, 61.69, 39.62, 14.16

## Preparation of 1-(2-ethoxyphenyl)ethanol (85)



85

To a dry tube filled with Ar was added NaOEt ( 3 eq., $50.8 \mathrm{mg}, 0.746 \mathrm{mmol}$ ) and anhydrous ethanol ( 1 mL ). Then, ethyl acetoacetate ( 2 eq., $62.8 \mu \mathrm{~L}, 0.497 \mathrm{mmol}$ ) was added and stirred at rt for $2 \mathrm{~min} . \mathrm{CuBr}(0.1$ eq., $3.57 \mathrm{mg}, 0.0249 \mathrm{mmol}$ ) and 2-bromo- $\alpha$-methylbenzyl alcohol ( $1 \mathrm{eq} ., 50 \mathrm{mg}, 0.249 \mathrm{mmol}$ ) were successively added. The reaction mixture was irradiated in microwaves under Ar at $150{ }^{\circ} \mathrm{C}$ for 15 min . The reaction mixture was concentrated in vacuo and acidified by $\mathrm{H}_{2} \mathrm{SO}_{4}$ (1M) to $\mathrm{pH} \sim 3$. The crude was extrated with EtOAc thrice. The combined organic phases were washed with brine and dried over anhydrous $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and filtered. The filtrate was concentrated in vacuo and purified by silica gel chromatography (Heptane:EtOAc $=$ $8: 1$ ) to afford $\mathbf{8 5}$ as a yellow oil ( $40 \mathrm{mg}, 97 \%$ ).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.27(\mathrm{~d}, J=7.5 \mathrm{~Hz}, 1 \mathrm{H}), 7.17(\mathrm{t}, J=7.8 \mathrm{~Hz}, 1 \mathrm{H}), 6.89$
(t, $J=7.5 \mathrm{~Hz}, 1 \mathrm{H}), 6.81(\mathrm{~d}, J=8.2 \mathrm{~Hz}, 1 \mathrm{H}), 5.04(\mathrm{q}, J=6.2 \mathrm{~Hz}, 1 \mathrm{H}), 4.04(\mathrm{q}, J=6.9$
$\mathrm{Hz}, 2 \mathrm{H}), 2.80(\mathrm{~s}, 1 \mathrm{H}), 1.47(\mathrm{~d}, J=6.5 \mathrm{~Hz}, 3 \mathrm{H}), 1.39(\mathrm{t}, J=6.9 \mathrm{~Hz}, 3 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 155.58,133.58,128.04,125.79,120.57,111.24$, 65.77, 63.53, 22.89, 14.72.

Rf: 0.3 (heptane: $E t O A c=2: 1$ ).

## Preparation of 2-bromo-3-methoxybenzoic acid (86)



86
The reaction was performed with 2-bromo-3-methoxybenzoic acid (1 eq., 200 mg , 0.866 mmol ), ethyl acetoacetate ( $2 \mathrm{eq} ., 0.219 \mathrm{~mL}, 1.73 \mathrm{mmol}$ ), NaOEt ( $4 \mathrm{eq} ., 235 \mathrm{mg}$, $3.46 \mathrm{mmol})$ and $\mathrm{CuBr}(0.1 \mathrm{eq} ., 12.4 \mathrm{mg}, 0.0866 \mathrm{mmol})$ in anhydrous ethanol ( 3.5 mL ) in 16 h according to typical procedure TP8, affording 86 as a brown solid ( 162 mg , 95 \%).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.72(\mathrm{dd}, J=7.7,1.9 \mathrm{~Hz}, 1 \mathrm{H}), 7.21-7.12(\mathrm{~m}, 2 \mathrm{H})$, $4.36(\mathrm{q}, J=7.1 \mathrm{~Hz}, 2 \mathrm{H}), 3.91(\mathrm{~s}, 3 \mathrm{H}), 1.46(\mathrm{t}, J=7.1 \mathrm{~Hz}, 3 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 165.74,152.25,147.25,124.93,124.10,122.75$, 117.56, 71.44, 56.35, 15.51.

## Preparation of ethyl 2-(2-benzoylphenyl)acetate (87)



87
A solution of $\mathrm{PhZnCl}(2$ eq., 0.5 M in THF, $6.66 \mathrm{~mL}, 3.33 \mathrm{mmol}$ ) was slowly added to a solution of $\mathbf{8 8}(1 \mathrm{eq} ., 500 \mathrm{mg}, 1.66 \mathrm{mmol})$ and $\mathrm{PdCl}_{2}\left(\mathrm{PPh}_{3}\right)_{2}(1 \%, 11.7 \mathrm{mg}, 0.0166$ $\mathrm{mmol})$ in toluene $(7 \mathrm{~mL})$ under Ar at rt . After stirred at rt for 5 h , the reaction was
quenched by the addition of saturated $\mathrm{NH}_{4} \mathrm{Cl}$ aqueous solution and extracted with EtOAc thrice. The combined organic phases were washed with brine, dried over anhydrous $\mathrm{Na}_{2} \mathrm{SO}_{4}$, and filtered. The filtrate was concentrated in vacuo and purified by silica gel chromatography (Heptane:EtOAc $=6: 1$ ) to afford $\mathbf{8 7}$ as a yellow oil (424 $\mathrm{mg}, 95$ \%).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.82(\mathrm{~d}, J=7.6 \mathrm{~Hz}, 2 \mathrm{H}), 7.57(\mathrm{t}, J=7.4 \mathrm{~Hz}, 1 \mathrm{H}), 7.51$ $-7.42(\mathrm{~m}, 3 \mathrm{H}), 7.42-7.30(\mathrm{~m}, 3 \mathrm{H}), 4.02(\mathrm{q}, J=7.1 \mathrm{~Hz}, 2 \mathrm{H}), 3.89(\mathrm{~s}, 2 \mathrm{H}), 1.11(\mathrm{t}, J=$ 7.1 Hz, 3H).

These data are consistent with the previously reported characterization. ${ }^{173}$

## Preparation of ethyl 2-(2-((phenylthio)carbonyl)phenyl)acetate (88)



88

EDCI ( $1.3 \mathrm{eq} ., 5.5 \mathrm{~g}, 28.1 \mathrm{mmol}$ ) was added portionwise to a mixture of $\mathbf{8 2 a}$ ( 1 eq ., $4.5 \mathrm{~g}, 21.6 \mathrm{mmol}$ ) and $\mathrm{HOBt}(1.3 \mathrm{eq} ., 3.8 \mathrm{~g}, 28.1 \mathrm{mmol})$ in $\mathrm{DCM}(50 \mathrm{~mL})$ at $0^{\circ} \mathrm{C}$. After stirred at $0^{\circ} \mathrm{C}$ for 30 min , thiophenol ( $1.3 \mathrm{eq} ., 2.87 \mathrm{~mL}, 28.1 \mathrm{mmol}$ ) was added slowly and the mixture was stirred at rt for 15 h . The reaction was quenched with saturated $\mathrm{NaHCO}_{3}$ aqueous solution and extracted with DCM thrice. The combined organic phases were washed with brine, dried over anhydrous $\mathrm{Na}_{2} \mathrm{SO}_{4}$, and filtered. The filtrate was concentrated in vacuo and purified by silica gel chromatography $($ Heptane:EtOAc $=10: 1)$ to afford $\mathbf{8 8}$ as a yellow solid ( $6.15 \mathrm{~g}, 95 \%$ ).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 8.08(\mathrm{~d}, J=7.7 \mathrm{~Hz}, 1 \mathrm{H}), 7.55-7.39(\mathrm{~m}, 7 \mathrm{H}), 7.31(\mathrm{~d}$, $J=7.5 \mathrm{~Hz}, 1 \mathrm{H}), 4.13(\mathrm{q}, J=7.1 \mathrm{~Hz}, 2 \mathrm{H}), 3.92(\mathrm{~s}, 2 \mathrm{H}), 1.22(\mathrm{t}, J=7.1 \mathrm{~Hz}, 3 \mathrm{H})$. Rf: 0.4 (heptane:EtOAc $=3: 1$ ).

These data are consistent with the previously reported characterization. ${ }^{173}$

## Preparation of phenylzinc(II) chloride (89)



89
To a dry flask was added $\mathrm{ZnCl}_{2}$ ( 1.4 eq., $1.56 \mathrm{~g}, 11.2 \mathrm{mmol}$ ) and sealed. After heated $\left(550^{\circ} \mathrm{C}, 15 \mathrm{~min}\right)$ by a heating gun under reduced pressure, the flask was cooled to rt and backfilled with argon thrice. Then THF ( 8 mL ) was added, the suspension was sonicated until it becam clear. After cooled to $0^{\circ} \mathrm{C}, \mathrm{PhMgBr}(1 \mathrm{eq} ., 1 \mathrm{M}$ in THF, 8 mL , 8 mmol ) was slowly added and a white precipitation formed. The mixture was stirred at rt for $\mathbf{3} \mathrm{h}$ to afford $\mathbf{8 9}$ in quantative yield ( 0.5 M in THF).

## Preparation of 2-(2-(hydroxy(phenyl)methyl)phenyl)ethanol (91)



91
Method 1: To a solution of $\mathbf{8 7}$ ( 1 eq., $200 \mathrm{mg}, 0.745 \mathrm{mmol}$ ) in EtOH ( 4 mL ) was added $\mathrm{NaBH}_{4}(4 \mathrm{eq} ., 112 \mathrm{mg}, 2.98 \mathrm{mmol})$ in small portions at rt . After stirred at rt for 1 h , the reaction was quenched water and concentrated in vacuo. The suspention was extracted with EtOAc thrice. The combined organic phases was washed with brine, dried over anhydrous $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and filtered. The filtrate was concentrated in vacuo to afford 91 as a white oil ( $160 \mathrm{mg}, 94 \%$ ).

Method 2: The mixture of $\mathbf{8 7}$ ( 1 eq., $60 \mathrm{mg}, 0.224 \mathrm{mmol}$ ), $\mathrm{Zn}(24 \mathrm{eq} ., 351 \mathrm{mg}, 5.37$ $\mathrm{mmol})$ and $\mathrm{NaOH}(6.25 \mathrm{eq} ., 55.9 \mathrm{mg}, 1.4 \mathrm{mmol})$ in $\mathrm{H}_{2} \mathrm{O}(0.7 \mathrm{~mL})$ was reflux for 20 h . The suspention was extracted with EtOAc thrice. The combined organic phases was washed with brine, dried over anhydrous $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and filtered. The filtrate was concentrated in vacuo to afford 91 as a white oil ( $51 \mathrm{mg}, 100 \%$ ).
${ }^{1} \mathrm{H}^{\mathrm{H}} \mathrm{NMR}\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right): \delta 7.30-7.08(\mathrm{~m}, 9 \mathrm{H}), 6.00(\mathrm{~s}, 1 \mathrm{H}), 3.82-3.64(\mathrm{~m}, 2 \mathrm{H})$,
$3.42(\mathrm{~s}, 1 \mathrm{H}), 2.98-2.72(\mathrm{~m}, 2 \mathrm{H}), 2.00(\mathrm{~s}, 1 \mathrm{H})$.
These data are consistent with the previously reported characterization. ${ }^{184}$

## Preparation of 1-phenylisochroman-3-one (92)



92
To a solution of $\mathbf{8 7}(1 \mathrm{eq} ., 2.5 \mathrm{~g}, 9.32 \mathrm{mmol})$ in THF ( 6 mL ) was added a solution of LiOH ( 1.5 eq., $0.335 \mathrm{~g}, 14 \mathrm{mmol}$ ) in $\mathrm{H}_{2} \mathrm{O}(6 \mathrm{~mL})$. After stirred at rt for 2 h , the mixture was concentrated under reduced pressure until dryness. The crude was dissolved in $\mathrm{MeOH}(50 \mathrm{~mL})$ followed by the addition of $\mathrm{NaBH}_{4}(4 \mathrm{eq} ., 1.41 \mathrm{~g}, 37.4$ $\mathrm{mmol})$ in small portions at $25^{\circ} \mathrm{C}$. After stirred at rt for $16 \mathrm{~h}, \mathrm{HCl}(1 \mathrm{M})$ was added dropwise to the mixture until $\mathrm{pH} \sim 3$ and stirred at rt for 1 h . The reaction mixture was concentrated in vacuo and extracted by EtOAc thrice. The combined organic phases were washed with brine, dried over anhydrous $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and filtered. The filtrate was concentrated in vacuo to afford 92 as a white solid ( $2.1 \mathrm{~g}, 100 \%$ ).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.43-7.22(\mathrm{~m}, 8 \mathrm{H}), 6.97(\mathrm{~d}, \mathrm{~J}=7.5 \mathrm{~Hz}, 1 \mathrm{H}), 6.39(\mathrm{~s}$, 1H), 3.74 ( $\mathrm{d}, \mathrm{J}=18.2 \mathrm{~Hz}, 1 \mathrm{H}$ ), 3.62 ( $\mathrm{d}, \mathrm{J}=18.2 \mathrm{~Hz}, 1 \mathrm{H}$ ).

These data are consistent with the previously reported characterization. ${ }^{185}$

## Preparation of $N$-benzylhydroxylamine (98)



98
$\mathrm{Na}(\mathrm{CN}) \mathrm{BH}_{3}$ ( 2.2 eq., $1.14 \mathrm{~g}, 18.2 \mathrm{mmol}$ ) was added in small portions to a solution of ( $E$ )-benzaldehyde oxime ( 1 eq., $1 \mathrm{~g}, 8.26 \mathrm{mmol}$ ) in $\mathrm{MeOH}(20 \mathrm{~mL})$ at rt . During the course of addition, pH was maintained around 2 by adding $\mathrm{H}_{2} \mathrm{SO}_{4}(2 \mathrm{M})$. After stirred
ar rt for $6 \mathrm{~h}, \mathrm{NaOH}(1 \mathrm{M})$ was added until $\mathrm{pH} \sim 9$. The reaction mixture was concentrated in vacuo and extracted with EtOAc thrice. The combined organic phases was washed with brine, dried over anhydrous $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and filtered. The filtrate was concentrated in vacuo to afford $\mathbf{9 8}$ as a yellow solid ( $0.98 \mathrm{~g}, 96 \%$ ).
${ }^{1} \mathrm{H}$ NMR ( 400 MHz, DMSO- $d^{6}$ ): $\delta 7.36-7.21$ (m, 5H), 6.07 (br, 1H), 3.87 (s, 2H). These data are consistent with the previously reported characterization. ${ }^{186}$

## Preparation of N -hydroxy-2-(2-(hydroxy(phenyl)methyl)phenyl)acetamide (101)



101
KOH ( 10 eq., $3.39 \mathrm{~g}, 60.4 \mathrm{mmol}$ ) was added to a cooled solution of hydroxylamine hydrochloride ( 10 eq., $4.2 \mathrm{~g}, 60.4 \mathrm{mmol}$ ) in $\mathrm{MeOH}\left(70.3 \mathrm{~mL}\right.$ ) at $0^{\circ} \mathrm{C}$. After stirred for 5 min , the suspension was filtered and filtrate was collected. 92 ( $1 \mathrm{eq} ., 1.36 \mathrm{~g}, 6.04$ mmol ) was then added to aforementioned filtrate and stirred at rt overnight. The mixture was concentrated in vacuo followed by the addition of THF and filtered through celite. The filtrate was concentrated in vacuo to afford $\mathbf{1 0 1}$ as a yellow oil ( $1.4 \mathrm{~g}, 90 \%$ ).
${ }^{1} \mathrm{H}$ NMR (400 MHz, DMSO-d $\mathrm{d}^{6}$ ): $\delta 9.69$ (s, 1H), 7.38 - $7.14(\mathrm{~m}, 9 \mathrm{H}), 6.07(\mathrm{~s}, 1 \mathrm{H})$, $3.42(\mathrm{~s}, 2 \mathrm{H}), 3.17(\mathrm{~s}, 1 \mathrm{H}), 1.70(\mathrm{~s}, 1 \mathrm{H})$.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{MeOD}-d^{4}$ ): $\delta 7.37-7.16(\mathrm{~m}, 9 \mathrm{H}), 6.10(\mathrm{~s}, 1 \mathrm{H}), 3.47(\mathrm{~s}, 2 \mathrm{H})$.

Preparation of ( $E$ )-1-phenylisochroman-3-one oxime (102) and 1-phenyl-4,5dihydrobenzo $[e][1,3]$ oxazepin-3(1H)-one (103)


102


103

Method 1: A solution of $\mathbf{1 0 1}$ (1 eq., $50 \mathrm{mg}, 0.194 \mathrm{mmol})$ in THF ( 4 mL ) was added dropwise to a solution of $\mathrm{PPh}_{3}(1.3$ eq., $66.3 \mathrm{mg}, 0.253 \mathrm{mmol}$ ) and DIAD ( 1.3 eq., $50.1 \mu \mathrm{~L}, 0.253 \mathrm{mmol})$ in THF $(4 \mathrm{~mL})$ at $0^{\circ} \mathrm{C}$ under Ar and stirred at rt over night. The reaction mixture was concentrated in vacuo and purified by reverse phase chromatography $\left(\mathrm{ACN} / \mathrm{H}_{2} \mathrm{O}\right)$ to afford $\mathbf{1 0 2}(8.2 \mathrm{mg}, 18 \%)$ and $\mathbf{1 0 3}(19 \mathrm{mg}, 41 \%)$ as white solids.

Method 2: To a solution of $\mathbf{1 0 1}(1 \mathrm{eq} ., 50 \mathrm{mg}, 0.117 \mathrm{mmol})$ in THF ( 2 mL ) was added CDI ( 2 eq., $37.8 \mathrm{mg}, 0.233 \mathrm{mmol}$ ) and the resulting mixture was stirred at rt for 16 h . The reaction mixture was then concentrated in vacuo and purified by reverse phase chromatography $\left(\mathrm{ACN} / \mathrm{H}_{2} \mathrm{O}\right)$ to afford $\mathbf{1 0 2}(15.6 \mathrm{mg}, 56 \%)$ and $103(7.5 \mathrm{mg}, 27 \%)$ as white solids.
${ }^{1} \mathrm{H}$ NMR ( 400 MHz, DMSO- $d^{6}$ ) of 102: $\delta 9.35(\mathrm{~s}, 1 \mathrm{H}), 7.49-7.33(\mathrm{~m}, 7 \mathrm{H}), 7.26(\mathrm{t}, J$ $=7.1 \mathrm{~Hz}, 1 \mathrm{H}), 6.83(\mathrm{~d}, J=7.5 \mathrm{~Hz}, 1 \mathrm{H}), 6.37(\mathrm{~s}, 1 \mathrm{H}), 3.69(\mathrm{~d}, J=17.2 \mathrm{~Hz}, 1 \mathrm{H}), 3.45$ (d, $J=17.2 \mathrm{~Hz}, 1 \mathrm{H}$ ).
${ }^{13} \mathrm{C}$ NMR ( 101 MHz, DMSO- $d^{6}$ ) of 102: $\delta$ 150.77, 137.83, 137.09, 132.46, 128.53, $128.40,128.35,127.35,126.89,126.60,125.26,78.98,30.10$.
${ }^{1} \mathrm{H}$ NMR ( 400 MHz, DMSO- $d^{6}$ ) of 103: $\delta 7.74(\mathrm{~s}, 1 \mathrm{H}), 7.50-7.30(\mathrm{~m}, 7 \mathrm{H}), 7.25(\mathrm{t}, J$ $=7.4 \mathrm{~Hz}, 1 \mathrm{H}), 6.80(\mathrm{~s}, 1 \mathrm{H}), 6.70(\mathrm{~d}, J=7.5 \mathrm{~Hz}, 1 \mathrm{H}), 4.64(\mathrm{~d}, J=14.8 \mathrm{~Hz}, 1 \mathrm{H}), 4.06$ (dd, $J=14.9,6.0 \mathrm{~Hz}, 1 \mathrm{H}$ ).
${ }^{13} \mathrm{C}$ NMR (101 MHz, DMSO- $d^{6}$ ) of 103: $\delta 154.59,139.22,138.32,137.39,128.51$, $128.38,128.11,127.85,127.77,127.16,127.05,77.61,43.70$.
phenyl)acetate (105) and methyl 2-(2-(methoxy(phenyl)methyl)phenyl)acetate (106)


105


106

A solution of $92(1 \mathrm{eq} ., 10 \mathrm{mg}, 0.0446 \mathrm{mmol})$ and $\mathrm{ZnCl}_{2}(0.1 \mathrm{eq} ., 0.608 \mathrm{mg}, 0.00446$ $\mathrm{mmol})$ in $\mathrm{SOCl}_{2}(0.2 \mathrm{~mL})$ was stirred at $70{ }^{\circ} \mathrm{C}$ for 16 h . After the solvent was removed under reduced pressure, $\mathrm{DCM}(0.4 \mathrm{~mL})$ and $\mathrm{MeOH}(1.5 \mathrm{eq} ., 2.71 \mu \mathrm{~L}, 0.0669$ mmol ) were added and stirred at rt for 1 h . The mixture was filtered through a silica gel pad with $\mathrm{DCM} / \mathrm{MeOH}$ (10:1), the filtrate was concentrated in vacuo at rt to afford the crude. The crude was dissolved in DMF $(0.2 \mathrm{~mL})$, followed by the addition of TEA ( 1.5 eq., $9.3 \mu \mathrm{~L}, 0.0669 \mathrm{mmol}$ ) and NHPI ( 1.3 eq., $9.46 \mathrm{mg}, 0.058 \mathrm{mmol}$ ). After stirred at rt for 4 h , the reaction mixture was purified by reverse phase chromatography $\left(\mathrm{ACN} / \mathrm{H}_{2} \mathrm{O}\right)$ to afford $\mathbf{1 0 5}$ as a yellow solid ( $8.4 \mathrm{mg}, 47 \%$ ) and 106 as a white solid ( $5.3 \mathrm{mg}, 44 \%$ ).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) of 105: $\delta 7.79-7.66(\mathrm{~m}, 5 \mathrm{H}), 7.55-7.51(\mathrm{~m}, 2 \mathrm{H}), 7.37$
$-7.30(\mathrm{~m}, 6 \mathrm{H}), 6.85(\mathrm{~s}, 1 \mathrm{H}), 3.93(\mathrm{~d}, J=16.0 \mathrm{~Hz}, 1 \mathrm{H}), 3.71(\mathrm{~d}, J=16.0 \mathrm{~Hz}, 1 \mathrm{H}), 3.53$ ( $\mathrm{s}, 3 \mathrm{H}$ ).
${ }^{13} \mathrm{C}$ NMR (101 MHz, $\mathrm{CDCl}_{3}$ ) of 105: $\delta 171.74,163.87,137.01,136.24,134.45$, $133.43,131.20,129.28,129.07,129.05,128.96,128.92,128.49,127.64,123.52$, 86.56, 52.11, 38.49.
${ }^{1} \mathrm{H}$ NMR $\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right)$ of 106: $\delta 7.36-7.32(\mathrm{~m}, 1 \mathrm{H}), 7.28-7.17(\mathrm{~m}, 8 \mathrm{H}), 5.42$ (s, 1H), $3.60(\mathrm{~d}, ~ J=3.2 \mathrm{~Hz}, 2 \mathrm{H}), 3.55(\mathrm{~s}, 3 \mathrm{H}), 3.32(\mathrm{~s}, 3 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) of 106: $\delta 171.95,140.74,139.83,132.74,131.50$, $128.41,128.28,128.03,127.64,127.52,127.50,82.97,57.24,51.99,38.41$.

## Preparation of (2-bromophenyl)(phenyl)methanol (107)



107
A solution of PhMgBr ( 1.2 eq., $1 \mathrm{M}, 6.49 \mathrm{~mL}, 6.49 \mathrm{mmol}$ ) in THF was added dropwise to a vigorously stirred solution of 2-bromobenzaldehyde (1 eq., $1 \mathrm{~g}, 0.633$ $\mathrm{mL}, 5.4 \mathrm{mmol})$ in $\mathrm{Et}_{2} \mathrm{O}(15 \mathrm{~mL})$ under Ar at $-30^{\circ} \mathrm{C}$. After stirred at $-30^{\circ} \mathrm{C}$ for 12 h , the reaction was quenched with saturated $\mathrm{NH}_{4} \mathrm{Cl}$ aqueous solution and extracted with EtOAc thrice. The combined organic phases were washed with brine, dried over anhydrous $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and filtered. The filtrate was concentrated under reduced pressure and purified by silica gel chromatography (Heptane:EtOAc $=15: 1$ ) to afford $\mathbf{1 0 7}$ as a yellow oil ( $1.2 \mathrm{~g}, 84 \%$ ).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.58$ (dd, $J=16.1,7.9 \mathrm{~Hz}, 2 \mathrm{H}$ ), $7.45-7.23$ (m, 6H), $7.16(\mathrm{t}, J=7.6 \mathrm{~Hz}, 1 \mathrm{H}), 6.19(\mathrm{~s}, 1 \mathrm{H}), 2.63(\mathrm{~s}, 1 \mathrm{H})$.

Rf: 0.3 (heptane:EtOAc = 3:1).
These data are consistent with the previously reported characterization. ${ }^{187}$

## Preparation of 2-((2-bromophenyl)(phenyl)methoxy)isoindoline-1,3-dione (108)



108
A mixture of $\mathbf{1 0 9}$ ( $1 \mathrm{eq} ., 120 \mathrm{mg}, 0.368 \mathrm{mmol}$ ), NHPI ( $1.1 \mathrm{eq} ., 66 \mathrm{mg}, 0.405 \mathrm{mmol}$ ) and TEA ( 2 eq., $0.102 \mathrm{~mL}, 0.736 \mathrm{mmol}$ ) in DMF ( 1 mL ) was stirred at rt overnight. After completion, water was added to the reaction mixture and acidified to $\mathrm{pH} \sim 3$ with $\mathrm{HCl}(1 \mathrm{M})$. The mixture was extracted with EtOAc thrice. The combined organic
phases were washed with brine, dried over anhydrous $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and filtered. The filtrate was concentrated in vacuo and purified by silica gel chromatography (Heptane:EtOAc $=5: 1$ ) to afford $\mathbf{1 0 8}$ as a white solid ( $147 \mathrm{mg}, 98 \%$ ).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 8.11(\mathrm{dd}, J=7.8,1.8 \mathrm{~Hz}, 1 \mathrm{H}), 7.79-7.73(\mathrm{~m}, 2 \mathrm{H})$, $7.73-7.67(\mathrm{~m}, 2 \mathrm{H}), 7.54-7.45(\mathrm{~m}, 4 \mathrm{H}), 7.38-7.27(\mathrm{~m}, 4 \mathrm{H}), 7.20(\mathrm{td}, J=7.7,1.8$ $\mathrm{Hz}, 1 \mathrm{H}), 6.91(\mathrm{~s}, 1 \mathrm{H})$.

Rf: 0.35 (heptane: $\mathrm{EtOAc}=5: 1$ ).

## Preparation of 1-bromo-2-(bromo(phenyl)methyl)benzene (109)



109
$\mathrm{PBr}_{3}$ ( 2 eq., $2.5 \mathrm{~mL}, 26.6 \mathrm{mmol}$ ) was added dropwise to a solution of 107 ( $1 \mathrm{eq} ., 3.5 \mathrm{~g}$, $13.3 \mathrm{mmol})$ in dry $\mathrm{DCM}(20 \mathrm{~mL})$ at $0^{\circ} \mathrm{C}$ and stirred at rt for 2 h . The reaction mixture was added slowly into ice water under stirration and extracted with DCM thrice. The combined organic phases were washed with saturated $\mathrm{NaHCO}_{3}$ aqueous soltion, dried over anhydrous $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and filtered. The filtrate was concentrated in vacuo to afford 109 as a yellow oil ( $4.3 \mathrm{~g}, 99$ \%).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.69(\mathrm{dd}, J=7.9,1.7 \mathrm{~Hz}, 1 \mathrm{H}$ ), $7.55(\mathrm{dd}, J=8.0,1.3$ $\mathrm{Hz}, 1 \mathrm{H}$ ), $7.50-7.43$ (m, 2 H ), $7.39-7.27$ (m, 4 H ), $7.18-7.10$ (m, 1 H$), 6.70$ (s, 1 H).

Rf: 0.7 (heptane: $E t O A c=3: 1$ ).
These data are consistent with the previously reported characterization. ${ }^{188}$

## Preparation of tert-butyl benzyl(hydroxy)carbamate (111)



111
A solution of $\mathrm{Boc}_{2} \mathrm{O}$ ( 1.1 eq., $976 \mathrm{mg}, 4.48 \mathrm{mmol}$ ) in THF ( 10 mL ) was added
dropwise to a solution of $\mathbf{9 8}(1 \mathrm{eq} ., 500 \mathrm{mg}, 4.06 \mathrm{mmol})$ in THF $(5 \mathrm{~mL})$ at $0{ }^{\circ} \mathrm{C}$. After stirred at $0^{\circ} \mathrm{C}$ for 1 h and at rt for 4 h , water was added to the reaction mixture and extracted with DCM thrice. The combined organic phases were washed with brine, dried over anhydrous $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and filtered. The filtrate was concentrated in vacuo and purified by silica gel chromatography (Heptane:EtOAc $=8: 1$ ) to afford 111 as a colorless oil ( $671 \mathrm{mg}, 74$ \%).
${ }^{1} \mathrm{H}$ NMR (400 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 7.35-7.27(\mathrm{~m}, 5 \mathrm{H}), 7.03(\mathrm{~s}, 1 \mathrm{H}), 4.65(\mathrm{~s}, 2 \mathrm{H}), 1.47(\mathrm{~s}$, 9 H ).

Rf: 0.5 (heptane: $E t O A c=2: 1$ ).
These data are consistent with the previously reported characterization. ${ }^{189}$

## Preparation of 2-(2-(((1,3-dioxoisoindolin-2-yl)oxy)(phenyl)methyl)phenyl)

 acetonitrile (113)

113
A mixture of $\mathbf{1 0 8}$ ( $1 \mathrm{eq} ., 15 \mathrm{mg}, 0.0367 \mathrm{mmol}$ ), sodium 2-cyanoacetate ( $1.5 \mathrm{eq} ., 5.9$ $\mathrm{mg}, 0.0551 \mathrm{mmol}),\left[\mathrm{Pd}(\mathrm{Cl})\left(\mathrm{C}_{3} \mathrm{H}_{5}\right)\right]_{2}(2 \%, 0.274 \mathrm{mg}, 0.000735 \mathrm{mmol})$ and SPhos $(6 \%$, $0.933 \mathrm{mg}, 0.0022 \mathrm{mmol}$ ) in toluene ( 1 mL ) was stirred under Ar at rt for 10 min and then stirred at $120^{\circ} \mathrm{C}$ for 16 h . The mixture was concentrated in vacuo and purified by reverse phase choromatography $\left(\mathrm{ACN} / \mathrm{H}_{2} \mathrm{O}\right)$ to afford 113 as a white solid $(4.6 \mathrm{mg}$, 34 \%).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.79-7.67(\mathrm{~m}, 4 \mathrm{H}), 7.61(\mathrm{~d}, J=7.4 \mathrm{~Hz}, 1 \mathrm{H}), 7.51-$ $7.29(\mathrm{~m}, 8 \mathrm{H}), 6.62(\mathrm{~s}, 1 \mathrm{H}), 4.29(\mathrm{~d}, J=19.0 \mathrm{~Hz}, 1 \mathrm{H}), 3.85(\mathrm{~d}, J=19.0 \mathrm{~Hz}, 1 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 163.86,136.09,134.98,134.69,130.74,130.66$, 130.07, 129.79, 129.29, 128.89, 128.86, 128.18, 128.14, 123.73, 118.15, 88.25, 21.77.

## Preparation of $\boldsymbol{O}$-((2-bromophenyl)(phenyl)methyl)hydroxylamine (115)



115
A solution of $\mathbf{1 0 8}(1 \mathrm{eq} ., 870 \mathrm{mg}, 2.13 \mathrm{mmol})$ and hydrazine hydrate $(15 \mathrm{eq} ., 3.1 \mathrm{~mL}$, 32 mmol ) in EtOH ( 20 mL ) was refluxed for 1 h and concentrated in vacuo. The crude was basifed with $10 \% \mathrm{Na}_{2} \mathrm{CO}_{3}$ aqueous solution to $\mathrm{pH} \sim 10$ and extracted with EtOAc thrice. The combined organic phases were washed brine, dried with anhydrous $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and filtered. The filtrate was concentrated in vacuo to afford 115 as a yellow oil ( $586 \mathrm{mg}, 99 \%$ ).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.45(\mathrm{dd}, J=24.3,7.8 \mathrm{~Hz}, 2 \mathrm{H}), 7.34-7.27(\mathrm{~m}, 3 \mathrm{H})$, $7.24-7.16(\mathrm{~m}, 3 \mathrm{H}), 7.11-7.05(\mathrm{~m}, 1 \mathrm{H}), 5.96(\mathrm{~s}, 1 \mathrm{H}), 5.42(\mathrm{~s}, 2 \mathrm{H})$.

These data are consistent with the previously reported characterization. ${ }^{190}$

Preparation of tert-butyl (2-bromophenyl)(phenyl)methoxycarbamate (117)


117
To a solution of $\mathbf{1 1 5}(1 \mathrm{eq} ., 268 \mathrm{mg}, 0.964 \mathrm{mmol})$ and TEA ( $1.5 \mathrm{eq} ., 0.201 \mathrm{~mL}, 1.45$ $\mathrm{mmol})$ in $\mathrm{DCM}(10 \mathrm{~mL})$ was added $\mathrm{Boc}_{2} \mathrm{O}(1.1 \mathrm{eq} ., 231 \mathrm{mg}, 1.06 \mathrm{mmol})$ and stirred at rt for 16 h . The reaction was concentrated in vacuo and purified by reverse phase chromatography $\left(\mathrm{MeOH} / \mathrm{H}_{2} \mathrm{O}\right)$ to afford $\mathbf{1 1 7}$ as a colorless oil ( $100 \mathrm{mg}, 27 \%$ ).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.66-7.55(\mathrm{~m}, 2 \mathrm{H}), 7.45-7.30(\mathrm{~m}, 6 \mathrm{H}), 7.20(\mathrm{td}, J=$ $7.7,1.7 \mathrm{~Hz}, 1 \mathrm{H}), 6.32(\mathrm{~s}, 1 \mathrm{H}), 1.51(\mathrm{~s}, 9 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 156.45,139.03,137.99,133.11,129.51,128.53$,
$128.42,128.39,127.76,123.82,87.50,82.00,28.31$.

Preparation of tert-butyl $N$-[(2-bromophenyl)(phenyl)methoxy]- $N$ - [(tert-butoxy) carbonyl]carbamate (119)


119
To a solution of $\mathbf{1 1 5}(1 \mathrm{eq} ., 187.5 \mathrm{mg}, 0.67 \mathrm{mmol})$ and TEA ( $4 \mathrm{eq} ., 0.37 \mathrm{~mL}, 2.7 \mathrm{mmol}$ ) in DCM ( 7 mL ) was added $\mathrm{Boc}_{2} \mathrm{O}(4$ eq., $588.49 \mathrm{mg}, 2.7 \mathrm{mmol})$ and stirred at rt for 16 h . The reaction was concentrated in vacuo and purified by reverse phase chromatography $\left(\mathrm{MeOH} / \mathrm{H}_{2} \mathrm{O}\right)$ to afford 119 as a colorless oil ( $306 \mathrm{mg}, 95 \%$ ).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.84(\mathrm{dd}, J=7.8,1.7 \mathrm{~Hz}, 1 \mathrm{H}), 7.52(\mathrm{dd}, J=8.0,1.3$ $\mathrm{Hz}, 1 \mathrm{H}), 7.41-7.35(\mathrm{~m}, 3 \mathrm{H}), 7.33-7.28(\mathrm{~m}, 3 \mathrm{H}), 7.17(\mathrm{td}, J=7.7,1.8 \mathrm{~Hz}, 1 \mathrm{H}), 6.45$ ( $\mathrm{s}, 1 \mathrm{H}$ ), 1.41 ( $\mathrm{s}, 18 \mathrm{H}$ ).
${ }^{13} \mathrm{C}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 150.57,138.59,137.24,132.77,129.78,129.56$, $129.15,128.55,128.29,127.47,123.55,87.05,83.86,28.00$.

## Preparation of (2-iodophenyl)(phenyl)methanone (121)



121
A mixture of 2-iodobenzoic acid ( $1 \mathrm{eq} ., 2 \mathrm{~g}, 8.06 \mathrm{mmol}^{2}$ ), $\mathrm{SOCl}_{2}$ ( $15.4 \mathrm{eq} ., 9 \mathrm{~mL}, 124$ mmol ) and DMF ( $1.6 \%, 0.01 \mathrm{~mL}, 0.129 \mathrm{mmol}$ ) was stirred at $70{ }^{\circ} \mathrm{C}$ for 0.5 h and then cooled to rt. After removal of $\mathrm{SOCl}_{2}$ under reduced pressure, benzene ( 11.2 eq., 8 $\mathrm{mL}, 90.1 \mathrm{mmol}$ ) and $\mathrm{AlCl}_{3}(1.1 \mathrm{eq} ., 1.18 \mathrm{~g}, 8.87 \mathrm{mmol})$ were added to the residue. The reaction mixture was stirred at $80^{\circ} \mathrm{C}$ for 1.5 h , cooled to rt , poured into ice water.
and extracted with EtOAc thrice. The combined organic phases were washed with saturated $\mathrm{NaHCO}_{3}$ aqueous solution, dried over anhydrous $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and filtered through a silica gel pad with EtOAc. The filtrate was concentrated in vacuo to afford 121 as a pale yellow oil ( $2.45 \mathrm{~g}, 99 \%$ ).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.93(\mathrm{~d}, J=7.9 \mathrm{~Hz}, 1 \mathrm{H}), 7.81(\mathrm{~d}, J=7.7 \mathrm{~Hz}, 2 \mathrm{H}), 7.61$ (t, $J=7.4 \mathrm{~Hz}, 1 \mathrm{H}), 7.46(\mathrm{q}, J=7.4 \mathrm{~Hz}, 3 \mathrm{H}), 7.30(\mathrm{~d}, J=7.5 \mathrm{~Hz}, 1 \mathrm{H}), 7.19(\mathrm{t}, J=7.7$ $\mathrm{Hz}, 1 \mathrm{H})$.

Rf: 0.6 (heptane: $\operatorname{EtOAc}=3: 2$ ).
These data are consistent with the previously reported characterization. ${ }^{191}$

## Preparation of (2-iodophenyl)(phenyl)methanol (122)



122
$\mathrm{NaBH}_{4}$ (4 eq., $1.066 \mathrm{~g}, 28.17 \mathrm{mmol}$ ) was added in portions to a solution of $\mathbf{1 2 1}(1 \mathrm{eq} .$, $2.17 \mathrm{~g}, 7.043 \mathrm{mmol})$ in $\mathrm{MeOH}(15 \mathrm{~mL}) /$ toluene $(7.5 \mathrm{~mL})$ at $0^{\circ} \mathrm{C}$. After stirred at rt for 1.5 h , the reaction mixture was quenched by $\mathrm{H}_{2} \mathrm{O}$ and extracted with EtOAc thrice. The combined organic phases were washed with brine, dried over anhydrous $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and filtered a silica gel pad with EtOAc. The filtrate was concentrated in vaccuo to afford $\mathbf{1 2 1}$ as a colorless oil ( $2.18 \mathrm{~g}, 100 \%$ ) .
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.84(\mathrm{~d}, J=7.9 \mathrm{~Hz}, 1 \mathrm{H}), 7.53(\mathrm{~d}, J=7.7 \mathrm{~Hz}, 1 \mathrm{H}), 7.44$ - $7.28(\mathrm{~m}, 6 \mathrm{H}), 6.99(\mathrm{t}, J=7.5 \mathrm{~Hz}, 1 \mathrm{H}), 6.07(\mathrm{~s}, 1 \mathrm{H}), 2.33(\mathrm{~s}, 1 \mathrm{H})$.

Rf: 0.5 (heptane: $E t O A c=3: 1$ ).
These data are consistent with the previously reported characterization. ${ }^{192}$


123
A mixture of 124 ( $1 \mathrm{eq} ., 700 \mathrm{mg}, 1.88 \mathrm{mmol}$ ), TEA ( $2 \mathrm{eq} ., 0.522 \mathrm{~mL}, 3.75 \mathrm{mmol}$ ), NHPI ( 1.1 eq., $336 \mathrm{mg}, 2.06 \mathrm{mmol}$ ) in DMF ( 5.1 mL ) was stirred at $50^{\circ} \mathrm{C}$ over night. After completion, water was added and acidified to $\mathrm{pH} \sim 3$ with HCl (1M). The mixture was extracted by EtOAc thrice. The combined organic phases were washed with brine, dried over anhydrous $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and filtered. The filtrate was concentrated in vacuo and purified by silica gel chromatography (Heptane:EtOAc $=4: 1$ ) to $\mathbf{1 2 3}$ as a white solid ( $740 \mathrm{mg}, 87 \%$ ).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 8.13-8.05(\mathrm{~m}, 1 \mathrm{H}), 7.83-7.68(\mathrm{~m}, 5 \mathrm{H}), 7.60-7.48$ $(\mathrm{m}, 3 \mathrm{H}), 7.39-7.31(\mathrm{~m}, 3 \mathrm{H}), 7.11-7.01(\mathrm{~m}, 1 \mathrm{H}), 6.78(\mathrm{~s}, 1 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 163.69,140.46,139.53,136.71,134.51,130.37$, $129.69,129.07,129.01,128.56,128.51,123.61,99.14,92.52$.

## Preparation of 1-(bromo(phenyl)methyl)-2-iodobenzene (124)



124
$\mathrm{PBr}_{3}$ ( 2 eq., $1.28 \mathrm{~mL}, 13.67 \mathrm{mmol}$ ) was added slowly to a solution of 122 ( $1 \mathrm{eq} ., 2.12$ $\mathrm{g}, 6.84 \mathrm{mmol})$ in dry $\mathrm{DCM}(10.28 \mathrm{~mL})$ at $0^{\circ} \mathrm{C}$. After stirred at rt for 2 h , the reaction mixture was slowly poured into ice water and extracted with DCM thrice. The combined organic phases were washed with saturated $\mathrm{NaHCO}_{3}$ aqueous solution, dried over anhydrous $\mathrm{Na}_{2} \mathrm{SO}_{4}$, and filtered. The filtrate was concentration in vacuo to afford gave $\mathbf{1 2 4}$ as a yellow oil ( $2.4 \mathrm{~g}, 94 \%$ ).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.85(\mathrm{dd}, J=7.9,1.1 \mathrm{~Hz}, 1 \mathrm{H}), 7.68$ (dd, $J=7.9,1.6$ $\mathrm{Hz}, 1 \mathrm{H}), 7.51-7.45(\mathrm{~m}, 2 \mathrm{H}), 7.39-7.28(\mathrm{~m}, 4 \mathrm{H}), 6.97(\mathrm{td}, J=7.7,1.7 \mathrm{~Hz}, 1 \mathrm{H}), 6.58$ ( $\mathrm{s}, 1 \mathrm{H}$ ).
${ }^{13} \mathrm{C}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 143.40,140.06,139.87,131.24,129.87,128.95$, 128.81, 128.72, 128.27, 99.35, 58.98.

Preparation of tert-butyl (2-iodophenyl)(phenyl)methoxycarbamate (125)


125

Method 1: A mixture of 127 ( 1 eq., $40 \mathrm{mg}, 0.0761 \mathrm{mmol}$ ), ethyl acetoacetate ( 3 eq., $28.9 \mu \mathrm{~L}, 0.228 \mathrm{mmol}$ ) , EtOH ( $3 \mathrm{eq} ., 13.3 \mu \mathrm{~L}, 0.228 \mathrm{mmol}$ ) , $\mathrm{K}_{3} \mathrm{PO}_{4}$ ( $3 \mathrm{eq} ., 48.5 \mathrm{mg}$, $0.228 \mathrm{mmol})$ and $\mathrm{CuI}(10 \%, 1.45 \mathrm{mg}, 0.00761 \mathrm{mmol})$ in DMSO $(0.5 \mathrm{~mL})$ was stirred at $80^{\circ} \mathrm{C}$ under Ar for 16 h . The reaction mixture was directly purified by reverse phase chromatography $\left(\mathrm{MeOH} / \mathrm{H}_{2} \mathrm{O}\right)$ to afford $\mathbf{1 2 5}$ as a colorless oil ( $15.8 \mathrm{mg}, 54 \%$ ).

Method 2: Asolution of (2-ethoxy-2-oxoethyl)zinc(II) bromide ( $1.5 \mathrm{eq} ., 0.51 \mathrm{M}, 0.224$ $\mathrm{mL}, 0.114 \mathrm{mmol})$ in THF was added slowly to a solution of $\mathbf{1 2 7}(1 \mathrm{eq} ., 40 \mathrm{mg}, 0.0761$ $\mathrm{mmol})$ and $\mathrm{PdCl}(\mathrm{Ph})\left(\mathrm{PPh}_{3}\right)_{2}(1 \%, 0.566 \mathrm{mg}, 0.000761 \mathrm{mmol})$ in THF $(0.5 \mathrm{~mL})$ under Ar at rt . The mixture was stirred at $60^{\circ} \mathrm{C}$ for 15 h and concentrated in vacuo. The crude was purified by reverse phase chromatography $\left(\mathrm{MeOH} / \mathrm{H}_{2} \mathrm{O}\right)$ to afford $\mathbf{1 2 5}$ as a colorless oil ( $32.4 \mathrm{mg}, 100 \%$ ).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.86(\mathrm{dd}, J=7.9,1.0 \mathrm{~Hz}, 1 \mathrm{H}), 7.56(\mathrm{dd}, J=7.8,1.6$ $\mathrm{Hz}, 1 \mathrm{H}), 7.46-7.38(\mathrm{~m}, 3 \mathrm{H}), 7.36-7.29(\mathrm{~m}, 3 \mathrm{H}), 7.10(\mathrm{~s}, 1 \mathrm{H}), 7.04(\mathrm{td}, J=7.7,1.7$ Hz, 1H), 6.16 (s, 1H), 1.50 ( $\mathrm{s}, 9 \mathrm{H}$ ).
${ }^{13} \mathrm{C}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 156.44,141.91,139.91,137.94,129.89,128.67$, $128.65,128.51,128.49,128.43,99.66,91.84,82.14,28.40$.

## Preparation of $\boldsymbol{O}$-((2-iodophenyl)(phenyl)methyl)hydroxylamine (126)



126
A solution of $\mathbf{1 2 3}$ ( $1 \mathrm{eq} ., 618 \mathrm{mg}, 1.36 \mathrm{mmol}$ ) and hydrazine hydrate ( $15 \mathrm{eq} ., 1.98 \mathrm{~mL}$, 20.4 mmol ) in EtOH ( 15 mL ) was refluxed for 1 h and concentrated in vacuo. The crude was basifed with $10 \% \mathrm{Na}_{2} \mathrm{CO}_{3}$ aqueous solution to $\mathrm{pH} \sim 10$ and extracted with EtOAc thrice. The combined organic phases were washed brine, dried with anhydrous $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and filtered. The filtrate was concentrated in vacuo to afford $\mathbf{1 2 6}$ as a yellow oil ( $436 \mathrm{mg}, 99 \%$ ).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.78$ (dd, $J=7.9,1.0 \mathrm{~Hz}, 1 \mathrm{H}$ ), $7.35-7.26(\mathrm{~m}, 5 \mathrm{H})$, $7.25-7.16(\mathrm{~m}, 2 \mathrm{H}), 6.94-6.88(\mathrm{~m}, 1 \mathrm{H}), 5.80(\mathrm{~s}, 1 \mathrm{H}), 5.43(\mathrm{~s}, 2 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 143.02,139.93,139.35,129.62,128.56,128.29$, 128.16, 128.06, 127.31, 99.90, 91.42 .

## Preparation of tert-butyl $N$-[(tert-butoxy)carbonyl]- $N$-[(2-iodophenyl)(phenyl) methoxy]carbamate (127)



127
TEA (4 eq., $0.675 \mathrm{~mL}, 4.86 \mathrm{mmol}$ ) was added to a solution of $\mathbf{1 2 6}(1 \mathrm{eq} ., 395 \mathrm{mg}$, 1.21 mmol ) and $\mathrm{Boc}_{2} \mathrm{O}$ (4 eq., $1.06 \mathrm{~g}, 4.86 \mathrm{mmol}$ ) in $\mathrm{DCM}(15 \mathrm{~mL})$ and stirred at rt for 16 h . The mixtrue was concentrated in vacuo and purified by reverse phase chromatography $\left(\mathrm{MeOH} / \mathrm{H}_{2} \mathrm{O}\right)$ to afford $\mathbf{1 2 7}$ as a colorless oil ( $485 \mathrm{mg}, 76 \%$ ).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.81$ (d, $J=8.0 \mathrm{~Hz}, 2 \mathrm{H}$ ), $7.44-7.37$ (m, 3H), $7.34-$
7.27 (m, 3H), 7.01 (td, $J=7.7,1.7 \mathrm{~Hz}, 1 \mathrm{H}), 6.31$ (s, 1H), 1.42 (s, 18H).
${ }^{13} \mathrm{C}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 150.48,141.39,139.40,137.02,129.82,129.51$, 129.38, 128.53, 128.25, 99.27, 91.41, 83.82, 27.99.

## Preparation of 1-(2-(2-hydroxyethyl)phenyl)-2-phenylethanol (131)



131
To a solution of $\mathbf{1 3 0}(1 \mathrm{eq} ., 170 \mathrm{mg}, 0.602 \mathrm{mmol})$ in $\mathrm{EtOH}(5 \mathrm{~mL})$ at $0^{\circ} \mathrm{C}$ was added $\mathrm{NaBH}_{4}$ (4 eq., $91.1 \mathrm{mg}, 2.41 \mathrm{mmol}$ ) and the resulting mixture was stirred rt for 3 h . After quenched by $\mathrm{H}_{2} \mathrm{O}$ and acidified by $\mathrm{H}_{2} \mathrm{SO}_{4}(1 \mathrm{M})$ to $\mathrm{pH} \sim 6$, the reaction mixture was extracted by EtOAc thrice. The combined organic phases were washed with brine, dried over anhydrous $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and filtered. The filtrate was concentrated in vacuo and purified by silica gel chromatography (heptane:EtOAc $=5: 1$ ) to afford $\mathbf{1 3 1}$ as a yellow oil ( $120 \mathrm{mg}, 82 \%$ ).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.49(\mathrm{~d}, J=7.1 \mathrm{~Hz}, 1 \mathrm{H}), 7.33-7.07(\mathrm{~m}, 8 \mathrm{H}), 5.13-$ $5.02(\mathrm{~m}, 1 \mathrm{H}), 3.74-3.49(\mathrm{~m}, 2 \mathrm{H}), 3.16(\mathrm{~s}, 1 \mathrm{H}), 3.08-2.97(\mathrm{~m}, 2 \mathrm{H}), 2.88-2.67(\mathrm{~m}$, $2 \mathrm{H}), 2.54(\mathrm{~s}, 1 \mathrm{H})$.

Rf: 0.25 (heptane:EtOAc $=2: 1$ ).
These data are consistent with the previously reported characterization. ${ }^{184}$

Preparation of 1-benzylisochroman-3-one (132)


132

To a solution of $\mathbf{1 3 0}(1$ eq., $34 \mathrm{mg}, 0.12 \mathrm{mmol})$ in $\mathrm{EtOH}(1 \mathrm{~mL})$ at $0{ }^{\circ} \mathrm{C}$ was added $\mathrm{NaBH}_{4}$ (4 eq., $18.2 \mathrm{mg}, 0.482 \mathrm{mmol}$ ) and stirred at $0{ }^{\circ} \mathrm{C}$ for 2 h . The reaction was quenched by $\mathrm{H}_{2} \mathrm{O}$ and acidified by $\mathrm{H}_{2} \mathrm{SO}_{4}(2 \mathrm{M})$ to $\mathrm{pH} \sim 1$. After stirred at rt for 20 min , the mixture was extracted by EtOAc thrice. The combined organic phases were washed with brine, dried over anhydrous $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and filtered. The filtrate was concentrated in vacuo to afford $\mathbf{1 3 2}$ as a white solid ( $27 \mathrm{mg}, 94 \%$ ).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.34-6.98(\mathrm{~m}, 9 \mathrm{H}), 5.70(\mathrm{t}, J=5.7 \mathrm{~Hz}, 1 \mathrm{H}), 3.48(\mathrm{~d}$, $J=19.5 \mathrm{~Hz}, 1 \mathrm{H}), 3.37(\mathrm{dd}, J=13.9,5.6 \mathrm{~Hz}, 1 \mathrm{H}), 3.22(\mathrm{dd}, J=13.9,5.6 \mathrm{~Hz}, 1 \mathrm{H}), 2.94$ (d, $J=19.4 \mathrm{~Hz}, 1 \mathrm{H}$ ).
These data are consistent with the previously reported characterization. ${ }^{193}$

## IX. Appendix

## IX. Appendix

## Appendix I. Crystallographic data and structure refinement

parameters of cpd 10a


Formula: $\mathrm{C}_{9} \mathrm{H}_{9} \mathrm{Cl}_{2} \mathrm{~N}_{3} \mathrm{O}$
Space group: P $21 / \mathrm{c}$ (14)
Cell lengths: a 11.7566(10) b 9.7544(10) c 9.4306(8)
Cell Angles: a 90 b 110.976(4) g 90
Cell Volume: 1009.82
Z: 4 Z': 0
R-factor (\%): 5.01
Atoms

| Number | Label | Charge | SybylType | Xfrac + ESD | Yfrac + ESD | Zfrac + ESD | Symm. op. |
| :--- | :--- | :--- | :--- | :--- | :--- | :--- | :--- |
| 1 | C1 | 0 | C. 2 | $0.9835(2)$ | $0.4100(3)$ | $0.2055(3)$ | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 2 | C2 | 0 | C.3 | $0.8579(3)$ | $0.3695(3)$ | $0.3589(3)$ | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 3 | H2A | 0 | H | 0.8935 | 0.4068 | 0.4632 | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 4 | H2B | 0 | H | 0.8065 | 0.2895 | 0.3603 | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 5 | C3 | 0 | C.3 | $0.7847(3)$ | $0.4756(4)$ | $0.2532(4)$ | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 6 | H3A | 0 | H | 0.7435 | 0.4331 | 0.1510 | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 7 | C4 | 0 | C.2 | $0.6900(4)$ | $0.5386(5)$ | $0.3046(5)$ | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 8 | C5 | 0 | C.2 | $0.5677(4)$ | $0.5138(5)$ | $0.2272(5)$ | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 9 | H5 | 0 | H | 0.5430 | 0.4601 | 0.1372 | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 10 | C6 | 0 | C.3 | $0.4807(4)$ | $0.5669(6)$ | $0.2799(6)$ | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 11 | C7 | 0 | C.3 | $0.5161(4)$ | $0.6468(6)$ | $0.4091(6)$ | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |


| 12 | C8 | 0 | C. 2 | 0.6371(4) | 0.6758(5) | 0.4851(5) | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 13 | H8 | 0 | H | 0.6611 | 0.7330 | 0.5724 | x,y,z |
| 14 | C9 | 0 | C. 2 | 0.7242(4) | $0.6207(5)$ | 0.4333(6) | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 15 | H9 | 0 | H | 0.8080 | 0.6396 | 0.4865 | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 16 | N1 | 0 | N. 2 | 0.9435(2) | 0.5344(2) | 0.1641(3) | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 17 | N2 | 0 | N. 3 | 0.9539(2) | 0.3296(3) | 0.3031(3) | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 18 | N3 | 0 | N. 3 | 1.0642(2) | 0.3579 (3) | 0.1475(3) | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 19 | Cl 1 | 0 | Cl | 0.32856(11) | $0.52574(17)$ | 0.17658(19) | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 20 | Cl 2 | 0 | Cl | 0.4058(2) | 0.7084(3) | 0.4754(3) | x,y,z |
| 21 | O1 | 0 | 0.3 | 0.8640(3) | 0.5841 (5) | 0.2397 (5) | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 22 | H2N | 0 | H | 0.974(3) | 0.251(4) | 0.309(4) | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 23 | H3C | 0 | H | 1.093(4) | 0.280(4) | 0.179(4) | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 24 | H3D | 0 | H | 1.070(3) | 0.398(4) | 0.069(4) | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 25 | H2C | 0 | H | 0.8833 | 0.3479 | 0.4685 | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 26 | H2D | 0 | H | 0.7828 | 0.3171 | 0.3044 | x,y,z |
| 27 | C3B | 0 | C. 3 | 0.8328(8) | 0.5195(10) | 0.3349(10) | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 28 | H3B | 0 | H | 0.9019 | 0.5690 | 0.4123 | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 29 | C4B | 0 | C. 3 | 0.7167(6) | 0.5671(9) | $0.3538(10)$ | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 30 | C5B | 0 | C. 3 | 0.6043(8) | 0.5242(9) | 0.2524(9) | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 31 | H5B | 0 | H | 0.6000 | 0.4700 | 0.1669 | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 32 | C6B | 0 | C. 3 | 0.4982(6) | 0.5604(11) | 0.2762(10) | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 33 | C7B | 0 | C. 3 | 0.5045(6) | $0.6396(11)$ | 0.4013(11) | x,y,z |
| 34 | C8B | 0 | C. 3 | 0.6169(7) | 0.6826(9) | 0.5027(9) | x,y,z |
| 35 | H8B | 0 | H | 0.6212 | 0.7367 | 0.5882 | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 36 | C9B | 0 | C. 3 | 0.7230(5) | 0.6464(9) | 0.4789(9) | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 37 | H9B | 0 | H | 0.7999 | 0.6757 | 0.5481 | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 38 | Cl1B | 0 | Cl | 0.3622(3) | 0.5090(5) | 0.1644(5) | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 39 | C12B | 0 | Cl | 0.3812(6) | 0.6872(8) | 0.4445(8) | x,y,z |
| 40 | O1B | 0 | 0.3 | 0.8272(9) | 0.5647(13) | 0.1925(13) | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |

Bonds

| Number | Atom1 | Atom2 | Type | Polymeric | Cyclicity | Length | SybylType |
| :--- | :--- | :--- | :--- | :--- | :--- | :--- | :--- |
| 1 | C1 | N1 | Unknown | no | cyclic | $1.309(3)$ | un |
| 2 | C1 | N2 | Unknown | no | cyclic | $1.346(4)$ | 1 |
| 3 | C1 | N3 | Unknown | no | acyclic | $1.352(4)$ | 1 |
| 4 | C2 | H2A | Unknown | no | acyclic | 0.990 | 1 |
| 5 | C2 | H2B | Unknown | no | acyclic | 0.990 | 1 |
| 6 | C2 | C3 | Unknown | no | cyclic | $1.480(4)$ | 1 |
| 7 | C2 | N2 | Unknown | no | cyclic | $1.459(5)$ | 1 |
| 8 | C3 | H3A | Unknown | no | acyclic | 1.001 | 1 |
| 9 | C3 | C4 | Unknown | no | acyclic | $1.496(7)$ | 1 |
| 10 | C3 | O1 | Unknown | no | cyclic | $1.446(6)$ | 1 |
| 11 | C4 | C5 | Unknown | no | cyclic | $1.381(6)$ | un |
| 12 | C4 | C9 | Unknown | no | cyclic | $1.388(7)$ | un |


| 13 | C5 | H5 | Unknown no | acyclic | 0.950 | 1 |
| :--- | :--- | :--- | :--- | :--- | :--- | :--- |
| 14 | C5 | C6 | Unknown | no | cyclic | $1.388(8)$ |
| 1 | cyclic | $1.379(8)$ | 1 |  |  |  |
| 15 | C6 | C7 | Unknown | no | acyclic | $1.750(4)$ |
| 1 | 1 |  |  |  |  |  |
| 16 | C6 | C11 | Unknown | no | cyclic | $1.374(6)$ |
| 17 | C7 | C8 | Unknown | no | acyclic | $1.736(6)$ |
| 1 |  |  |  |  |  |  |
| 18 | C7 | C12 | Unknown | no | acyclic | 0.950 |
| 19 | C8 | H8 | Unknown | 1 |  |  |
| 20 | C8 | C9 | Unknown | no | cyclic | $1.391(8)$ |
| un |  |  |  |  |  |  |
| 21 | C9 | H9 | Unknown | no | acyclic | 0.950 |
| 22 | N1 | O1 | Unknown | no | cyclic | $1.447(6)$ |
| 1 |  |  |  |  |  |  |
| 23 | N2 | H2N | Unknown | no | acyclic | $0.80(4)$ |
| 24 | N3 | H3C | Unknown | no | acyclic | $0.84(4)$ |
| 25 | N3 | H3D | Unknown | no | acyclic | $0.86(4)$ |

Symmetry

| Number | Symm. Op. | Description | Detailed Description | Order | Type |
| :--- | :--- | :--- | :--- | :--- | :--- |
| 1 | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ | Identity | Identity | 1 | 1 |
| 2 | $-\mathrm{x}, 1 / 2+\mathrm{y}$, | Screw axis | 2-fold screw axis with direction $[0,1,0]$ at $0, \mathrm{y}, 1 / 4$ | 2 | 2 |
|  | $1 / 2-\mathrm{z}$ | $(2-$ fold $)$ | with screw component $[0,1 / 2,0]$ |  |  |
| 3 | $-\mathrm{x},-\mathrm{y},-\mathrm{z}$ | Inversion | Inversion at $[0,0,0]$ | 2 | -1 |
|  |  | centre | Glide plane | Glide plane perpendicular to $[0,1,0]$ with glide | 2 |

Angles

| Number | Atom1 | Atom2 | Atom3 | Angle |
| :--- | :--- | :--- | :--- | :--- |
| 1 | N1 | C1 | N2 | $126.2(3)$ |
| 2 | N1 | C1 | N3 | $117.2(3)$ |
| 3 | N2 | C1 | N3 | $116.6(3)$ |
| 4 | H2A | C2 | H2B | 108.6 |
| 5 | H2A | C2 | C3 | 110.4 |
| 6 | H2A | C2 | N2 | 110.5 |
| 7 | H2B | C2 | C3 | 110.5 |
| 8 | H2B | C2 | N2 | 110.4 |
| 9 | C3 | C2 | N2 | $106.4(3)$ |
| 10 | C2 | C3 | H3A | 108.9 |
| 11 | C2 | C3 | C4 | $112.9(3)$ |
| 12 | C2 | C3 | O1 | $109.5(3)$ |
| 13 | H3A | C3 | C4 | 108.8 |
| 14 | H3A | C3 | O1 | 108.9 |
| 15 | C4 | C3 | O1 | $107.8(3)$ |
| 16 | C3 | C4 | C5 | $120.8(4)$ |
| 17 | C3 | C4 | C9 | $120.3(4)$ |
| 18 | C5 | C4 | C9 | $119.0(4)$ |


| 19 | C4 | C5 | H5 | 119.7 |
| :--- | :--- | :--- | :--- | :--- |
| 20 | C4 | C5 | C6 | $120.4(5)$ |
| 21 | H5 | C5 | C6 | 119.8 |
| 22 | C5 | C6 | C7 | $120.0(5)$ |
| 23 | C5 | C6 | Cl1 | $116.9(4)$ |
| 24 | C7 | C6 | Cl1 | $123.1(4)$ |
| 25 | C6 | C7 | C8 | $120.4(5)$ |
| 26 | C6 | C7 | Cl2 | $119.1(4)$ |
| 27 | C8 | C7 | Cl2 | $120.5(4)$ |
| 28 | C7 | C8 | H8 | 120.3 |
| 29 | C7 | C8 | C9 | $119.5(5)$ |
| 30 | H8 | C8 | C9 | 120.3 |
| 31 | C4 | C9 | C8 | $120.7(5)$ |
| 32 | C4 | C9 | H9 | 119.7 |
| 33 | C8 | C9 | H9 | 119.6 |
| 34 | C1 | N1 | O1 | $112.9(3)$ |
| 35 | C1 | N2 | C2 | $120.9(3)$ |
| 36 | C1 | N2 | H2N | $118(3)$ |
| 37 | C2 | N2 | H2N | $119(3)$ |
| 38 | C1 | N3 | H3C | $117(3)$ |
| 39 | C1 | N3 | H3D | $117(2)$ |
| 40 | H3C | N3 | H3D | $125(4)$ |
| 41 | C3 | O1 | N1 | $110.4(3)$ |


| Torsions |  |  |  |  |  |
| :--- | :--- | :--- | :--- | :--- | :--- |
| Number | Atom1 | Atom2 | Atom3 | Atom4 | Torsion |
| 1 | N2 | C1 | N1 | O1 | $2.3(4)$ |
| 2 | N3 | C1 | N1 | O1 | $-176.2(3)$ |
| 3 | N1 | C1 | N2 | C2 | $8.4(4)$ |
| 4 | N1 | C1 | N2 | H2N | $169(3)$ |
| 5 | N3 | C1 | N2 | C2 | $-173.1(3)$ |
| 6 | N3 | C1 | N2 | H2N | $-12(3)$ |
| 7 | N1 | C1 | N3 | H3C | $176(3)$ |
| 8 | N1 | C1 | N3 | H3D | $-17(3)$ |
| 9 | N2 | C1 | N3 | H3C | $-3(3)$ |
| 10 | N2 | C1 | N3 | H3D | $165(3)$ |
| 11 | H2A | C2 | C3 | H3A | -174.7 |
| 12 | H2A | C2 | C3 | C4 | -53.8 |
| 13 | H2A | C2 | C3 | O1 | 66.3 |
| 14 | H2B | C2 | C3 | H3A | -54.6 |
| 15 | H2B | C2 | C3 | C4 | 66.4 |
| 16 | H2B | C2 | C3 | O1 | -173.5 |
| 17 | N2 | C2 | C3 | H3A | 65.3 |
| 18 | N2 | C2 | C3 | C4 | $-173.7(3)$ |


| 19 | N2 | C2 | C3 | O1 | -53.6(4) |
| :---: | :---: | :---: | :---: | :---: | :---: |
| 20 | H2A | C2 | N2 | C1 | -101.8 |
| 21 | H2A | C2 | N2 | H2N | 97 |
| 22 | H2B | C2 | N2 | C1 | 138.0 |
| 23 | H2B | C2 | N2 | H2N | -23 |
| 24 | C3 | C2 | N2 | C1 | 18.1(4) |
| 25 | C3 | C2 | N2 | H2N | -143(3) |
| 26 | C2 | C3 | C4 | C5 | -110.6(5) |
| 27 | C2 | C3 | C4 | C9 | 68.0(5) |
| 28 | H3A | C3 | C4 | C5 | 10.4 |
| 29 | H3A | C3 | C4 | C9 | -171.0 |
| 30 | O1 | C3 | C4 | C5 | 128.3(5) |
| 31 | O1 | C3 | C4 | C9 | -53.1(5) |
| 32 | C2 | C3 | O1 | N1 | 67.3(4) |
| 33 | H3A | C3 | O1 | N1 | -51.6 |
| 34 | C4 | C3 | O1 | N1 | -169.5(3) |
| 35 | C3 | C4 | C5 | H5 | -3.3 |
| 36 | C3 | C4 | C5 | C6 | 176.7(4) |
| 37 | C9 | C4 | C5 | H5 | 178.1 |
| 38 | C9 | C4 | C5 | C6 | -1.9(7) |
| 39 | C3 | C4 | C9 | C8 | -177.7(4) |
| 40 | C3 | C4 | C9 | H9 | 2.4 |
| 41 | C5 | C4 | C9 | C8 | 0.9(7) |
| 42 | C5 | C4 | C9 | H9 | -179.0 |
| 43 | C4 | C5 | C6 | C7 | 1.0(8) |
| 44 | C4 | C5 | C6 | Cl1 | -178.3(4) |
| 45 | H5 | C5 | C6 | C7 | -178.9 |
| 46 | H5 | C5 | C6 | Cl1 | 1.8 |
| 47 | C5 | C6 | C7 | C8 | 0.9(8) |
| 48 | C5 | C6 | C7 | Cl 2 | -178.4(4) |
| 49 | Cl1 | C6 | C7 | C8 | -179.8(4) |
| 50 | Cl1 | C6 | C7 | Cl 2 | 0.9(7) |
| 51 | C6 | C7 | C8 | H8 | 178.2 |
| 52 | C6 | C7 | C8 | C9 | -1.8(8) |
| 53 | Cl 2 | C7 | C8 | H8 | -2.6 |
| 54 | Cl 2 | C7 | C8 | C9 | 177.4(4) |
| 55 | C7 | C8 | C9 | C4 | 1.0(8) |
| 56 | C7 | C8 | C9 | H9 | -179.1 |
| 57 | H8 | C8 | C9 | C4 | -179.1 |
| 58 | H8 | C8 | C9 | H9 | 0.8 |
| 59 | C1 | N1 | O1 | C3 | -39.4(4) |

## Appendix II. Crystallographic data and structure refinement

## parameters of cpd 10b



Formula: $\mathrm{C}_{12} \mathrm{H}_{15} \mathrm{~N}_{3} \mathrm{O}$
Space group: P 21 (4)
Cell lengths: a 8.2172(2) b 6.5985(2) c 11.2773(3)
Cell Angles: a 90 b 103.3510(10) g 90
Cell Volume: 594.943
Z: 2 Z': 0
R-factor (\%): 3.01

| Atoms |  |  |  |  |  |  |  |
| :--- | :--- | :--- | :--- | :--- | :--- | :--- | :--- |
| Number | Label | Charge | SybylType | Xfrac + ESD | Yfrac + ESD | Zfrac + ESD | Symm. op. |
| 1 | C1 | 0 | C.3 | $0.7032(2)$ | $0.7257(4)$ | $0.01324(18)$ | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 2 | H1A | 0 | H | 0.6489 | 0.6603 | -0.0649 | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 3 | H1B | 0 | H | 0.7625 | 0.8488 | -0.0041 | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 4 | C2 | 0 | C.3 | $0.5728(3)$ | $0.7793(4)$ | $0.0870(2)$ | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 5 | H2A | 0 | H | 0.5872 | 0.9210 | 0.1165 | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 6 | H2B | 0 | H | 0.4578 | 0.7626 | 0.0365 | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 7 | C3 | 0 | C.3 | $0.6057(3)$ | $0.6306(4)$ | $0.19424(19)$ | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 8 | H3A | 0 | H | 0.5770 | 0.6915 | 0.2670 | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 9 | H3B | 0 | H | 0.5410 | 0.5039 | 0.1729 | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 10 | C4 | 0 | C.3 | $0.7926(2)$ | $0.5917(3)$ | $0.21567(17)$ | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 11 | H4 | 0 | H | 0.8539 | 0.7112 | 0.2590 | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 12 | C5 | 0 | C.3 | $0.8610(2)$ | $0.4003(3)$ | $0.28438(16)$ | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 13 | H5 | 0 | H | 0.9859 | 0.4054 | 0.3034 | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 14 | C6 | 0 | C. 2 | $0.8611(2)$ | $0.4030(3)$ | $0.04676(15)$ | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 15 | C7 | 0 | C.2 | $0.8047(2)$ | $0.3744(3)$ | $0.40216(17)$ | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 16 | C8 | 0 | C. 2 | $0.8828(3)$ | $0.4868(4)$ | $0.50276(18)$ | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |


| 17 | H8 | 0 | H | 0.9689 | 0.5794 | 0.4963 | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| :--- | :--- | :--- | :--- | :--- | :--- | :--- | :--- |
| 18 | C9 | 0 | C.2 | $0.8369(3)$ | $0.4656(4)$ | $0.6127(2)$ | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 19 | H9 | 0 | H | 0.8914 | 0.5439 | 0.6811 | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 20 | C10 | 0 | C.2 | $0.7131(3)$ | $0.3321(4)$ | $0.62335(19)$ | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 21 | H10 | 0 | H | 0.6822 | 0.3170 | 0.6990 | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 22 | C11 | 0 | C.2 | $0.6338(3)$ | $0.2200(5)$ | $0.5235(2)$ | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 23 | H11 | 0 | H | 0.5475 | 0.1278 | 0.5303 | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 24 | C12 | 0 | C.2 | $0.6793(3)$ | $0.2411(4)$ | $0.41317(18)$ | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 25 | H12 | 0 | H | 0.6240 | 0.1635 | 0.3447 | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 26 | N1 | 0 | N.3 | $0.82045(18)$ | $0.5841(2)$ | $0.09168(14)$ | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 27 | N2 | 0 | N.2 | $0.87942(19)$ | $0.2305(3)$ | $0.10345(14)$ | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 28 | N3 | 0 | N.3 | $0.8875(2)$ | $0.4081(3)$ | $-0.06902(14)$ | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 29 | O1 | 0 | O.3 | $0.80620(16)$ | $0.2293(2)$ | $0.20873(11)$ | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 30 | H1N | 0 | H | $0.946(3)$ | $0.512(5)$ | $-0.087(2)$ | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 31 | H2N | 0 | H | $0.922(4)$ | $0.287(5)$ | $-0.090(2)$ | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |

Bonds

| Number | Atom1 | Atom2 | Type | Polymeric | Cyclicity | Length | SybylType |
| :--- | :--- | :--- | :--- | :--- | :--- | :--- | :--- |
| 1 | C1 | H1A | Unknown | no | acyclic | 0.990 | 1 |
| 2 | C1 | H1B | Unknown | no | acyclic | 0.990 | 1 |
| 3 | C1 | C2 | Unknown | no | cyclic | $1.542(3)$ | 1 |
| 4 | C1 | N1 | Unknown | no | cyclic | $1.480(2)$ | 1 |
| 5 | C2 | H2A | Unknown | no | acyclic | 0.990 | 1 |
| 6 | C2 | H2B | Unknown | no | acyclic | 0.990 | 1 |
| 7 | C2 | C3 | Unknown | no | cyclic | $1.532(3)$ | 1 |
| 8 | C3 | H3A | Unknown | no | acyclic | 0.990 | 1 |
| 9 | C3 | H3B | Unknown | no | acyclic | 0.990 | 1 |
| 10 | C3 | C4 | Unknown | no | cyclic | $1.520(3)$ | 1 |
| 11 | C4 | H4 | Unknown | no | acyclic | 1.000 | 1 |
| 12 | C4 | C5 | Unknown | no | cyclic | $1.520(3)$ | 1 |
| 13 | C4 | N1 | Unknown | no | cyclic | $1.469(3)$ | 1 |
| 14 | C5 | H5 | Unknown | no | acyclic | 0.999 | 1 |
| 15 | C5 | C7 | Unknown | no | acyclic | $1.514(3)$ | 1 |
| 16 | C5 | O1 | Unknown | no | cyclic | $1.423(2)$ | 1 |
| 17 | C6 | N1 | Unknown | no | cyclic | $1.369(2)$ | 1 |
| 18 | C6 | N2 | Unknown | no | cyclic | $1.297(3)$ | un |
| 19 | C6 | N3 | Unknown | no | acyclic | $1.373(2)$ | 1 |
| 20 | C7 | C8 | Unknown | no | cyclic | $1.383(3)$ | un |
| 21 | C7 | C12 | Unknown | no | cyclic | $1.382(3)$ | un |
| 22 | C8 | H8 | Unknown | no | acyclic | 0.950 | 1 |
| 23 | C8 | C9 | Unknown | no | cyclic | $1.384(3)$ | un |
| 24 | C9 | H9 | Unknown | no | acyclic | 0.950 | 1 |
| 25 | C9 | C10 | Unknown | no | cyclic | $1.372(4)$ | un |
| 26 | C10 | H10 | Unknown | no | acyclic | 0.950 | 1 |


| 27 | C10 | C11 | Unknown | no | cyclic | $1.379(3)$ |
| :--- | :--- | :--- | :--- | :--- | :--- | :--- |
| un |  |  |  |  |  |  |
| 28 | C11 | H11 | Unknown | no | acyclic | 0.951 |
| 29 | C11 | C12 | Unknown | no | cyclic | $1.386(3)$ |
| un |  |  |  |  |  |  |
| 30 | C12 | H12 | Unknown | no | acyclic | 0.950 |
| 31 | N2 | O1 | Unknown | no | cyclic | $1.450(2)$ |
| 32 | N3 | H1N | Unknown | no | acyclic | $0.89(3)$ |
| 3 | 1 |  |  |  |  |  |
| 33 | N3 | H2N | Unknown | no | acyclic | $0.90(3)$ |

Symmetry

| Number | Symm. <br> Op. | Description | Detailed Description | Order | Type |  |
| :--- | :--- | :--- | :--- | :--- | :--- | :--- |
| 1 | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ | Identity |  | Identity |  |  |
| 2 | $-\mathrm{x}, 1 / 2+\mathrm{y}$, | Screw | axis | 2-fold screw axis with direction $[0,1,0]$ at $0, \mathrm{y}, 0$ | 2 | 2 |
|  | -z | (2-fold) |  | with screw component $[0,1 / 2,0]$ | 1 |  |


| Angles |  |  |  |  |
| :--- | :--- | :--- | :--- | :--- |
| Number | Atom1 | Atom2 | Atom3 | Angle |
| 1 | H1A | C1 | H1B | 108.9 |
| 2 | H1A | C1 | C2 | 110.7 |
| 3 | H1A | C1 | N1 | 110.7 |
| 4 | H1B | C1 | C2 | 110.7 |
| 5 | H1B | C1 | N1 | 110.7 |
| 6 | C2 | C1 | N1 | $105.1(2)$ |
| 7 | C1 | C2 | H2A | 110.7 |
| 8 | C1 | C2 | H2B | 110.7 |
| 9 | C1 | C2 | C3 | $105.1(2)$ |
| 10 | H2A | C2 | H2B | 108.8 |
| 11 | H2A | C2 | C3 | 110.7 |
| 12 | H2B | C2 | C3 | 110.7 |
| 13 | C2 | C3 | H3A | 111.2 |
| 14 | C2 | C3 | H3B | 111.2 |
| 15 | C2 | C3 | C4 | $102.8(2)$ |
| 16 | H3A | C3 | H3B | 109.1 |
| 17 | H3A | C3 | C4 | 111.2 |
| 18 | H3B | C3 | C4 | 111.2 |
| 19 | C3 | C4 | H4 | 108.7 |
| 20 | C3 | C4 | C5 | $117.5(2)$ |
| 21 | C3 | C4 | N1 | $103.2(2)$ |
| 22 | H4 | C4 | C5 | 108.7 |
| 23 | H4 | C4 | N1 | 108.7 |
| 24 | C5 | C4 | N1 | $109.7(1)$ |
| 25 | C4 | C5 | H5 | 108.8 |
| 26 | C4 | C5 | C7 | $112.9(2)$ |
| 27 | C4 | C5 | O1 | $108.9(1)$ |
|  |  |  |  |  |


| 28 | H5 | C5 | C7 | 108.8 |
| :--- | :--- | :--- | :--- | :--- |
| 29 | H5 | C5 | O1 | 108.8 |
| 30 | C7 | C5 | O1 | $108.5(1)$ |
| 31 | N1 | C6 | N2 | $126.4(2)$ |
| 32 | N1 | C6 | N3 | $115.9(2)$ |
| 33 | N2 | C6 | N3 | $117.7(2)$ |
| 34 | C5 | C7 | C8 | $118.8(2)$ |
| 35 | C5 | C7 | C12 | $122.4(2)$ |
| 36 | C8 | C7 | C12 | $118.8(2)$ |
| 37 | C7 | C8 | H8 | 119.6 |
| 38 | C7 | C8 | C9 | $120.7(2)$ |
| 39 | H8 | C8 | C9 | 119.7 |
| 40 | C8 | C9 | H9 | 119.8 |
| 41 | C8 | C9 | C10 | $120.3(2)$ |
| 42 | H9 | C9 | C10 | 119.9 |
| 43 | C9 | C10 | H10 | 120.2 |
| 44 | C9 | C10 | C11 | $119.6(2)$ |
| 45 | H10 | C10 | C11 | 120.2 |
| 46 | C10 | C11 | H11 | 119.9 |
| 47 | C10 | C11 | C12 | $120.3(2)$ |
| 48 | H11 | C11 | C12 | 119.8 |
| 49 | C7 | C12 | C11 | $120.4(2)$ |
| 50 | C7 | C12 | H12 | 119.8 |
| 51 | C11 | C12 | H12 | 119.8 |
| 52 | C1 | N1 | C4 | $108.9(1)$ |
| 53 | C1 | N1 | C6 | $120.7(2)$ |
| 54 | C4 | N1 | C6 | $119.1(1)$ |
| 55 | C6 | N2 | O1 | $112.7(2)$ |
| 56 | C6 | N3 | H1N | $117(2)$ |
| 57 | C6 | N3 | H2N | $111(2)$ |
| 58 | H1N | N3 | H2N | $114(3)$ |
| 59 | C5 | O1 | N2 | $110.7(1)$ |
|  |  |  |  |  |

Torsions

| Number | Atom1 | Atom2 | Atom3 | Atom4 | Torsion |
| :--- | :--- | :--- | :--- | :--- | :--- |
| 1 | H1A | C1 | C2 | H2A | -131.5 |
| 2 | H1A | C1 | C2 | H2B | -10.7 |
| 3 | H1A | C1 | C2 | C3 | 108.9 |
| 4 | H1B | C1 | C2 | H2A | -10.7 |
| 5 | H1B | C1 | C2 | H2B | 110.1 |
| 6 | H1B | C1 | C2 | C3 | -130.3 |
| 7 | N1 | C1 | C2 | H2A | 108.9 |
| 8 | N1 | C1 | C2 | H2B | -130.3 |
| 9 | N1 | C1 | C2 | C3 | $-10.7(2)$ |


| 10 | H1A | C1 | N1 | C4 | -133.6 |
| :---: | :---: | :---: | :---: | :---: | :---: |
| 11 | H1A | C1 | N1 | C6 | 9.8 |
| 12 | H1B | C1 | N1 | C4 | 105.6 |
| 13 | H1B | C1 | N1 | C6 | -111.1 |
| 14 | C2 | C1 | N1 | C4 | -14.0(2) |
| 15 | C2 | C1 | N1 | C6 | 129.4(2) |
| 16 | C1 | C2 | C3 | H3A | 149.4 |
| 17 | C1 | C2 | C3 | H3B | -88.8 |
| 18 | C1 | C2 | C3 | C4 | 30.3(2) |
| 19 | H2A | C2 | C3 | H3A | 29.7 |
| 20 | H2A | C2 | C3 | H3B | 151.5 |
| 21 | H2A | C2 | C3 | C4 | -89.4 |
| 22 | H2B | C2 | C3 | H3A | -91.0 |
| 23 | H2B | C2 | C3 | H3B | 30.8 |
| 24 | H2B | C2 | C3 | C4 | 149.9 |
| 25 | C2 | C3 | C4 | H4 | 76.7 |
| 26 | C2 | C3 | C4 | C5 | -159.4(2) |
| 27 | C2 | C3 | C4 | N1 | -38.6(2) |
| 28 | H3A | C3 | C4 | H4 | -42.4 |
| 29 | H3A | C3 | C4 | C5 | 81.5 |
| 30 | H3A | C3 | C4 | N1 | -157.7 |
| 31 | H3B | C3 | C4 | H4 | -164.2 |
| 32 | H3B | C3 | C4 | C5 | -40.3 |
| 33 | H3B | C3 | C4 | N1 | 80.5 |
| 34 | C3 | C4 | C5 | H5 | -171.0 |
| 35 | C3 | C4 | C5 | C7 | -50.1(2) |
| 36 | C3 | C4 | C5 | O1 | 70.5(2) |
| 37 | H4 | C4 | C5 | H5 | -47.1 |
| 38 | H4 | C4 | C5 | C7 | 73.8 |
| 39 | H4 | C4 | C5 | O1 | -165.5 |
| 40 | N1 | C4 | C5 | H5 | 71.6 |
| 41 | N1 | C4 | C5 | C7 | -167.5(1) |
| 42 | N1 | C4 | C5 | O1 | -46.8(2) |
| 43 | C3 | C4 | N1 | C1 | 33.3(2) |
| 44 | C3 | C4 | N1 | C6 | -110.7(2) |
| 45 | H4 | C4 | N1 | C1 | -82.0 |
| 46 | H4 | C4 | N1 | C6 | 134.0 |
| 47 | C5 | C4 | N1 | C1 | 159.3(1) |
| 48 | C5 | C4 | N1 | C6 | 15.3(2) |
| 49 | C4 | C5 | C7 | C8 | -78.0(2) |
| 50 | C4 | C5 | C7 | C12 | 102.7(2) |
| 51 | H5 | C5 | C7 | C8 | 42.9 |
| 52 | H5 | C5 | C7 | C12 | -136.5 |
| 53 | O1 | C5 | C7 | C8 | 161.1(2) |


| 54 | O1 | C5 | C7 | C12 | -18.2(2) |
| :---: | :---: | :---: | :---: | :---: | :---: |
| 55 | C4 | C5 | O1 | N2 | 65.9(2) |
| 56 | H5 | C5 | O1 | N2 | -52.6 |
| 57 | C7 | C5 | O1 | N2 | -170.8(1) |
| 58 | N2 | C6 | N1 | C1 | -140.1(2) |
| 59 | N2 | C6 | N1 | C4 | -0.4(3) |
| 60 | N3 | C6 | N1 | C1 | 41.1(2) |
| 61 | N3 | C6 | N1 | C4 | -179.1(2) |
| 62 | N1 | C6 | N2 | O1 | 16.9(3) |
| 63 | N3 | C6 | N2 | O1 | -164.3(2) |
| 64 | N1 | C6 | N3 | H1N | 42(2) |
| 65 | N1 | C6 | N3 | H2N | 175(2) |
| 66 | N2 | C6 | N3 | H1N | -137(2) |
| 67 | N2 | C6 | N3 | H2N | -4(2) |
| 68 | C5 | C7 | C8 | H8 | 0.9 |
| 69 | C5 | C7 | C8 | C9 | -179.0(2) |
| 70 | C12 | C7 | C8 | H8 | -179.7 |
| 71 | C12 | C7 | C8 | C9 | 0.3(3) |
| 72 | C5 | C7 | C12 | C11 | 178.9(2) |
| 73 | C5 | C7 | C12 | H12 | -1.1 |
| 74 | C8 | C7 | C12 | C11 | -0.4(3) |
| 75 | C8 | C7 | C12 | H12 | 179.6 |
| 76 | C7 | C8 | C9 | H9 | -179.9 |
| 77 | C7 | C8 | C9 | C10 | 0.1(4) |
| 78 | H8 | C8 | C9 | H9 | 0.2 |
| 79 | H8 | C8 | C9 | C10 | -179.8 |
| 80 | C8 | C9 | C10 | H10 | 179.6 |
| 81 | C8 | C9 | C10 | C11 | -0.4(4) |
| 82 | H9 | C9 | C10 | H10 | -0.4 |
| 83 | H9 | C9 | C10 | C11 | 179.6 |
| 84 | C9 | C10 | C11 | H11 | -179.7 |
| 85 | C9 | C10 | C11 | C12 | 0.3(4) |
| 86 | H10 | C10 | C11 | H11 | 0.3 |
| 87 | H10 | C10 | C11 | C12 | -179.7 |
| 88 | C10 | C11 | C12 | C7 | 0.1(4) |
| 89 | C10 | C11 | C12 | H12 | -179.9 |
| 90 | H11 | C11 | C12 | C7 | -179.9 |
| 91 | H11 | C11 | C12 | H12 | 0.1 |
| 92 | C6 | N2 | O1 | C5 | -50.3(2) |

## Appendix III. Crystallographic data and structure refinement

## parameters of cpd 48



Formula: $\mathrm{C}_{16} \mathrm{H}_{28} \mathrm{~N}_{3} \mathrm{O}, \mathrm{Br}$
Space group: $\mathrm{P} 2_{1} / \mathrm{c}$ (14)
Cell lengths: a 11.8270(4) b 6.8408(2) c 23.5402(9)
Cell Angles: a 90 b 102.434(2) g 90
Cell Volume: 1859.88
Z: $4 \mathbf{Z}$ ': 0
R-factor (\%): 3.41

Atoms

| Number | Label | Charge | SybylType | Xfrac + ESD | Yfrac + ESD | Zfrac + ESD | Symm. op. |
| :--- | :--- | :--- | :--- | :--- | :--- | :--- | :--- |
| 1 | C1 | 0 | C.3 | $0.35796(15)$ | $0.6005(2)$ | $0.41942(7)$ | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 2 | H1 | 0 | H | 0.3105 | 0.6228 | 0.3794 | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 3 | C2 | 0 | C.3 | $0.48331(15)$ | $0.6279(3)$ | $0.41841(7)$ | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 4 | H2A | 0 | H | 0.4946 | 0.7556 | 0.4006 | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 5 | H2B | 0 | H | 0.5307 | 0.6261 | 0.4586 | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 6 | C3 | 0 | C.2 | $0.44898(15)$ | $0.3208(2)$ | $0.36353(7)$ | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 7 | C4 | 0 | C.3 | $0.24872(16)$ | $0.1927(3)$ | $0.35780(9)$ | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |


| 8 | H4A | 0 | H | 0.2086 | 0.1312 | 0.3860 | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 9 | H4B | 0 | H | 0.2636 | 0.0896 | 0.3308 | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 10 | C5 | 0 | C. 2 | 0.17172(17) | 0.3439(3) | 0.32413 (8) | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 11 | H5 | 0 | H | 0.2025 | 0.4166 | 0.2965 | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 12 | C6 | 0 | C. 2 | 0.06413(18) | 0.3882(3) | 0.32861(10) | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 13 | C7 | 0 | C. 3 | -0.0012(2) | 0.2921 (4) | 0.36867 (13) | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 14 | H7A | 0 | H | 0.0504 | 0.2029 | 0.3948 | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 15 | H7B | 0 | H | -0.0664 | 0.2184 | 0.3458 | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 16 | H7C | 0 | H | -0.0303 | 0.3921 | 0.3917 | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 17 | C8 | 0 | C. 3 | -0.0020(2) | 0.5443(4) | 0.29034 (14) | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 18 | H8A | 0 | H | 0.0474 | 0.6019 | 0.2663 | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 19 | H8B | 0 | H | -0.0258 | 0.6461 | 0.3146 | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 20 | H8C | 0 | H | -0.0708 | 0.4866 | 0.2652 | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 21 | C9 | 0 | C. 2 | 0.30980(16) | 0.7226(3) | 0.46157(8) | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 22 | C10 | 0 | C. 2 | 0.37529(19) | 0.8323(3) | 0.50217(9) | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 23 | H10A | 0 | H | 0.4568 | 0.8360 | 0.5055 | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 24 | H10B | 0 | H | 0.3407 | 0.9072 | 0.5279 | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 25 | C11 | 0 | C. 3 | 0.18019(18) | 0.7140(3) | 0.45240 (10) | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 26 | H11A | 0 | H | 0.1551 | 0.7913 | 0.4825 | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 27 | H11B | 0 | H | 0.1558 | 0.5779 | 0.4547 | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 28 | H11C | 0 | H | 0.1452 | 0.7672 | 0.4140 | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 29 | C12 | 0 | C. 3 | 0.62511(16) | 0.5020(3) | 0.36189(9) | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 30 | H12A | 0 | H | 0.6053 | 0.5804 | 0.3258 | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 31 | H12B | 0 | H | 0.6558 | 0.3747 | 0.3521 | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 32 | C13 | 0 | C. 2 | 0.71619(17) | 0.6054(3) | $0.40474(8)$ | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 33 | H13 | 0 | H | 0.7371 | 0.5508 | 0.4427 | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 34 | C14 | 0 | C. 2 | 0.77072(16) | 0.7664(3) | 0.39488(9) | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 35 | C15 | 0 | C. 3 | 0.7450(3) | 0.8794(5) | 0.33971 (16) | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 36 | H15A | 0 | H | 0.8101 | 0.8680 | 0.3203 | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 37 | H15B | 0 | H | 0.7331 | 1.0172 | 0.3482 | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 38 | H15C | 0 | H | 0.6748 | 0.8275 | 0.3143 | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 39 | C16 | 0 | C. 3 | 0.8687(2) | 0.8471(5) | 0.43993 (13) | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 40 | H16A | 0 | H | 0.8738 | 0.7765 | 0.4766 | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 41 | H16B | 0 | H | 0.8552 | 0.9862 | 0.4459 | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 42 | H16C | 0 | H | 0.9414 | 0.8314 | 0.4268 | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 43 | N1 | 0 | N. 3 | 0.36011(13) | 0.2728(2) | 0.38938 (6) | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 44 | N2 | 0 | N. 3 | 0.51932(12) | 0.4684(2) | $0.38424(6)$ | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 45 | N3 | 0 | N. 3 | 0.46773(15) | 0.2092(3) | 0.32060(7) | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 46 | O1 | 0 | 0.3 | 0.34567(11) | 0.39552(17) | 0.43548 (5) | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 47 | H1N | 0 | H | 0.5130(19) | 0.248 (3) | 0.2997(9) | x,y,z |
| 48 | H2N | 0 | H | 0.430(2) | $0.106(4)$ | 0.3118(10) | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 49 | Br1 | 0 | Br | $0.35034(2)$ | 0.77807(3) | 0.27258(2) | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |

## Bonds

| Number | Atom1 | Atom2 | Type | Polymeric | Cyclicity | Length | SybylType |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1 | C1 | H1 | Unknown | no | acyclic | 0.999 | 1 |
| 2 | C1 | C2 | Unknown | no | cyclic | 1.500(3) | 1 |
| 3 | C1 | C9 | Unknown | no | acyclic | 1.500(3) | 1 |
| 4 | C1 | O1 | Unknown | no | cyclic | 1.468(2) | 1 |
| 5 | C2 | H2A | Unknown | no | acyclic | 0.990 | 1 |
| 6 | C2 | H2B | Unknown | no | acyclic | 0.990 | 1 |
| 7 | C2 | N2 | Unknown | no | cyclic | 1.472(2) | 1 |
| 8 | C3 | N1 | Unknown | no | cyclic | 1.363(2) | 1 |
| 9 | C3 | N2 | Unknown | no | cyclic | 1.332(2) | 1 |
| 10 | C3 | N3 | Unknown | no | acyclic | $1.323(2)$ | 1 |
| 11 | C4 | H4A | Unknown | no | acyclic | 0.989 | 1 |
| 12 | C4 | H4B | Unknown | no | acyclic | 0.990 | 1 |
| 13 | C4 | C5 | Unknown | no | acyclic | 1.489(3) | 1 |
| 14 | C4 | N1 | Unknown | no | acyclic | 1.472(2) | 1 |
| 15 | C5 | H5 | Unknown | no | acyclic | 0.951 | 1 |
| 16 | C5 | C6 | Unknown | no | acyclic | 1.334(3) | un |
| 17 | C6 | C7 | Unknown | no | acyclic | 1.494(4) | 1 |
| 18 | C6 | C8 | Unknown | no | acyclic | 1.503(3) | 1 |
| 19 | C7 | H7A | Unknown | no | acyclic | 0.981 | 1 |
| 20 | C7 | H7B | Unknown | no | acyclic | 0.980 | 1 |
| 21 | C7 | H7C | Unknown | no | acyclic | 0.980 | 1 |
| 22 | C8 | H8A | Unknown | no | acyclic | 0.979 | 1 |
| 23 | C8 | H8B | Unknown | no | acyclic | 0.980 | 1 |
| 24 | C8 | H8C | Unknown | no | acyclic | 0.980 | 1 |
| 25 | C9 | C10 | Unknown | no | acyclic | $1.326(3)$ | un |
| 26 | C9 | C11 | Unknown | no | acyclic | 1.502(3) | 1 |
| 27 | C10 | H10A | Unknown | no | acyclic | 0.951 | 1 |
| 28 | C10 | H10B | Unknown | no | acyclic | 0.951 | 1 |
| 29 | C11 | H11A | Unknown | no | acyclic | 0.980 | 1 |
| 30 | C11 | H11B | Unknown | no | acyclic | 0.980 | 1 |
| 31 | C11 | H11C | Unknown | no | acyclic | 0.980 | 1 |
| 32 | C12 | H12A | Unknown | no | acyclic | 0.989 | 1 |
| 33 | C12 | H12B | Unknown | no | acyclic | 0.990 | 1 |
| 34 | C12 | C13 | Unknown | no | acyclic | 1.487(3) | 1 |
| 35 | C12 | N2 | Unknown | no | acyclic | 1.476(3) | 1 |
| 36 | C13 | H13 | Unknown | no | acyclic | 0.951 | 1 |
| 37 | C13 | C14 | Unknown | no | acyclic | 1.322(3) | un |
| 38 | C14 | C15 | Unknown | no | acyclic | $1.485(4)$ | 1 |
| 39 | C14 | C16 | Unknown | no | acyclic | 1.498(3) | 1 |
| 40 | C15 | H15A | Unknown | no | acyclic | 0.979 | 1 |
| 41 | C15 | H15B | Unknown | no | acyclic | 0.980 | 1 |
| 42 | C15 | H15C | Unknown | no | acyclic | 0.979 | 1 |
| 43 | C16 | H16A | Unknown | no | acyclic | 0.980 | 1 |


| 44 | C16 | H16B | Unknown | no | acyclic | 0.980 | 1 |
| :--- | :--- | :--- | :--- | :--- | :--- | :--- | :--- |
| 45 | C16 | H16C | Unknown | no | acyclic | 0.980 | 1 |
| 46 | N1 | O1 | Unknown | no | cyclic | $1.411(2)$ | 1 |
| 47 | N3 | H1N | Unknown | no | acyclic | $0.84(2)$ | 1 |
| 48 | N3 | H2N | Unknown | no | acyclic | $0.84(3)$ | 1 |

Symmetry

| Number | Symm. Op. | Description | Detailed Description | Order | Type |
| :--- | :--- | :--- | :--- | :--- | :---: |
| 1 | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ | Identity | Identity | 1 | 1 |
| 2 | $-\mathrm{x}, 1 / 2+\mathrm{y}$, | Screw axis | 2-fold screw axis with direction $[0,1,0]$ at $0, \mathrm{y}, 1 / 4$ | 2 | 2 |
|  | $1 / 2-\mathrm{z}$ | $(2$-fold $)$ | with screw component $[0,1 / 2,0]$ |  |  |
| 3 | $-\mathrm{x},-\mathrm{y},-\mathrm{z}$ | Inversion | Inversion at $[0,0,0]$ | 2 | -1 |
|  |  | centre | Glide plane | Glide plane perpendicular to $[0,1,0]$ with glide | 2 |

Angles

| Number | Atom1 | Atom2 | Atom3 | Angle |
| :--- | :--- | :--- | :--- | :--- |
| 1 | H1 | C1 | C2 | 108.8 |
| 2 | H1 | C1 | C9 | 108.8 |
| 3 | H1 | C1 | O1 | 108.8 |
| 4 | C2 | C1 | C9 | $117.3(1)$ |
| 5 | C2 | C1 | O1 | $106.1(1)$ |
| 6 | C9 | C1 | O1 | $106.8(1)$ |
| 7 | C1 | C2 | H2A | 109.9 |
| 8 | C1 | C2 | H2B | 110.0 |
| 9 | C1 | C2 | N2 | $108.6(1)$ |
| 10 | H2A | C2 | H2B | 108.4 |
| 11 | H2A | C2 | N2 | 110.0 |
| 12 | H2B | C2 | N2 | 110.0 |
| 13 | N1 | C3 | N2 | $120.0(1)$ |
| 14 | N1 | C3 | N3 | $118.3(2)$ |
| 15 | N2 | C3 | N3 | $121.5(2)$ |
| 16 | H4A | C4 | H4B | 107.8 |
| 17 | H4A | C4 | C5 | 109.0 |
| 18 | H4A | C4 | N1 | 109.0 |
| 19 | H4B | C4 | C5 | 109.0 |
| 20 | H4B | C4 | N1 | 109.0 |
| 21 | C5 | C4 | N1 | $112.9(2)$ |
| 22 | C4 | C5 | H5 | 116.5 |
| 23 | C4 | C5 | C6 | $126.9(2)$ |
| 24 | H5 | C5 | C6 | 116.6 |
| 25 | C5 | C6 | C7 | $125.6(2)$ |
| 26 | C5 | C6 | C8 | $119.7(2)$ |


| 27 | C7 | C6 | C8 | 114.7(2) |
| :---: | :---: | :---: | :---: | :---: |
| 28 | C6 | C7 | H7A | 109.5 |
| 29 | C6 | C7 | H7B | 109.4 |
| 30 | C6 | C7 | H7C | 109.4 |
| 31 | H7A | C7 | H7B | 109.5 |
| 32 | H7A | C7 | H7C | 109.4 |
| 33 | H7B | C7 | H7C | 109.5 |
| 34 | C6 | C8 | H8A | 109.5 |
| 35 | C6 | C8 | H8B | 109.5 |
| 36 | C6 | C8 | H8C | 109.4 |
| 37 | H8A | C8 | H8B | 109.4 |
| 38 | H8A | C8 | H8C | 109.5 |
| 39 | H8B | C8 | H8C | 109.4 |
| 40 | C1 | C9 | C10 | 123.1(2) |
| 41 | C1 | C9 | C11 | 113.8(2) |
| 42 | C10 | C9 | C11 | 123.0(2) |
| 43 | C9 | C10 | H10A | 119.9 |
| 44 | C9 | C10 | H10B | 120.0 |
| 45 | H10A | C10 | H10B | 120.1 |
| 46 | C9 | C11 | H11A | 109.5 |
| 47 | C9 | C11 | H11B | 109.4 |
| 48 | C9 | C11 | H11C | 109.5 |
| 49 | H11A | C11 | H11B | 109.5 |
| 50 | H11A | C11 | H11C | 109.5 |
| 51 | H11B | C11 | H11C | 109.5 |
| 52 | H12A | C12 | H12B | 107.9 |
| 53 | H12A | C12 | C13 | 109.1 |
| 54 | H12A | C12 | N2 | 109.2 |
| 55 | H12B | C12 | C13 | 109.2 |
| 56 | H12B | C12 | N2 | 109.1 |
| 57 | C13 | C12 | N2 | 112.2(2) |
| 58 | C12 | C13 | H13 | 117.0 |
| 59 | C12 | C13 | C14 | 125.9(2) |
| 60 | H13 | C13 | C14 | 117.0 |
| 61 | C13 | C14 | C15 | 124.8(2) |
| 62 | C13 | C14 | C16 | 121.0(2) |
| 63 | C15 | C14 | C16 | 114.1(2) |
| 64 | C14 | C15 | H15A | 109.4 |
| 65 | C14 | C15 | H15B | 109.5 |
| 66 | C14 | C15 | H15C | 109.4 |
| 67 | H15A | C15 | H15B | 109.5 |
| 68 | H15A | C15 | H15C | 109.5 |
| 69 | H15B | C15 | H15C | 109.5 |
| 70 | C14 | C16 | H16A | 109.5 |


| 71 | C14 | C16 | H16B | 109.5 |
| :--- | :--- | :--- | :--- | :--- |
| 72 | C14 | C16 | H16C | 109.5 |
| 73 | H16A | C16 | H16B | 109.5 |
| 74 | H16A | C16 | H16C | 109.4 |
| 75 | H16B | C16 | H16C | 109.4 |
| 76 | C3 | N1 | C4 | $123.8(1)$ |
| 77 | C3 | N1 | O1 | $115.6(1)$ |
| 78 | C4 | N1 | O1 | $111.5(1)$ |
| 79 | C2 | N2 | C3 | $122.0(1)$ |
| 80 | C2 | N2 | C12 | $116.5(1)$ |
| 81 | C3 | N2 | C12 | $119.9(1)$ |
| 82 | C3 | N3 | H1N | $120(1)$ |
| 83 | C3 | N3 | H2N | $121(2)$ |
| 84 | H1N | N3 | H2N | $119(2)$ |
| 85 | C1 | O1 | N1 | $109.6(1)$ |


| Torsions |  |  |  |  |  |
| :--- | :--- | :--- | :--- | :--- | :--- |
| Number | Atom1 | Atom2 | Atom3 | Atom4 | Torsion |
| 1 | H1 | C1 | C2 | H2A | 52.3 |
| 2 | H1 | C1 | C2 | H2B | 171.5 |
| 3 | H1 | C1 | C2 | N2 | -68.1 |
| 4 | C9 | C1 | C2 | H2A | -71.7 |
| 5 | C9 | C1 | C2 | H2B | 47.5 |
| 6 | C9 | C1 | C2 | N2 | $168.0(1)$ |
| 7 | O1 | C1 | C2 | H2A | 169.2 |
| 8 | O1 | C1 | C2 | H2B | -71.6 |
| 9 | O1 | C1 | C2 | N2 | $48.8(2)$ |
| 10 | H1 | C1 | C9 | C10 | -132.9 |
| 11 | H1 | C1 | C9 | C11 | 45.3 |
| 12 | C2 | C1 | C9 | C10 | $-8.9(3)$ |
| 13 | C2 | C1 | C9 | C11 | $169.3(2)$ |
| 14 | O1 | C1 | C9 | C10 | $109.8(2)$ |
| 15 | O1 | C1 | C9 | C11 | $-71.9(2)$ |
| 16 | H1 | C1 | O1 | N1 | 47.2 |
| 17 | C2 | C1 | O1 | N1 | $-69.7(2)$ |
| 18 | C9 | C1 | O1 | N1 | $164.5(1)$ |
| 19 | C1 | C2 | N2 | C3 | $-5.2(2)$ |
| 20 | C1 | C2 | N2 | C12 | $160.5(1)$ |
| 21 | H2A | C2 | N2 | C3 | -125.5 |
| 22 | H2A | C2 | N2 | C12 | 40.2 |
| 23 | H2B | C2 | N2 | C3 | 115.2 |
| 24 | H2B | C2 | N2 | C12 | -79.1 |
| 25 | N2 | C3 | N1 | C4 | $147.9(2)$ |
| 26 | N2 | C3 | N1 | O1 | $3.7(2)$ |


| 27 | N3 | C3 | N1 | C4 | -36.8(2) |
| :---: | :---: | :---: | :---: | :---: | :---: |
| 28 | N3 | C3 | N1 | O1 | 179.0(1) |
| 29 | N1 | C3 | N2 | C2 | -23.7(2) |
| 30 | N1 | C3 | N2 | C12 | 171.1(2) |
| 31 | N3 | C3 | N2 | C2 | 161.1(2) |
| 32 | N3 | C3 | N2 | C12 | -4.1(2) |
| 33 | N1 | C3 | N3 | H1N | 168(2) |
| 34 | N1 | C3 | N3 | H2N | -6(2) |
| 35 | N2 | C3 | N3 | H1N | -17(2) |
| 36 | N2 | C3 | N3 | H2N | 169(2) |
| 37 | H4A | C4 | C5 | H5 | 177.7 |
| 38 | H4A | C4 | C5 | C6 | -2.3 |
| 39 | H4B | C4 | C5 | H5 | -64.9 |
| 40 | H4B | C4 | C5 | C6 | 115.1 |
| 41 | N1 | C4 | C5 | H5 | 56.4 |
| 42 | N1 | C4 | C5 | C6 | -123.6(2) |
| 43 | H4A | C4 | N1 | C3 | 162.2 |
| 44 | H4A | C4 | N1 | O1 | -52.3 |
| 45 | H4B | C4 | N1 | C3 | 44.8 |
| 46 | H4B | C4 | N1 | O1 | -169.7 |
| 47 | C5 | C4 | N1 | C3 | -76.5(2) |
| 48 | C5 | C4 | N1 | O1 | 69.0(2) |
| 49 | C4 | C5 | C6 | C7 | -0.4(4) |
| 50 | C4 | C5 | C6 | C8 | -179.2(2) |
| 51 | H5 | C5 | C6 | C7 | 179.6 |
| 52 | H5 | C5 | C6 | C8 | 0.8 |
| 53 | C5 | C6 | C7 | H7A | 7.2 |
| 54 | C5 | C6 | C7 | H7B | -112.8 |
| 55 | C5 | C6 | C7 | H7C | 127.1 |
| 56 | C8 | C6 | C7 | H7A | -174.0 |
| 57 | C8 | C6 | C7 | H7B | 66.0 |
| 58 | C8 | C6 | C7 | H7C | -54.1 |
| 59 | C5 | C6 | C8 | H8A | -2.6 |
| 60 | C5 | C6 | C8 | H8B | -122.6 |
| 61 | C5 | C6 | C8 | H8C | 117.5 |
| 62 | C7 | C6 | C8 | H8A | 178.5 |
| 63 | C7 | C6 | C8 | H8B | 58.5 |
| 64 | C7 | C6 | C8 | H8C | -61.4 |
| 65 | C1 | C9 | C10 | H10A | 0.0 |
| 66 | C1 | C9 | C10 | H10B | -180.0 |
| 67 | C11 | C9 | C10 | H10A | -178.0 |
| 68 | C11 | C9 | C10 | H10B | 1.9 |
| 69 | C1 | C9 | C11 | H11A | 177.1 |
| 70 | C1 | C9 | C11 | H11B | 57.1 |


| 71 | C1 | C9 | C11 | H11C | -62.9 |
| :--- | :--- | :--- | :--- | :--- | :--- |
| 72 | C10 | C9 | C11 | H11A | -4.6 |
| 73 | C10 | C9 | C11 | H11B | -124.7 |
| 74 | C10 | C9 | C11 | H11C | 115.3 |
| 75 | H12A | C12 | C13 | H13 | 173.9 |
| 76 | H12A | C12 | C13 | C14 | -6.1 |
| 77 | H12B | C12 | C13 | H13 | -68.4 |
| 78 | H12B | C12 | C13 | C14 | 111.7 |
| 79 | N2 | C12 | C13 | H13 | 52.7 |
| 80 | N2 | C12 | C13 | C14 | $-127.2(2)$ |
| 81 | H12A | C12 | N2 | C2 | -81.7 |
| 82 | H12A | C12 | N2 | C3 | 84.3 |
| 83 | H12B | C12 | N2 | C2 | 160.6 |
| 84 | H12B | C12 | N2 | C3 | -33.4 |
| 85 | C13 | C12 | N2 | C2 | $39.4(2)$ |
| 86 | C13 | C12 | N2 | C3 | $-154.5(2)$ |
| 87 | C12 | C13 | C14 | C15 | $3.9(4)$ |
| 88 | C12 | C13 | C14 | C16 | $-174.3(2)$ |
| 89 | H13 | C13 | C14 | C15 | -176.1 |
| 90 | H13 | C13 | C14 | C16 | 5.7 |
| 91 | C13 | C14 | C15 | H15A | -111.8 |
| 92 | C13 | C14 | C15 | H15B | 128.2 |
| 93 | C13 | C14 | C15 | H15C | 8.2 |
| 94 | C16 | C14 | C15 | H15A | 66.5 |
| 95 | C16 | C14 | C15 | H15B | -53.5 |
| 96 | C16 | C14 | C15 | H15C | -173.4 |
| 97 | C13 | C14 | C16 | H16A | -9.2 |
| 98 | C13 | C14 | C16 | H16B | -129.2 |
| 99 | C13 | C14 | C16 | H16C | 110.8 |
| 100 | C15 | C14 | C16 | H16A | 172.4 |
| 101 | C15 | C14 | C16 | H16B | 52.3 |
| 102 | C15 | C14 | C16 | H16C | -67.7 |
| 103 | C3 | N1 | O1 | C1 | $43.2(2)$ |
| 104 | C4 | N1 | O1 | C1 | $-105.2(1)$ |
|  |  |  |  |  |  |
| 98 |  |  |  | C15 |  |

## Appendix IV. Crystallographic data and structure refinement

 parameters of cpd 102

Formula: $2\left(\mathrm{C}_{15} \mathrm{H}_{13} \mathrm{~N} \mathrm{O}_{2}\right), \mathrm{H}_{2} \mathrm{O}$
Space group: Pb c n (60)
Cell lengths: a 16.1722(9) b 22.6903(13) c 6.9291(3)
Cell Angles: a 90 b 90 g 90
Cell Volume: 2542.65
Z: $4 \mathbf{Z}$ ': 0
R-factor (\%): 8.36

| Atoms |  |  |  |  |  |  |  |
| :--- | :--- | :--- | :--- | :--- | :--- | :--- | :--- |
| Number | Label | Charge | SybylType | Xfrac + ESD | Yfrac + ESD | Zfrac + ESD | Symm. op. |
| 1 | C1 | 0 | C. 2 | $0.17894(16)$ | $0.29276(13)$ | $0.3331(4)$ | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 2 | C2 | 0 | C. 2 | $0.15250(17)$ | $0.30886(13)$ | $0.5164(4)$ | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 3 | H2 | 0 | H | 0.1718 | 0.3445 | 0.5728 | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 4 | C3 | 0 | C.2 | $0.09828(19)$ | $0.27323(15)$ | $0.6169(5)$ | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 5 | H3 | 0 | H | 0.0811 | 0.2841 | 0.7431 | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 6 | C4 | 0 | C.2 | $0.0690(2)$ | $0.22198(15)$ | $0.5350(5)$ | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 7 | H4 | 0 | H | 0.0308 | 0.1979 | 0.6032 | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 8 | C5 | 0 | C.2 | $0.09559(18)$ | $0.20579(14)$ | $0.3535(5)$ | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 9 | H5 | 0 | H | 0.0755 | 0.1705 | 0.2967 | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 10 | C6 | 0 | C.2 | $0.15113(17)$ | $0.24049(13)$ | $0.2537(5)$ | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |


| 11 | H6 | 0 | H | 0.1703 | 0.2284 | 0.1303 | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| :--- | :--- | :--- | :--- | :--- | :--- | :--- | :--- |
| 12 | C7 | 0 | C. 3 | $0.23099(17)$ | $0.33295(13)$ | $0.2126(4)$ | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 13 | H7 | 0 | H | 0.2616 | 0.3086 | 0.1159 | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 14 | C8 | 0 | C. 2 | $0.18213(19)$ | $0.37932(13)$ | $0.1059(4)$ | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 15 | C9 | 0 | C. 2 | $0.0973(2)$ | $0.37573(15)$ | $0.0761(5)$ | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 16 | H9 | 0 | H | 0.0668 | 0.3436 | 0.1274 | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 17 | C10 | 0 | C. 2 | $0.0575(2)$ | $0.41903(17)$ | $-0.0283(6)$ | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 18 | H10 | 0 | H | -0.0005 | 0.4165 | -0.0494 | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 19 | C11 | 0 | C. 2 | $0.1012(3)$ | $0.46589(17)$ | $-0.1019(6)$ | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 20 | H11 | 0 | H | 0.0735 | 0.4954 | -0.1746 | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 21 | C12 | 0 | C. 2 | $0.1854(3)$ | $0.47006(16)$ | $-0.0700(5)$ | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 22 | H12 | 0 | H | 0.2153 | 0.5029 | -0.1184 | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 23 | C13 | 0 | C. 2 | $0.2262(2)$ | $0.42654(14)$ | $0.0319(4)$ | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 24 | C14 | 0 | C.3 | $0.3170(2)$ | $0.42742(15)$ | $0.0711(5)$ | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 25 | H14A | 0 | H | 0.3384 | 0.4680 | 0.0545 | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 26 | H14B | 0 | H | 0.3457 | 0.4016 | -0.0225 | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 27 | C15 | 0 | C. 2 | $0.33474(18)$ | $0.40663(13)$ | $0.2726(5)$ | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 28 | N1 | 0 | N. 2 | $0.38840(16)$ | $0.43299(12)$ | $0.3736(4)$ | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 29 | O1 | 0 | O.3 | $0.29140(12)$ | $0.36058(9)$ | $0.3415(3)$ | $\mathrm{x,y,z}$ |
| 30 | O2 | 0 | O.3 | $0.39803(15)$ | $0.40761(11)$ | $0.5558(4)$ | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 31 | H2O | 0 | H | $0.434(2)$ | $0.4293(15)$ | $0.623(5)$ | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 32 | O3 | 0 | O.3 | 0.5000 | $0.48223(14)$ | 0.7500 | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 33 | H1W | 0 | H | $0.463(2)$ | $0.5076(15)$ | $0.797(5)$ | $\mathrm{x,y,z}$ |
| 34 | H1W | 0 | H | $0.537(2)$ | $0.5076(15)$ | $0.703(5)$ | $1-x, y, 1.5-z$ |

Bonds

| Number | Atom1 | Atom2 | Type | Polymeric | Cyclicity | Length | SybylType |
| :--- | :--- | :--- | :--- | :--- | :--- | :--- | :--- |
| 1 | C1 | C2 | Unknown | no | cyclic | $1.389(4)$ | un |
| 2 | C1 | C6 | Unknown | no | cyclic | $1.383(4)$ | un |
| 3 | C1 | C7 | Unknown | no | acyclic | $1.496(4)$ | 1 |
| 4 | C2 | H2 | Unknown | no | acyclic | 0.951 | 1 |
| 5 | C2 | C3 | Unknown | no | cyclic | $1.381(4)$ | un |
| 6 | C3 | H3 | Unknown | no | acyclic | 0.950 | 1 |
| 7 | C3 | C4 | Unknown | no | cyclic | $1.378(5)$ | un |
| 8 | C4 | H4 | Unknown | no | acyclic | 0.951 | 1 |
| 9 | C4 | C5 | Unknown | no | cyclic | $1.379(5)$ | un |
| 10 | C5 | H5 | Unknown | no | acyclic | 0.950 | 1 |
| 11 | C5 | C6 | Unknown | no | cyclic | $1.380(4)$ | un |
| 12 | C6 | H6 | Unknown | no | acyclic | 0.950 | 1 |
| 13 | C7 | H7 | Unknown | no | acyclic | 1.000 | 1 |
| 14 | C7 | C8 | Unknown | no | cyclic | $1.509(4)$ | 1 |
| 15 | C7 | O1 | Unknown | no | cyclic | $1.465(3)$ | 1 |
| 16 | C8 | C9 | Unknown | no | cyclic | $1.390(4)$ | un |
| 17 | C8 | C13 | Unknown | no | cyclic | $1.385(4)$ | un |


| 18 | C9 | H9 | Unknown | no | acyclic | 0.949 | 1 |
| :--- | :--- | :--- | :--- | :--- | :--- | :--- | :--- |
| 19 | C9 | C10 | Unknown | no | cyclic | $1.379(5)$ | un |
| 20 | C10 | H10 | Unknown | no | acyclic | 0.951 | 1 |
| 21 | C10 | C11 | Unknown | no | cyclic | $1.375(6)$ | un |
| 22 | C11 | H11 | Unknown | no | acyclic | 0.950 | 1 |
| 23 | C11 | C12 | Unknown | no | cyclic | $1.383(7)$ | un |
| 24 | C12 | H12 | Unknown | no | acyclic | 0.949 | 1 |
| 25 | C12 | C13 | Unknown | no | cyclic | $1.382(5)$ | un |
| 26 | C13 | C14 | Unknown | no | cyclic | $1.493(5)$ | 1 |
| 27 | C14 | H14A | Unknown | no | acyclic | 0.990 | 1 |
| 28 | C14 | H14B | Unknown | no | acyclic | 0.990 | 1 |
| 29 | C14 | C15 | Unknown | no | cyclic | $1.501(5)$ | 1 |
| 30 | C15 | N1 | Unknown | no | acyclic | $1.265(4)$ | un |
| 31 | C15 | O1 | Unknown | no | cyclic | $1.346(4)$ | 1 |
| 32 | N1 | O2 | Unknown | no | acyclic | $1.396(4)$ | 1 |
| 33 | O2 | H2O | Unknown | no | acyclic | $0.89(3)$ | 1 |
| 34 | O3 | H1W | Unknown | no | acyclic | 0.89 | 1 |
| 35 | O3 | H1W | Unknown | no | acyclic | 0.89 | 1 |

Symmetry

| Number | Symm. Op. | Description | Detailed Description | Order | Type |
| :---: | :---: | :---: | :---: | :---: | :---: |
| 1 | x,y,z | Identity | Identity | 1 | 1 |
| 2 | $\begin{aligned} & 1 / 2+\mathrm{x}, 1 / 2-\mathrm{y}, \\ & -\mathrm{z} \end{aligned}$ | $\begin{array}{ll} \text { Screw } & \text { axis } \\ \text { (2-fold) } & \end{array}$ | 2 -fold screw axis with direction $[1,0,0]$ at $\mathrm{x}, 1 / 4$, 0 with screw component [ $1 / 2,0,0$ ] | 2 | 2 |
| 3 | -x, y, 1/2-z | $\begin{aligned} & \text { Rotation axis } \\ & \text { (2-fold) } \end{aligned}$ | 2 -fold rotation axis with direction $[0,1,0]$ at $0, \mathrm{y}$, 1/4 | 2 | 2 |
| 4 | $\begin{aligned} & 1 / 2-x, \quad 1 / 2-y, \\ & 1 / 2+z \end{aligned}$ | $\begin{array}{ll} \text { Screw } & \text { axis } \\ \text { (2-fold) } & \end{array}$ | 2 -fold screw axis with direction $[0,0,1]$ at $1 / 4$, $1 / 4, \mathrm{z}$ with screw component $[0,0,1 / 2$ ] | 2 | 2 |
| 5 | -x, -y, -z | Inversion centre | Inversion at [ $0,0,0$ ] | 2 | -1 |
| 6 | $1 / 2-x, 1 / 2+y,$ | Glide plane | Glide plane perpendicular to $[1,0,0]$ with glide component [0, 1/2, 0] | 2 | -2 |
| 7 | x, -y, 1/2+z | Glide plane | Glide plane perpendicular to $[0,1,0]$ with glide component $[0,0,1 / 2]$ | 2 | -2 |
| 8 | $\begin{aligned} & 1 / 2+x, \\ & 1 / 2+y, 1 / 2-z \end{aligned}$ | Glide plane | Glide plane perpendicular to $[0,0,1]$ with glide component [1/2, $1 / 2,0$ ] | 2 | -2 |


| Angles |  |  |  |  |
| :--- | :--- | :--- | :--- | :--- |
| Number | Atom1 | Atom2 | Atom3 | Angle |
| 1 | C2 | C1 | C6 | $119.3(3)$ |
| 2 | C2 | C1 | C7 | $121.6(2)$ |
| 3 | C6 | C1 | C7 | $118.9(3)$ |
| 4 | C1 | C2 | H2 | 119.9 |
| 5 | C1 | C2 | C3 | $120.2(3)$ |
| 6 | H2 | C2 | C3 | 119.9 |


| 7 |  |  | C2 | H3 |
| :--- | :--- | :--- | :--- | :--- |
| 8 | C2 | C3 | C4 | 119.9 |
| 9 | H3 | C3 | C4 | $119.3(3)$ |
| 10 | C3 | C4 | H4 | 120.2 |
| 11 | C3 | C4 | C5 | $119.6(3)$ |
| 12 | H4 | C4 | C5 | 120.2 |
| 13 | C4 | C5 | H5 | 119.7 |
| 14 | C4 | C5 | C6 | $120.5(3)$ |
| 15 | H5 | C5 | C6 | 119.7 |
| 16 | C1 | C6 | C5 | $120.1(3)$ |
| 17 | C1 | C6 | H6 | 120.0 |
| 18 | C5 | C6 | H6 | 119.9 |
| 19 | C1 | C7 | H7 | 108.4 |
| 20 | C1 | C7 | C8 | $113.8(2)$ |
| 21 | C1 | C7 | O1 | $107.2(2)$ |
| 22 | H7 | C7 | C8 | 108.4 |
| 23 | H7 | C7 | O1 | 108.4 |
| 24 | C8 | C7 | O1 | $110.5(2)$ |
| 25 | C7 | C8 | C9 | $123.3(3)$ |
| 26 | C7 | C8 | C13 | $116.8(3)$ |
| 27 | C9 | C8 | C13 | $119.9(3)$ |
| 28 | C8 | C9 | H9 | 120.2 |
| 29 | C8 | C9 | C10 | $119.8(3)$ |
| 30 | H9 | C9 | C10 | 120.1 |
| 31 | C9 | C10 | H10 | 119.9 |
| 32 | C14 | C9 | C10 | C11 |
| 33 | H10 | C10 | C11 | $120.4(4)$ |
| 34 | C10 | C11 | H11 | 119.8 |
| 48 | C10.0 | C15 | C11 | C12 |


| 51 | N1 | C15 | O1 | $121.9(3)$ |
| :--- | :--- | :--- | :--- | :--- |
| 52 | C15 | N1 | O2 | $112.4(3)$ |
| 53 | C7 | O1 | C15 | $117.6(2)$ |
| 54 | N1 | O2 | H2O | $108(2)$ |
| 55 | H1W | O3 | H1W | 100 |

Torsions

| Number | Atom1 | Atom2 | Atom3 | Atom4 | Torsion |
| :---: | :---: | :---: | :---: | :---: | :---: |
| 1 | C6 | C1 | C2 | H2 | 179.3 |
| 2 | C6 | C1 | C2 | C3 | -0.7(4) |
| 3 | C7 | C1 | C2 | H2 | -6.0 |
| 4 | C7 | C1 | C2 | C3 | 174.0(3) |
| 5 | C2 | C1 | C6 | C5 | 2.1(4) |
| 6 | C2 | C1 | C6 | H6 | -177.8 |
| 7 | C7 | C1 | C6 | C5 | -172.7(3) |
| 8 | C7 | C1 | C6 | H6 | 7.3 |
| 9 | C2 | C1 | C7 | H7 | 157.2 |
| 10 | C2 | C1 | C7 | C8 | -82.0(3) |
| 11 | C2 | C1 | C7 | O1 | 40.4(3) |
| 12 | C6 | C1 | C7 | H7 | -28.1 |
| 13 | C6 | C1 | C7 | C8 | 92.7(3) |
| 14 | C6 | C1 | C7 | O1 | -144.9(3) |
| 15 | C1 | C2 | C3 | H3 | 178.9 |
| 16 | C1 | C2 | C3 | C4 | -1.0(5) |
| 17 | H2 | C2 | C3 | H3 | -1.0 |
| 18 | H2 | C2 | C3 | C4 | 179.0 |
| 19 | C2 | C3 | C4 | H4 | -178.7 |
| 20 | C2 | C3 | C4 | C5 | 1.4(5) |
| 21 | H3 | C3 | C4 | H4 | 1.3 |
| 22 | H3 | C3 | C4 | C5 | -178.6 |
| 23 | C3 | C4 | C5 | H5 | -180.0 |
| 24 | C3 | C4 | C5 | C6 | -0.0(5) |
| 25 | H4 | C4 | C5 | H5 | 0.1 |
| 26 | H4 | C4 | C5 | C6 | -179.9 |
| 27 | C4 | C5 | C6 | C1 | -1.7(5) |
| 28 | C4 | C5 | C6 | H6 | 178.2 |
| 29 | H5 | C5 | C6 | C1 | 178.2 |
| 30 | H5 | C5 | C6 | H6 | -1.8 |
| 31 | C1 | C7 | C8 | C9 | -17.4(4) |
| 32 | C1 | C7 | C8 | C13 | 164.2(3) |
| 33 | H7 | C7 | C8 | C9 | 103.4 |
| 34 | H7 | C7 | C8 | C13 | -75.1 |
| 35 | O1 | C7 | C8 | C9 | -138.0(3) |
| 36 | O1 | C7 | C8 | C13 | 43.5(3) |


| 37 | C1 | C7 | O1 | C15 | -167.8(2) |
| :---: | :---: | :---: | :---: | :---: | :---: |
| 38 | H7 | C7 | O1 | C15 | 75.4 |
| 39 | C8 | C7 | O1 | C15 | -43.3(3) |
| 40 | C7 | C8 | C9 | H9 | 2.1 |
| 41 | C7 | C8 | C9 | C10 | -177.9(3) |
| 42 | C13 | C8 | C9 | H9 | -179.5 |
| 43 | C13 | C8 | C9 | C10 | 0.5(5) |
| 44 | C7 | C8 | C13 | C12 | 179.0(3) |
| 45 | C7 | C8 | C13 | C14 | -1.9(4) |
| 46 | C9 | C8 | C13 | C12 | 0.5(5) |
| 47 | C9 | C8 | C13 | C14 | 179.6(3) |
| 48 | C8 | C9 | C10 | H10 | 179.6 |
| 49 | C8 | C9 | C10 | C11 | -0.4(5) |
| 50 | H9 | C9 | C10 | H10 | -0.4 |
| 51 | H9 | C9 | C10 | C11 | 179.6 |
| 52 | C9 | C10 | C11 | H11 | 179.5 |
| 53 | C9 | C10 | C11 | C12 | -0.6(6) |
| 54 | H10 | C10 | C11 | H11 | -0.6 |
| 55 | H10 | C10 | C11 | C12 | 179.4 |
| 56 | C10 | C11 | C12 | H12 | -178.6 |
| 57 | C10 | C11 | C12 | C13 | 1.5(6) |
| 58 | H11 | C11 | C12 | H12 | 1.4 |
| 59 | H11 | C11 | C12 | C13 | -178.5 |
| 60 | C11 | C12 | C13 | C8 | -1.5(5) |
| 61 | C11 | C12 | C13 | C14 | 179.4(3) |
| 62 | H12 | C12 | C13 | C8 | 178.6 |
| 63 | H12 | C12 | C13 | C14 | -0.5 |
| 64 | C8 | C13 | C14 | H14A | -160.1 |
| 65 | C8 | C13 | C14 | H14B | 81.5 |
| 66 | C8 | C13 | C14 | C15 | -39.3(4) |
| 67 | C12 | C13 | C14 | H14A | 19.0 |
| 68 | C12 | C13 | C14 | H14B | -99.3 |
| 69 | C12 | C13 | C14 | C15 | 139.9(3) |
| 70 | C13 | C14 | C15 | N1 | -138.3(3) |
| 71 | C13 | C14 | C15 | O1 | 40.6(4) |
| 72 | H14A | C14 | C15 | N1 | -17.4 |
| 73 | H14A | C14 | C15 | O1 | 161.5 |
| 74 | H14B | C14 | C15 | N1 | 100.9 |
| 75 | H14B | C14 | C15 | O1 | -80.2 |
| 76 | C14 | C15 | N1 | O2 | -179.2(3) |
| 77 | O1 | C15 | N1 | O2 | 2.0(4) |
| 78 | C14 | C15 | O1 | C7 | 1.4(4) |
| 79 | N1 | C15 | O1 | C7 | -179.7(3) |
| 80 | C15 | N1 | O 2 | H2O | -176(2) |

Appendix V. Crystallographic data and structure refinement parameters of cpd 81


Formula: $\mathrm{C}_{15} \mathrm{H}_{13} \mathrm{~N} \mathrm{O}_{2}$
Space group: $\mathrm{P} 2_{1} / \mathrm{c}$ (14)
Cell lengths: a 5.6544(4) b 13.9616(9) c $15.2825(8)$
Cell Angles: a 90 b 91.623(3) g 90
Cell Volume: 1205.98
Z: 4 Z': 0
R-factor (\%): 4.45

| Atoms |  |  |  |  |  |  |  |
| :--- | :--- | :--- | :--- | :--- | :--- | :--- | :--- |
| Number | Label | Charge | SybylType | Xfrac + ESD | Yfrac + ESD | Zfrac + ESD | Symm. op. |
| 1 | C1 | 0 | C. 2 | $0.0901(2)$ | $0.61428(9)$ | $0.27821(7)$ | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 2 | C2 | 0 | C. 2 | $0.2825(2)$ | $0.58878(8)$ | $0.22740(7)$ | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 3 | C3 | 0 | C.2 | $0.3534(2)$ | $0.65005(9)$ | $0.16084(8)$ | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 4 | H3 | 0 | H | 0.4882 | 0.6341 | 0.1281 | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 5 | C4 | 0 | C.2 | $0.2308(3)$ | $0.73362(10)$ | $0.14174(9)$ | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 6 | H4 | 0 | H | 0.2811 | 0.7745 | 0.0962 | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 7 | C5 | 0 | C.2 | $0.0353(3)$ | $0.75715(10)$ | $0.18922(9)$ | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 7 | H5 | 0 | H | -0.0530 | 0.8132 | 0.1751 | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 8 | C6 | 0 | C.2 | $-0.0323(2)$ | $0.69878(9)$ | $0.25765(8)$ | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 9 | H6 | 0 | H | -0.1643 | 0.7165 | 0.2912 | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |


| 11 | C7 | 0 | C. 3 | 0.0137(2) | 0.55724(9) | 0.35739(8) | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 12 | H7A | 0 | H | -0.1140 | 0.5921 | 0.3869 | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 13 | H7B | 0 | H | -0.0499 | 0.4945 | 0.3378 | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 14 | C8 | 0 | C. 2 | 0.2183(2) | 0.54141(8) | $0.42157(7)$ | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 15 | C9 | 0 | C. 3 | 0.4170(2) | 0.49523(9) | 0.23587 (7) | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 16 | H9 | 0 | H | 0.5902 | 0.5096 | 0.2397 | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 17 | C10 | 0 | C. 2 | 0.3699(2) | 0.42640 (9) | $0.16056(8)$ | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 18 | C11 | 0 | C. 2 | 0.1635(2) | 0.42983(10) | 0.10922(9) | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 19 | H11 | 0 | H | 0.0496 | 0.4784 | 0.1192 | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 20 | C12 | 0 | C. 2 | 0.1222(3) | $0.36257(11)$ | 0.04328(9) | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 21 | H12 | 0 | H | -0.0194 | 0.3654 | 0.0084 | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 22 | C13 | 0 | C. 2 | 0.2871(3) | $0.29165(11)$ | 0.02850(9) | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 23 | H13 | 0 | H | 0.2589 | 0.2457 | -0.0165 | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 24 | C14 | 0 | C. 2 | 0.4921 (3) | 0.28771 (11) | 0.07909(9) | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 25 | H14 | 0 | H | 0.6054 | 0.2390 | 0.0689 | x,y,z |
| 26 | C15 | 0 | C. 2 | 0.5341(2) | 0.35474 (10) | 0.14501(8) | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 27 | H15 | 0 | H | 0.6760 | 0.3515 | 0.1797 | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 28 | N1 | 0 | N.am | 0.3990(2) | 0.49119(8) | $0.38976(7)$ | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 29 | O1 | 0 | O. 2 | $0.22959(16)$ | 0.57590 (6) | 0.49591(6) | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 30 | O2 | 0 | O. 3 | 0.35434(17) | 0.43952(6) | $0.31206(5)$ | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |
| 31 | H1N | 0 | H | 0.517(3) | 0.4675(12) | 0.4240(11) | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ |

## Bonds

| Number | Atom1 | Atom2 | Type | Polymeric | Cyclicity | Length | SybylType |
| :--- | :--- | :--- | :--- | :--- | :--- | :--- | :--- |
| 1 | C1 | C2 | Unknown | no | cyclic | $1.400(2)$ | un |
| 2 | C1 | C6 | Unknown | no | cyclic | $1.399(2)$ | un |
| 3 | C1 | C7 | Unknown | no | cyclic | $1.521(2)$ | 1 |
| 4 | C2 | C3 | Unknown | no | cyclic | $1.397(2)$ | un |
| 5 | C2 | C9 | Unknown | no | cyclic | $1.515(2)$ | 1 |
| 6 | C3 | H3 | Unknown | no | acyclic | 0.950 | 1 |
| 7 | C3 | C4 | Unknown | no | cyclic | $1.384(2)$ | un |
| 8 | C4 | H4 | Unknown | no | acyclic | 0.950 | 1 |
| 9 | C4 | C5 | Unknown | no | cyclic | $1.379(2)$ | un |
| 10 | C5 | H5 | Unknown | no | acyclic | 0.950 | 1 |
| 11 | C5 | C6 | Unknown | no | cyclic | $1.388(2)$ | un |
| 12 | C6 | H6 | Unknown | no | acyclic | 0.950 | 1 |
| 13 | C7 | H7A | Unknown | no | acyclic | 0.990 | 1 |
| 14 | C7 | H7B | Unknown | no | acyclic | 0.990 | 1 |
| 15 | C7 | C8 | Unknown | no | cyclic | $1.512(2)$ | 1 |
| 16 | C8 | N1 | Unknown | no | cyclic | $1.342(2)$ | un |
| 17 | C8 | O1 | Unknown | no | acyclic | $1.234(1)$ | 2 |
| 18 | C9 | H9 | Unknown | no | acyclic | 1.000 | 1 |
| 19 | C9 | C10 | Unknown | no | acyclic | $1.517(2)$ | 1 |
| 20 | C9 | O2 | Unknown | no | cyclic | $1.452(1)$ | 1 |


| 21 | C10 | C11 | Unknown | no | cyclic | $1.389(2)$ | un |
| :--- | :--- | :--- | :--- | :--- | :--- | :--- | :--- |
| 22 | C10 | C15 | Unknown | no | cyclic | $1.390(2)$ | un |
| 23 | C11 | H11 | Unknown | no | acyclic | 0.950 | 1 |
| 24 | C11 | C12 | Unknown | no | cyclic | $1.392(2)$ | un |
| 25 | C12 | H12 | Unknown | no | acyclic | 0.950 | 1 |
| 26 | C12 | C13 | Unknown | no | cyclic | $1.383(2)$ | un |
| 27 | C13 | H13 | Unknown | no | acyclic | 0.951 | 1 |
| 28 | C13 | C14 | Unknown | no | cyclic | $1.376(2)$ | un |
| 29 | C14 | H14 | Unknown | no | acyclic | 0.950 | 1 |
| 30 | C14 | C15 | Unknown | no | cyclic | $1.391(2)$ | un |
| 31 | C15 | H15 | Unknown | no | acyclic | 0.950 | 1 |
| 32 | N1 | O2 | Unknown | no | cyclic | $1.406(1)$ | 1 |
| 33 | N1 | H1N | Unknown | no | acyclic | $0.90(2)$ | 1 |

Symmetry

| Number | Symm. Op. | Description | Detailed Description | Order | Type |
| :---: | :---: | :---: | :---: | :---: | :---: |
| 1 | $\mathrm{x}, \mathrm{y}, \mathrm{z}$ | Identity | Identity | 1 | 1 |
| 2 | $\begin{aligned} & -x, \quad 1 / 2+y, \\ & 1 / 2-z \end{aligned}$ | $\begin{aligned} & \text { Screw } \quad \text { axis } \\ & (2 \text {-fold) } \end{aligned}$ | 2-fold screw axis with direction $[0,1,0]$ at $0, \mathrm{y}, 1 / 4$ with screw component $[0,1 / 2,0]$ | 2 | 2 |
| 3 | $-\mathrm{x},-\mathrm{y},-\mathrm{z}$ | Inversion centre | Inversion at [0, 0, 0] | 2 | -1 |
| 4 | $\begin{aligned} & x, \quad 1 / 2-y, \\ & 1 / 2+z \end{aligned}$ | Glide plane | Glide plane perpendicular to $[0,1,0]$ with glide component $[0,0,1 / 2$ ] | 2 | -2 |


| Angles |  |  |  | Angle |
| :--- | :--- | :--- | :--- | :--- |
| Number | Atom1 | Atom2 | Atom3 | C1 |
| 1 | C2 | C1 | C6 | $118.5(1)$ |
| 2 | C2 | C1 | C7 | $123.4(1)$ |
| 3 | C6 | C1 | C7 | $118.0(1)$ |
| 4 | C1 | C2 | C3 | $119.5(1)$ |
| 5 | C1 | C2 | C9 | $124.6(1)$ |
| 6 | C3 | C2 | C9 | $115.9(1)$ |
| 7 | C2 | C3 | H3 | 119.4 |
| 8 | C2 | C3 | C4 | $121.2(1)$ |
| 9 | H3 | C3 | C4 | 119.4 |
| 10 | C3 | C4 | H4 | 120.2 |
| 11 | C3 | C4 | C5 | $119.6(1)$ |
| 12 | H4 | C4 | C5 | 120.2 |
| 13 | C4 | C5 | H5 | 120.1 |
| 14 | C4 | C5 | C6 | $119.9(1)$ |
| 15 | H5 | C5 | C6 | 120.0 |
| 16 | C1 | C6 | C5 | $121.3(1)$ |
| 17 | C1 | C6 | H6 | 119.3 |
| 18 | C5 | C6 | H6 | 119.4 |


| 19 | C1 | C7 | H7A | 109.4 |
| :---: | :---: | :---: | :---: | :---: |
| 20 | C1 | C7 | H7B | 109.4 |
| 21 | C1 | C7 | C8 | 111.3(1) |
| 22 | H7A | C7 | H7B | 108.0 |
| 23 | H7A | C7 | C8 | 109.3 |
| 24 | H7B | C7 | C8 | 109.4 |
| 25 | C7 | C8 | N1 | 114.7(1) |
| 26 | C7 | C8 | O1 | 124.0(1) |
| 27 | N1 | C8 | O1 | 121.2(1) |
| 28 | C2 | C9 | H9 | 108.7 |
| 29 | C2 | C9 | C10 | 113.8(1) |
| 30 | C2 | C9 | O2 | 113.38(9) |
| 31 | H9 | C9 | C10 | 108.8 |
| 32 | H9 | C9 | O2 | 108.7 |
| 33 | C10 | C9 | O2 | 103.14(9) |
| 34 | C9 | C10 | C11 | 122.2(1) |
| 35 | C9 | C10 | C15 | 118.8(1) |
| 36 | C11 | C10 | C15 | 118.9(1) |
| 37 | C10 | C11 | H11 | 119.8 |
| 38 | C10 | C11 | C12 | 120.4(1) |
| 39 | H11 | C11 | C12 | 119.8 |
| 40 | C11 | C12 | H12 | 120.0 |
| 41 | C11 | C12 | C13 | 120.1(1) |
| 42 | H12 | C12 | C13 | 120.0 |
| 43 | C12 | C13 | H13 | 120.1 |
| 44 | C12 | C13 | C14 | 119.9(1) |
| 45 | H13 | C13 | C14 | 120.1 |
| 46 | C13 | C14 | H14 | 119.8 |
| 47 | C13 | C14 | C15 | 120.3(1) |
| 48 | H14 | C14 | C15 | 119.9 |
| 49 | C10 | C15 | C14 | 120.5(1) |
| 50 | C10 | C15 | H15 | 119.8 |
| 51 | C14 | C15 | H15 | 119.8 |
| 52 | C8 | N1 | O2 | 117.0(1) |
| 53 | C8 | N1 | H1N | 123(1) |
| 54 | O2 | N1 | H1N | 115(1) |
| 55 | C9 | O2 | N1 | 111.11(9) |


| Torsions |  |  |  |  |  |
| :--- | :--- | :--- | :--- | :--- | :--- |
| Number | Atom1 | Atom2 | Atom3 | Atom4 | Torsion |
| 1 | C6 | C1 | C2 | C3 | $3.0(2)$ |
| 2 | C6 | C1 | C2 | C9 | $-173.8(1)$ |
| 3 | C7 | C1 | C2 | C3 | $-174.1(1)$ |
| 4 | C7 | C1 | C2 | C9 | $9.1(2)$ |


| 5 | C2 | C1 | C6 | C5 | -0.7(2) |
| :---: | :---: | :---: | :---: | :---: | :---: |
| 6 | C2 | C1 | C6 | H6 | 179.3 |
| 7 | C7 | C1 | C6 | C5 | 176.6(1) |
| 8 | C7 | C1 | C6 | H6 | -3.5 |
| 9 | C2 | C1 | C7 | H7A | 173.8 |
| 10 | C2 | C1 | C7 | H7B | -68.1 |
| 11 | C2 | C1 | C7 | C8 | 52.9(1) |
| 12 | C6 | C1 | C7 | H7A | -3.3 |
| 13 | C6 | C1 | C7 | H7B | 114.8 |
| 14 | C6 | C1 | C7 | C8 | -124.3(1) |
| 15 | C1 | C2 | C3 | H3 | 177.2 |
| 16 | C1 | C2 | C3 | C4 | -2.8(2) |
| 17 | C9 | C2 | C3 | H3 | -5.7 |
| 18 | C9 | C2 | C3 | C4 | 174.3(1) |
| 19 | C1 | C2 | C9 | H9 | -130.8 |
| 20 | C1 | C2 | C9 | C10 | 107.8(1) |
| 21 | C1 | C2 | C9 | O2 | -9.8(2) |
| 22 | C3 | C2 | C9 | H9 | 52.3 |
| 23 | C3 | C2 | C9 | C10 | -69.1(1) |
| 24 | C3 | C2 | C9 | O2 | 173.4(1) |
| 25 | C2 | C3 | C4 | H4 | -179.9 |
| 26 | C2 | C3 | C4 | C5 | 0.1(2) |
| 27 | H3 | C3 | C4 | H4 | 0.1 |
| 28 | H3 | C3 | C4 | C5 | -179.9 |
| 29 | C3 | C4 | C5 | H5 | -177.7 |
| 30 | C3 | C4 | C5 | C6 | 2.2(2) |
| 31 | H4 | C4 | C5 | H5 | 2.3 |
| 32 | H4 | C4 | C5 | C6 | -177.8 |
| 33 | C4 | C5 | C6 | C1 | -1.9(2) |
| 34 | C4 | C5 | C6 | H6 | 178.1 |
| 35 | H5 | C5 | C6 | C1 | 178.0 |
| 36 | H5 | C5 | C6 | H6 | -1.9 |
| 37 | C1 | C7 | C8 | N1 | -61.6(1) |
| 38 | C1 | C7 | C8 | O1 | 114.2(1) |
| 39 | H7A | C7 | C8 | N1 | 177.4 |
| 40 | H7A | C7 | C8 | O1 | -6.8 |
| 41 | H7B | C7 | C8 | N1 | 59.4 |
| 42 | H7B | C7 | C8 | O1 | -124.9 |
| 43 | C7 | C8 | N1 | O2 | -15.9(1) |
| 44 | C7 | C8 | N1 | H1N | -168(1) |
| 45 | O1 | C8 | N1 | O2 | 168.2(1) |
| 46 | O1 | C8 | N1 | H1N | 16(1) |
| 47 | C2 | C9 | C10 | C11 | -24.2(2) |
| 48 | C2 | C9 | C10 | C15 | 158.8(1) |


| 49 | H9 | C9 | C10 | C11 | -145.6 |
| :---: | :---: | :---: | :---: | :---: | :---: |
| 50 | H9 | C9 | C10 | C15 | 37.4 |
| 51 | O2 | C9 | C10 | C11 | 99.1(1) |
| 52 | O2 | C9 | C10 | C15 | -77.9(1) |
| 53 | C2 | C9 | O2 | N1 | -59.4(1) |
| 54 | H9 | C9 | O2 | N1 | 61.6 |
| 55 | C10 | C9 | O2 | N1 | 176.97(9) |
| 56 | C9 | C10 | C11 | H11 | 2.9 |
| 57 | C9 | C10 | C11 | C12 | -177.0(1) |
| 58 | C15 | C10 | C11 | H11 | 179.9 |
| 59 | C15 | C10 | C11 | C12 | -0.0(2) |
| 60 | C9 | C10 | C15 | C14 | 177.1(1) |
| 61 | C9 | C10 | C15 | H15 | -2.8 |
| 62 | C11 | C10 | C15 | C14 | 0.0(2) |
| 63 | C11 | C10 | C15 | H15 | -179.9 |
| 64 | C10 | C11 | C12 | H12 | -180.0 |
| 65 | C10 | C11 | C12 | C13 | 0.0(2) |
| 66 | H11 | C11 | C12 | H12 | 0.1 |
| 67 | H11 | C11 | C12 | C13 | -179.9 |
| 68 | C11 | C12 | C13 | H13 | 180.0 |
| 69 | C11 | C12 | C13 | C14 | -0.0(2) |
| 70 | H12 | C12 | C13 | H13 | -0.0 |
| 71 | H12 | C12 | C13 | C14 | 180.0 |
| 72 | C12 | C13 | C14 | H14 | -180.0 |
| 73 | C12 | C13 | C14 | C15 | 0.0(2) |
| 74 | H13 | C13 | C14 | H14 | 0.1 |
| 75 | H13 | C13 | C14 | C15 | -180.0 |
| 76 | C13 | C14 | C15 | C10 | -0.0(2) |
| 77 | C13 | C14 | C15 | H15 | 179.9 |
| 78 | H14 | C14 | C15 | C10 | 180.0 |
| 79 | H14 | C14 | C15 | H15 | -0.1 |
| 80 | C8 | N1 | O2 | C9 | 93.6(1) |
| 81 | H1N | N1 | O 2 | C9 | -112(1) |

## Appendix VI. 2D NMRs of cpd 48

1. COSY in DMSO- $d^{6}$

2. NOESY in DMSO- $\boldsymbol{d}^{6}$


## 3. HSQC in DMSO- $d^{6}$



## 4. HMBC in DMSO- $\boldsymbol{d}^{6}$



## Appendix VII. NOESY and HMBC of cpd 45 and 43

1. NOESY of cpd 45 in DMSO- $d^{6}$

2. HMBC of cpd 45 in DMSO- $d^{6}$

3. NOESY of cpd 43 in DMSO- $d^{6}$


## 4. HMBC of cpd 43 in DMSO- $d^{6}$



Appendix VIII. Dioxygenation of styrenes with molecular oxygen in water

# Dioxygenation of styrenes with molecular oxygen in water 

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#### Abstract

Employing Triton X-100 as a surfactant, the tert-butyl hydroperoxide-mediated dioxygenation of styrene with molecular oxygen and $N$-hydroxyphthalimide was achieved in water at room temperature, providing the corresponding dioxygenated products in $9-93 \%$ yield. This facile method is eco-friendly, feasible on gram scale, and applicable to a wide range of styrene derivatives with a variety of functional groups.


 © 2018 Elsevier Ltd. All rights reserved.The environmental impact of the chemical industry is a major issue; approximately $80 \%$ of the chemical waste from a reaction mixture corresponds to organic solvents. ${ }^{1}$ One of the main research fields is the development of alternatives to organic solvents, with expected outputs in terms of health, safety and environmental impacts. Solvent-free alternatives represent the best solution, however, most organic reactions require a medium to enable matter and heat transfer. Ionic liquids, supercritical media and other non-conventional media have been described as efficient alternatives to conventional organic solvents, but the use of water appears to be one of the best solutions in terms of safety and environmental impact. ${ }^{2}$ Unfortunately, most organic reactants have poor solubility in water, leading to low yields and poor reaction rate. The development of organic synthesis in aqueous medium using surfactants represents an efficient ecofriendly strategy. ${ }^{3}$ Indeed, due to their amphiphilic nature, surfactants in water undergo spontaneous self-assembly into micelles, which act as nanoreactors, and their hydrophobic cores play the role of reaction vessels in which organic transformations involving water-insoluble reagents can occur. By using versatile nonionic surfactants, such as TPGS-750M , a set of chemical transformations has been developed under micellar conditions, including nucleophilic substitution, ${ }^{4}$ oxidation, ${ }^{5}$ reduction, ${ }^{6,7}$ olefin metathesis, ${ }^{8}$ and Pd-catalyzed cross-coupling, ${ }^{9}$ as well as solution phase peptide synthesis in water. ${ }^{10}$ Recently, our group developed an efficient and versatile method for the Buchwald-Hartwig cross-coupling reaction and the Ull-mann-type amination reaction in water with the assistance of

[^1]the non-ionic surfactant TPGS-750-M. ${ }^{11-14}$ The adoption of surfactants in these reactions resulted in significant benefits across the entire synthetic route, not just from an environment standpoint, but also from an economic and productivity perspective. ${ }^{15}$

1,2-Dioxygenated structures are present in many biologically active molecules. ${ }^{16-18}$ In view of the importance of such structures, Xia and co-workers have developed efficient radical methods for styrene 1,2-dioxygenation using $N$-hydroxyphthalimide (NHPI, Scheme 1). ${ }^{19,20}$ Although these methods furnished 2 in good to excellent yields, optimal yields were obtained in dichloroethane (DCE), a chlorinated organic solvent which is a known human carcinogen and highly hazardous for the environment. Accordingly, the development of an "in water" method is desirable to avoid the use of such a toxic solvent. Inspired by the work of Xia and co-workers, and in continuation of our efforts in the development of reactions in water, ${ }^{19,20}$ we considered whether it was possible to perform the radical dioxygenation of styrene with NHPI under micellar conditions in water. Herein, we disclose the radical dioxygenation of styrene derivatives in an aqueous solution including Triton X-100-based micelles.

Following Xia and co-workers conditions which were published in 2015, ${ }^{20}$ we initiated our studies with styrene $\mathbf{1 a}$ as a model substrate for the synthesis of 2-(2-hydroxy-2-phenylethoxy)-2,3-dihy-dro- 1 H -isoindoline-1,3-dione 2a using commercially available NHPI, catalytic PTSA, and excess TBHP under air in an aqueous solution of TPGS-750-M ( $2 \mathrm{wt} \%$ ) at room temperature (Table 1, entries 1 and 2). The reaction without surfactant was carried out in parallel as a control. Disappointedly, unsatisfactory yields were obtained ( $5 \%$ without surfactant and $9 \%$ in the TPGS-750-M solution), which prompted us to run subsequent reactions under $\mathrm{O}_{2}$


Xia and co-workers ${ }^{19}$
Scheme 1. Reported methods from Xia and co-workers.
with different types of surfactants (Table 1, entries 3-9). To our delight, the reaction proceeded well in the aqueous solution of Triton X-100 ( $2 \mathrm{wt} \%$ ) and produced 2a in $87 \%$ yield. Other surfactants did not produce better yields (58\% TPGS-750-M, 73\% Brij 30, 83\% TPGS-1000, 14\% SPGS-550-M, 57\% Tween-80, 15\% SDS). Interestingly, when the structures of these surfactants were compared (ESI, Fig. S1), it was noticeable that all the surfactants bearing one terminal hydroxyl group (Brij 30, TPGS-1000, Triton X-100) were favorable to the reaction except for Tween 80. In contrast with most of the reactions reported so far, surfactants bearing terminal ether groups such as TPGS-750-M or SPGS-550-M, appeared less efficient. Lipshutz and co-workers proposed that the size of the micelle may have an impact on the reaction. ${ }^{3-10}$ According to Lipshutz and co-workers, with a diameter of about 50 nm , micelles formed by TPGS-750-M are suitable for micellar chemistry. ${ }^{5,9}$ In
contrast, TPGS-1000 and Triton X-100 lead to micelles with a small diameter of 15 nm and 10 nm , respectively, while micelles resulting from Brij-30 have a diameter of 110 nm (ESI, Table S1). ${ }^{5,9,21,22}$ In this work, the good yields obtained with TPGS-1000, Triton X100 and Brij-30 indicate that micelle diameter does not significantly influence the reaction. The common point of these three nonionic surfactants is the presence of a hydroxyl group at the terminus of the PEG moiety. Further work will be necessary to explain the role of this hydroxyl group in this reaction under micellar conditions. Triton X-100 and TPGS-1000 are both stable and biodegradable surfactants, ${ }^{23}$ but since triton $\mathrm{X}-100$ is much cheaper than TPGS-1000, it was preferred for the following reactions in water.

When the concentration of Triton X-100 was increased from 2 $\mathrm{wt} \%$ to $5 \mathrm{wt} \%$ or decreased to $1 \mathrm{wt} \%$ (Table 1, entries 10 and 11), the yields decreased to $51 \%$ and $73 \%$, respectively, suggesting the dependence of the reaction on the concentration of Triton X-100. Surprisingly, the absence of the PTSA catalyst did not have a significant impact on the reaction and produced 2a in 88\% yield (Table 1, entry 12). On another hand, decreasing 1a or TBHP to 2 equivalents led to a significant decrease in yield ( $55 \%$ and $51 \%$, respectively, Table 1, entries 13 and 14).

In an effort to accelerate the reaction, the temperature was raised to $50^{\circ} \mathrm{C}$ (Table 1, entry 15), resulting in an exacerbation of side reactions and producing $\mathbf{2 a}$ in only $62 \%$ yield. Several other catalyst/oxidant combinations also have been reported in the alkene 1,2-dioxygenation with NHPI. ${ }^{20,24-28}$ Herein, we tested several used combinations TBAI/TBHP, $\mathrm{CuBr}_{2} / \mathrm{DTBP}, \mathrm{CuCl}, \mathrm{Cu}$ $(\mathrm{OAc})_{2} / \mathrm{TBHP}, \mathrm{FeCl}_{3}$ and $\mathrm{PhI}(\mathrm{OAc})_{2}$. However, except for TBAI/ TBHP which led to trace amounts of $\mathbf{2 a}$, most did not give the desired product.

To examine the scope of the established method, various styrene derivatives were investigated as substrates to react with NHPI under the optimized conditions (Table 1, entry 12). As shown in Scheme 2, the electronic properties and positions of the sub-

Table 1
Optimization of the reaction conditions. ${ }^{\text {a }}$


| Entry | 1a <br> (equiv.) | TBHP <br> (equiv.) | PTSA <br> (mol\%) | Surfactant <br> (\% w/w in $\mathrm{H}_{2} \mathrm{O}$ ) | Yield $(\%)^{c}$ |
| :---: | :---: | :---: | :---: | :---: | :---: |
| $1{ }^{\text {b }}$ | 3 | 4 | 10 | - | 5 |
| $2^{\text {b }}$ | 3 | 4 | 10 | TPGS-750-M (2) | 9 |
| 3 | 3 | 4 | 10 | TPGS-750-M (2) | 58 |
| 4 | 3 | 4 | 10 | Brij 30 (2) | 73 |
| 5 | 3 | 4 | 10 | TPGS-1000 (2) | 83 |
| 6 | 3 | 4 | 10 | Triton X-100 (2) | 87 |
| 7 | 3 | 4 | 10 | SPGS-550-M (2) | 14 |
| 8 | 3 | 4 | 10 | Tween 80 (2) | 57 |
| 9 | 3 | 4 | 10 | SDS (2) | 15 |
| 10 | 3 | 4 | 10 | Triton X-100 (5) | 51 |
| 11 | 3 | 4 | 10 | Triton X-100 (1) | 73 |
| 12 | 3 | 4 | - | Triton X-100 (2) | 88 |
| 13 | 2 | 4 | - | Triton X-100 (2) | 55 |
| 14 | 3 | 2 | - | Triton X-100 (2) | 51 |
| $15^{\text {d }}$ | 3 | 4 | - | Triton X-100 (2) | 62 |

[^2]

2a, $88 \%$


2e, 59\%


2i, 26\%


2m, 81\%


2b, $93 \%$


2f, $72 \%$


2ja, 49\% (syn : anti = $3: 1$ )


2n, $51 \%$


2c, 64\%


2g, $74 \%$


2d, 89\%


2h, 52\%

$\mathbf{2 k}^{\mathbf{b}}, 25 \%$ (syn)


21, 9\% (syn)

Scheme 2. Scope of the reaction of styrene derivatives with NHPI in water. Reactions were carried out in a vial on a bioshaker ( 1800 rpm ) using $\mathbf{1 a}$ ( 0.366 mmol ), NHPI
 chromatography are given. ${ }^{\mathrm{a}}$ trans configuration of the starting material. ${ }^{\mathrm{b}}$ cis configuration of the starting material.


Scheme 3. Gram-scale synthesis of 2a.
stituents on styrene have a large influence on the reactivity. The dioxygenation reaction of 2-vinylnaphthalene proceeded in excellent yield ( $93 \% \mathbf{2 b}$ ). The presence of a chlorine atom on the styrene moiety was well tolerated, producing moderate yields for the ortho-position ( $64 \% \mathbf{2 c}$ ) and para-position ( $59 \% \mathbf{2 e}$ ). However, a significant improvement in yield occured when the chlorine atom was present at the meta-position ( $89 \%$ 2d). Substrates with fluorine or bromine atom on the styrene moiety were also well tolerated ( $72 \% \mathbf{2 f}, 74 \% \mathbf{2 g}$ ). Disappointingly, the introduction of electrondonating groups, such as a methoxy group, at the ortho- or paraposition of the aromatic ring produced less satisfactory results $(52 \% \mathbf{2 h}, 26 \% \mathbf{2 i})$. The efficiency of the dioxygenation reaction was affected by the steric hindrance of a substituent at the $\beta$-position of the double bond. The methyl group significantly lowered the reactivity ( $49 \% \mathbf{2 j}$ compared to $88 \% \mathbf{2 a}$ ). With a phenyl group at the $\beta$-position, the reaction proceeded sluggishly and compound $\mathbf{2 k}$ was obtained in only $25 \%$ yield. Finally, starting from indene, compound 21 was obtained in $9 \%$ yield after purification. The configuration of compound $\mathbf{2 j}, \mathbf{2 k}$ and $\mathbf{2 l}$ were deduced by comparing
the coupling constant of the $\alpha$ proton with the corresponding diols reported in the literature. ${ }^{19,20,29,30}$ Indeed, syn-diols show a coupling constant of about $4-5 \mathrm{~Hz}$ versus $7-8 \mathrm{~Hz}$ for anti-diols. In contrast, the presence of either a methyl or a phenyl group at the $\alpha$ position of styrene did not alter the dioxygenation reaction, leading to $\mathbf{2 m}(81 \%), \mathbf{2 n}(51 \%)$, and 20 ( $78 \%$ ).

Remarkably, this in water dioxygenation reaction could be performed on the gram scale with mechanical stirring. Treatment of 1a ( $2.1 \mathrm{~mL}, 18.3 \mathrm{mmol}$ ) with NHPI ( $1.0 \mathrm{~g}, 6.1 \mathrm{mmol}$ ) and TBHP ( $2.3 \mathrm{~mL}, 24.4 \mathrm{mmol}$ ) in a 2 wt \% Triton $\mathrm{X}-100$ aqueous solution $(100 \mathrm{~mL})$ afforded product 2a in excellent yield ( $92 \%$, Scheme 3 ).

In summary, a convenient and eco-friendly protocol was developed for the dioxygenation of styrene derivatives with NHPI, resulting in the direct synthesis of substituted alcohols in moderate to good yields. This reaction is effective in water at room temperature; in the absence of any metal catalyst or organic solvent. Moreover, the reaction proceeded well on the gram scale and produced an excellent yield. The products 2 can be further transformed into $\beta$-hydroxy- $N$-alkoxyamines using hydrazine or diols using $\mathrm{Mo}(\mathrm{CO})_{6}$, which are useful difunctionalized substrates in the synthesis of complex scaffolds. ${ }^{26,27,31}$ Further investigations will be carried out by replacing NHPI with $N$-hydroxybenzotriazole or $N$-hydroxysuccinimide. ${ }^{32}$

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## A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.tetlet.2018.03.009.

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# Supporting Information 

## Dioxygenation of Styrenes with Molecular Oxygen in Water

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## General information

All reagents were purchased commercially without further purification. Compounds were purified using Armen spot flash chromatography on silica gel Merck 60 (particle size $0.040-0.063 \mathrm{~mm}$ ). The obtained compounds were characterized by ${ }^{1} \mathrm{H}-\mathrm{NMR}$ and ${ }^{13} \mathrm{C}-\mathrm{NMR}$ spectra, which were recorded on a Bruker Advance III NMR spectrometer in $\mathrm{CDCl}_{3}$ at $400 \mathrm{MHz} / 500 \mathrm{MHz}$ and 100 MHz , respectively. High resolution mass spectra (HRMS) were recorded on an Agilent Accurate Mass QToF 6520.


TPGS-750-M


TPGS-1000


SPGS-550-M


Brij 30


Triton X-100


SDS


Tween 80

Fig. S1. Structures of the surfactants

Table S1. Size of micelle

| Surfactant | Average diameter (nm) | Reference |
| :---: | :---: | :---: |
| TPGS-750-M | 49 | 1 |
| Brij 30 | 110 | 2 |
| Triton X-100 | 10 | 3 |
| TPGS-1000 | 15 | 1 |
| SDS | 17 | 2 |
| SPGS-550-M | 46 | 1 |
| Tween 80 | 8 | 4 |

## Typical experiment procedures

## Synthesis of 2-(2-hydroxy-2-phenylethoxy)-2,3-dihydro-1H-isoindoline-1,3-dione (2a)

A solution of $\mathbf{1 a}(42 \mu \mathrm{~L}, 0.366 \mathrm{mmol}, 3$ equiv.), NHPI ( $20 \mathrm{mg}, 0.122 \mathrm{mmol}, 1$ equiv.) and TBHP ( $46 \mu \mathrm{~L}, 0.488 \mathrm{mmol}, 4$ equiv.) in an aqueous solution of $2 \mathrm{wt} \%$ Trion X-100 ( 2 mL ) was vibrated (1800 rpm) under $\mathrm{O}_{2}$ (balloon)on a bioshaker at room temperature for 20 h . Purification of the concentrated crude reaction mixture by flash chromatography $\left(\mathrm{MeCN}-\mathrm{H}_{2} \mathrm{O}, 10: 90\right.$ to 50:50 in 40 min ) afforded the product $\mathbf{2 a}$ as a white solid ( $30.6 \mathrm{mg}, 88 \%$ ).

## Gram scale synthesis of 2a

A solution of $\mathbf{1 a}(2.1 \mathrm{~mL}, 18.3 \mathrm{mmol}, 3$ equiv), NHPI ( $1 \mathrm{~g}, 6.1 \mathrm{mmol}, 1$ equiv.) and TBHP ( 2.3 mL , $24.4 \mathrm{mmol}, 4$ equiv.) in an aqueous solution of $2 \mathrm{wt} \%$ Trion X-100 $(100 \mathrm{~mL})$ was mechanically stirred (2000 rpm) under $\mathrm{O}_{2}$ (balloon) at room temperature for 4 d . Purification of the concentrated crude reaction mixture by column chromatography (heptane-EtOAc, $4: 1$ ) afforded the product $\mathbf{2 a}$ as a white solid ( $1.6 \mathrm{~g}, 92 \%$ ).

## Analytical data

The NMR spectra of $\mathbf{2 a - 2 0}$ except $\mathbf{2 h}$ and $\mathbf{2 l}$ were characterized according to the literatures. ${ }^{5,6}$


2-(2-hydroxy-2-(2-methoxyphenyl)ethoxy)isoindoline-1,3-dione (2h)
White solid, ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 9.61(\mathrm{~s}, 1 \mathrm{H}), 7.88-7.84(\mathrm{~m}, 2 \mathrm{H}), 7.79-7.76(\mathrm{~m}, 2 \mathrm{H})$, 7.45-7.43 (m, 1H), 7.31-7.26(m, 1H), $6.96(\mathrm{t}, J=7.5 \mathrm{~Hz}, 1 \mathrm{H}), 6.87(\mathrm{~d}, J=8.2 \mathrm{~Hz}, 1 \mathrm{H}), 5.80(\mathrm{dd}, J$ $=2.3,8.4 \mathrm{~Hz}, 1 \mathrm{H}), 4.55-4.28(\mathrm{~m}, 2 \mathrm{H}), 3.80(\mathrm{~s}, 3 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 162.1,154.6$, $132.9,127.8,127.0,125.7,122.2,121.9,118.9,108.7,79.5,76.8,53.6$; HRMS (ESI) $m / z$ : calcd. for $\mathrm{C}_{17} \mathrm{H}_{15} \mathrm{NO}_{5}\left[\mathrm{M}+\mathrm{H}_{2} \mathrm{O}+\mathrm{H}^{+}, 332.1056\right.$, found 332.1123.


2-((1-hydroxy-2,3-dihydro-1H-inden-2-yl)oxy)isoindoline-1,3-dione (21)
White solid, ${ }^{1} \mathrm{H}$ NMR ( $500 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.88-7.86(\mathrm{~m}, 2 \mathrm{H}), 7.79-7.77(\mathrm{~m}, 2 \mathrm{H}), 7.39-7.38(\mathrm{~m}$, $1 \mathrm{H}), 7.29-7.26(\mathrm{~m}, 2 \mathrm{H}), 7.21-7.19(\mathrm{~m}, 1 \mathrm{H}), 5.53(\mathrm{~d}, J=5.8 \mathrm{~Hz}, 1 \mathrm{H}), 4.86-4.82(\mathrm{~m}, 1 \mathrm{H}), 3.46-3.41$ $(\mathrm{m}, 1 \mathrm{H}), 3.22-3.17(\mathrm{~m}, 1 \mathrm{H}), 2.98(\mathrm{~s}, 1 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( $500 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 164.28,140.65,137.43$, 134.77, 128.82, 127.63, 124.86, 124.18, 123.83, 96.91, 78.93, 34.4; HRMS (ESI) $\mathrm{m} / \mathrm{z}$ : calcd. for $\mathrm{C}_{17} \mathrm{H}_{13} \mathrm{NO}_{4}[\mathrm{M}+\mathrm{H}]^{+}, 296.0845$, found 296.0910

## Dioxygenation of Styrenes with Molecular Oxygen in Water (supporting information)

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Appendix IX. Fukuyama cross-coupling approach to isoprekinamycin: discovery of the highly active and bench-stable palladium precatalyst POxAP

# Fukuyama Cross-Coupling Approach to Isoprekinamycin: Discovery of the Highly Active and Bench-Stable Palladium Precatalyst POxAP 

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## S Supporting Information


#### Abstract

An efficient and user-friendly palladium(II) precatalyst, POxAP (post-oxidative-addition precatalyst), was identified for use in Fukuyama cross-coupling reactions. Suitable for storage under air, the POxAP precatalyst allowed reaction between thioesters and organozinc reagents with turnover numbers of $\sim 90000$. A series of 23 ketones were obtained with yields ranging from 53 to $99 \%$. As proof of efficacy, an alternative approach was developed for the synthesis of a key precursor of the natural product isoprekinamycin. 


Benzo[a]fluorenes, including isoprekinamycin (IPK) and fluostatins $\mathrm{A}-\mathrm{Q}$, represent an interesting class of natural products. ${ }^{1}$ IPK is particularly noteworthy as it bears a diazo group at the 5 -position, which plays a crucial role in its cytotoxicity against cancer cell lines. ${ }^{2}$ To date, only one total synthesis of IPK has been reported (Figure 1), ${ }^{2 \mathrm{e}}$ where the key


Figure 1. Synthetic strategies to the key IPK precursor.
step involved formation of precursor 1 through a SuzukiMiyaura cross-coupling reaction (CCR). While the transformation of $\mathbf{1}$ into IPK was efficiently achieved over nine steps and in a $23 \%$ overall yield, the synthesis of $\mathbf{1}$ appeared less efficient, with 16 steps being required to give an overall yield of $3 \%$. Thus, we herein propose an alternative approach based on the Fukuyama cross-coupling reaction, ${ }^{3}$ where a palladium precatalyst POxAP, of generic formula $\operatorname{PdX}(\mathrm{Ar})\left(\mathrm{PPh}_{3}\right)_{2}$, is employed to efficiently generate ketones.

Initially, we investigated the preparation of an unsubstituted version of the key precursor of IPK, as outlined in Table 1. Starting from commercially available 2-bromobenzoic acid, a copper-mediated acetylation was easily performed to obtain 2a in $98 \%$ yield. ${ }^{4}$ A coupling reaction with EDCI/HOBt led to thioester 3a, a classical substrate of the Fukuyama reaction. Surprisingly, under standard conditions, the Fukuyama reaction between 3a and benzylzinc bromide afforded the expected compound $\mathbf{4 a}$ in a poor $8 \%$ yield (Table 1, entry 2 ), while naphthalenediol 5 was recovered as the main product ( $62 \%$ yield). A dropwise addition of benzylzinc bromide at 25 ${ }^{\circ} \mathrm{C}$ still gave a mixture of $\mathbf{4 a}$ and $\mathbf{5}$ in yields of $9 \%$ and $27 \%$, respectively (Table 1, entry 1 ). It was therefore considered that the Fukuyama reaction was relatively slow, thereby allowing any unreacted BnZnBr to act as a base toward ketone 4a, speeding up the Dieckman condensation reaction and yielding compound 5. Consequently, other catalytic conditions described previously in the literature were investigated for the Fukuyama CCR, with palladium-, nickel-, and iron-based catalysts being employed in the presence of various ligands or additives (Table 1, entries $3-8$ ). ${ }^{5}$ All conditions favored the formation of 5 , which we expect may be due to the slow formation of $\operatorname{Pd}(0)$ from $\operatorname{Pd}(\mathrm{II})$. Indeed, during the past decade, significant effort has been focused on the development of stable $\operatorname{Pd}(\mathrm{II})$ precatalysts, which can be easily transformed in situ into $\operatorname{Pd}(0) .{ }^{6}$ In the Fukuyama CCR, fourth-generation palladacycles from Buchwald's group led to traces of 4a, while PEPPSI-IPr precatalyst from Organ's group afforded ketone 4a in a $15 \%$ yield (Table 1, entries 9 and 10). It is important to highlight that these two precatalysts have been optimized for the Negishi $\mathrm{CCR}^{7}$ and may require different ligands for Fukuyama CCR. We then examined an alternative palladium

[^3]Table 1. Fukuyama CCR on a Model System


| entry ${ }^{\text {a }}$ | cat. | $\begin{aligned} & \text { temp } \\ & \left({ }^{\circ} \mathrm{C}\right) \end{aligned}$ | $\begin{gathered} \text { time } \\ (\mathrm{min}) \end{gathered}$ | yield ${ }^{\text {b }}$ (\%) |  |
| :---: | :---: | :---: | :---: | :---: | :---: |
|  |  |  |  | 4a | 5 |
| 1 | $\mathrm{PdCl}_{2}\left(\mathrm{PPh}_{3}\right)_{2}$ | 25 | 15 | 9 | 27 |
| 2 | $\mathrm{PdCl}_{2}\left(\mathrm{PPh}_{3}\right)_{2}$ | 50 | 15 | 8 | 62 |
| $3^{\text {c }}$ | $\mathrm{Pd}(\mathrm{dba})_{2} / \mathrm{P}(\mathrm{Fu})_{3}$ | 50 | 45 | 19 | 14 |
| $4^{d}$ | $\mathrm{Pd}_{2}(\mathrm{dba})_{3} / \mathrm{PCy}_{3} / \mathrm{ZnCl}_{2}$ | 50 | 45 | 31 | 53 |
| $5^{e}$ | $\mathrm{Ni}(\mathrm{acac}){ }_{2}$ | 50 | 45 | 0 | 0 |
| 6 | $\mathrm{NiCl}\left(\mathrm{PPh}_{3}\right)_{2}$ | 50 | 45 | 19 | 44 |
| 7 | $\mathrm{Cu}(\mathrm{TMHD})_{2}$ | 50 | 45 | 27 | 41 |
| 8 | $\mathrm{Fe}(\mathrm{acac})_{3}$ | 50 | 45 | 15 | 22 |
| 9 | XPhos-Pd-G4 | 50 | 30 | trace | 0 |
| 10 | PEPPSI-IPr | 50 | 30 | 15 | 51 |
| $11^{f}$ | $\mathrm{PdCl}(\mathrm{Ph})\left(\mathrm{PPh}_{3}\right)_{2}$ | 50 | 5 | 95 | 0 |

${ }^{a}$ Reaction conditions: thioester 3a $(0.14 \mathrm{mmol})$, catalyst ( $1 \mathrm{~mol} \%$ ), BnZnBr ( $0.21 \mathrm{mmol}, 0.82 \mathrm{M}$ in THF), toluene ( 0.26 mL ), rt. ${ }^{b}$ Isolated yield. ${ }^{c} 1.4 \mathrm{~mol} \%$ of $\mathrm{P}(\mathrm{Fu})_{3} . d_{2} \mathrm{~mol} \%$ of $\mathrm{PCy}_{3}$ and 1 equiv of $\mathrm{ZnCl}_{2}$ were used. ${ }^{e} 10 \mathrm{~mol} \%$ of $\mathrm{Ni}(\mathrm{acac})_{2} .{ }^{f_{0}} 0.1 \mathrm{~mol} \%$ of $\mathrm{PdCl}(\mathrm{Ph})\left(\mathrm{PPh}_{3}\right)_{2}\left(0.1 \mathrm{~mL}, 1.4 \times 10^{-3} \mathrm{M}\right.$ in THF/toluene $)$ was used.
precatalyst, $\mathrm{PdCl}(\mathrm{Ph})\left(\mathrm{PPh}_{3}\right)_{2}$, which we recently identified and referred to by a generic name, POxAP (i.e., a post-oxidative-addition precatalyst). Indeed, $\mathrm{PdX}(\mathrm{Ar})\left(\mathrm{PPh}_{3}\right)_{2}$ precatalysts respect the criteria of Pd-based OACs (oxidative addition complexes) recently described by Ingoglia and Buchwald. ${ }^{8}$ This palladium complex is well-known in the literature, as it is formed through the first oxidative addition between $\mathrm{Pd}(0) \mathrm{Ln}$ and PhCl and is common in the majority of palladium-catalyzed CCRs. ${ }^{9}$ While this complex has been extensively cited in various mechanistic studies, it has been scarcely described per se as a catalyst. We have only found three papers published in the 1970s, at the very beginning of the palladium-catalyzed CCR era, in which $\operatorname{PdI}(\mathrm{Ph})\left(\mathrm{PPh}_{3}\right)_{2}$ was used in only one example of Heck CCR ${ }^{10}$ and Negishi CCR. ${ }^{11}$ In 1976, Sekiya and Ishikawa reported that $\mathrm{PdI}(\mathrm{Ph})$ $\left(\mathrm{PPh}_{3}\right)_{2}$ could be used as a catalyst in the Kumada CCR between ArI and ArMgX , with yields ranging from 32 to $82 \%{ }^{12}$ Yet $\mathrm{PdCl}(\mathrm{Ph})\left(\mathrm{PPh}_{3}\right)_{2}$ complex is a bench-stable $\mathrm{Pd}(\mathrm{II})$ complex that can be both stored and manipulated under air and is easily obtained from $\mathrm{Pd}\left(\mathrm{PPh}_{3}\right)_{4} \cdot{ }^{13}$ In the presence of an organozinc reagent $\mathrm{R}^{1} \mathrm{ZnX}$, this complex follows a Negishi-like initiation step and provides $\mathrm{PhR}^{1}$ as well as a reactive $\operatorname{Pd}(0)$ entity, which is then available for a subsequent Fukuyama catalytic cycle (Figure 2).

Thus, using Flemming's procedure, ${ }^{13} \mathrm{PdCl}(\mathrm{Ph})\left(\mathrm{PPh}_{3}\right)_{2}$ was obtained in a high yield, and was employed with a loading of $0.1 \mathrm{~mol} \%$ in the Fukuyama CCR featured in Table 1. Pleasingly, ketone 4 a was obtained in a $95 \%$ yield after only 5 min , without any trace of naphthalenediol 5 being observed


Figure 2. Comparison of the reaction mechanisms involved where $\mathrm{PdCl}_{2}\left(\mathrm{PPh}_{3}\right)_{2}$ and the $\operatorname{POxAP} \operatorname{PdCl}(\mathrm{Ph})\left(\mathrm{PPh}_{3}\right)_{2}$ are employed.
(Table 1, entry 11). To better determine the reactivity of this new precatalyst, we synthesized three derivatives, namely $\left(\mathrm{PdCl}(4-\mathrm{CN}-\mathrm{Ph})\left(\mathrm{PPh}_{3}\right)_{2}, \mathrm{PdCl}(4-\mathrm{MeO}-\mathrm{Ph})\left(\mathrm{PPh}_{3}\right)_{2}\right.$, and $\mathrm{PdI}-$ (4-MeO-Ph) $\left.\left(\mathrm{PPh}_{3}\right)_{2}\right)$, in which electron-donating or -withdrawing groups were added to the phenyl ring or where chlorine was substituted with iodine. These potential POxAPs were compared in a kinetic study based on the Fukuyama CCR, as shown in Table 2. Interestingly, with a loading of only $0.001 \mathrm{~mol} \%, \operatorname{PdCl}(\mathrm{Ph})\left(\mathrm{PPh}_{3}\right)_{2}$ catalyzed the formation of ketone $\mathbf{4 b}$ in a $92 \%$ yield with a turnover number (TON) of 92000 (Table 2, entry 2). In comparison, classical $\mathrm{PdCl}_{2}\left(\mathrm{PPh}_{3}\right)_{2}$ led to a poor yield of $12 \%$ (Table 2, entry 1), while other POxAPs gave similar yields and TONs to

Table 2. Kinetic Study ${ }^{a}$ into the Fukuyama CCR Using Various Precatalysts of Generic Formula $\operatorname{PdX}(\mathbf{A r})\left(\mathbf{P P h}_{3}\right)_{2}$


3b
4b

|  |  |  | TOF $\left(\mathrm{s}^{-1}\right)$ |  |  |
| :---: | :--- | :--- | :---: | :---: | :---: |
| entry | cat. or POxAP <br> $(0.001 \mathrm{~mol} \%)$ | TON | initial <br> rate ${ }^{b}$ | cruising $^{\text {rate }}$ | yield <br> $(\%)$ |
| 1 | $\mathrm{PdCl}_{2}\left(\mathrm{PPh}_{3}\right)_{2}$ | 12000 | 0.55 | 0.21 | 12 |
| 2 | $\mathrm{PdCl}(\mathrm{Ph})\left(\mathrm{PPh}_{3}\right)_{2}$ | 92000 | 5.55 | 1.46 | 92 |
| 3 | $\mathrm{PdCl}(4-\mathrm{CN}-\mathrm{Ph})\left(\mathrm{PPh}_{3}\right)_{2}$ | 83000 | 2.22 | 1.53 | 83 |
| 4 | $\mathrm{PdCl}(4-\mathrm{MeO}-\mathrm{Ph})\left(\mathrm{PPh}_{3}\right)_{2}$ | 89000 | 8.89 | 1.60 | 89 |
| 5 | $\mathrm{PdI}(4-\mathrm{MeO}-\mathrm{Ph})\left(\mathrm{PPh}_{3}\right)_{2}$ | 91000 | 12.78 | 1.53 | 91 |

${ }^{a}$ Reaction conditions: thioester $\mathbf{3 b}$ ( 0.14 mmol$)$, [Pd] ( $0.001 \mathrm{~mol} \%$ ), $\mathrm{BnZnBr}\left(0.21 \mathrm{mmol}, 0.82 \mathrm{M}\right.$ in THF), toluene $(0.26 \mathrm{~mL})$, rt. ${ }^{b}$ Initial rate was measured between 0 and 30 min . ${ }^{c}$ Cruising rate was measured between 4 and 8 h . ${ }^{d}$ Yield of $\mathbf{4 b}$ was determined from the average of two independent experiments by HPLC/UV using caffeine as an internal standard.

## Scheme 1. Scope of the Fukuyama $\mathbf{C C R}^{a}$ Using $\operatorname{POxAP} \operatorname{PdCl}(\mathbf{P h})\left(\mathbf{P P h}_{3}\right)_{2}$



${ }^{a}$ Reaction conditions: thioester $3(1 \mathrm{mmol}), \mathrm{PdCl}(\mathrm{Ph})\left(\mathrm{PPh}_{3}\right)_{2}(0.1 \mathrm{~mol} \%), \mathrm{R}^{2} \mathrm{ZnBr} 6(1.5 \mathrm{mmol}$ in THF$)$, toluene $(2.5 \mathrm{~mL}), \mathrm{rt}, 1-3 \mathrm{~h}$.
$\operatorname{PdCl}(\mathrm{Ph})\left(\mathrm{PPh}_{3}\right)_{2}$ (Table 2, entries 3-5). However, differences in reactivity appeared when measuring the turnover frequencies (TOF). Initial rates were determined for the first 30 min of the reaction, and it was found that the presence of an aryl moiety bearing an electron-withdrawing group (i.e., 4-CN$\mathrm{Ph}, 2.22$ vs $5.55 \mathrm{~s}^{-1}$ for Ph ) decreased the initial rate, while the presence of an electron-donating group (i.e., $4-\mathrm{OMe}-\mathrm{Ph}, 8.89$ vs $5.55 \mathrm{~s}^{-1}$ for Ph ) increased this rate (Table 2, entries 3-5). This result is fully consistent with our proposed mechanism. Indeed, compared with electron-poor compounds, reductive elimination is favored by electron-rich compounds. Furthermore, the replacement of chlorine by iodine led also to an initial rate increase (i.e., 8.89 vs $12.8 \mathrm{~s}^{-1}$ ) as iodine is more easily substituted by the organozinc reagent than chlorine (Table 2, entries 4 and 5). However, these differences in the initial rates disappeared between 4 and 8 h (i.e., the cruising rate), where rates ranging from 1.46 to $1.6 \mathrm{~s}^{-1}$ were recorded. Indeed, following our concept, all four POxAPs led to the same catalytic entity $\operatorname{Pd}(0) \mathrm{Ln}$, which is consistent with observation of similar cruising rates following the initial stages of the reaction.

Further proof of the proposed mechanism shown in Figure 2 is the fact that 3-phenylpyridine ( $\mathrm{Ph}-\mathrm{R}^{1}$ ) was detected by mass spectroscopy, which resulted from the Negishi-like initiation step in the presence of pyridin-3-ylzinc bromide. All POxAPs were bench-stable for several weeks, and could be both manipulated and stored under air.

Metal-catalyzed formation of ketones is still a very prolific area of scientific investigation, ${ }^{14}$ as ketone-containing products are numerous in many fields of chemistry.

Using $\mathrm{PdCl}(\mathrm{Ph})\left(\mathrm{PPh}_{3}\right)_{2}$, we then investigated the scope of the Fukuyama CCR at the 1 mmol scale, synthesizing 23 ketones in yields ranging from 53 to $99 \%$ (Scheme 1). As shown, aryl, heteroaryl, and alkyl thioesters were easily coupled to aryl or alkyl organozinc reagents in high yields. Even bulky
ketone $4 \mathbf{k}$ was obtained in $82 \%$ yield despite the steric hindrance on both the thioester and the organozinc reagent. In addition, the use of $0.1 \mathrm{~mol} \%$ of $\mathrm{PdCl}(\mathrm{Ph})\left(\mathrm{PPh}_{3}\right)_{2}$ produced a range of ketones over $1-3 \mathrm{~h}$ at room temperature. Furthermore, with a $0.001 \mathrm{~mol} \%$ loading of $\mathrm{PdI}(4-\mathrm{MeO}-$ $\mathrm{Ph})\left(\mathrm{PPh}_{3}\right)_{2}$, an extended reaction time of 36 h transformed 10 mmol of thioester $\mathbf{3 b}$ into the corresponding ketone $\mathbf{4 b}$ in $96 \%$ yield (Scheme 2a).

Scheme 2. Scale-up (a) and in Situ Generation of $\operatorname{PdCl}(\mathbf{P h})\left(\mathbf{P P h}_{3}\right)_{2}(b)$


Interestingly, POxAP can also be generated in situ starting from $\mathrm{PdCl}_{2}\left(\mathrm{PPh}_{3}\right)_{2}$. Indeed, in 2006, Yasuda et al. reported that $\mathrm{PdCl}_{2}\left(\mathrm{PPh}_{3}\right)_{2}$ reacts with phenolate to afford $\mathrm{PdCl}(\mathrm{Ph})$ $\left(\mathrm{PPh}_{3}\right)_{2}$ in a low yield $(\sim 10 \%) .{ }^{15}$ Moreover, through the use of equimolar amounts of $\mathrm{PdCl}_{2}\left(\mathrm{PPh}_{3}\right)_{2}$ and PhOH in the presence of organozinc reagents, the $\operatorname{POxAP} \operatorname{PdCl}(\mathrm{Ph})\left(\mathrm{PPh}_{3}\right)_{2}$ was generated in situ, as confirmed by NMR spectroscopy (see the SI), and compound $\mathbf{4 a}$ was obtained in $94 \%$ yield (Scheme 2b), without any trace of naphthalenediol 5 .

With the efficient precatalyst POxAP in hand, we attempted to complete the synthesis of the IPK precursor (Scheme 3) following the strategy proposed in Figure 1. Starting from 2,5dimethylphenol, the perbromination of positions 3,4 , and 6 ,

Scheme 3. Total Synthesis of the IPK Precursor 1

followed by the debromination of positions 4 and 6 by $\mathrm{AlCl}_{3}$, led to the desired 3-bromo-2,5-dimethylphenol. Following a subsequent O-methylation step, 7 was obtained in a $74 \%$ overall yield (three steps). Radical bromination of the methyl group at position 2 then gave organozinc $\mathbf{6 c}$, which was stored in THF. Subsequently, 2-bromo-3-methoxybenzoic acid was coupled to ethyl acetoacetate in the presence of a catalytic amount of copper bromide. While sodium ethanolate is required for the copper-mediated coupling reaction, it also promoted an in situ deacetylation to afford $\mathbf{2 b}$ in a $94 \%$ yield. Following formation of the thioester $\mathbf{3 j}$ under standard conditions, a Fukuyama CCR was performed with organozinc 6c using POxAP $\operatorname{PdCl}(\mathrm{Ph})\left(\mathrm{PPh}_{3}\right)_{2}$ to give $\mathbf{4 k}$ in $82 \%$ yield, which was oxidized by $\mathrm{SeO}_{2}$ in AcOH . ${ }^{16}$ Several conditions were then attempted for the subsequent cyclization. While TEA in hot ethanol produced 9a (Table 1), the unsubstituted analogue of $\mathbf{9 b}$, the steric hindrance imparted by both aromatic rings of $\mathbf{8 b}$ prevented the formation of $\mathbf{9 b}$ itself. Several conditions were examined (see the SI), but only the use of DBU in hot DMSO led to indanone $\mathbf{9 b}$ in an excellent yield. Finally, a palladium-catalyzed cyanation reaction led to the desired IPK precursor $\mathbf{1}$. This compound was synthesized over 11 steps and in an overall yield of $29 \%$. This compares to a $3 \%$ overall yield from 16 steps as reported previously. ${ }^{2 e}$

In conclusion, we demonstrated that the POxAPs of generic formula $\mathrm{PdX}(\mathrm{Ar})\left(\mathrm{PPh}_{3}\right)_{2}$, prepared from the oxidative addition of $\operatorname{Pd}(0)$ with $\operatorname{ArX}$, constituted efficient $\mathrm{Pd}(\mathrm{II})$ precatalysts. Indeed, these bench stable POxAPs could be employed in particularly low quantities ( $0.001 \mathrm{~mol} \%$ ) to perform Fukuyama CCRs and generate a large diversity of ketones. This efficacy was demonstrated through the development of a convenient route to IPK. The use of these POxAP are not limited to the Fukuyama CCR, and their efficacies in other palladium-catalyzed CCRs are currently under investigation.

## ASSOCIATED CONTENT

## (S) Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00031.

Full experimental details; ${ }^{1} \mathrm{H}$ and ${ }^{13} \mathrm{C}$ NMR spectra (PDF)

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## Notes

The authors declare no competing financial interest.

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# Fukuyama Cross-Coupling Approach to Isoprekinamycin: Discovery of the Highly Active and Bench Stable Palladium Precatalyst POxAP 

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## Supporting Information

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## I. General Information

All commercial reagents were used without additional purification. Analytical TLC was performed using silica gel plates Merck $60 \mathrm{~F}_{254}$ and plates were visualized by exposure to ultraviolet light ( 254 nm ). Compounds were purified on silica gel Merck 60 (particle size 0.040-0.063 nm).
${ }^{1} \mathrm{H}$ and ${ }^{13} \mathrm{C}$ NMR spectra were recorded on Bruker Avance Spectrometer operating at 400 or 500 MHz and 100 or 125 MHz , respectively. All chemical shift values $\delta$ and coupling constants J are quoted in ppm and in Hz , respectively, multiplicity ( $\mathrm{s}=$ singulet, $\mathrm{d}=$ doublet, $\mathrm{t}=$ triplet, $\mathrm{q}=$ quartet, quin $=$ quintet, $\mathrm{sex}=$ sextet $\mathrm{m}=$ multiplet, $\mathrm{br}=$ broad).

Analytical RP-HPLC-MS was performed using a LC 1200 Agilent with quadrupole-time-of-flight (QTOF) (Agilent Accurate Mass QToF 6520) with a Zorbax Agilent C18-column (C18, $50 \mathrm{~mm} \times 2.1$ $\mathrm{mm} ; 1.8 \mu \mathrm{~m})$ using the following parameters: 1) The solvent system: A $(0.05 \%$ of formic acid in acetonitrile) and $\mathrm{B}\left(0.05 \%\right.$ of formic acid in $\left.\mathrm{H}_{2} \mathrm{O}\right) ; 2$ ) A linear gradient: $\mathrm{t}=0 \mathrm{~min}, 98 \% \mathrm{~B} ; \mathrm{t}=8 \mathrm{~min}, 0 \%$ $\mathrm{B} ; \mathrm{t}=12.5 \mathrm{~min}, 0 \% \mathrm{~B} ; \mathrm{t}=12.6 \mathrm{~min}, 98 \% \mathrm{~B} ; \mathrm{t}=13 \mathrm{~min}, 98 \% \mathrm{~B} ; 3$ ) Flow rate of $0.5 \mathrm{~mL} / \mathrm{min} ; 4$ ) Column temperature: $35^{\circ} \mathrm{C}$; 5) DAD scan from 190 nm to 700 nm ; 6) Ionization mode : $\mathrm{ESI}^{+}$or $\mathrm{ESI}^{-}$. HPLC were performed using a Dionex UltiMate 3000 using the following parameters: Flow rate of 0.5 $\mathrm{mL} / \mathrm{min}$, column temperature: $30^{\circ} \mathrm{C}$, solvent system: $\mathrm{A}(\mathrm{MeOH})$ and $\mathrm{B}(0.05 \%$ of TFA in H 2 O$), \mathrm{t}=0$ $\min$ to $1 \mathrm{~min}: 50$ to $60 \%$ of $B$, then $t=1 \mathrm{~min}$ to $t=10 \mathrm{~min}: 60$ to $100 \%$ of $B$ and $t=10 \mathrm{~min}$ to $t=15 \mathrm{~min}$ : $100 \%$ of B.

## II. Preparation of POxAPs

$\mathrm{PdCl}(\mathrm{Ph})\left(\mathrm{PPh}_{3}\right)_{2}, \mathrm{PdCl}(4-\mathrm{CN}-\mathrm{Ph})\left(\mathrm{PPh}_{3}\right)_{2}, \mathrm{PdCl}(4-\mathrm{MeO}-\mathrm{Ph})\left(\mathrm{PPh}_{3}\right)_{2}$ and $\mathrm{PdI}(4-\mathrm{MeO}-\mathrm{Ph})\left(\mathrm{PPh}_{3}\right)_{2}$ were synthesized according to the previous reported methods. ${ }^{1}$

1. Preparation of $\mathbf{P d C l}(\mathbf{P h})(\mathbf{P P h})_{2}$ 2: The mixture of $\operatorname{Pd}\left(\mathrm{PPh}_{3}\right)_{4}$ (1 equiv, $480 \mathrm{mg}, 0.41 \mathrm{mmol}$ ) and PhBr (3.4 equiv, $146 \mu \mathrm{~L}, 1.39 \mathrm{mmol}$ ) in degassed benzene ( 3.2 mL ) was stirred at $80^{\circ} \mathrm{C}$ under Ar for 16 h . The reaction mixture was concentrated in vacuo, the residue was washed with ether and then dissolved into a vial charged with the mixture of $\mathrm{CH}_{2} \mathrm{Cl}_{2}(3 \mathrm{~mL})$ and saturated KCl aqueous solution ( 3 mL ), then capped and vibrated on a bioshaker ( 1800 rpm ) for 30 min . The aqueous layer was separated and disposed of, the organic phase was treated with another 3 mL of saturated KCl aqueous solution and vibrated ( 1800 rpm ) for another 30 min . After repeated this procedure for 8 times, the organic phase was separated, dried over anhydrous $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and filtered through a $0.22 \mu \mathrm{~m}$ filter. Ether ( 10 mL ) was added to the filtrate, the mixture was left overnight and then filtered to obtain $\mathrm{PdCl}(\mathrm{Ph})\left(\mathrm{PPh}_{3}\right)_{2}$ as a yellow solid $(287 \mathrm{mg}, 94 \%)$.
2. Preparation of $\mathbf{P d C l}(\mathbf{4} \mathbf{- C N}-\mathbf{P h})(\mathbf{P P h} 3)_{2}$ : The mixture of $\operatorname{Pd}\left(\mathrm{PPh}_{3}\right)_{4}(1$ equiv, $260 \mathrm{mg}, 0.22 \mathrm{mmol})$ and 4-chlorobenzonitrile ( 1.2 equiv, $36.8 \mathrm{mg}, 0.27 \mathrm{mmol}$ ) in degassed benzene ( 3 mL ) was stirred at $100^{\circ} \mathrm{C}$ under Ar for 16 h . The reaction mixture was concentrated in vacuo and $\mathrm{Et}_{2} \mathrm{O}(5 \mathrm{~mL})$ was added. The suspension was filtered, the residue was washed with $\mathrm{Et}_{2} \mathrm{O}(5 \mathrm{~mL})$ thrice and dried under vacuum to afford $\mathrm{PdCl}(4-\mathrm{CN}-\mathrm{Ph})\left(\mathrm{PPh}_{3}\right)_{2}$ as a white solid (164 mg, 96\%).
3. Preparation of $\operatorname{PdI}(4-\mathbf{M e O}-\mathbf{P h})(\mathbf{P P h} 3)_{2}$ : The mixture of $\operatorname{Pd}\left(\mathrm{PPh}_{3}\right)_{4}$ ( 1 equiv, $379 \mathrm{mg}, 0.33 \mathrm{mmol}$ ) and 4-iodoanisole ( 1.2 equiv, $91 \mathrm{mg}, 0.39 \mathrm{mmol}$ ) in degassed toluene ( 6 mL ) was stirred at rt under Ar for 16 h. The reaction mixture was concentrated in vacuo and $\mathrm{Et}_{2} \mathrm{O}(5 \mathrm{~mL})$ was added. The suspension was filtered, the residue was washed with $\mathrm{Et}_{2} \mathrm{O}(5 \mathrm{~mL})$ thrice and dried under vacuum to afford $\mathrm{PdI}(4-\mathrm{MeO}-$ $\mathrm{Ph})\left(\mathrm{PPh}_{3}\right)_{2}$ as a white solid ( $250 \mathrm{mg}, 89 \%$ ).
4. Preparation of $\mathbf{P d C l}(4-\mathbf{M e O}-\mathbf{P h})\left(\mathbf{P P h}_{3}\right)_{2}$ : To the solution of $\mathrm{PdI}(4-\mathrm{MeO}-\mathrm{Ph})\left(\mathrm{PPh}_{3}\right)_{2}$ ( 1 equiv, 150 mg , 0.17 mmol ) in $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ ( 2 mL ) was added tetrabutylammonium chloride ( 7 equiv, $337 \mathrm{mg}, 1.2 \mathrm{mmol}$ ) under Ar at $0^{\circ} \mathrm{C}$ and stirred at rt for 30 min . The reaction mixture was concentrated in vacuo and then $\mathrm{MeOH}(3 \mathrm{~mL})$ was added. The suspension was filtered, the residue was washed with $\mathrm{MeOH}(3 \mathrm{~mL})$ thrice, dried under reduced pressure to afford $\mathrm{PdCl}(4-\mathrm{MeO}-\mathrm{Ph})\left(\mathrm{PPh}_{3}\right)_{2}$ as a white solid $(130 \mathrm{mg}, 97 \%)$.

## III. Kinetic Study of POxAPs

$1.4 \times 10^{-2} \mathrm{mmol}$ POxAPs was added to a 20 mL microwave tube charged with 10 mL THF/toluene (1:1) and sonicated until the solution became clear $\left(1.4 \times 10^{-3} \mathrm{M}\right)$. From this solution, $100 \mu \mathrm{l}$ were taken to a second 20 mL microwave tube and diluted with $900 \mu \mathrm{LTHF} /$ toluene $(1: 1)\left(1.4 \times 10^{-4} \mathrm{M}\right)$. Then, $100 \mu \mathrm{~L}$ from this last solution were taken and diluted with $900 \mu \mathrm{~L}$ THF/toluene (1:1) in a third 20 mL microwave tube $\left(1.4 \times 10^{-5} \mathrm{M}\right)$. The microwave tubes were sealed, degassed and backfilled with Ar thrice.
To the solution of $\mathbf{3 b}$ ( 1 equiv, $30 \mathrm{mg}, 0.14 \mathrm{mmol}$ ) in toluene ( 0.26 mL ) was added the corresponding catalyst solution ( $10^{-3} \mathrm{~mol} \%, 100 \mu \mathrm{~L}, 1.4 \times 10^{-6} \mathrm{mmol}, 1.4 \times 10^{-5} \mathrm{M}$ in THF/toluene), degassed and backfilled with argon thrice. Then, the solution of the organozinc reagent $\mathbf{6 a}$ ( 1.5 equiv, $0.26 \mathrm{~mL}, 0.21$ mmol, 0.82 M in THF) was added and stirred at $25^{\circ} \mathrm{C}$ for the given time. Yields of $\mathbf{4 b}$ were determined from the average of two independent experiments by HPLC/UV using caffeine as an internal standard (Table S1).

TON and TOF were calculated with the formulas in Figure S1.

Table S1. Yield (\%) of 4b under different catalyst at $25^{\circ} \mathrm{C}$.


|  | 3b | 6a | 4b |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| Time (h) | $\mathrm{PdCl}_{2}\left(\mathrm{PPh}_{3}\right)_{2}$ | $\mathrm{PdCl}(\mathrm{Ph})\left(\mathrm{PPh}_{3}\right)_{2}$ | $\mathrm{PdCl}(4-\mathrm{CN}-\mathrm{Ph})\left(\mathrm{PPh}_{3}\right)_{2}$ | $\mathrm{PdCl}(4-\mathrm{MeO}-\mathrm{Ph})\left(\mathrm{PPh}_{3}\right)_{2}$ | $\mathrm{PdI}(4-\mathrm{MeO}-\mathrm{Ph})\left(\mathrm{PPh}_{3}\right)_{2}$ |
| 0.5 | 1 | 10 | 4 | 16 | 23 |
| 4 | 3 | 35 | 27 | 44 | 56 |
| 8 | 6 | 56 | 49 | 67 | 78 |
| 16 | 10 | 81 | 77 | 86 | 88 |
| 40 | 12 | 92 | 83 | 89 | 91 |



Figure S1. Calculation of TON and TOF (See Table 2, article).

## IV. POxAPs Catalyzed Fukuyama Cross-Coupling Reactions

## 1. Typical procedure for the synthesis of thioester (TP1)

To an ice-cooled solution of carboxylic acid ( 1 equiv, 5.0 mmol ) and EDCI ( $1.3 \mathrm{eq} ., 1.27 \mathrm{mg}, 6.5 \mathrm{mmol}$ ) in DCM ( 15 mL ) was added $\mathrm{HOBt}(1.3 \mathrm{eq} ., 0.88 \mathrm{~g}, 6.5 \mathrm{mmol})$ The mixture was stirred at $0{ }^{\circ} \mathrm{C}$ for 10 min and then thiophenol ( 1.1 equiv, $562 \mu \mathrm{~L}, 5.5 \mathrm{mmol}$ ) was added. The ice bath was removed and the resulting solution was stirred at room temperature for 5 h . After completion (HPLC or TLC monitoring), water (30 mL ) was added and the mixture was extracted with $\mathrm{DCM}(20 \mathrm{~mL})$ thrice. The combined organic phases were washed with brine, dried over anhydrous $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and concentrated in vacuo. The crude was purified by silica gel chromatography (heptane/EtOAc) to afford corresponding thioester.

## 2. Typical procedures for the synthesis of organozinc reagents

(1) Typical procedure 2 (TP2):

An oven-dried 20 mL microwave vial equipped with a magnetic stirrer was charged with zinc ( 1.5 equiv, $392 \mathrm{mg}, 6 \mathrm{mmol})$. The vial was properly capped and the vessel was heated using a heat gun ( $350{ }^{\circ} \mathrm{C}, 10$ $\min$ ) under reduced pressure, the tube was cooled to room temperature, degassed and backfilled with argon thrice. Then THF ( 4.0 mL ) was added followed by 1,2-dibromoethane ( $5 \%, 17.3 \mu \mathrm{~L}, 0.2 \mathrm{mmol}$ ) and chlorotrimethylsilane ( $5 \%, 25.6 \mu \mathrm{~L}, 0.2 \mathrm{mmol})$. The suspension was heated $\left(50^{\circ} \mathrm{C}, 1 \mathrm{~min}\right)$ until the suspension became clear and grey precipitates formed. After cooling to room temperature, the corresponding bromide ( 1 equiv, 4 mmol ) was added dropwise at $0^{\circ} \mathrm{C}$ (solid bromides were dissolved in 1 mL THF before adding). The resulted solution was stirred at room temperature overnight to afford the corresponding organozinc reagent. The concentration and yield of the organozinc reagent were determined by iodometric titration of the supernatant solution. ${ }^{2}$

## (2) Typical procedure 3 (TP3):

An oven-dried 20 mL microwave vial equipped with a magnetic stirrer was charged with $\mathrm{ZnCl}_{2}$ (1.4 equiv, $779 \mathrm{mg}, 5.6 \mathrm{mmol})$. The vial was properly capped and the vessel was heated using a heat gun ( $550{ }^{\circ} \mathrm{C}, 15$ min ) under reduced pressure, the tube was cooled to room temperature, degassed and backfilled with argon thrice. Then THF ( 4 mL ) was added and the mixture was ultrasonicated until it became a clear solution. The corresponding organomagnesium bromide ( 1 equiv, 4 mmol ) was added to the forementioned solution slowly at $0^{\circ} \mathrm{C}$ and a white precipitate was observed. The resulting mixture was stirred at room temperature for additional 3 h to afford the corresponding organozinc reagent, which was used directly without titration.

## 3. Typical procedure for the synthesis of ketone (TP4):

A solution of thioester ( 1 equiv, 1 mmol ) and $\mathrm{PdCl}(\mathrm{Ph})\left(\mathrm{PPh}_{3}\right)_{2}(0.1 \mathrm{~mol} \%, 0.74 \mathrm{mg}, 0.001 \mathrm{mmol})$ in toluene ( 2.5 mL ) was degassed and backfilled with argon thrice. Then, the solution of organozinc reagent ( 1.5 equiv, 1.5 mmol ) in THF was added dropwise at the given temperature. After stirring for the given time, the reaction mixture was quenched with saturated $\mathrm{NH}_{4} \mathrm{Cl}$ solution ( 10 mL ) and extracted with EtOAc ( 10 mL ) thrice. The combined organic phases were dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and concentrated in vacuo. The crude was purified by silica gel chromatography to afford the corresponding ketone.

## Preparation of ethyl 2-(2-((phenylthio)carbonyl)phenyl)acetate (3a)



3a
The reaction was performed with $\mathbf{2 a}$ ( 1 equiv, $1.04 \mathrm{~g}, 5 \mathrm{mmol}$ ) according to TP1, the crude was purified silica gel chromatography (heptane: $\mathrm{EtOAc}=10: 1$ ) to afford $\mathbf{3 a}$ as a yellow solid $(1.43 \mathrm{~g}, 95 \%)$.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 8.08(\mathrm{~d}, \mathrm{~J}=7.7 \mathrm{~Hz}, 1 \mathrm{H}), 7.56-7.38(\mathrm{~m}, 7 \mathrm{H}), 7.31(\mathrm{~d}, \mathrm{~J}=7.5 \mathrm{~Hz}, 1 \mathrm{H})$, 4.14 (q, J = 7.0 Hz, 2H), 3.93 (s, 2H), 1.23 (t, J = 7.1 Hz, 3H).
${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 192.09,170.98$, 136.87, 135.00, 133.47, 132.41, 132.33, 129.53, 129.28, 129.23, 128.11, 127.55, 60.88, 39.51, 14.26.

HRMS (ESI): m/z calcd. for $\mathrm{C}_{17} \mathrm{H}_{16} \mathrm{O}_{3} \mathrm{~S}[\mathrm{M}]^{+}: 300.0820$, found: 300.0805.

## Preparation of S-phenyl benzothioate (3b)



## 3b

The reaction was performed with benzoic acid ( 1 equiv $611 \mathrm{mg}, 5 \mathrm{mmol}$ ) according to TP1, the crude was purified silica gel chromatography (heptane:EtOAc $=4: 1$ ) to afford $\mathbf{4 c}$ as a yellow solid ( 1.05 g , 98\%).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 8.04(\mathrm{~d}, \mathrm{~J}=7.9 \mathrm{~Hz}, 2 \mathrm{H}), 7.62(\mathrm{t}, \mathrm{J}=7.3 \mathrm{~Hz}, 1 \mathrm{H}), 7.56-7.43(\mathrm{~m}, 7 \mathrm{H})$. These data are consistent with the previously reported characterization. ${ }^{3}$

## Preparation of S-phenyl 4-chlorobenzothioate (3c)



3c

The reaction was performed with 4-chlorobenzoic acid (1 equiv, $0.78 \mathrm{~g}, 5 \mathrm{mmol}$ ) according to TP1, the crude was purified silica gel chromatography (heptane: $\mathrm{EtOAc}=18: 1$ ) to afford $\mathbf{3 c}$ as a white solid (1.16 g, $93 \%$ ).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 8.02-7.94(\mathrm{~m}, 2 \mathrm{H}), 7.57-7.43(\mathrm{~m}, 7 \mathrm{H})$.
These data are consistent with the previously reported characterization. ${ }^{4}$

## Preparation of S-phenyl 3-chlorobenzothioate (3d)



3d
The reaction was performed with 3-chlorobenzoic acid (1 equiv, $0.78 \mathrm{~g}, 5 \mathrm{mmol}$ ) according to TP1, the crude was purified silica gel chromatography (heptane: $\mathrm{EtOAc}=18: 1$ ) to afford $\mathbf{3 d}$ as a colorless oil ( 1.22 g, $98 \%$ ).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 8.02(\mathrm{t}, \mathrm{J}=2.0 \mathrm{~Hz}, 1 \mathrm{H}), 7.93(\mathrm{dt}, \mathrm{J}=7.8,1.4 \mathrm{~Hz}, 1 \mathrm{H}), 7.60-7.46(\mathrm{~m}$, 6 H ), 7.42 (t, J = $7.9 \mathrm{~Hz}, 1 \mathrm{H}$ ).

These data are consistent with the previously reported characterization. ${ }^{4}$

## Preparation of S-phenyl 2-chlorobenzothioate (3e)



3 e
The reaction was performed with 2-chlorobenzoic acid (1 equiv, $0.78 \mathrm{~g}, 5 \mathrm{mmol}$ ) according to TP1, the crude was purified silica gel chromatography (heptane $: \mathrm{EtOAc}=18: 1$ ) to afford $\mathbf{3 e}$ as a yellow solid (1.19 g, $96 \%$ ).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.77(\mathrm{~d}, \mathrm{~J}=7.5 \mathrm{~Hz}, 1 \mathrm{H}), 7.59-7.53(\mathrm{~m}, 2 \mathrm{H}), 7.51-7.40(\mathrm{~m}, 5 \mathrm{H}), 7.36$ (t, J = 7.3 Hz, 1H).

These data are consistent with the previously reported characterization. ${ }^{5}$

## Preparation of S-phenyl 2-bromobenzothioate (3f)


$3 f$

The reaction was performed with 2-bromobenzoic acid (1 equiv, $1.01 \mathrm{~g}, 5 \mathrm{mmol}$ ) according to TP1, the crude was purified silica gel chromatography (heptane: $\mathrm{EtOAc}=18: 1$ ) to afford $\mathbf{3 f}$ as a yellow solid (1.31 g, $89 \%$ ).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.73(\mathrm{~d}, \mathrm{~J}=7.5 \mathrm{~Hz}, 1 \mathrm{H}), 7.67(\mathrm{~d}, \mathrm{~J}=7.8 \mathrm{~Hz}, 1 \mathrm{H}), 7.60-7.53(\mathrm{~m}, 2 \mathrm{H})$, $7.52-7.44(\mathrm{~m}, 3 \mathrm{H}), 7.43-7.31(\mathrm{~m}, 2 \mathrm{H})$.

These data are consistent with the previously reported characterization. ${ }^{6}$

## Preparation of S-phenyl 2-methoxybenzothioate (3g)



3 g
The reaction was performed with 2-methoxybenzoic acid (1 equiv, $0.76 \mathrm{~g}, 5 \mathrm{mmol}$ ) according to TP1, the crude was purified silica gel chromatography (heptane:EtOAc $=18: 1$ ) to afford $\mathbf{3 g}$ as a colorless oil ( $1.05 \mathrm{~g}, 86 \%$ ).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.87(\mathrm{~d}, \mathrm{~J}=7.6 \mathrm{~Hz}, 1 \mathrm{H}), 7.64-7.38(\mathrm{~m}, 6 \mathrm{H}), 7.11-6.94(\mathrm{~m}, 2 \mathrm{H}), 3.96$ ( $\mathrm{s}, 3 \mathrm{H}$ ).
These data are consistent with the previously reported characterization. ${ }^{4}$

## Preparation of S-phenyl 2-cyanobenzothioate (3h)



## 3h

The reaction was performed with 2-cyanobenzoic acid (1 equiv, $0.74 \mathrm{~g}, 5 \mathrm{mmol}$ ) according to TP1, the crude was purified silica gel chromatography (heptane: $\mathrm{EtOAc}=15: 1$ ) to afford $\mathbf{3 h}$ as a white solid (1.06 g, $89 \%$ ).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 8.18(\mathrm{dd}, \mathrm{J}=7.7,1.5 \mathrm{~Hz}, 1 \mathrm{H}), 7.84(\mathrm{dd}, \mathrm{J}=7.3,1.7 \mathrm{~Hz}, 1 \mathrm{H}), 7.79-7.66$ (m, 2H), 7.63-7.40 (m, 5H).
${ }^{13} \mathrm{C}$ NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 188.29,139.19,135.25,135.02,132.98,132.79,130.12,129.57,129.27$, 126.35, 117.23, 110.58.

HRMS (ESI): m/z calcd. for $\mathrm{C}_{14} \mathrm{H}_{9} \mathrm{NOS}[\mathrm{M}]^{+}: 239.0405$, found: 239.0393.

## Preparation of S-phenyl 2-nitrobenzothioate (3i)


$3 i$
The reaction was performed with 2-nitrobenzoic acid (1 equiv, $0.84 \mathrm{~g}, 5 \mathrm{mmol}$ ) according to TP1, the crude was purified silica gel chromatography (heptane:EtOAc $=6: 1$ ) to afford $\mathbf{3 i}$ as a yellow solid ( 1.21 g, 93\%).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 8.08(\mathrm{~d}, \mathrm{~J}=8.0 \mathrm{~Hz}, 1 \mathrm{H}), 7.78-7.62(\mathrm{~m}, 3 \mathrm{H}), 7.61-7.54(\mathrm{~m}, 2 \mathrm{H}), 7.51-$ 7.42 (m, 3H).
${ }^{13} \mathrm{C}$ NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 190.20,146.26,134.83,133.72,131.79,131.73,130.15,129.64,128.54$, 126.81, 124.86.

HRMS (ESI): m/z calcd. for $\mathrm{C}_{13} \mathrm{H}_{9} \mathrm{NO}_{3} \mathrm{~S}[\mathrm{M}]^{+}: 259.0303$, found: 259.0288 .

## Preparation of ethyl 2-(2-methoxy-6-((phenylthio)carbonyl)phenyl)acetate (3j)



3j
The reaction was performed with $\mathbf{2 b}$ ( 1 equiv, $1.19 \mathrm{~g}, 5 \mathrm{mmol}$ ) according to TP1, the crude was purified silica gel chromatography (heptane:EtOAc $=14: 1$ ) to afford $\mathbf{3 j}$ as a yellow solid $(1.52 \mathrm{~g}, 92 \%)$.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.61(\mathrm{dd}, \mathrm{J}=7.8,1.0 \mathrm{~Hz}, 1 \mathrm{H}$ ), $7.53-7.43(\mathrm{~m}, 5 \mathrm{H}), 7.38(\mathrm{t}, \mathrm{J}=8.1 \mathrm{~Hz}$, $1 \mathrm{H}), 7.09(\mathrm{~d}, \mathrm{~J}=8.2 \mathrm{~Hz}, 1 \mathrm{H}), 4.12(\mathrm{q}, \mathrm{J}=7.1 \mathrm{~Hz}, 2 \mathrm{H}), 3.94(\mathrm{~s}, 2 \mathrm{H}), 3.85(\mathrm{~s}, 3 \mathrm{H}), 1.22(\mathrm{t}, \mathrm{J}=7.1 \mathrm{~Hz}, 3 \mathrm{H})$. ${ }^{13} \mathrm{C}$ NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 192.44,171.32,158.40,138.50,134.97,129.60,129.35,128.31,128.26$, 122.37, 120.91, 114.41, 60.71, 56.18, 31.87, 14.35.

HRMS (ESI): m/z calcd. for $\mathrm{C}_{17} \mathrm{H}_{18} \mathrm{O}_{4} \mathrm{~S}[\mathrm{M}]^{+}: 330.0926$, found: 330.0909 .

## Preparation of S-phenyl benzofuran-2-carbothioate (3k)



## 3k

The reaction was performed with benzofuran-2-carboxylic acid (1 equiv, $0.81 \mathrm{~g}, 5 \mathrm{mmol}$ ) according to TP1, the crude was purified silica gel chromatography (heptane:EtOAc $=6: 1$ ) to afford $\mathbf{3 k}$ as a white solid ( $1.26 \mathrm{~g}, 99 \%$ ).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.72(\mathrm{dt}, \mathrm{J}=7.8,1.0 \mathrm{~Hz}, 1 \mathrm{H}), 7.65-7.59(\mathrm{~m}, 2 \mathrm{H}), 7.58-7.53(\mathrm{~m}, 2 \mathrm{H})$, $7.53-7.46(\mathrm{~m}, 4 \mathrm{H}), 7.37-7.31(\mathrm{~m}, 1 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 180.55,155.77$, 150.87, 135.17, 129.91, 129.47, 128.40, 127.08, 126.25, 124.23, 123.35, 112.61, 111.94.

HRMS (ESI): m/z calcd. for $\mathrm{C}_{15} \mathrm{H}_{10} \mathrm{O}_{2} \mathrm{~S}[\mathrm{M}]^{+}: 254.0402$, found: 254.0385 .

## Preparation of S-phenyl quinoline-3-carbothioate (31)



31
The reaction was performed with quinoline-3-carboxylic acid ( 1 equiv, $0.87 \mathrm{~g}, 5 \mathrm{mmol}$ ) according to TP1, the crude was purified silica gel chromatography (heptane: $\mathrm{EtOAc}=3: 1$ ) to afford $\mathbf{3 1}$ as a white solid ( 1.31 g, 99\%).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 9.44(\mathrm{~d}, \mathrm{~J}=2.2 \mathrm{~Hz}, 1 \mathrm{H}), 8.83(\mathrm{~d}, \mathrm{~J}=2.0 \mathrm{~Hz}, 1 \mathrm{H}), 8.22-8.14(\mathrm{~m}, 1 \mathrm{H})$, 8.02-7.94 (m, 1H), 7.92-7.83 (m, 1H), 7.70-7.62 (m, 1H), 7.60-7.53 (m, 2H), 7.52-7.46(m, 3H).
${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 188.79,150.35,148.03,136.49,135.18,132.31,129.99,129.73,129.54$, 129.47, 129.41, 127.91, 126.93, 126.63.

HRMS (ESI): m/z calcd. for $\mathrm{C}_{16} \mathrm{H}_{11} \mathrm{NOS}[\mathrm{M}]^{+}: 265.0561$, found: 265.0549.

## Preparation of S-phenyl 1H-indole-2-carbothioate (3m)



## 3m

The reaction was performed with 1 H -indole-2-carboxylic acid (1 equiv, $0.81 \mathrm{~g}, 5 \mathrm{mmol}$ ) according to TP1, the crude was purified silica gel chromatography (heptane:EtOAc $=3: 1$ ) to afford $\mathbf{3 m}$ as a white solid ( $1.23 \mathrm{~g}, 97 \%$ ).
${ }^{1} \mathrm{H}$ NMR ( 400 MHz, DMSO-d ) : $\delta 12.06(\mathrm{~s}, 1 \mathrm{H}), 7.78-7.71(\mathrm{~m}, 1 \mathrm{H}), 7.59-7.45(\mathrm{~m}, 7 \mathrm{H}), 7.35-7.29(\mathrm{~m}$, 1H), 7.16-7.10 (m, 1H).
These data are consistent with the previously reported characterization. ${ }^{7}$

## Preparation of S-phenyl furan-3-carbothioate (3n)



## 3n

The reaction was performed with furan-3-carboxylic acid (1 equiv, $0.56 \mathrm{~g}, 5 \mathrm{mmol}$ ) according to $\mathbf{T P 1}$, the crude was purified silica gel chromatography (heptane:EtOAc $=15: 1$ ) to afford $\mathbf{3 n}$ as a colorless oil ( $1.01 \mathrm{~g}, 99 \%$ ).
${ }^{1}{ }^{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 8.17(\mathrm{dd}, \mathrm{J}=1.6,0.8 \mathrm{~Hz}, 1 \mathrm{H}), 7.53-7.43(\mathrm{~m}, 6 \mathrm{H}), 6.82(\mathrm{dd}, \mathrm{J}=1.9,0.9$ $\mathrm{Hz}, 1 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta$ 183.08, 146.26, 144.31, 135.00, 129.65, 129.33, 126.86, 126.55, 108.52.

HRMS (ESI): m/z calcd. for C11H8O2S [M] ${ }^{+}$: 204.0245, found: 204.0231.

## Preparation of S-phenyl 4-methylthiazole-5-carbothioate (3o)



30
The reaction was performed with 4-methylthiazole-5-carboxylic acid ( 1 equiv, $0.72 \mathrm{~g}, 5 \mathrm{mmol}$ ) according to TP1, the crude was purified silica gel chromatography (heptane: $\mathrm{EtOAc}=3: 1$ ) to afford $\mathbf{3 o}$ as a white solid ( $1.15 \mathrm{~g}, 98 \%$ ).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 8.78$ ( $\mathrm{s}, 1 \mathrm{H}$ ), $7.53-7.43(\mathrm{~m}, 5 \mathrm{H}), 2.78(\mathrm{~s}, 3 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 181.97,158.95,154.90,135.00,130.03,129.47,129.43,127.12,18.22$. HRMS (ESI): m/z calcd. for $\mathrm{C}_{11} \mathrm{H}_{9} \mathrm{NOS}_{2}[\mathrm{M}]^{+}: 235.0126$, found: 235.0110.

## Preparation of S-phenyl pyridine-3-carbothioate (3p)



3p
The reaction was performed with nicotinic acid ( 1 equiv, $0.62 \mathrm{~g}, 5 \mathrm{mmol}$ ) according to TP1, the crude was purified silica gel chromatography (heptane:EtOAc $=3: 1$ ) to afford $\mathbf{3 p}$ as a colorless oil ( 1.02 g , 95\%).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 9.23(\mathrm{~s}, 1 \mathrm{H}), 8.80(\mathrm{~d}, \mathrm{~J}=3.9 \mathrm{~Hz}, 1 \mathrm{H}), 8.27-8.21(\mathrm{~m}, 1 \mathrm{H}), 7.54-7.37(\mathrm{~m}$, 6 H ).

These data are consistent with the previously reported characterization. ${ }^{8}$

## Preparation of S-phenyl 2-(p-tolyl)ethanethioate (3q)



3q
The reaction was performed with 2-(p-tolyl)acetic acid (1 equiv, $0.75 \mathrm{~g}, 5 \mathrm{mmol}$ ) according to TP1, the crude was purified silica gel chromatography (heptane: $\mathrm{EtOAc}=10: 1$ ) to afford $\mathbf{3 q}$ as a colorless oil ( 1.16 g, 96\%).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.39(\mathrm{~s}, 5 \mathrm{H}), 7.28-7.15(\mathrm{~m}, 4 \mathrm{H}), 3.89(\mathrm{~s}, 2 \mathrm{H}), 2.37(\mathrm{~s}, 3 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 195.61,137.37,134.54,130.36,129.67,129.54,129.43,129.23,128.07$, 49.92, 21.26.

HRMS (ESI): m/z calcd. for $\mathrm{C}_{15} \mathrm{H}_{14} \mathrm{OS}[\mathrm{M}]^{+}: 242.0765$, found: 242.0761 .

## Preparation of S-phenyl 2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)ethanethioate (3r)

(moc O-S
3r
The reaction was performed with Fmoc-glycine ( 1 equiv, $1.49 \mathrm{~g}, 5 \mathrm{mmol}$ ) according to TP1, the crude was purified silica gel chromatography (heptane: $\mathrm{EtOAc}=3: 1$ ) to afford $\mathbf{3 r}$ as a white solid $(1.79 \mathrm{~g}, 92 \%)$. ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.78(\mathrm{~d}, \mathrm{~J}=7.5 \mathrm{~Hz}, 2 \mathrm{H}), 7.63(\mathrm{~d}, \mathrm{~J}=7.4 \mathrm{~Hz}, 2 \mathrm{H}), 7.48-7.36(\mathrm{~m}, 7 \mathrm{H})$, $7.32(\mathrm{t}, \mathrm{J}=7.9 \mathrm{~Hz}, 2 \mathrm{H}), 5.48(\mathrm{~s}, 1 \mathrm{H}), 4.48(\mathrm{~d}, \mathrm{~J}=7.0 \mathrm{~Hz}, 2 \mathrm{H}), 4.27(\mathrm{t}, \mathrm{J}=7.0 \mathrm{~Hz}, 1 \mathrm{H}), 4.22(\mathrm{~d}, \mathrm{~J}=6.1$ $\mathrm{Hz}, 2 \mathrm{H})$.
These data are consistent with the previously reported characterization. ${ }^{9}$

## Preparation of (S)-tert-butyl 2-((phenylthio)carbonyl)pyrrolidine-1-carboxylate (3s)



3s
The reaction was performed with N-Boc-L-proline ( 1 equiv, $1.08 \mathrm{~g}, 5 \mathrm{mmol}$ ) according to TP1, the crude was purified silica gel chromatography (heptane $\mathrm{EtOAc}=6: 1$ ) to afford 3 s as a white solid $(1.48 \mathrm{~g}, 96 \%)$. ${ }^{1}{ }^{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.42-7.37(\mathrm{dd}, \mathrm{J}=6.0,3.5 \mathrm{~Hz}, 5 \mathrm{H}), 4.61-4.39(\mathrm{~m}, 1 \mathrm{H}), 3.72-3.40(\mathrm{~m}$, $2 \mathrm{H}), 2.34-1.84(\mathrm{~m}, 4 \mathrm{H}), 1.51(\mathrm{~s}, 3 \mathrm{H}), 1.49(\mathrm{~s}, 6 \mathrm{H})$.
These data are consistent with the previously reported characterization. ${ }^{10}$

## Preparation of benzylzinc(II) bromide (6a)


$6 \mathbf{a}$
According to TP2, 6a was prepared from (bromomethyl)benzene ( 1 equiv, $0.48 \mathrm{~mL}, 4 \mathrm{mmol}$ ). Titration against iodine indicates a concentration of $0.82 \mathrm{M}(92 \%)$.

## Preparation of phenylzinc(II) bromide (6b)



6b
According to TP3, 6b was prepared from phenylmagnesium bromide ( 1 equiv, $4 \mathrm{~mL}, 4 \mathrm{mmol}, 1 \mathrm{M}$ in THF). The concentration of $\mathbf{6 b}$ was 0.5 M .

## Preparation of (2-bromo-6-methoxy-4-methylbenzyl)zinc(II) bromide (6c)


$6 c$
The corresponding bromide was prepared from 2,5-dimethylphenol according to the previous reported methods (4 overall steps, 59\%). ${ }^{11}$

According to TP2, 6c was prepared from the corresponding bromide (1 equiv, $1.18 \mathrm{~g}, 4 \mathrm{mmol}$ ) in THF $(1 \mathrm{~mL})$. Titration against iodine indicates a concentration of $0.57 \mathrm{M}(86 \%)$.

## Preparation of adamantan-1-ylzinc(II) chloride (6d)



6d
6d was prepared according to a previous reported method. ${ }^{12}$ An oven-dried 20 mL microwave vial equipped with a magnetic stirrer was charged with $\mathrm{LiCl}(1.1$ equiv, $163 \mathrm{mg}, 3.85 \mathrm{mmol})$. The vial was capped and heated $\left(450{ }^{\circ} \mathrm{C}, 5 \mathrm{~min}\right)$ by an heat gun under reduced pressure. The vial was then cooled to room temperature and backfilled with argon. Mg ( 2 equiv, $170 \mathrm{mg}, 7 \mathrm{mmol}$ ) was added, the tube was properly sealed and heated under reduced pressure ( $90^{\circ} \mathrm{C}, 3 \mathrm{~min}$ ). After cooling to room temperature, the tube was backfilled with argon thrice. THF ( 5 mL ) was added, followed by DBE ( 0.05 equiv, $15.1 \mu \mathrm{~L}$, $0.19 \mathrm{mmol})$ and $\mathrm{TMSCl}(0.03$ equiv, $13.4 \mu \mathrm{~L}, 0.11 \mathrm{mmol})$. Then, a solution of $\mathrm{ZnCl}_{2}$ ( 1.1 equiv, 525 mg , 3.85 mmol ) in THF ( 3.85 mL ) was added followed by a solution of 1-bromoadamantane (1 equiv, 753 $\mathrm{mg}, 3.5 \mathrm{mmol})$ in THF ( 1 mL ). The reaction mixture was stirred at room temperature overnight to afford adamantan-1-ylzinc(II) chloride. Titration against iodine indicates a concentration of $0.23 \mathrm{M}(73 \%)$.

## Preparation of ([1,1'-biphenyl]-3-ylmethyl)zinc(II) bromide (6e)


$6 e$
According to TP2, $\mathbf{6 e}$ was prepared from the solution of 3-(bromomethyl)-1,1'-biphenyl (1 equiv, 0.99 g , $4 \mathrm{mmol})$ in THF ( 1 mL ). Titration against iodine indicates a concentration of $0.55 \mathrm{M}(83 \%)$.

## Preparation of (naphthalen-2-ylmethyl)zinc(II) bromide (6f)


$6 f$

According to TP2, $\mathbf{6 f}$ was prepared from the solution of 2-(bromomethyl)naphthalene (1 equiv, $0.88 \mathrm{~g}, 4$ $\mathrm{mmol})$ in THF ( 1 mL ). Titration against iodine indicates a concentration of $0.59 \mathrm{M}(89 \%)$.

## Preparation of pyridin-3-ylzinc(II) bromide ( 6 g )

## $\mathrm{Br}^{-\mathrm{Zn}}$

6 g
$\mathbf{6 g}$ was prepared according to a previous reported method. ${ }^{13}$ An oven-dried 20 mL microwave tube equipped with a magnetic stirrer was charged with $\mathrm{LiCl}\left(1.5\right.$ equiv, $191 \mathrm{mg}, 4.5 \mathrm{mmol}$ ), $\mathrm{ZnCl}_{2}$ ( 1.1 equiv, $450 \mathrm{mg}, 3.3 \mathrm{mmol}$. The vial was capped and heated $\left(550{ }^{\circ} \mathrm{C}, 15 \mathrm{~min}\right)$ by an heat gun under reduced pressure, the tube was cooled to room temperature and backfilled with argon. Mg ( 2.47 equiv, 180 mg , 7.41 mmol ) was added, the tube was sealed and heated under reduced pressure ( $90^{\circ} \mathrm{C}, 3 \mathrm{~min}$ ). After cooling to room temperature, the tube was backfilled with argon thrice. THF ( 6 mL ) was added, and the mixture was stirred for 30 min at room temperature. Then, 3-bromopyridine ( 1 equiv, $0.29 \mathrm{~mL}, 3 \mathrm{mmol}$ ) was added in one portion at $25^{\circ} \mathrm{C}$. The reaction mixture was stirred for at room temperature overnight to afford pyridin-3-ylzinc(II) bromide. Titration against iodine indicates a concentration of 0.3 M ( $64 \%$ ).

## Preparation of (2-ethoxy-2-oxoethyl)zinc(II) bromide (6h)

$\mathrm{Br}^{-2 \mathrm{Zn}} \mathrm{CO}_{2} \mathrm{Et}$
6h
According to TP2, 6h was prepared from ethyl 2-bromoacetate (1 equiv, $0.44 \mathrm{~mL}, 4 \mathrm{mmol}$ ). Titration against iodine indicates a concentration of $0.74 \mathrm{M}(83 \%)$.

## Preparation of prop-1-en-2-ylzinc(II) bromide (6i)

$\mathrm{Br}^{-2 n} \pi$
$6 i$
According to TP3, $\mathbf{6 i}$ was prepared from prop-1-en-2-ylmagnesium bromide (1 equiv, $8 \mathrm{~mL}, 4 \mathrm{mmol}, 0.5$ M in THF). The concentration of $\mathbf{6 i}$ was 0.33 M .

## Preparation of (3,4-dichlorophenyl)zinc(II) bromide ( $\mathbf{6 j}$ )



6j
(3,4-dichlorophenyl)magnesium bromide was prepared according to a previous reported method ( 0.74 M , $92 \%) .{ }^{14}$

According to TP3, $\mathbf{6 j}$ was prepared from (3,4-dichlorophenyl)magnesium bromide (1 equiv, $5.4 \mathrm{~mL}, 4$ $\mathrm{mmol}, 0.74 \mathrm{M}$ in THF). The concentration of $\mathbf{6 j}$ was 0.43 M .

## Preparation of ethyl 2-(2-(2-phenylacetyl)phenyl)acetate (4a)


$4 \mathbf{a}$
The cross-coupling reaction of $\mathbf{3 a}$ ( 1 equiv, $300 \mathrm{mg}, 1 \mathrm{mmol}$ ) with $\mathbf{6 a}(1.5$ equiv, $1.83 \mathrm{~mL}, 1.5 \mathrm{mmol}$, 0.82 M in THF) was performed according to TP4 at room temperature in 1 h . the crude was purified by silica gel chromatography (heptane: $\mathrm{EtOAc}=9: 1$ ) to afford $\mathbf{4 a}$ as a yellow solid ( $268 \mathrm{mg}, 95 \%$ ).

Synthesis of 4 a with $\mathbf{P d C l}_{2}\left(\mathbf{P P h}_{3}\right)_{2}$ with the addition of $\mathbf{P h O H}$ : A solution of $\mathbf{3 a}$ (1 equiv, $300 \mathrm{mg}, 1$ $\mathrm{mmol}), \mathrm{PhOH}(1 \mathrm{~mol} \%, 0.94 \mathrm{mg}, 0.01 \mathrm{mmol})$ and $\mathrm{PdCl}_{2}\left(\mathrm{PPh}_{3}\right)_{2}(1 \mathrm{~mol} \%, 7.02 \mathrm{mg}, 0.01 \mathrm{mmol})$ in toluene ( 2.5 mL ) was degassed and backfilled with argon thrice. Then, $\mathbf{6 a}(1.5$ equiv, $1.83 \mathrm{~mL}, 1.5 \mathrm{mmol}$, 0.82 M in THF) was added slowly at room temperature. After stirring at $50^{\circ} \mathrm{C}$ for 25 min , the reaction mixture was quenched with saturated $\mathrm{NH}_{4} \mathrm{Cl}$ solution $(10 \mathrm{~mL})$ and extracted with $\mathrm{EtOAc}(10 \mathrm{~mL})$ thrice. The combined organic phases were dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and concentrated in vacuo. The crude was purified by silica gel chromatography (heptane: $\mathrm{EtOAc}=9: 1$ ) to afford $\mathbf{4 a}$ as a yellow solid $(265 \mathrm{mg}, 94 \%)$.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.86(\mathrm{~d}, \mathrm{~J}=7.7 \mathrm{~Hz}, 1 \mathrm{H}$ ), $7.48-7.27(\mathrm{~m}, 8 \mathrm{H}), 4.28(\mathrm{~s}, 2 \mathrm{H}), 4.14(\mathrm{q}, \mathrm{J}=$ $7.1 \mathrm{~Hz}, 2 \mathrm{H}), 3.92(\mathrm{~s}, 2 \mathrm{H}), 1.25(\mathrm{t}, \mathrm{J}=7.2 \mathrm{~Hz}, 3 \mathrm{H})$.

These data are consistent with the previously reported characterization. ${ }^{15}$

## Preparation of 1,2-diphenylethanone (4b)



4b
The cross-coupling reaction of $\mathbf{3 b}$ ( 1 equiv, $214 \mathrm{mg}, 1 \mathrm{mmol}$ ) with $\mathbf{6 a}$ ( 1.5 equiv, $1.83 \mathrm{~mL}, 1.5 \mathrm{mmol}$, 0.82 M in THF) was performed according to TP4 at room temperature in 1 h . The crude was purified silica gel chromatography (heptane $: E t O A c=15: 1$ ) to afford 4b as a white solid ( $192 \mathrm{mg}, 98 \%$ ).

Synthesis of 4b in $\mathbf{1 0} \mathbf{~ m m o l}$ scale: To the solution of $\mathbf{3 b}$ ( 1 equiv, $2.14 \mathrm{~g}, 10 \mathrm{mmol}$ ) in toluene ( 18.3 mL ) was added $\operatorname{PdI}(4-\mathrm{MeO}-\mathrm{Ph})\left(\mathrm{PPh}_{3}\right)_{2}\left(0.001 \mathrm{~mol} \%, 71.4 \mu \mathrm{~L}, 10^{-4} \mathrm{mmol}, 1.4 \times 10^{-3} \mathrm{M}\right.$ in THF/toluene $)$. The resulting mixture was then degassed and backfilled with argon thrice. $\mathbf{6 a}(1.5$ equiv, $18.3 \mathrm{~mL}, 15 \mathrm{mmol}$, 0.82 M in THF) was added dropwise at room temperature. After stirring for 36 h , the reaction mixture was quenched with saturated $\mathrm{NH}_{4} \mathrm{Cl}$ solution $(40 \mathrm{~mL})$ and extracted with EtOAc $(40 \mathrm{~mL})$ thrice. The
combined organic phases were dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and concentrated in vacuo. The crude was purified by silica gel chromatography (heptane $: E t O A c=15: 1)$ to afford $\mathbf{4 b}$ as a white solid $(1.88 \mathrm{~g}, 96 \%)$.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 8.09-8.02(\mathrm{~m}, 2 \mathrm{H}), 7.55(\mathrm{t}, \mathrm{J}=7.3 \mathrm{~Hz}, 1 \mathrm{H}), 7.45(\mathrm{t}, \mathrm{J}=7.7 \mathrm{~Hz}, 2 \mathrm{H}), 7.38$ - 7.26 (m, 5H), 4.29 (s, 2H).

These data are consistent with the previously reported characterization. ${ }^{16}$

## Preparation of 1-(4-chlorophenyl)-2-phenylethanone (4c)


$4 c$
The cross-coupling reaction of $\mathbf{3 c}$ ( 1 equiv, $249 \mathrm{mg}, 1 \mathrm{mmol}$ ) with $\mathbf{6 a}(1.5$ equiv, $1.83 \mathrm{~mL}, 1.5 \mathrm{mmol}, 0.82$ M in THF) was performed according to TP4 at room temperature in 1 h . The crude was purified silica gel chromatography (heptane: $\mathrm{EtOAc}=40: 1$ ) to afford $\mathbf{4 c}$ as a colorless oil $(226 \mathrm{mg}, 98 \%)$.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 8.13-7.84(\mathrm{~m}, 2 \mathrm{H}), 7.52-7.39(\mathrm{~m}, 2 \mathrm{H}), 7.39-7.21(\mathrm{~m}, 5 \mathrm{H}), 4.25(\mathrm{~s}$, 2 H ).
These data are consistent with the previously reported characterization. ${ }^{17}$

## Preparation of 1-(3-chlorophenyl)-2-phenylethanone (4d)



4d
The cross-coupling reaction of $\mathbf{3 d}$ ( 1 equiv, $249 \mathrm{mg}, 1 \mathrm{mmol}$ ) with $\mathbf{6 a}$ ( 1.5 equiv, $1.83 \mathrm{~mL}, 1.5 \mathrm{mmol}$, 0.82 M in THF) was performed according to TP4 at room temperature in 1 h . The crude was purified silica gel chromatography (heptane $: E t O A c=40: 1)$ to afford $\mathbf{4 d}$ as a white solid ( $224 \mathrm{mg}, 97 \%$ ).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.96(\mathrm{t}, \mathrm{J}=2.0 \mathrm{~Hz}, 1 \mathrm{H}), 7.86(\mathrm{dt}, \mathrm{J}=7.8,1.4 \mathrm{~Hz}, 1 \mathrm{H}), 7.54-7.47(\mathrm{~m}$, 1H), $7.41-7.19$ (m, 7H), 4.24 (s, 2H).

These data are consistent with the previously reported characterization. ${ }^{18}$

## Preparation of 1-(2-chlorophenyl)-2-phenylethanone (4e)



4e

The cross-coupling reaction of $\mathbf{3 e}$ ( 1 equiv, $249 \mathrm{mg}, 1 \mathrm{mmol}$ ) with $\mathbf{6 a}(1.5$ equiv, $1.83 \mathrm{~mL}, 1.5 \mathrm{mmol}, 0.82$ M in THF) was performed according to TP4 at room temperature in 1 h . The crude was purified silica gel chromatography (heptane:EtOAc $=25: 1$ ) to afford $\mathbf{4 e}$ as a colorless oil $(229 \mathrm{mg}, 99 \%)$.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.45-7.21$ (m, 9H), 4.26 ( $\mathrm{s}, 2 \mathrm{H}$ ).
These data are consistent with the previously reported characterization. ${ }^{19}$

## Preparation of 1-(2-bromophenyl)-2-phenylethanone (4f)


$4 f$
The cross-coupling reaction of $\mathbf{3 f}$ ( 1 equiv, $293 \mathrm{mg}, 1 \mathrm{mmol}$ ) with $\mathbf{6 a}(1.5$ equiv, $1.83 \mathrm{~mL}, 1.5 \mathrm{mmol}, 0.82$ M in THF) was performed according to TP4 at room temperature in 1 h . The crude was purified silica gel chromatography (heptane: $\mathrm{EtOAc}=25: 1$ ) to afford $\mathbf{4 f}$ as a colorless oil $(261 \mathrm{mg}, 95 \%)$.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.54(\mathrm{~d}, \mathrm{~J}=7.8 \mathrm{~Hz}, 1 \mathrm{H}), 7.29-7.19(\mathrm{~m}, 8 \mathrm{H}), 4.19(\mathrm{~s}, 2 \mathrm{H})$.
These data are consistent with the previously reported characterization. ${ }^{20}$

## Preparation of 1-(2-methoxyphenyl)-2-phenylethanone (4g)



4g
The cross-coupling reaction of $\mathbf{3 g}$ ( 1 equiv, $244 \mathrm{mg}, 1 \mathrm{mmol}$ ) with $\mathbf{6 a}$ ( 1.5 equiv, $1.83 \mathrm{~mL}, 1.5 \mathrm{mmol}$, 0.82 M in THF) was performed according to TP4 at room temperature in 1 h . The crude was purified silica gel chromatography (heptane: $\mathrm{EtOAc}=15: 1$ ) to afford $\mathbf{4 g}$ as a white solid ( $205 \mathrm{mg}, 91 \%$ ).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.68(\mathrm{dd}, \mathrm{J}=7.7,1.8 \mathrm{~Hz}, 1 \mathrm{H}), 7.46(\mathrm{td}, \mathrm{J}=8.7,7.4,1.9 \mathrm{~Hz}, 1 \mathrm{H}), 7.34-$ 7.21 (m, 5H), $7.02-6.94(\mathrm{~m}, 2 \mathrm{H}), 4.32(\mathrm{~s}, 2 \mathrm{H}), 3.92(\mathrm{~s}, 3 \mathrm{H})$.

These data are consistent with the previously reported characterization. ${ }^{21}$

## Preparation of 2-(2-phenylacetyl)benzonitrile (4h)



4h
The cross-coupling reaction of $\mathbf{3 h}$ ( 1 equiv, $239 \mathrm{mg}, 1 \mathrm{mmol}$ ) with $\mathbf{6 a}$ ( 1.5 equiv, $1.83 \mathrm{~mL}, 1.5 \mathrm{mmol}$, 0.82 M in THF) was performed according to TP4 at room temperature in 1 h . The crude was purified silica gel chromatography (heptane: $\mathrm{EtOAc}=40: 1$ ) to afford $\mathbf{4 h}$ as a yellow solid $(210 \mathrm{mg}, 95 \%)$.
${ }^{1} \mathrm{H}$ NMR ( $500 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.97-7.93(\mathrm{~m}, 1 \mathrm{H}), 7.83-7.79(\mathrm{~m}, 1 \mathrm{H}), 7.67(\mathrm{td}, \mathrm{J}=7.7,1.5 \mathrm{~Hz}, 1 \mathrm{H})$, 7.62 (td, J = 7.5, $1.4 \mathrm{~Hz}, 1 \mathrm{H}), 7.36-7.31(\mathrm{~m}, 2 \mathrm{H}), 7.29-7.25(\mathrm{~m}, 3 \mathrm{H}), 4.34(\mathrm{~s}, 2 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR (126 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 196.31,139.73,135.49,133.33,132.65,132.49,129.83,129.61,129.01$, 127.44, 118.10, 111.53, 46.91.

HRMS (ESI): m/z calcd. for $\mathrm{C}_{15} \mathrm{H}_{11} \mathrm{NO}[\mathrm{M}]^{+}: 221.0841$, found: 221.0829.

## Preparation of (2-nitrophenyl)(phenyl)methanone (4i)



4i
The cross-coupling reaction of $\mathbf{3 i}$ ( 1 equiv, $259 \mathrm{mg}, 1 \mathrm{mmol}$ ) with $\mathbf{6 b}$ ( 1.5 equiv, $3 \mathrm{~mL}, 1.5 \mathrm{mmol}, 0.5 \mathrm{M}$ in THF) was performed according to TP4 at $-10{ }^{\circ} \mathrm{C}$ in 3 h . The crude was purified silica gel chromatography (heptane: $\mathrm{EtOAc}=7: 1$ ) to afford $\mathbf{4 i}$ as a yellow solid ( $148 \mathrm{mg}, 65 \%$ ).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 8.22(\mathrm{~d}, \mathrm{~J}=8.3 \mathrm{~Hz}, 1 \mathrm{H}), 7.83-7.72(\mathrm{~m}, 3 \mathrm{H}), 7.67(\mathrm{t}, \mathrm{J}=7.9 \mathrm{~Hz}, 1 \mathrm{H})$, $7.58(\mathrm{t}, \mathrm{J}=7.4 \mathrm{~Hz}, 1 \mathrm{H}), 7.50-7.41(\mathrm{~m}, 3 \mathrm{H})$.

These data are consistent with the previously reported characterization. ${ }^{22}$

## Preparation of ethyl 2-(2-benzoylphenyl)acetate (4j)



4j
The cross-coupling reaction of $\mathbf{3 a}$ ( 1 equiv, $300 \mathrm{mg}, 1 \mathrm{mmol}$ ) with $\mathbf{6 b}$ ( 1.5 equiv, $3 \mathrm{~mL}, 1.5 \mathrm{mmol}, 0.5 \mathrm{M}$ in THF) was performed according to TP4 at room temperature in 1 h . The crude was purified silica gel chromatography (heptane: $\mathrm{EtOAc}=6: 1$ ) to afford $\mathbf{4 j}$ as a yellow oil $(255 \mathrm{mg}, 95 \%)$.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.82(\mathrm{~d}, \mathrm{~J}=7.8 \mathrm{~Hz}, 2 \mathrm{H}), 7.61-7.54(\mathrm{~m}, 1 \mathrm{H}), 7.51-7.42(\mathrm{~m}, 3 \mathrm{H}), 7.41$ - $7.30(\mathrm{~m}, 3 \mathrm{H}), 4.02(\mathrm{q}, \mathrm{J}=7.1 \mathrm{~Hz}, 2 \mathrm{H}), 3.89$ (s, 2H), 1.11 (t, J = 7.1 Hz, 3H).

These data are consistent with the previously reported characterization. ${ }^{23}$

Preparation of ethyl 2-(2-(2-(2-bromo-6-methoxy-4-methylphenyl)acetyl)-6methoxyphenyl)acetate ( 4 k )


4k

The cross-coupling reaction of $\mathbf{3 j}$ ( 1 equiv, $330 \mathrm{mg}, 1 \mathrm{mmol}$ ) with $\mathbf{6 c}$ ( 1.5 equiv, $2.63 \mathrm{~mL}, 1.5 \mathrm{mmol}, 0.57$ M in THF) was performed according to TP4 at room temperature in 1 h . the crude was purified silica gel chromatography (heptane: $\mathrm{EtOAc}=5: 1$ ) to afford $\mathbf{4 k}$ as a white solid $(357 \mathrm{mg}, 82 \%)$.
${ }^{1} \mathrm{H}^{2}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.35-7.33(\mathrm{~m}, 2 \mathrm{H}), 7.07-7.01(\mathrm{~m}, 2 \mathrm{H}), 6.66(\mathrm{~d}, \mathrm{~J}=1.4 \mathrm{~Hz}, 1 \mathrm{H}), 4.15$ (s, 2H), 4.13 (q, J = 7.1 Hz, 2H), 3.95 (s, 2H), 3.83 ( $\mathrm{s}, 3 \mathrm{H}$ ), 3.79 ( $\mathrm{s}, 3 \mathrm{H}$ ), 2.27 ( $\mathrm{s}, 3 \mathrm{H}$ ), 1.24 (t, J = 7.1 Hz, 3 H ).
${ }^{13} \mathrm{C}$ NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 201.27,171.89,158.34,139.44,133.90,128.04,125.77,125.65,125.56$, $123.11,120.62,113.93,110.76,60.70,56.11,55.91,47.91,31.40,15.57,14.37$.

HRMS (ESI): m/z calcd. for $\mathrm{C}_{21} \mathrm{H}_{23} \mathrm{BrO}_{5}[M]^{+}: 434.0729$, found: 434.0709.

## Preparation of adamantan-1-yl(benzofuran-2-yl)methanone (41)



## 41

The cross-coupling reaction of $\mathbf{3 k}$ ( 1 equiv, $254 \mathrm{mg}, 1 \mathrm{mmol}$ ) with $\mathbf{6 d}$ ( 1.5 equiv, $6.5 \mathrm{~mL}, 1.5 \mathrm{mmol}, 0.23$ M in THF) was performed according to TP4 at room temperature in 3 h . The crude was purified silica gel chromatography (heptane:EtOAc $=8: 1$ ) to afford $\mathbf{4 I}$ as a white solid ( $149 \mathrm{mg}, 53 \%$ ).
${ }^{1} \mathrm{H}$ NMR ( $500 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.29-7.14(\mathrm{~m}, 4 \mathrm{H}), 6.94-6.85(\mathrm{~m}, 1 \mathrm{H}), 1.97-1.30(\mathrm{~m}, 15 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $126 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 202.32,134.74,129.46,129.23,128.92,127.11,121.16,110.11,86.48$, 58.76, 43.75, 39.78, 39.19, 36.90, 36.30, 36.11, 30.11, 28.64, 28.40.

HRMS (ESI): m/z calcd. for $\mathrm{C}_{19} \mathrm{H}_{20} \mathrm{O}_{2}[\mathrm{M}]^{+}: 280.1463$, found: 280.1472 .

## Preparation of 2-([1,1'-biphenyl]-3-yl)-1-(quinolin-3-yl)ethanone (4m)



## 4m

The cross-coupling reaction of $\mathbf{3 1}$ ( 1 equiv, $265 \mathrm{mg}, 1 \mathrm{mmol}$ ) with $\mathbf{6 e}$ ( 1.5 equiv, $2.73 \mathrm{~mL}, 1.5 \mathrm{mmol}, 0.55$ M in THF) was performed according to TP4 at room temperature in 3 h . The crude was purified silica gel chromatography (heptane: $\mathrm{EtOAc}=2: 1$ ) to afford $\mathbf{4 m}$ as a yellow solid $(265 \mathrm{mg}, 82 \%)$.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 9.50(\mathrm{~d}, \mathrm{~J}=2.3 \mathrm{~Hz}, 1 \mathrm{H}), 8.80(\mathrm{~d}, \mathrm{~J}=1.8 \mathrm{~Hz}, 1 \mathrm{H}), 8.19-8.13(\mathrm{~m}, 1 \mathrm{H})$, 7.94 (dd, J = 8.2, $1.4 \mathrm{~Hz}, 1 \mathrm{H}$ ), 7.84 (dtd, J = 8.5, $6.9,1.5 \mathrm{~Hz}, 1 \mathrm{H}$ ), 7.63 (dtd, J = 8.1, 6.9, $1.2 \mathrm{~Hz}, 1 \mathrm{H}$ ), $7.59-7.54(\mathrm{~m}, 3 \mathrm{H}), 7.51(\mathrm{dt}, \mathrm{J}=7.7,1.5 \mathrm{~Hz}, 1 \mathrm{H}), 7.45-7.40(\mathrm{~m}, 3 \mathrm{H}), 7.37-7.29(\mathrm{~m}, 2 \mathrm{H}), 4.48(\mathrm{~s}, 2 \mathrm{H})$. ${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 196.40,149.98,149.56,142.11,140.94,137.80,134.38,132.23,129.64$, $129.55,129.43,129.03,128.89,128.45,128.44,127.73,127.57,127.35,127.03,126.26,46.15$.

HRMS (ESI): $\mathrm{m} / \mathrm{z}$ calcd. for $\mathrm{C}_{23} \mathrm{H}_{17} \mathrm{NO}[\mathrm{M}]^{+}: 323.1310$, found: 323.1295 .

## Preparation of (1H-indol-2-yl)(phenyl)methanone (4n)



4n
The cross-coupling reaction of $\mathbf{3 m}$ ( 1 equiv, $259 \mathrm{mg}, 1 \mathrm{mmol}$ ) with $\mathbf{6 b}$ ( 1.5 equiv, $3 \mathrm{~mL}, 1.5 \mathrm{mmol}, 0.5$ M in THF) was performed according to TP4 at room temperature in 1 h . The crude was purified silica gel chromatography (heptane: $\mathrm{EtOAc}=6: 1$ ) to afford $\mathbf{4 n}$ as a white solid ( $210 \mathrm{mg}, 95 \%$ ).
${ }^{1}{ }^{H}$ NMR ( 400 MHz, DMSO-d ${ }_{6}$ ): $\delta 11.99$ (s, 1H), $7.98-7.90(\mathrm{~m}, 2 \mathrm{H}), 7.74-7.64$ (m, 2H), $7.62-7.50$ (m, 3H), 7.32 (dtd, J = 8.3, 6.9, 1.2 Hz, 1H), $7.16-7.07(\mathrm{~m}, 2 \mathrm{H})$.

These data are consistent with the previously reported characterization. ${ }^{24}$

## Preparation of furan-3-yl(phenyl)methanone (40)



40
The cross-coupling reaction of $\mathbf{3 n}$ ( 1 equiv, $204 \mathrm{mg}, 1 \mathrm{mmol}$ ) with $\mathbf{6 b}$ ( 1.5 equiv, $3 \mathrm{~mL}, 1.5 \mathrm{mmol}, 0.5 \mathrm{M}$ in THF) was performed according to TP4 at room temperature in 1 h . The crude was purified silica gel chromatography (heptane: $\mathrm{EtOAc}=8: 1$ ) to afford 40 as a colorless oil $(160 \mathrm{mg}, 93 \%)$.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.91(\mathrm{dd}, \mathrm{J}=1.4,0.9 \mathrm{~Hz}, 1 \mathrm{H}), 7.87-7.81(\mathrm{~m}, 2 \mathrm{H}), 7.61-7.53(\mathrm{~m}, 1 \mathrm{H})$, $7.50-7.44$ (m, 3H), 6.90 (dd, J = 1.9, $0.8 \mathrm{~Hz}, 1 \mathrm{H}$ ).
These data are consistent with the previously reported characterization. ${ }^{25}$

## Preparation of 1-(4-methylthiazol-5-yl)-2-(naphthalen-2-yl)ethanone (4p)



4p
The cross-coupling reaction of $\mathbf{3 o}$ ( 1 equiv, $235 \mathrm{mg}, 1 \mathrm{mmol}$ ) with $\mathbf{6 f}(1.5$ equiv, $2.54 \mathrm{~mL}, 1.5 \mathrm{mmol}, 0.59$ M in THF) was performed according to TP4 at room temperature in 1 h . The crude was purified silica gel chromatography (heptane: $\mathrm{EtOAc}=4: 1$ ) to afford $\mathbf{4 p}$ as a white solid ( $205 \mathrm{mg}, 77 \%$ ).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 8.93(\mathrm{~s}, 1 \mathrm{H}), 7.90-7.71(\mathrm{~m}, 4 \mathrm{H}), 7.52-7.46(\mathrm{~m}, 2 \mathrm{H}), 7.38(\mathrm{dd}, \mathrm{J}=8.4$, $1.8 \mathrm{~Hz}, 1 \mathrm{H}), 4.31$ (s, 2H), $2.80(\mathrm{~s}, 3 \mathrm{H})$.

[^4]
## Preparation of phenyl(pyridin-3-yl)methanone (4q)


$4 q$
The cross-coupling reaction of $\mathbf{3 b}$ ( 1 equiv, $214 \mathrm{mg}, 1 \mathrm{mmol}$ ) with $\mathbf{6 g}$ ( 1.5 equiv, $5 \mathrm{~mL}, 1.5 \mathrm{mmol}, 0.3 \mathrm{M}$ in THF) was performed according to TP4 at room temperature in 3 h . The crude was purified silica gel chromatography (heptane: $\mathrm{EtOAc}=2: 1$ ) to afford $\mathbf{4 q}$ as a colorless oil $(161 \mathrm{mg}, 88 \%)$.
${ }^{1} \mathrm{H}^{\mathrm{N}} \mathrm{NRR}\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right): \delta 8.99(\mathrm{~s}, 1 \mathrm{H}), 8.87-8.76(\mathrm{~m}, 1 \mathrm{H}), 8.11(\mathrm{dt}, \mathrm{J}=7.9,2.0 \mathrm{~Hz}, 1 \mathrm{H}), 7.85-$ 7.78 (m, 2H), $7.66-7.60(\mathrm{~m}, 1 \mathrm{H}), 7.56-7.48(\mathrm{~m}, 2 \mathrm{H}), 7.44$ (dd, J = 7.7, $4.9 \mathrm{~Hz}, 1 \mathrm{H})$.

These data are consistent with the previously reported characterization. ${ }^{26}$

## Preparation of di(pyridin-3-yl)methanone (4r)



4 r
The cross-coupling reaction of $\mathbf{3 p}$ ( 1 equiv, $215 \mathrm{mg}, 1 \mathrm{mmol}$ ) with $\mathbf{6 g}$ ( 1.5 equiv, $5 \mathrm{~mL}, 1.5 \mathrm{mmol}, 0.3 \mathrm{M}$ in THF) was performed according to TP4 at room temperature in 3 h . The crude was purified silica gel chromatography ( $\mathrm{DCM}: \mathrm{MeOH}=30: 1$ ) to afford $\mathbf{4 r}$ as a white solid ( $136 \mathrm{mg}, 74 \%$ ).
${ }^{1} \mathrm{H}$ NMR ( 400 MHz , Methanol-d4): $\delta 8.96$ (dd, J $=2.2,0.9 \mathrm{~Hz}, 2 \mathrm{H}$ ), 8.82 (dd, J = 5.0, $1.7 \mathrm{~Hz}, 2 \mathrm{H}$ ), 8.29 -8.22 (m, 2H), 7.68-7.61 (m, 2H).

These data are consistent with the previously reported characterization. ${ }^{27}$

## Preparation of 1-(naphthalen-2-yl)-3-(p-tolyl)propan-2-one (4s)



4s
The cross-coupling reaction of $\mathbf{3 q}$ ( 1 equiv, $242 \mathrm{mg}, 1 \mathrm{mmol}$ ) with $\mathbf{6 f}(1.5$ equiv, $2.54 \mathrm{~mL}, 1.5 \mathrm{mmol}, 0.59$ M in THF) was performed according to TP4 at room temperature in 1 h . The crude was purified silica gel chromatography (heptane:EtOAc $=10: 1$ ) to afford 4 s as a yellow solid $(236 \mathrm{mg}, 86 \%)$.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.88-7.76(\mathrm{~m}, 3 \mathrm{H}), 7.65-7.59(\mathrm{~m}, 1 \mathrm{H}), 7.54-7.43(\mathrm{~m}, 2 \mathrm{H}), 7.29(\mathrm{dd}$, $\mathrm{J}=8.4,1.8 \mathrm{~Hz}, 1 \mathrm{H}), 7.19-7.04(\mathrm{~m}, 4 \mathrm{H}), 3.89(\mathrm{~s}, 2 \mathrm{H}), 3.73(\mathrm{~s}, 2 \mathrm{H}), 2.36(\mathrm{~s}, 3 \mathrm{H})$.

[^5]
## Preparation of ethyl 4-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-oxobutanoate (4t)

$\xrightarrow{\mathrm{Fmoc}}{ }^{\mathrm{O}}$

## $4 t$

The cross-coupling reaction of $\mathbf{3 r}$ ( 1 equiv, $390 \mathrm{mg}, 1 \mathrm{mmol}$ ) with $\mathbf{6 h}$ ( 1.5 equiv, $2.03 \mathrm{~mL}, 1.5 \mathrm{mmol}$, 0.74 M in THF) was performed according to TP4 at room temperature for 2 h . The crude was purified silica gel chromatography (heptane: $\mathrm{EtOAc}=3: 1$ ) to afford $\mathbf{4 t}$ as a yellow solid ( $320 \mathrm{mg}, 87 \%$ ).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.77(\mathrm{~d}, \mathrm{~J}=7.5 \mathrm{~Hz}, 2 \mathrm{H}), 7.60(\mathrm{~d}, \mathrm{~J}=7.4 \mathrm{~Hz}, 2 \mathrm{H}), 7.40(\mathrm{t}, \mathrm{J}=7.3 \mathrm{~Hz}, 2 \mathrm{H})$, $7.34-7.29(\mathrm{~m}, 2 \mathrm{H}), 5.47(\mathrm{~s}, 1 \mathrm{H}), 4.41(\mathrm{~d}, \mathrm{~J}=7.0 \mathrm{~Hz}, 2 \mathrm{H}), 4.25-4.18(\mathrm{~m}, 5 \mathrm{H}), 3.49(\mathrm{~s}, 2 \mathrm{H}), 1.30(\mathrm{~d}, \mathrm{~J}=$ 7.1 Hz, 3H).

These data are consistent with the previously reported characterization. ${ }^{28}$

## Preparation of (9H-fluoren-9-yl)methyl (3-methyl-2-oxobut-3-en-1-yl)carbamate (4u)



4u
The cross-coupling reaction of $\mathbf{3 r}$ ( 1 equiv, $390 \mathrm{mg}, 1 \mathrm{mmol}$ ) with $\mathbf{6 i}$ ( 1.5 equiv, $4.55 \mathrm{~mL}, 1.5 \mathrm{mmol}, 0.33$ M in THF) was performed according to TP4 at room temperature for 1 h . The crude was purified silica gel chromatography (heptane: $\mathrm{EtOAc}=6: 1$ ) to afford $\mathbf{4 u}$ as a yellow solid $(286 \mathrm{mg}, 89 \%)$.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.77(\mathrm{~d}, \mathrm{~J}=7.5 \mathrm{~Hz}, 2 \mathrm{H}), 7.62(\mathrm{~d}, \mathrm{~J}=7.5 \mathrm{~Hz}, 2 \mathrm{H}), 7.43-7.38(\mathrm{~m}, 2 \mathrm{H})$, $7.35-7.29$ (m, 2H), 6.03 (s, 1H), 5.87 ( $\mathrm{s}, 1 \mathrm{H}$ ), 5.69 ( $\mathrm{s}, 1 \mathrm{H}$ ), 4.45 (d, J = $4.5 \mathrm{~Hz}, 2 \mathrm{H}$ ), 4.40 (d, J = 7.2 Hz , $2 \mathrm{H}), 4.25(\mathrm{t}, \mathrm{J}=7.2 \mathrm{~Hz}, 1 \mathrm{H}), 1.94$ ( $\mathrm{s}, 3 \mathrm{H}$ ).
${ }^{13} \mathrm{C}$ NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta$ 195.66, 156.34, 144.01, 142.38, 141.43, 127.82, 127.19, 125.83, 125.23, 120.09, 77.48, 77.16, 76.84, 67.28, 47.31, 47.07, 17.48.

HRMS (ESI): m/z calcd. for $\mathrm{C}_{20} \mathrm{H}_{19} \mathrm{NO}_{3}[\mathrm{M}]^{+}: 321.1365$, found: 321.1361.

Preparation of (9H-fluoren-9-yl)methyl (2-(3,4-dichlorophenyl)-2-oxoethyl)carbamate (4v)


4v

The cross-coupling reaction of $\mathbf{3 r}$ ( 1 equiv, $390 \mathrm{mg}, 1 \mathrm{mmol}$ ) with $\mathbf{6 j}$ ( 1.5 equiv, $3.49 \mathrm{~mL}, 1.5 \mathrm{mmol}, 0.43$ M in THF) was performed according to TP4 at room temperature in 1 h . The crude was purified silica gel chromatography (heptane: $\mathrm{EtOAc}=5: 1$ ) to afford $\mathbf{4 v}$ as a white solid ( $358 \mathrm{mg}, 84 \%$ ).
${ }^{1} \mathrm{H}^{\mathrm{NMR}}\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right): \delta 8.06(\mathrm{~d}, \mathrm{~J}=2.0 \mathrm{~Hz}, 1 \mathrm{H}), 7.81-7.75(\mathrm{~m}, 3 \mathrm{H}), 7.65-7.59(\mathrm{~m}, 3 \mathrm{H}), 7.41(\mathrm{t}$, $\mathrm{J}=7.3 \mathrm{~Hz}, 2 \mathrm{H}), 7.33(\mathrm{t}, \mathrm{J}=7.3 \mathrm{~Hz}, 2 \mathrm{H}), 5.75(\mathrm{~s}, 1 \mathrm{H}), 4.69(\mathrm{~d}, \mathrm{~J}=4.6 \mathrm{~Hz}, 2 \mathrm{H}), 4.44(\mathrm{~d}, \mathrm{~J}=7.1 \mathrm{~Hz}, 2 \mathrm{H})$, $4.26(\mathrm{t}, \mathrm{J}=7.0 \mathrm{~Hz}, 1 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 192.29,156.35,143.97,141.51,138.99,134.06,134.03,131.26,130.06$, 127.91, 127.26, 126.94, 125.23, 120.16, 67.48, 48.06, 47.36.

HRMS (ESI): m/z calcd. for $\mathrm{C}_{23} \mathrm{H}_{17} \mathrm{Cl}_{2} \mathrm{NO}_{3}[\mathrm{M}]^{+}: 425.0585$, found: 425.0564 .

Preparation of (S)-tert-butyl 2-benzoylpyrrolidine-1-carboxylate (4w)


## 4w

The cross-coupling reaction of $\mathbf{3 s}$ ( 1 equiv, $307 \mathrm{mg}, 1 \mathrm{mmol}$ ) with $\mathbf{6 b}$ ( 1.5 equiv, $3 \mathrm{~mL}, 1.5 \mathrm{mmol}, 0.5 \mathrm{M}$ in THF) was performed according to TP4 at room temperature in 1 h . The crude was purified silica gel chromatography (heptane: $\mathrm{EtOAc}=15: 1$ ) to afford $\mathbf{4 w}$ as a white solid $(242 \mathrm{mg}, 88 \%)$.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 8.01-7.90(\mathrm{~m}, 2 \mathrm{H}), 7.60-7.51(\mathrm{~m}, 1 \mathrm{H}), 7.50-7.39(\mathrm{~m}, 2 \mathrm{H}), 5.32(\mathrm{dd}$, $\mathrm{J}=9.3,2.9 \mathrm{~Hz}, 0.4 \mathrm{H}$ ), $5.18(\mathrm{dd}, \mathrm{J}=8.7,3.7 \mathrm{~Hz}, 0.6 \mathrm{H}), 3.73-3.41(\mathrm{~m}, 2 \mathrm{H}), 2.42-2.19(\mathrm{~m}, 1 \mathrm{H}), 2.01-$ $1.85(\mathrm{~m}, 3 \mathrm{H}), 1.45(\mathrm{~s}, 3.5 \mathrm{H}), 1.25(\mathrm{~s}, 5.5 \mathrm{H})$.
These data are consistent with the previously reported characterization. ${ }^{29}$

## V. Generation of POxAPs with the Addition of PhOH

(A) An oven-dried 20 mL microwave vial equipped with a magnetic stirrer was charged with phenol ( 1 equiv, 13.4 mg , $0.14 \mathrm{mmol}), \mathrm{PdCl}_{2}\left(\mathrm{PPh}_{3}\right)_{2}$ ( 1 equiv, $100 \mathrm{mg}, 0.14 \mathrm{mmol}$ ), THF $(2 \mathrm{~mL})$ and toluene $(2 \mathrm{~mL})$. The vial was properly sealed and the mixture vessel was evacuated and backfilled with argon thrice. After stirring for $1 \mathrm{~h}, 0.5 \mathrm{~mL}$ of the reaction mixture was transferred into an argon-prefilled NMR tube by syringe and the solvent was removed under high vacuum. The NMR tube was then backfilled with argon and $0.5 \mathrm{~mL} \mathrm{CDCl}_{3}$ was added. ${ }^{1} \mathrm{H}$ NMR of this crude showed phenol did not react with $\mathrm{PdCl}_{2}\left(\mathrm{PPh}_{3}\right)_{2}$ in the absence of organozinc reagent (Figure S2 A).
(B) An oven-dried 20 mL microwave tube equipped with a magnetic stirrer was charged with phenol ( 1 equiv, 13.4 mg , 0.14 mmol ), $\mathrm{PdCl}_{2}\left(\mathrm{PPh}_{3}\right)_{2}$ ( 1 equiv, $100 \mathrm{mg}, 0.14 \mathrm{mmol}$ ), THF $(2 \mathrm{~mL})$, toluene $(2 \mathrm{~mL})$ and sealed. The vial was properly sealed and the mixture vessel was evacuated and backfilled with argon thrice. $6 \mathbf{a}$ ( 1 equiv $0.17 \mathrm{~mL}, 0.14 \mathrm{mmol}, 0.82 \mathrm{M}$ in THF) was added dropwise to the mixture at room temperature. After stirring for $1 \mathrm{~h}, 0.5 \mathrm{~mL}$ of the reaction mixture was transferred

(C) $\mathrm{PdCl}(\mathrm{Ph})\left(\mathrm{PPh}_{3}\right)_{2}$


10

Figure S2. Generation of POxAPs with PhOH and BnZnBr into an argon-prefilled NMR tube by syringe and the solvent was removed under high vacuum. The NMR tube was then backfilled with argon and $0.5 \mathrm{~mL} \mathrm{CDCl}_{3}$ was added. ${ }^{1} \mathrm{H}$ NMR of this crude showed the formation of a new compound compared to the control group (Figure S2 B).
(C) The rest of the forementioned reaction mixture was concentrated in vacuo. Toluene ( 5 mL ) was added to the crude and cooled to $0^{\circ} \mathrm{C}$. The suspension was filtered. The filtrate was evaporated to dryness, the resulting product was washed with ether $(2 \times 5 \mathrm{~mL})$ and dried under reduced pressure. Recrystallization from a $\mathrm{CHCl}_{3}-\mathrm{Et}_{2} \mathrm{O}$ solution at room temperature gave yellow crystals ( $11.5 \mathrm{mg}, 11 \%$ ). The ${ }^{1} \mathrm{H}$ NMR and X-ray crystallography results were consistent with the previously reported data, indicating that the identity of these crystals was $\mathrm{PdCl}(\mathrm{Ph})\left(\mathrm{PPh}_{3}\right)_{2}$ (Figure $\mathbf{S 2} \mathbf{C}$ ).

## VI. Synthesis of the unsubstituted IPK precursor 9a



## Preparation of 2-(2-ethoxy-2-oxoethyl)benzoic acid (2a)



2a
To a dry flask filled with Ar was added EtONa (3 equiv, $1.52 \mathrm{~g}, 22.4 \mathrm{mmol}$ ) and anhydrous EtOH (30 mL ). The suspension was sonicated until it became a clear solution. Ethyl acetoacetate ( 2 equiv, 1.89 mL , 14.9 mmol ) was added and the mixture was stirred at room temperature for 10 min . Then, $\mathrm{CuBr}(0.1 \mathrm{eq}$., $107 \mathrm{mg}, 0.75 \mathrm{mmol}$ ) and 2-bromo-3-methoxybenzoic acid ( 1 equiv, $1.5 \mathrm{~g}, 7.46 \mathrm{mmol}$ ) were added and the reaction mixture was reflux under Ar at $80^{\circ} \mathrm{C}$ for 16 h . After completion, the reaction mixture was concentrated in vacuo, then acidified by $1 \mathrm{~N} \mathrm{HCl}(50 \mathrm{~mL})$ and extracted with $\mathrm{EtOAc}(3 \times 20 \mathrm{~mL})$. The combined organic phase was washed with brine, dried over anhydrous $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and filtered through a celite pad. The filtrate was concentrated in vacuo to afford $\mathbf{2 a}$ as a white solid ( $1.52 \mathrm{~g}, 98 \%$ ).
${ }^{1}{ }^{H} \mathrm{NMR}\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right): \delta 8.13(\mathrm{~d}, \mathrm{~J}=7.8 \mathrm{~Hz}, 1 \mathrm{H}), 7.54(\mathrm{t}, \mathrm{J}=7.5 \mathrm{~Hz}, 1 \mathrm{H}), 7.40(\mathrm{t}, \mathrm{J}=7.6 \mathrm{~Hz}, 1 \mathrm{H})$, $7.28(\mathrm{~d}, \mathrm{~J}=7.6 \mathrm{~Hz}, 1 \mathrm{H}), 4.17(\mathrm{q}, \mathrm{J}=7.1 \mathrm{~Hz}, 2 \mathrm{H}), 4.04(\mathrm{~s}, 2 \mathrm{H}), 1.26(\mathrm{t}, \mathrm{J}=7.1 \mathrm{~Hz}, 3 \mathrm{H})$.
These data are consistent with the previously reported characterization. ${ }^{30}$

## Preparation of 3a, BnZnBr and 4a see Part IV. POxAPs Catalyzed Fuyayama Cross-Coupling Reactions.

## Preparation of 2-phenylnaphthalene-1,3-diol (5a)



5a
The solution of 3a (1 equiv, $50 \mathrm{mg}, 0.17 \mathrm{mmol})$ and $\mathrm{PdCl}_{2}\left(\mathrm{PPh}_{3}\right)_{2}\left(1 \mathrm{~mol} \%, 1.2 \mathrm{mg}, 1.7 \times 10^{-3} \mathrm{mmol}\right)$ in toluene ( 0.3 mL ) was degassed and backfilled with argon thrice. Then, a solution of benzyl zinc bromide 6a ( 1.5 equiv, $0.3 \mathrm{~mL}, 0.25 \mathrm{mmol}, 0.82 \mathrm{M}$ in THF ) in THF was added dropwise at room temperature.

After stirring at $50^{\circ} \mathrm{C}$ for 15 min , the reaction mixture was quenched with saturated $\mathrm{NH}_{4} \mathrm{Cl}$ solution ( 5 mL ) and extracted with EtOAc ( 5 mL ) thrice. The combined organic phases were dried over anhydrous $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and concentrated in vacuo. The crude was purified by silica gel column (heptane:EtOAc $=3: 1$ ) to afford $5 \mathbf{5}$ as an yellow solid ( $24.9 \mathrm{mg}, 62 \%$ ), along with $8.1 \mathrm{mg} \mathbf{3 a}$ and $10.7 \mathrm{mg} \mathbf{4 a}$.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 8.14(\mathrm{~d}, \mathrm{~J}=8.3 \mathrm{~Hz}, 1 \mathrm{H}), 7.70-7.60(\mathrm{~m}, 3 \mathrm{H}), 7.55-7.43(\mathrm{~m}, 4 \mathrm{H}), 7.34$ (t, J = 7.6 Hz, 1H), $6.96(\mathrm{~s}, 1 \mathrm{H}), 5.45(\mathrm{~s}, 1 \mathrm{H}), 4.89(\mathrm{~s}, 1 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 151.08$, 149.29, 134.74, 131.29, 131.06, 130.57, 129.59, 127.39, 126.30, 123.19, 122.62, 119.82, 113.43, 102.34.

HRMS (ESI): m/z calcd. for $\mathrm{C}_{16} \mathrm{H}_{12} \mathrm{O}_{2}[\mathrm{M}]^{+}: 236.0837$, found: 236.0839

## Preparation of ethyl 2-(2-(2-oxo-2-phenylacetyl)phenyl)acetate (8a)



8a
A solution of $\mathbf{4 a}$ ( 1 equiv, $200 \mathrm{mg}, 0.71 \mathrm{mmol}$ ) and $\mathrm{SeO}_{2}$ ( 2 equiv, $157 \mathrm{mg}, 1.42 \mathrm{mmol}$ ) in acetic acid ( 5 mL ) was stirred at $100^{\circ} \mathrm{C}$ for 2 h . The reaction mixture was filtered through a silica gel pad with EtOAc, the filtrate was concentrated in vacuo to afford $\mathbf{8 a}$ as a yellow solid ( $206 \mathrm{mg}, 98 \%$ ).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 8.03-7.90(\mathrm{~m}, 2 \mathrm{H}), 7.70(\mathrm{~d}, \mathrm{~J}=7.8 \mathrm{~Hz}, 1 \mathrm{H}), 7.64(\mathrm{t}, \mathrm{J}=7.4 \mathrm{~Hz}, 1 \mathrm{H})$, $7.61-7.55(\mathrm{~m}, 1 \mathrm{H}), 7.51(\mathrm{t}, \mathrm{J}=7.7 \mathrm{~Hz}, 2 \mathrm{H}), 7.38(\mathrm{t}, \mathrm{J}=6.9 \mathrm{~Hz}, 2 \mathrm{H}), 4.21(\mathrm{q}, \mathrm{J}=7.1 \mathrm{~Hz}, 2 \mathrm{H}), 4.13(\mathrm{~s}$, 2H), 1.29 ( $\mathrm{t}, \mathrm{J}=7.1 \mathrm{~Hz}, 3 \mathrm{H}$ ).
${ }^{13} \mathrm{C}$ NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 196.87$, 194.50, 171.19, 136.99, 134.89, 134.29, 133.97, 133.42, 133.27, 131.66, 130.19, 129.12, 127.78, 61.07, 40.72, 14.38.

HRMS (ESI): m/z calcd. for $\mathrm{C}_{18} \mathrm{H}_{16} \mathrm{O}_{4}[\mathrm{M}]^{+}: 296.1049$, found: 296.1044.

## Preparation of ethyl 1-oxo-2-phenyl-1H-indene-3-carboxylate (9a)



9a
A solution of $\mathbf{8 a}$ ( 1 equiv, $200 \mathrm{mg}, 0.68 \mathrm{mmol}$ ) and TEA ( 5 equiv, $0.47 \mathrm{~mL}, 3.37 \mathrm{mmol}$ ) in anhydrous $\mathrm{EtOH}(5 \mathrm{~mL})$ was stirred at $100^{\circ} \mathrm{C}$ for 5 h . The mixture was concentrated in vacuo and purified by silica gel column (Heptane:EtOAc=15:1) to afford 9a as an orange solid ( $179 \mathrm{mg}, 95 \%$ ).
${ }^{1} \mathrm{H}^{\mathrm{NMR}}\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right): \delta 7.56(\mathrm{dd}, \mathrm{J}=12.6,7.3 \mathrm{~Hz}, 2 \mathrm{H}), 7.49-7.38(\mathrm{~m}, 6 \mathrm{H}), 7.29(\mathrm{t}, \mathrm{J}=7.4 \mathrm{~Hz}$, $1 \mathrm{H}), 4.32(\mathrm{q}, \mathrm{J}=7.1 \mathrm{~Hz}, 2 \mathrm{H}), 1.23(\mathrm{t}, \mathrm{J}=7.1 \mathrm{~Hz}, 3 \mathrm{H})$.

These data are consistent with the previously reported characterization. ${ }^{31}$

## VII. Synthesis of IPK precursor 1



Preparation of 2-(2-ethoxy-2-oxoethyl)-3-methoxybenzoic acid (2b)


2b
To an oven-dried flask filled with Argon was added EtONa (3 equiv, $1.33 \mathrm{~g}, 19.5 \mathrm{mmol}$ ) and anhydrous $\mathrm{EtOH}(25 \mathrm{~mL})$. The suspension was sonicated until it became a clear solution. Ethyl acetoacetate ( 2 equiv, $1.64 \mathrm{~mL}, 13 \mathrm{mmol}$ ) was added and the mixture was stirred at room temperature for 10 min . Then, CuBr ( 0.1 eq., $93.1 \mathrm{mg}, 0.65 \mathrm{mmol}$ ) and 2-bromo-3-methoxybenzoic acid ( 1 equiv, $1.5 \mathrm{~g}, 6.49 \mathrm{mmol}$ ) were added and the reaction mixture was reflux under Ar at $80^{\circ} \mathrm{C}$ for 16 h . After completion, the reaction mixture was concentrated in vacuo, then acidified by $1 \mathrm{~N} \mathrm{HCl}(50 \mathrm{~mL})$ and extracted with $\mathrm{EtOAc}(3 \times 20$ mL ). The combined organic phase was washed with brine, dried over anhydrous $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and filtered through a celite pad. The filtrate was concentrated in vacuo to afford $\mathbf{2 b}$ as a white solid ( $1.45 \mathrm{~g}, 94 \%$ ). ${ }^{1} \mathrm{H}^{2} \mathrm{NMR}\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right): \delta 7.69(\mathrm{~d}, \mathrm{~J}=7.8 \mathrm{~Hz}, 1 \mathrm{H}), 7.34(\mathrm{t}, \mathrm{J}=8.1 \mathrm{~Hz}, 1 \mathrm{H}), 7.11(\mathrm{~d}, \mathrm{~J}=8.2 \mathrm{~Hz}, 1 \mathrm{H})$, $4.20-4.13(\mathrm{~d}, \mathrm{~J}=6.9 \mathrm{~Hz}, 4 \mathrm{H}), 3.85(\mathrm{~s}, 3 \mathrm{H}), 1.26(\mathrm{t}, \mathrm{J}=7.1 \mathrm{~Hz}, 3 \mathrm{H})$.

These data are consistent with the previously reported characterization. ${ }^{32}$

## Preparation of 3j, 6c and 4 k see Part IV. POxAPs Catalyzed Fuyayama Cross-Coupling

## Reactions.

## Preparation of 2-(2-bromo-6-methoxy-4-methylphenyl)-3-hydroxy-5-methoxynaphthalene-1,4dione (5b)



5b
The solution of $\mathbf{3 j}$ ( 1 equiv, $50 \mathrm{mg}, 0.15 \mathrm{mmol}$ ) and $\mathrm{PdCl}_{2}\left(\mathrm{PPh}_{3}\right)_{2}\left(1 \mathrm{~mol} \%, 1.1 \mathrm{mg}, 1.5 \times 10^{-3} \mathrm{mmol}\right)$ in toluene ( 0.4 mL ) was degassed and backfilled with argon thrice. Then, a solution of $\mathbf{6 c}(1.5$ equiv, 0.4 $\mathrm{mL}, 0.23 \mathrm{mmol}, 0.57 \mathrm{M}$ in THF) in THF was added dropwise at room temperature. After stirring at $50^{\circ} \mathrm{C}$ for 25 min , the reaction mixture was quenched with saturated $\mathrm{NH}_{4} \mathrm{Cl}$ solution ( 5 mL ) and extracted with EtOAc ( 5 mL ) thrice. The combined organic phases were dried over anhydrous $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and concentrated in vacuo. The crude was purified by silica gel column (heptane:EtOAc $=1: 1$ ) to afford $\mathbf{5 b}$ as a red solid ( $44 \mathrm{mg}, 72 \%$ ), along with $9.2 \mathrm{mg} \mathbf{3 j}$ and $5.2 \mathrm{mg} \mathbf{4 k}$.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.86(\mathrm{~d}, \mathrm{~J}=7.1 \mathrm{~Hz}, 1 \mathrm{H}), 7.73(\mathrm{t}, \mathrm{J}=8.1 \mathrm{~Hz}, 1 \mathrm{H}), 7.28(\mathrm{~d}, \mathrm{~J}=8.4 \mathrm{~Hz}, 1 \mathrm{H})$, $7.12(\mathrm{~s}, 1 \mathrm{H}), 6.73(\mathrm{~s}, 1 \mathrm{H}), 4.06(\mathrm{~s}, 3 \mathrm{H}), 3.72(\mathrm{~s}, 3 \mathrm{H}), 2.36(\mathrm{~s}, 3 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 182.40,179.99,160.46,158.11,153.74,141.36,136.68,135.54,125.40$, 124.57, 120.27, 118.66, 118.19, 117.40, 116.89, 111.20, 56.70, 56.23, 21.65.

HRMS (ESI): m/z calcd. for $\mathrm{C}_{19} \mathrm{H}_{15} \mathrm{BrO}_{5}[\mathrm{M}]^{+}: 402.0103$, found: 402.0086

## Preparation of ethyl 2-(2-(2-(2-bromo-6-methoxy-4-methylphenyl)-2-oxoacetyl)-6methoxyphenyl)acetate ( 8 b )



## 8b

A solution of $\mathbf{4 k}$ ( 1 equiv, $300 \mathrm{mg}, 0.69 \mathrm{mmol}$ ) and $\mathrm{SeO}_{2}$ ( 2 equiv, $152 \mathrm{mg}, 1.38 \mathrm{mmol}$ ) in acetic acid ( 5 mL ) was stirred at $100^{\circ} \mathrm{C}$ for 2 h . The reaction mixture was filtered through a silica gel pad with EtOAc, the filtrate was concentrated in vacuo to afford $\mathbf{8 b}$ as a yellow solid ( $304 \mathrm{mg}, 98 \%$ ).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 7.45(\mathrm{dd}, \mathrm{J}=7.9,1.1 \mathrm{~Hz}, 1 \mathrm{H}), 7.37(\mathrm{t}, \mathrm{J}=8.0 \mathrm{~Hz}, 1 \mathrm{H}), 7.18-7.09(\mathrm{~m}$, 2H), 6.68
$(\mathrm{s}, 1 \mathrm{H}), 4.13(\mathrm{q}, \mathrm{J}=7.1 \mathrm{~Hz}, 2 \mathrm{H}), 4.07(\mathrm{~s}, 2 \mathrm{H}), 3.87(\mathrm{~s}, 3 \mathrm{H}), 3.61(\mathrm{~s}, 3 \mathrm{H}), 2.36(\mathrm{~s}, 3 \mathrm{H}), 1.23(\mathrm{t}, \mathrm{J}=7.1 \mathrm{~Hz}$, 3 H ).
${ }^{13} \mathrm{C}$ NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 192.14,171.45,160.42,158.49,145.31,132.68,127.71,127.70,125.95$, 125.16, 123.52, 122.66, 115.37, 111.81, 60.63, 56.23, 56.21, 32.08, 21.86, 14.38.

HRMS (ESI): m/z calcd. for $\mathrm{C}_{21} \mathrm{H}_{21} \mathrm{BrO}_{6}[\mathrm{M}]^{+}: 448.0522$, found: 448.0495 .

## Preparation of ethyl 2-(2-bromo-6-methoxy-4-methylphenyl)-4-methoxy-1-oxo-1H-indene-3carboxylate (9b)

Several conditions were tried for the preparation of $\mathbf{9 b}$ from $\mathbf{8 b}$ (Table S2). With TEA/EtOH, which was used in the synthesis of $\mathbf{9 a}$, we did not obtain $\mathbf{9 b}$, but $\mathbf{9 c}$ in $94 \%$ yield (Table S2, entry 1). With the addition of PTSA or DBU to $\mathbf{9 c}$ no formation of $9 \mathbf{b}$ was observed (Table S2, entries 2 and 3). Strong bases such as EtONa or NaH produced a mixture of $\mathbf{9 c}$ and $9 \mathbf{d}$ (Table S2, entries 4 and 5). Finally, DBU in hot DMSO were tried and furnished 9b in $94 \%$ yield.

Table S2. Cyclization of 8b


| Entry | Conditions | 9b (\%) | 9c (\%) | 9d (\%) |
| :---: | :---: | :--- | :--- | :--- |
| $\mathbf{1}$ | $\mathrm{TEA}, \mathrm{EtOH}, 100^{\circ} \mathrm{C}$ | 0 | 94 | 0 |
| $\mathbf{2}$ | $(1) \mathrm{TEA}, \mathrm{EtOH}, 100^{\circ} \mathrm{C} ;(2) \mathrm{PTSA}$, toluene or $\mathrm{EtOH}, 100{ }^{\circ} \mathrm{C}$ | 0 | 92 | 0 |
| $\mathbf{3}$ | $(1) \mathrm{TEA}, \mathrm{EtOH}, 100^{\circ} \mathrm{C} ;(2) \mathrm{DBU}$, toluene, $80^{\circ} \mathrm{C}$ | 0 | 96 | 0 |
| $\mathbf{4}$ | $\mathrm{EtONa}, \mathrm{EtOH}, 100^{\circ} \mathrm{C}$ | 0 | 73 | 13 |
| $\mathbf{5}$ | $\mathrm{NaH}, \mathrm{THF}, \mathrm{rt}$ | 0 | 65 | 9 |
| $\mathbf{6}$ | $\mathrm{DBU}, \mathrm{DMSO}, 100^{\circ} \mathrm{C}$ | $\mathbf{9 4}$ | 0 | 0 |



9b
A solution of $\mathbf{8 b}$ ( 1 equiv, $300 \mathrm{mg}, 0.67 \mathrm{mmol}$ ) and DBU ( 1.2 equiv, $0.12 \mathrm{~mL}, 0.8 \mathrm{mmol}$ ) in anhydrous DMSO ( 5 mL ) was stirred at $100{ }^{\circ} \mathrm{C}$ for 8 h . The mixture was concentrated under high vacuum and purified by silica gel column (Heptane: $\mathrm{EtOAc}=4: 1$ ) to afford $\mathbf{9 b}$ as a yellow solid ( $271 \mathrm{mg}, 94 \%$ ). ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{MeOD}$ ) $\delta 7.37$ (dd, J = 8.5, $7.0 \mathrm{~Hz}, 1 \mathrm{H}$ ), 7.23 (dd, J = 8.5, $0.8 \mathrm{~Hz}, 1 \mathrm{H}$ ), 7.16 (dd, J $=7.0,0.8 \mathrm{~Hz}, 1 \mathrm{H}), 7.07(\mathrm{dd}, \mathrm{J}=1.5,0.8 \mathrm{~Hz}, 1 \mathrm{H}), 6.84(\mathrm{~s}, 1 \mathrm{H}), 4.19(\mathrm{q}, \mathrm{J}=7.1 \mathrm{~Hz}, 2 \mathrm{H}), 3.88(\mathrm{~s}, 3 \mathrm{H}), 3.73$ (s, 3H), 2.36 ( $\mathrm{s}, 3 \mathrm{H}$ ), 1.15 (t, J = 7.1 Hz, 3H).
${ }^{13}$ C NMR (101 MHz, MeOD) $\delta 196.12,166.70,160.14,154.59,149.63,143.06,133.89,133.00,132.28$, $129.10,125.81,125.28,120.80,119.09,117.48,111.84,62.33,56.63,56.49,21.44,14.28$.

HRMS (ESI): m/z calcd. for $\mathrm{C}_{21} \mathrm{H}_{19} \mathrm{BrO}_{5}[\mathrm{M}]^{+}: 430.0416$, found: 430.0428 .

## Preparation of ethyl 2-(2-(cyanomethyl)-6-methoxy-4-methylphenyl)-4-methoxy-1-oxo-1H-indene-3-carboxylate (1)



1
A mixture of 9b ( 1 equiv, $180 \mathrm{mg}, 0.417 \mathrm{mmol}$ ), sodium 2-cyanoacetate ( 1.5 equiv, $67 \mathrm{mg}, 0.626 \mathrm{mmol}$ ), allylpalladium(II) chloride dimer ( $2 \mathrm{~mol} \%, 3.12 \mathrm{mg}, 0.00835 \mathrm{mmol}$ ) and SPhos ( $6 \mathrm{~mol} \%, 10.6 \mathrm{mg}, 0.025$ mmol ) in mesitylene ( 3 mL ) was stirred under Argon at room temperature for 10 min and then stirred in a preheated heating plate at $120^{\circ} \mathrm{C}$ for 16 h . The reaction mixture was loaded to the silica gel column and flushed with heptane ( 300 mL ) to remove mesitylene, then eluted with heptane:EtOAc $=3: 1$ to afford $\mathbf{1}$ as an orange solid ( $140 \mathrm{mg}, 0.358 \mathrm{mmol}, 86 \%$ ).
${ }^{1}{ }^{H} \mathrm{NMR}\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right): \delta 7.30(\mathrm{dd}, \mathrm{J}=8.4,7.1 \mathrm{~Hz}, 1 \mathrm{H}), 7.20(\mathrm{dd}, \mathrm{J}=7.0,0.8 \mathrm{~Hz}, 1 \mathrm{H}), 7.06-7.01$ $(\mathrm{m}, 1 \mathrm{H}), 6.97(\mathrm{~s}, 1 \mathrm{H}), 6.69(\mathrm{~s}, 1 \mathrm{H}), 4.28-4.18(\mathrm{~m}, 2 \mathrm{H}), 3.86(\mathrm{~s}, 3 \mathrm{H}), 3.78-3.61(\mathrm{~m}, 5 \mathrm{H}), 2.38(\mathrm{~s}, 3 \mathrm{H})$, 1.19 (t, J = $7.1 \mathrm{~Hz}, 3 \mathrm{H}$ ).
${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 195.36,165.56,158.33,153.06,148.97,141.12,131.87,131.39,131.02$, $130.56,128.22,121.24,119.13,118.05,117.14,115.39,111.51,61.60,56.07,55.98,22.12,21.92,14.11$. HRMS (ESI): m/z calcd. for $\mathrm{C}_{23} \mathrm{H}_{21} \mathrm{NO}_{5}[\mathrm{M}]^{+}: 391.1420$, found: 391.1416.

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## Abstract

Keywords : 3-amino-1,2,4-oxadiazine ; benzo-2,3-oxazepin-4-one ; alchornedine ; green chemsitry ; POxAP

Heterocycles including two adjacent nitrogen atoms were very popular in medicinal chemistry. More particularly, the five-membered ring pyrazole, as well as both six-membered rings pyridazine and 1,2,4triazine, were extensively used in drug design. Indeed, thanks to the nitrogen atoms, these three aromatic scaffolds exhibit 2 to 3 H -bond acceptors, capable to interact with target proteins. Moreover, these nitrogen atoms allow to decrease the lipophilicity of these heterocycles in comparison with benzene. However, due to their aromatic character, these scaffolds have still a planar geometry, which constitutes a significant limitation in the search for complex molecular structures. In 2009, Franck Lovering from Wyeth proposed the concept "Escape from Flatland", which means to avoid aromatics, in favour of saturated carbon bonds and chiral $\mathrm{sp}^{3}$ carbon atoms. The rational of this approach is that these non-planar molecules will be more natural productlike, and more amenable to explore additional areas of chemical space. Moreover, significant gains are expected in terms of ADME properties (solubility, biological selectivity, lipophilicity, etc). Despite the fivemembered $\mathrm{N}-\mathrm{O}$ heterocycles such as isoxazole or isooxazoline are well known, the corresponding six and seven-membered non-aromatic heterocycles exhibiting a N-O moiety are pretty rare in the literature. Besides the interesting non-planar geometry, the presence of the oxygen atom will strongly decrease the basicity of the adjacent nitrogen atom, endowing these N-O heterocycles particular physicochemical properties. Furthermore, the oximes ethers (=N-O-) possess a good resistance to protonation, which gives them better intrinsic stabilities towards hydrolysis than hydrazones or imines. Untill now, several alkoxyamides are under clinic trails.

In this project, new non-planar N-O heterocycles, 3-amino-1,2,4-oxadiazine and benzo-2,3-oxazepin-4-one would be synthesized and their physicochemical properties would be measured. During this course, a radical reaction in water was established to introduce N-O moiety and a novel precatalyst was developed for Fukuyama cross-coupling reaction. Futhermore, we also attempted to synthesize the natural product alchornedine with the established synthetic methods for 3-amino-1,2,4-oxadiazine scaffold.


3-amino-1,2,4-oxadiazine

benzo-2,3-oxazepin-4-one

## Shuang-Qi TANG <br> Synthèse d'hétérocycles non planaires à 6 ou 7 chaînons présentant une liaison N - O

## Résumé

Mots-clés: 3-amino-1,2,4-oxadiazine ; benzo-2,3-oxazepin-4-one ; alchornedine ; chimie verte; POxAP
Les hétérocycles présentant 2 atomes d'azote adjacents sont très populaires en chimie médicinale. Ainsi, le cycle à 5 de type pyrazole, ainsi que les cycles à 6 de type pyridazine et 1,2,4-triazine ont été intensivement étudiés en drug design. En effet, la présence des atomes d'azote permet à ces systèmes hétérocycliques aromatiques de présenter 2 à 3 sites potentiels d'interactions de type accepteur de liaison hydrogène avec une cible protéique. De plus, la présence d'atomes d'azote permet de diminuer la lipophilie de ces systèmes aromatiques en comparaison avec le benzène. Toutefois, le caractère aromatique de ces hétérocycles leur confère une géométrie planaire, ce qui constitue une limitation importante dans la recherche de structures moléculaires complexes. En 2009, Franck Lovering de Wyeth a proposé le concept "Escape from flatland", dans lequel il présente l'intérêt d'éviter les structures aromatiques pour privilégier des cycles saturés présentant des carbones $\mathrm{sp}^{3}$. Le rationnel de cette approche repose sur le fait que ces molécules non aromatiques sont plus proches des produits naturels, et que leur géométrie non-planaire permet une plus grande exploration de l'espace chimique tridimensionnel, tout en améliorant les propriétés d'ADME (solubilité, sélectivité, lipophilie, etc). Dans ce projet de thèse, nous proposons de développer de nouveaux hétérocycles non aromatiques et non planaires présentant une liaison N-O. Si les cycles à 5 (isoxazole ou isoxazoline) sont bien connus, les cycles à 6 ou 7 chaînons présentant un motif N-O sont particulièrement rares ou inexistants dans la littérature. Outre l'intérêt géométrique de ces hétérocycles, la présence de l'oxygène en alpha de l'azote permet de fortement diminuer la basicité de ce dernier, conférant à l'hétérocycles des propriétés physico-chimiques particulières. Par ailleurs, les oximes ethers ( $=\mathrm{N}-\mathrm{O}-$ ) présentent une bonne résistance à la protonation, ce qui leur confère une stabilité intrinsèque à l'hydrolyse bien meilleure que celle observée avec les hydrazones ou les imines. Enfin, plusieurs alkoxyamides sont actuellement en essai clinique.
Durant cette thèse, nous avons focaliser nos travaux sur la synthèse et propriétés physicochimiques de 3-amino-1,2,4-oxadiazine et benzo-2,3-oxazepin-4-one. Pendant ce cours, une réaction radicalaire dans l'eau a été établie pour introduire un fragment $\mathrm{N}-\mathrm{O}$ et un nouveau précatalyseur a été développé pour la réaction de couplage croisé de Fukuyama. De plus, nous avons également tenté de synthétiser le produit naturel alchornédine avec les méthodes de synthèse établies pour l'échafaudage 3-amino-1,2,4-oxadiazine.


3-amino-1,2,4-oxadiazine

benzo-2,3-oxazepin-4-one


[^0]:    (S)-2-Me-CBS

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[^2]:    ${ }^{\text {a }}$ Reactions were carried out in a vial on a bioshaker ( 1800 rpm ) using NHPI ( $0.122 \mathrm{mmol}, 1$ equiv.), styrene ( $\mathbf{1 a}$ ), PTSA, TBHP, and the surfactant in water ( 2 mL ) under an $\mathrm{O}_{2}$ balloon at r.t. for 19 h , unless otherwise noted.
    ${ }^{\mathrm{b}}$ Reaction performed under air.
    ${ }^{\text {c }}$ Yield of 2a based on NHPI was determined by HPLC/UV using caffeine as an internal standard.
    ${ }^{\text {d }}$ Reaction performed at $50^{\circ} \mathrm{C}$ for 9 h .

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[^4]:    ${ }^{13} \mathrm{C}$ NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 190.53,135.05,133.67,132.78,130.83,129.61,128.75,128.57,127.87$, 127.84, 127.42, 126.53, 126.26, 125.94, 50.47, 17.93.

    HRMS (ESI): m/z calcd. for $\mathrm{C}_{16} \mathrm{H}_{13} \mathrm{NOS}[\mathrm{M}]^{+}: 267.0718$, found: 267.0702 .

[^5]:    ${ }^{13} \mathrm{C}$ NMR (101 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 205.97$, 136.86, 133.70, 132.59, 131.79, 131.06, 129.58, 129.54, 128.48, $128.40,127.81,127.75,127.65,126.32,125.94,49.24,49.01,21.20$.

    HRMS (ESI): m/z calcd. for $\mathrm{C}_{20} \mathrm{H}_{18} \mathrm{O}$ [M] ${ }^{+}: 274.1358$, found: 274.135.

