

### Sustainable functionalization of cyclic amides and imides with ruthenium catalysts: development, scope and mechanisms

Yu-Chao Yuan

### ► To cite this version:

Yu-Chao Yuan. Sustainable functionalization of cyclic amides and imides with ruthenium catalysts: development, scope and mechanisms. Catalysis. Université de Rennes, 2019. English. NNT: 2019REN1S059. tel-02508308

### HAL Id: tel-02508308 https://theses.hal.science/tel-02508308

Submitted on 14 Mar 2020  $\,$ 

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers. L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.





### THESE DE DOCTORAT DE

L'UNIVERSITE DE RENNES 1 Comue Universite Bretagne Loire

ECOLE DOCTORALE N° 596 Matière Molécules et Matériaux Spécialité : Chimie Moléculaire et Macromoléculaire



### Sustainable Functionalization of Cyclic Amides and Imides with Ruthenium Catalysts: Development, Scope and Mechanisms

Thèse présentée et soutenue à Rennes, le 29 Octobre 2019 Unité de recherche : UMR6226, CNRS, Université de Rennes 1, Institut des Sciences Chimiques de Rennes

#### Rapporteurs avant soutenance :

Giovanni POLI Professeur, Sorbonne Université Paris

Lukas J. GOOSSEN Professeur, Ruhr-Universität Bochum

#### Composition du Jury :

Giovanni POLI Professeur, Sorbonne Université Paris

Lukas J. GOOSSEN Professeur, Ruhr-Universität Bochum

Francine AGBOSSOU-NIEDERCORN Directrice de Recherche CNRS, Université de Lille

Christian BRUNEAU Chercheur Emérite, Université de Rennes 1

#### **Rafael GRAMAGE-DORIA**

Chargé de Recherche CNRS, Université de Rennes 1 Directeur de thèse

#### Acknowledgments

Time flies! First, I would like to say some words to my PhD supervisors. I would like to sincerely thank Dr. Christian Bruneau for offering me the opportunity to apply for a CSC PhD fellowship to join the group, especially for allowing me independently free exploration and giving me generous support and scientific advices. His kindness and interest in my well-being helped me considerably during some difficult time in my work. I feel myself very fortunate to be associated with Dr. Rafael Gramage-Doria, whose care, support, enthusiasm, tolerance have no bounds when and where needed. I have learned a lot from him and I am grateful for his guidance in using experimental devices and showing useful materials. During these three years, he taught me not only chemistry and experimentation, but also how to do research, work efficiently and give a good presentation.

I would like to express my deep sense of gratitude to Emer. Prof. Pierre H. Dixneuf for giving me this wonderful opportunity to work in Rennes as he is the first person I was lucky enough to contact for the CSC PhD fellowship.

I would like to thank my thesis committee whom I appreciate for accepting to referee my PhD thesis: Prof. Dr. Giovanni Poli, Dr. Francine Agboussou Niedercorn, and Prof. Dr. Lukas J. Goossen. Thanks to them for spending their valuable time in reading and carefully evaluating my PhD thesis as well as travelling long distances to attend my PhD viva.

I am also thankful to Prof. Dr. Christophe Darcel, Dr. Henri Doucet, Dr. Jean-François Soulé, Dr. Cédric Fischmeister, Dr. Mathieu Achard, Dr. Sylvie Dérien and Jérôme Ollivier, all permanent members in the group, for their kind help in research and interesting catalysis lessons I discovered during the past three years.

I am grateful to the Rennes Metropole mobility program for offering me the

opportunity to work abroad from October to November 2017, and I thank Dr. Marcos García Suero for accepting me in his group at ICIQ (Taragona- Spain), as well as the labmates in ICIQ for a wonderful atmosphere.

I would like to thank Dr. Thierry Roisnel and Dr. Vincent Dorcet from the X-Ray diffraction Center here in Rennes, for their kind help in performing detailed X-Ray diffraction analysis. Thanks also to Dr. Philippe Jéhan and his team for the help in HRMS analysis at the CRMPO in Rennes. I would like to thank as well Thierry Labasque from Geosciences Rennes for helping us with GC gas phase analysis.

I would like to thank Mrs. Béatrice Mahi and Mrs. Christèle Vallerie, and all the secretary staff, for their help in the administrative tasks.

I would like to associate these thanks to all my "international" labmates and friends Dr. Paolo Zardi, Dr. Antoine Bruneau-Voisine, Dr. Changsheng Wang, Dr. Shengdong Wang, Duo Wei, Julien Hervochon, Arpan Sasmal, Xinzhe Shi, Haoran Li, Zhuan Zhang, Sitthichok Kasemthaveechok, Haiyun Huang, Chakkrit Netkavev, Harikrishnan Jayaprakash, Yixuan Cao, Weiheng Huang, Shuxin Mao, Luciana Sarmento Fernandes, Gabriel Matos Viera, Thalita Soares Galhardo, Shaymaa Shehimy, Christophe Besnard, Lucas Jacquet and Marion Goujon. They have all created cooperative and cordial atmosphere in the lab during this project of research.

I am very thankful to all my friends outside the lab for their moral support, encouragements and caring attitude.

The largest contribution in shaping my present comes from the faith, hope, encouragement and affection of my parents, my sisters and my beloved Dandan, who also assisted me with their meticulous efforts.

I am also extremely thankful to the China Scholarship Council for the award of a PhD fellowship within this project.

AcknowledgmentsI
------------------

# Chapter 1: Merging transition metal catalysis with phthalimides: a new entry to useful building blocks

1.1 Introduction	1
1.2 Partial carbonyl reduction	3
1.3 Full carbonyl reduction	8
1.4 Aromatic ring reduction	12
1.5 Five-membered ring opening	17
1.6 Conclusion	.26
1.7 References	27

# Chapter 2: Ruthenium-catalyzed protodecarbonylation of N-substituted phthalimide derivatives

2.1 Introduction	
2.2 Results and discussion	
2.2.1 Ruthenium-catalyzed protodecarbonylation of N-subs derivatives: search for optimal reaction conditions	tituted phthalimide 35
2.2.2 Scope and limitations of the ruthenium-catalyzed proto	odecarbonylation of
N-substituted phthalimide derivatives	
2.3 Mechanistic studies	44
2.4 Conclusion	49
2.5 Experimental details	
2.6 References	81

## Chapter 3: Ruthenium-catalyzed selective C-H bond hydroxylation of cyclic imides

3.1 Introduction	87
3.2 Results and discussion	91
3.2.1 Optimization of the Ru-catalyzed site-selective aromatic hydroxylation using cyclic imides as weak directing groups	<i>C-H bond</i> 91
3.2.2 Scope and limitations of the Ru-catalyzed site-selective aromat	ic C-H bond
hydroxylation of different substituted aryl cyclic imides	
3.3 Mechanistic studies	97
3.4 Post-functionalization reactions	
3.5 Conclusion	
3.6 Experimental details	
3.7 References	

# Chapter 4: Ruthenium-catalyzed selective C(sp<sup>2</sup>)-H bond benzoxylation of biologically appealing N-arylisoindolinones

4.1 Introduction	
4.2 Results and discussion	
4.2.1 Optimization of ruthenium-catalyzed C-H bond isoindolinone	benzoxylation of 130
4.2.2 Scope and limitations of the Ru(II)-catalyzed C-H box	nd benzoxylation of
isoindolinones	
4.3 Mechanistic studies	
4.4 Conclusion	
4.5 Experimental details	
4.6 References	

### Chapter 5: Site-selective Ruthenium-catalyzed C-H bond alkenylations with the biologically relevant isoindolinone core as a weak directing group

5.1 Introduction	
5.2 Results and discussion	
5.2.1 Optimization of the site-sele with the isoindolinone frage	ective ruthenium-catalyzed C-H bond alkenylation nent serving as a weak directing group160
5.2.2 Scope and limitations of t alkenylation with different t	he ruthenium-catalyzed site-selective C-H bond erminal alkenes162
5.3 Mechanistic studies	
5.4 Derivatization reactions	
5.5 Conclusion	
5.6 Experimental details	
5.7 References	

## Chapter 6: Selective Ruthenium-catalyzed C-H bond arylation with the isoindolinones serving as a weak directing group

6.1 Introduction	
6.2 Results and discussion	
6.2.1 Optimization of selective Ru-catalyzed C-H bond aryla isoindolinone serving as a weak directing group	ation with the 197
6.2.2 Scope and limitations of selective Ru-catalyzed C-H bond ar	ylation with the
isoindolinone serving as a weak directing group	199
6.3 Preliminary mechanistic studies	204
6.4 Additional experiments with other aryl sources	205
6.5 Conclusion	207
6.6 Experimental details	
6.7 References	

# Chapter 7: C-H bond alkylation of cyclic amides with maleimides via a site-selective-determining six-membered ruthenacycle

1 Introduction	226
2 Results and discussion	.228
7.2.1 Optimization of the site-selective Ru-catalyzed C-H bond alkylation of cy amides with maleimides	vclic .228
7.2.2 Evaluation of the scope for the site-selective Ru-catalyzed C-H b alkylation of cyclic amides with maleimides	oond 230
3 Mechanistic studies	.233
4 Investigation of different directing groups in the Ru-catalyzed C-H bond alkyla	ition
with maleimides	.235
5 Conclusion	.237
6 Experimental details	.238
7 References	.250

<b>Conclusions and Per</b>	rspectives	
conclusions and 1 er	<i>specuves</i>	

## Each chapter contains independent numbering of compounds and independent citation of references.

#### **General Introduction**

Over the past few decades, homogeneous catalysis plays a pivotal role to cover the demands of our society.<sup>1</sup> For instance, the synthesis of many daily life chemicals (drugs, pesticides, OLED materials, commodities, polymers, etc.) comprise at least one step involving transition metal catalysed transformations and many reactions nowadays are being conducted in industry at the multi-ton scale.<sup>2</sup> For example, the rhodium-catalyzed hydroformylation reaction enables the synthesis of biologically-relevant aldehydes starting from alkenes derived from oil cracking/reforming.<sup>3</sup> For that, the fundamental understanding of metal's reactivity and the discovery of new chemical reactions are extremely appealing in view to generate sustainable and environmentally benign processes in academic and industrial laboratories.

Well-defined, transition metal complexes derived from platinum, rhodium, iridium and palladium are, by far, the most widely used and versatile ones due to their ability to reach multiple oxidation states and multiple coordination geometries that can affect the reactivity of given substrates. However, these metals are extremely expensive, very scarce on the Earth's crust and their related complexes are in general unstable towards air and moisture.<sup>4</sup> It seems convenient then, to turn the attention to more abundant, affordable and stable metal complexes. As such, ruthenium seems promising since it displays a large number of oxidation states (from +8 to -2) and coordination geometries comparable to most of the precious metals, which makes this metal interesting to replace the less abundant ones. In addition, the reactivity of ruthenium complexes for fine chemical synthesis has been well-established during the last decades.<sup>5</sup> The most relevant breakthroughs in this context are (1) the asymmetric hydrogenation of ketones into chiral alcohols with Ru-BINAP-diamine complexes by Novori,<sup>6</sup> (2) the olefin metathesis reaction with RuCl<sub>2</sub>(PCy<sub>3</sub>)<sub>2</sub>(CHPh) as pre-catalyst by Grubbs<sup>7</sup> and (3) the C-H bond functionalization of phenyl moieties with RuH<sub>2</sub>(CO)(PPh3)<sub>3</sub> as pre-catalyst by Murai using ketones as directing groups (Scheme 1).<sup>8</sup>



Scheme 1 Relevant breakthroughs with ruthenium catalysts.

In this PhD project, the main focus is the development of readily available catalytic systems based on ruthenium complexes to target new chemical transformations. Particular emphasis was devoted to react long time believed inert chemical bonds such as C-H bonds in order (1) to transform them into more useful carbon-carbon and/or carbon-oxygen bonds in a selective manner; as well as (2) to discover new type of chemical disconnections that could enable the synthesis of difficult molecules in a more straightforward manner. As such, it is expected to provide new synthetic routes towards chemical diversity as well as understanding the mechanisms associated to these catalytic reactions. The general aim of this PhD is the development of ruthenium-based catalytic systems enabling site-, regio- and chemo-selective functionalizations with biologically-relevant cyclic imides and cyclic amides together with experimental mechanistic studies.

In this context, it is relevant to emphasize the different strategies that enable C-H bond activation and functionalization employing transition metal catalysts. For instance, a classic approach relies on the use of so-called directing groups (DGs) that are located

at close proximity of the C-H bond that is desired to be functionalized.<sup>9</sup> Typically, nitrogen-containing DGs (e.g. pyridines, diazines, diazoles) are considered the strongest ones as they bind tightly to the metal catalyst guiding the activation in the most proximally-located C-H bond. In the case of aromatic C-H bonds, such approach gives exclusively rise to ortho-selectivity thanks to the formation of 5-membered metallacycle intermediates (Scheme 2).<sup>9</sup> The key C-H bond activation elementary step occurs via a concerted-metallation deprotonation (CMD), in which an anionic ligand (usually a base) attached to the metal catalyst enables deprotonation in an intramolecular fashion. However, an alternative intermolecular deprotonation via a three-center electrophilic mechanism analogous to an intermolecular S<sub>E</sub>3 mechanism has been evoked as well (Scheme 2).<sup>10</sup> Depending on the chemical nature of the coupling partner employed during the C-H bond functionalization different chemical bonds can be formed. For example, C-aryl bonds can be formed when employing aryl halides or aryl boronates as aryl sources (Scheme 2), and C-alk(en)yl bonds can be formed when using olefin-containing partners depending on the reaction conditions (redox reagents, pH, etc.). Other synthetically useful DGs include amides, esters and carboxylic acids.<sup>11</sup>



Scheme 2 DG-controlled *ortho*-selectivity exemplified for ruthenium catalysts in a C-H bond arylation with some postulated intermediates. L = p-cymene or 2phenylpyridine.

#### General Introduction

Alternatively, weak coordinating groups such as ketones or tertiary amides can be used as well as DGs for C-H bond functionalizations (Figure 1).<sup>11</sup> These DGs coordinate in a labile manner *via* the oxygen lone pair to the catalyst (Figure 1), which in principle, may result in a catalytic system more effective with respect to the turnover numbers. On the other hand, the metal center within the catalyst should be electrophilic enough to enable transient coordination to the ketone group and to prevent catalytically unproductive full catalyst de-coordination.



**Figure 1** Simplified, generally-accepted order of coordination strength of DGs in transition metal-catalyzed C-H bond functionalizations.

In some cases, the DG is already in the molecule of interest to be functionalized. This is particular appealing in the case of late-stage functionalization as it enables a high degree of diversification without the need of re-starting and re-designing the synthesis of the target structures.<sup>12</sup> In other cases, the DG can be cleaved, typically using sacrificial harsh reagents as exemplified in Scheme 3.<sup>13</sup>



Scheme 3 Synthetic sequence enabling C-H bond functionalization followed by DG cleavage reported by Ackermann and co-workers.<sup>14</sup>

In general, the DG is difficult to be removed or transformed due to the covalent nature of the chemical bonds present in the starting material. Consequently, recent strategies have emerged in the last years in which traceless or easy-to-remove DGs have been developed.<sup>15</sup> For example, DGs can react and be transformed in the course of the C-H bond functionalization reaction leading to complex molecules, e.g. intramolecular rearrangements, cleavage of the directing group, etc. (Scheme 4). In this direction, an interesting strategy is the use of catalytic amounts of a reagent that forms the DG *in situ* within an initially DG-free substrate. This is typically achieved with dynamic covalent chemistry, in which covalent bonds are simultaneously being formed and cleaved. A representative example is the formation of imine bonds as DGs. In this way, at the end of the reaction, the DG-free substrate is recovered again after being functionalized (Scheme 5). Alternatively, there are examples of one-pot directing group formation followed by C-H bond functionalization (Scheme 6). These domino sequences are known involving transition metal-catalyzed processes or purely organic transformations in the first step.<sup>16</sup>



Scheme 4 Example of the carboxylic acid as a transformable DG in C-H bond functionalization reported by Goossen and co-workers: two products can form depending on the reaction conditions.<sup>17</sup>



Scheme 5 Example of a transient DG-controlled, Rh-catalyzed C-H bond functionalization reported by Jun and co-workers.<sup>18</sup>



**Scheme 6** Example of a one-pot directing group formation/C-H bond functionalization with two different transition metal catalysts reported by our group.<sup>19</sup>

As above-mentioned, these strategies mainly lead to proximal selectivity. In order to tackle the more difficult remote selectivity, three approaches are usually envisaged:

(1) The first one is based on the design of large and rigid DGs that guide the metal catalyst further than *ortho*-selectivity for the case of aromatic C-H bonds (Scheme 7). In a pioneer series of examples Yu and co-workers, and Maiti and co-workers, independently, demonstrated that highly sophisticated nitrile containing DGs specifically locate the catalytically active palladium center in order to achieve *meta* or *para* selectivity depending on the length and geometry of the DG.<sup>20</sup> This strategy suffers from an important lack of prediction as very subtle small changes in the nature of the DG (i.e. torsion angles) can lead to very different catalytic outcomes. This was further extended to the use of so-called templates. These are molecules bearing bifunctional coordinating groups. On one hand, a site containing a palladium center for interacting with a pyridine substrate and in the other side, a nitrile coordinating group for interacting with the catalytically active palladium center. Overall, an overstoichiometric amount of palladium is required in this approach.<sup>21</sup>



Scheme 7 Examples of remote selectivity of C-H bonds by highly-elaborated DGs (top) and templates (bottom) reported by Yu and co-workers.<sup>22</sup>

#### General Introduction

(2) A second strategy relies on the use of non-covalent interactions (hydrogen bonding, ion pair, etc.) between the catalyst and the substrate in order to preorganize the substrate and locate the desired C-H bond nearby the metal catalyst. Interesting examples have been reported by Kanai, Phipps, Nakao, and others for iridium-catalyzed C-H borylation reactions (Scheme 8).<sup>23</sup> Such concept is reminiscent from enzymes, in which smartly-designed weak non-covalent interactions enable high levels of activity and selectivity. On the other hand, the reaction conditions have to be compatible with the persistence of such non-covalent interactions, which is not always trivial.



**Scheme 8** Example of a C-H bond functionalization in which the regio-selectivity is controlled by non-covalent hydrogen bonding reported by Kanai and co-workers.<sup>24</sup>

(3) A third strategy enabling remote selectivity is based on the formation of metalsubstrate complexes, in which the C-H bonds that are not activated by the metal can undergo functionalization *via* radical mechanisms (Scheme 9). This has been elegantly shown for sulfonation, alkylation, nitration and halogenation reactions mostly, and the selectivity is controlled by the inner nature of the substrate imposed by electronic effects of the metal-substrate complex.<sup>25</sup>



Scheme 9 Example of *meta*-selective C-H bond sulfonation enabled by a rutheniumsubstrate complex reported by Frost and co-workers.<sup>26</sup>

Besides DG-controlled C-H bond functionalizations, there are substrate that *per se* are prone to undergo a C-H bond activation without any need of DGs. In particular, C-H bond activations can take place *via* Heck-type processes, in which a C=C double bond within a substrate coordinates to the metal, followed by migratory insertion leading to a new C-M bond formation. This scenario is usually observed for the C-H bond functionalization of small heteroaromatic molecules (pyrroles, furans, thiophenes, etc.) in which their C=C double bonds are polarized to some extent due to the close presence of heteroatoms such as N, O, S, Se, etc (Scheme 10). Once a C-M bond is catalytically formed, subsequent reaction with a coupling partner enables the formation of a new chemical bond. In other cases, the C-H bonds within the molecule are sufficiently acidic for deprotonation in the presence of a base, however, the presence of a metal catalyst is required for the bond-forming elementary steps within the catalytic cycle.<sup>27</sup>



Scheme 10 Example of a substrate-controlled C-H bond arylation with palladium catalysis reported by Ohta and co-workers.<sup>28</sup>

An important parameter to be controlled, besides the selectivity of the C-H bond functionalization, is the control over mono- *versus* bis-functionalization. Usually, the use of stoichiometric (or slightly over-stoichiometric) amounts of coupling partner gives mono-functionalization whereas an excess leads to bis-functionalization. In some cases, after mono-functionalization, the resulting product is sterically congested in such a way that it geometrically prevents a second C-H bond activation to occur, even in the presence of excess of both reagents and metal catalyst.

Obviously, it is highly important to develop C-H bond functionalizations with useful synthetic motifs. An in-depth survey in the literature shows an important gap in the amide-directed C-H bond functionalization with transition metal catalysts. Whereas primary amides and secondary amides are widely used as DGs, the use of tertiary amides still remains scarce. This is likely a consequence of the tautomeric nature of the formers with respect to the latter. In the case of the primary and the secondary amides, multiple possibilities are feasible to access metallacycle intermediates considering the deprotonation event as well. On the contrary, in the case of tertiary amides only two intermediates are expected to behave as DG for coordinating the metal catalyst in the C-H bond activation step (Scheme 11).<sup>29</sup>



Scheme 11 Comparison of general coordinating ability between acyclic amides as DGs.

In addition, cyclic amides and cyclic imides are important motifs found in many molecular scaffolds ranging from biology to materials sciences.<sup>30</sup> Moreover, *N*-aryl isoindolinone and *N*-arylphthalimides (and their derivatives) may impose site-selectivity issues in the case of successful C-H bond functionalizations, as two chemically different aromatic C-H bonds are present within these molecular structures (Scheme 12). In contrast to acyclic tertiary amides (Scheme 11), the cyclic ones are expected to behave as DGs *via* the exploitation of the oxygen lone pair, which is significantly weaker compared to the nitrogen one (Scheme 12).



Scheme 12 Representative cyclic tertiary amide studied in this PhD as DG for C-H bond functionalizations with ruthenium catalysts and plausible intermediates involved in the activation step.

In this PhD thesis, benchmark and robust ruthenium catalysts are being used to tackle unprecedented transformations with cyclic a/imides including the selective cleavage of C-C and C-N bonds (chapter 2), C-O bond forming (chapters 3-4) and C-C bond forming processes (chapter 5-7) *via* C-H bond functionalization strategies. Important differences in reactivity and mono- *versus* bis-functionalization introduced by the cyclic amide and imide directing groups will be highlighted in this thesis, exemplified in various C-C and C-O bond formation reactions.

The content of this thesis manuscript is as follows:

**Chapter 1:** This chapter is an overview that summarizes the useful chemical transformations that have been accomplished by the scientific community employing phthalimides as key synthons towards more complex molecular structures under transition metal catalysis.

**Chapter 2:** This chapter is devoted to describe the unprecedented transformation of a wide range of synthetically appealing phthalimides into secondary amides in a single-step operation in high yields and short reaction times using a ruthenium catalyst. Preliminary mechanistic studies revealed a unique, homogeneous pathway involving five-membered ring opening and CO<sub>2</sub> release with water being the source of protons.

**Chapter 3:** This chapter deals with the ability of cyclic imides to behave as weak directing groups for selective hydroxylation reactions using ruthenium catalysts. Whereas acyclic amides are known to promote the hydroxylation of the  $C(sp^2)$ -H bond enabling five-membered ring ruthenacycle intermediates, the cyclic imides studied herein enabled the hydroxylation of the  $C(sp^2)$ -H bond *via* larger six-membered ruthenacycle intermediates. Furthermore, mono-hydroxylated products were exclusively obtained (even in the presence of over-stoichiometric amounts of reagents), which was rationalized by the difficulty to accommodate co-planar intermediates once the first hydroxyl group was introduced into the substrate. The same reactivity was observed in the presence of palladium catalysts.

**Chapter 4:** In this part of the manuscript, site- and regio-selective aromatic C-H bond benzoxylations were found to take place using biologically appealing *N*-arylisoindolinones (a type of cyclic amides) under ruthenium(II) catalysis in the presence of (hetero)aromatic carboxylic acid derivatives as coupling partners. Besides the presence of two potential  $C(sp^2)$ -H sites available for functionalization in the substrates, exclusive *ortho* selectivity was achieved in the phenyl ring attached to the nitrogen atom. The reactions took place in a selective manner as only monofunctionalized products were formed and a large number of functional groups were tolerated. In contrast, the more sterically demanding cyclic imides were unreactive under identical reaction conditions.

**Chapter 5:** This chapter is dedicated to the development of a general Ru-catalyzed C-H bond alkenylation using *N*-arylisoindolinones (cyclic amides) as weak coordinating groups. Selective mono-alkenylations in the *ortho* position with respect to the nitrogen atom were observed with a readily available ruthenium catalyst. The scalability, versatility and high functional group tolerance of the catalysis enabled the late-stage functionalization of biologically relevant indoprofen and further derivatizations. Some mechanistic studies indicate that subtle stereo-electronic differences associated to

cyclic amides and imides, respectively, are responsible for the different results obtained. The isolation of an unprecedented off-cycle ruthenium complex is presented and discussed as well.

**Chapter 6:** This part of the manuscript shows that *N*-arylisoindolinones (cyclic amides) underwent arylation reactions under ruthenium catalysis *via* C-H bond functionalization. The reactions exclusively led to mono-arylated products and only *ortho* selectivity was observed in the aromatic ring connected to the nitrogen atom with no C-H bond functionalization occurring in the other benzene ring being in *ortho* position with respect to the carbonyl group. This ruthenium-catalyzed reaction displayed a high functional group tolerance, and it employed readily available and benchmark stable boronic acid and potassium aryltrifluoroborate derivatives as coupling partners. An appealing late-stage functionalization of indoprofen applying this methodology is showcased.

**Chapter 7:** The last chapter of the manuscript is focused on the development of ruthenium-catalyzed  $C(sp^2)$ -H bond alkylations using *N*-substituted maleimides as coupling partners and biologically appealing isoindolinones. The cyclic tertiary amide core acted as a weak directing group enabling the formation of six-membered cycloruthenated species responsible of the control of the regio- and site-selectivity of the catalysis. The reactions displayed an excellent functional group tolerance, which paved the way for late-stage functionalizations. This reaction constitutes the first example of an aromatic C-H bond alkylation enabled by six-membered ruthenacycles.

#### References

- [1] R. Noyori, *Nature Chem.* **2009**, *1*, 5.
- [2] (a) K. Sanderson, *Nature* 2011, 469, 18. (b) R. A. Sheldon, *Chem. Soc. Rev.* 2012, 41, 1437. (c) G. Rothenberg, *Catalysis: Concepts and Green Applications*, Wiley-VCH, Weinheim, 2008. (d) M. Beller, *Chem. Soc. Rev.* 2011, 40, 4891.
- [3] R. Franke, D. Selen, A. Borner, Chem. Rev. 2012, 112, 5675.
- [4] (a) S. E. Livingstone, *The Chemistry of Ruthenium, Rhodium, Palladium, Osmium, Iridium and Platinum*, Pergamon Texts in Inorganic Chemistry, Elsevier, 1973. (b)
  J. F. Hartwig, *Organotransition Metal Chemistry: From Bonding to Catalysis*, University Science Books, Sausalito, 2009. (c) M. Beller, C. Bolm, *Transition Metals for Organic Synthesis*, Wiley-VCH, Weinheim, 2004. (d) A. de Meijere, F. Diederich, *Metal-Catalyzed Cross-Coupling Reactions, 2nd ed.*, Wiley-VCH, Weinheim, 2004. (e) A. de Meijere, S. Braese, M. Oestreich, *Metal-Catalyzed Cross-Coupling Reactions and More*, Wiley-VCH, Weinheim, 2014.
- [5] (a) E. A. Seddon, K. R. Seddon, *The Chemistry of Ruthenium*, Elsevier Science, 1984.
  (b) S.-I. Murahashi, *Ruthenium in Organic Synthesis*, Wiley-VCH, Weinheim, Germany 2004.
- [6] (a) R. Noyori, S. Hashiguchi, Acc. Chem. Res. 1997, 30, 97. (b) R. Noyori, T. Okhuma, Angew. Chem. Int. Ed. 2001, 40, 40.
- [7] (a) T. M. Trnka, R. H. Grubbs, Acc. Chem. Res. 2001, 34, 18. (b) R. H. Grubbs, Tetrahedron 2004, 60, 7117.
- [8] S. Murai, F. Kakiuchi, S. Sekine, Y. Tanaka, A. Kamatani, M. Sonoda, N. Chatani, *Nature* 1993, 366, 529.
- [9] (a) *C–H Activation*, in: *Topics in Current Chemistry*, Vol. 292, (Eds.: J.-Q. Yu, Z. Shi), Springer, Berlin, **2010**. (b) J. Yamaguchi, A. Yamaguchi, K. Itami, *Angew. Chem. Int. Ed.* **2012**, *51*, 8960. (c) D. A. Colby, R. G. Bergman, J. A. Ellman, *Chem. Rev.* **2010**, *110*, 624. (d) E. M. Beck, M. J. Gaunt, *Top. Curr. Chem.* **2010**, *292*, 85. (e) P. Sehnal, R. J. K. Taylor, I. J. S. Fairlamb, *Chem. Rev.* **2010**, *110*, 824.

(f) C. L. Sun, B. J. Li, Z. J. Shi, *Chem. Commun.* 2010, 46, 677. (g) L. Ackermann, *Acc. Chem. Res.* 2014, 47, 281. (h) P. B. Arockiam, C. Bruneau, P. H. Dixneuf, *Chem. Rev.* 2012, *112*, 5879. (i) S. R. Neufeldt, M. S. Sanford, *Acc. Chem. Res.* 2012, 45, 936. (j) J. F. Hartwig, *Nature* 2008, 455, 314. (k) J. Wencel-Delord, F. Glorius, *Nature Chem.* 2013, 5, 369. (l) J. Wencel-Delord, T. Droege, F. Liu, F. Glorius, *Chem. Soc. Rev.* 2011, 40, 4740. (m) K. Gao, N. Yoshikai, *Acc. Chem. Res.* 2014, 47, 1208. (n) M. Moselage, J. Li, L. Ackermann, *ACS Catal.* 2016, 6, 498. (o) G.-F. Zha, H. L. Qin, E. A. B. Kantchev, *RSC Adv.* 2016, 6, 30875.

- [10] For mechanisms with ruthenium in C-H bond functionalization, see : (a) L. Ackermann, *Chem. Rev.* 2011, *111*, 1315. (b) L. Ackermann, *Acc. Chem. Res.* 2014, *47*, 281. (c) I. Fabre, N. von Wolff, G. Le Duc, E. Ferrer Flegeau, C. Bruneau, P. H. Dixneuf, A. Jutand, *Chem. Eur. J.* 2013, *19*, 7595. (d) E. Ferrer Flegeau, C. Bruneau, P. H. Dixneuf, A. Jutand, *J. Am. Chem. Soc.* 2011, *133*, 10161. (e) C. Shan, L. Zhu, L.-B. Qu, R. Bai, Y. Lan, *Chem. Soc. Rev.* 2018, *47*, 7552. (f) M. Simonetti, R. Kuniyil, S. A. Macgregor, I. Larrosa, *J. Am. Chem. Soc.* 2018, *140*, 11836. (g) M. Simonetti, D. M. Cannas, X. Just-Baringo, I. J. Vitorica-Yrezabal, I. Larrosa, *Nature Chem.* 2018, *10*, 724. (h) D. L. Davies, S. A. Macgregor, C. L. McMullin, *Chem. Rev.* 2017, *117*, 8649. (i) F. M. Miloserdov, D. McKay, B. K. Munoz, H. Samouei, S. A. MacGregor, V. V. Grushin, *Angew. Chem. Int. Ed.* 2015, *54*, 8466.
- [11] (a) R.-Y. Zhu, M. E. Farmer, Y.-Q. Chen, J.-Q. Yu, *Angew. Chem. Int. Ed.* 2016, 55, 10578. (b) C. Sambiagio, D. Schönbauer, R. Blieck, T. Dao-Huy, G. Pototschnig, P. Schaaf, T. Wiesinger, M. Farooq Zia, J. Wencel-Delord, T. Besset, B. U. W. Maes, M. Schnürch, *Chem. Soc. Rev.* 2018, 47, 6603. (c) M. Font, J. M. Quibell, G. J. P. Perry, I. Larrosa, *Chem. Commun.* 2017, 53, 5584. (d) M. Pichette Drapeau, L. J. Goossen, *Chem. Eur. J.* 2016, 22, 18654. (e) Z. Huang, H. N. Lim, F. Mo, M. C. Younga, G. Dong, *Chem. Soc. Rev.* 2015,44, 7764. (f) Q.-Z. Zheng, N. Jiao, *Tet. Lett.* 2014, 55, 1121.

- [12] T. Cernak, K. D. Dykstra, S. Tyagarajan, P. Vachal, S. W. Krska, *Chem. Soc. Rev.* 2016, 45, 546.
- [13] (a) F. Zhang, D. R. Spring, *Chem. Soc. Rev.* 2014, 43, 6906. (b) G. Rousseau, Bernhard Breit, *Angew. Chem. Int. Ed.* 2011, 50, 2450.
- [14] K. Raghuvanshi, K. Rauch, L. Ackermann, Chem. Eur. J. 2015, 21, 1790.
- [15] (a) Q. Zhao, T. Poisson, X. Pannecoucke, T. Besset, *Synthesis* 2017, *49*, 4808. (b)
  P. Gandeepan1, L. Ackermann, *Chem* 2018, *4*, 199.
- [16] (a) R. K. Arigela, R. Kumar, T. Joshi, R. Mahar, B. Kundu, *RSC Adv.* 2014, *4*, 57749. (b) K. Muralirajan, R. Haridharan, S. Prakash, C.-H. Cheng, *Adv. Synth. Catal.* 2015, *357*, 761. (c) Y. Liu, Y. Zhang, M. Huang, J.-P. Wan, *RSC Adv.* 2015, 5, 46192. (d) L. Zheng, R. Hua, *Chem. Eur. J.* 2014, *20*, 2352. (e) L. Qiu, D. Huang, G. Xu, Z. Dai, J. Sun, *Org. Lett.* 2015, *17*, 1810. (f) A. Bartoszewicz, B. Martin-Matute, *Org. Lett.* 2009, *11*, 1749. (g) A. J. A. Watson, A. C. Maxwell, J. M. J. Williams, *Org. Lett.* 2010, *12*, 3856. (h) d) B. Li, C. Darcel, P. H. Dixneuf, *Chem. Commun.* 2014, *50*, 5970. (i) L. Ackermann, R. Jeyachandran, H. K. Potukuchi, P. Nova, L. Bgttner, *Org. Lett.* 2010, *12*, 2056. (j) B. Li, C. B. Bheeter, C. Darcel, P. H. Dixneuf, *ACS Catal.* 2011, *1*, 1221. (k) L. Ackermann, R. Born, P. Alvarez-Bercedo, *Angew. Chem. Int. Ed.* 2007, *46*, 6364.
- [17] L. Huang, A. Biafora, G. Zhang, V. Bragoni, L. J. Goossen, *Angew. Chem. Int. Ed.***2016**, *55*, 6933.
- [18] C.-H. Jun, H. Lee, J.-B. Hong, J. Org. Chem. 1997, 62, 1200.
- [19] C. Bruneau, R. Gramage-Doria, Adv. Synth. Catal. 2016, 358, 3847.
- [20] (a) L. Ping, D. S. Chung, J. Bouffard, S.-G. Lee, *Chem. Soc. Rev.* 2017, 46, 4299.
  (b) A. Dey, S. K. Sinha, T. K. Achar, D. Maiti, *Angew. Chem. Int. Ed.* 2019, 58, 10820. (c) J. Yang, *Org. Biomol. Chem.* 2015, 13, 1930.
- [21] M. Ghosh, S. De Sarkar, Asian J. Org. Chem. 2018, 7, 1236.
- [22] (a) D. Leow, G. Li, T.-S. Mei, J.-Q. Yu, *Nature* 2012, 486, 518. (b) Z. Zhang, K. Tanaka, J.-Q. Yu, *Nature* 2017, 543, 538.

- [23] (a) H. J. Davisa, R. J. Phipps, *Chem. Sci.* 2017, *8*, 864. (b) M. T. Mihai, G. R. Genova, R. J. Phipps, *Chem. Soc. Rev.* 2018, *47*, 149. (c) L. Yang, K. Semba, Y. Nakao, *Angew. Chem. Int. Ed.* 2017, *56*, 4853. (d) L. Yang, N. Uemura, Y. Nakao, *J. Am. Chem. Soc.* 2019, *141*, 7972.
- [24] Y. Kuninobu, H. Ida, M. Nishi, M. Kanai, Nature Chem. 2015, 7, 712.
- [25] (a) J. A. Leitch, C. G. Frost, *Chem. Soc. Rev.* 2017, 46, 7145. (b) C. J. Teskey, A. Y. W. Lui, M. F. Greaney, Angew. Chem. Int. Ed. 2015, 54, 11677. (c) Q. Yu, L. Hu, Y. Wang, S. Zheng, J. Huang, *Angew. Chem. Int. Ed.* 2015, 54, 15284. (d) C. Whiteoak, O. Planas, A. Company, X. Ribas, *Adv. Synth. Catal.* 2016, 358, 1679.
- [26] O. Saidi, J. Marafie, A. E. W. Ledger, P. Man Liu, M. F. Mahon, G. Kociok-Koehn,M. K. Whittlesey, C. G. Frost, J. Am. Chem. Soc. 2011, 133, 19298.
- [27] (a) C. B. Bheeter, L. Chen, J.-F. Soule, H. Doucet, *Catal. Sci. Technol.* 2016, 6, 2005. (b) S. I. Gorelsky, *Coord. Chem. Rev.* 2013, 257, 153. (c) I. V. Seregin, V. Gevorgyan, *Chem. Soc. Rev.* 2007, 36, 1173. (d) G. P. McGlacken, L. M. Bateman, *Chem. Soc. Rev.* 2009, 38, 2447. (e) L. Ackermann, R. Vicente, A. R. Kapdi, *Angew. Chem. Int. Ed.* 2009, 48, 9792.
- [28] A. Ohta, Y. Akita, T. Ohkuwa, M. Chiba, R. Fukunaga, A. Miyafuji, T. Nakata, N. Tani, Y. Aoyagi, *Heterocycles* 1990, *31*, 1951.
- [29] (a) P. Nareddy, F. Jordan, S. E. Brenner-Moyer, M. Szostak, ACS Catal. 2016, 6, 4755. (b) Y. Hashimoto, T. Ortloff, K. Hirano, T. Satoh, C. Bolm, M. Miura, Chem. Lett. 2012, 41, 151. (c) R. Das, M. Kapur, Chem. Eur. J. 2016, 22, 16986. (d) R. Das, M. Kapur, Chem. Asian J. 2015, 10, 1505. (e) Z. Yang, F.-C. Qiu, J. Gao, Z.-W. Li, B.-T. Guan, Org. Lett. 2015, 17, 4316. (f) P. Nareddy, F. Jordan, M. Szostak, Chem. Sci. 2017, 8, 3204. (g) N. Y. More, K. Padala, M. Jeganmohan, J. Org. Chem. 2017, 82, 12691. (h) R. Manikandan, P. Madasamy, M. Jeganmohan, ACS Catal. 2016, 6, 230.
- [30] (a) S. Nomura, K. Endo-Umeda, A. Aoyama, M. Makishima, Y. Hashimoto, M. Ishikawa, ACS Med. Chem. Lett. 2015, 6, 902. (b) S. Nomura, K. Endo-Umeda,

M. Makishima, Y. Hashimoto, M. Ishikawa, *ChemMedChem* 2016, *11*, 2347. (c)
S. Nomura, K. Endo-Umeda, S. Fujii, M. Makishima, Y. Hashimoto, M. Ishikawa, *Bioorg. Med. Chem. Lett.* 2018, *28*, 796. (d) M. R. Lunn, D. E. Root, A. M. Martino,
S. P. Flaherty, B. P. Kelley, D. D. Coovert, A. H. Burghes, N. T. Man, G. E. Morris,
J. Zhou, E. J. Androphy, C. J. Sumner, B. R. Stockwell, *Chem. Biol.* 2004, *11*, 1489.

[Part of this chapter has been published in Synthesis 2018, 50, 4216-4228]

### Chapter 1. Merging transition metal catalysis with phthalimides: a new entry to useful building blocks

#### 1.1. Introduction

Multi-functionalized molecules conveniently synthesized from readily available building blocks represent the central core of chemical synthesis and, consequently, it has helped in the advancement and progress of our societies.<sup>1</sup> As such, chemical motifs displaying unique physical and biological features have been targeted by chemists all over the years. New synthetic routes are always appealing to generate the desired molecules in an efficient manner.<sup>2</sup> From a sustainable point of view, it is more than welcome to generate highly functionalized molecules starting from readily available building blocks (hydrocarbons, aminoacids, etc.) and benign reagents (O<sub>2</sub>, H<sub>2</sub>O, CO<sub>2</sub>, etc.).<sup>3</sup> Nevertheless, there are molecules that are easily obtained in large quantities and that actually constitute a suitable starting point for a desired synthetic pathway.

In this respect, phthalimides and their derivatives are particularly interesting. They are bicyclic structures consisting on an aromatic ring fused with a five-membered ring bearing a cyclic imide (Scheme 1.1). Probably, the most important reason why synthetic chemists, either in the industry or in academia, employ the phthalimide backbone is to introduce at will primary amines after deprotection with hydrazine as reagent (Gabriel synthesis)<sup>4</sup> or with the NaBH4/HCl method.<sup>5</sup> On one hand, phthalimides are well recognized for multiple purposes and some representative derivatives are depicted in Scheme 1.1. They have found applications in biology<sup>6</sup> and as chemical motifs for dyes,<sup>7</sup> organic solar cells<sup>8</sup> and porous solids.<sup>9</sup> Polymers containing the phthalimide skeleton are also actively studied for multiple applications.<sup>10</sup> Furthermore, phthalimide derivatives are excellent candidates as redox-active ester (RAE) reagents for challenging organic transformations<sup>11</sup> and their use as organocatalysts is just starting.<sup>12</sup>



Scheme 1.1 Molecular structure of a phthalimide backbone surrounded by useful examples containing this chemical motif.

On the other hand, an interesting approach is to consider the phthalimide backbone as a starting point for a given synthetic pathway. This is apparently due to the high density of chemical information lying in such a very small molecular fragment. Unfortunately, most of the phthalimide transformations are based on the use of hazardous reagents employed in an over-stoichiometric manner such as hydride salts (BH<sub>3</sub>, NaBH<sub>4</sub>, LiAlH<sub>4</sub>, DIBAL-H, etc.), alkyl lithium salts (RLi), Grignard reagents (RMgX) or metallic Zn and Sn in the presence of acids (HCl, HOAc, etc.).<sup>13</sup> Such reagents, although efficient, are extremely air and moisture sensitive. They also generate large amounts of toxic by-products. From a sustainable point of view, it seems more convenient to find alternative pathways that could find real applications in industry and academic laboratories.

The last decade has witnessed the potential of transition metal catalysts in these directions under more benign conditions. Moreover, in some cases, they enabled unprecedented chemical disconnections that could find further implementation in fine chemistry. In this chapter, a summary about the multiple organic molecules that have

been so far obtained starting from phthalimides by employing catalytic systems based on transition metals are discussed (Scheme 1.2). For comparison purposes, other relevant non-metal catalyzed transformations are also included. Transformations of phthalimides with organocatalysts are beyond the scope of this summary.



Scheme 1.2 Overview of the transformations reviewed in this chapter.

#### 1.2 Partial carbonyl reduction

Selective hydrogenation of one carbonyl group of the phthalimide skeleton is expected to give rise to hydroxy lactam derivatives, which are interesting motifs in organic synthesis. This was pioneered by Bergens and co-workers who reported in 2010 the first examples in which *N*-methyl, *N*-phenyl and *N*-benzyl phthalimides, respectively, were monohydrogenated in the presence of a transition metal catalyst leading to the corresponding hydroxy lactams in good yields (Scheme 1.3).<sup>14</sup> Such transformations were accomplished by employing as little as 1 mol% of Noyori-type ruthenium-dihydride catalyst based on BINAP and diamine ligands with only 4 bar of H<sub>2</sub> gas and 9 mol% of *t*-BuOK as base at 30 °C for 3 hours. The relevance of the

ruthenium catalyst design was evidenced as replacing the ethylenediamine ligand by the (R,R)-1,2-diphenylethylenediamine ligand led to significantly lower yield (55%) for *N*-methylphthalimide as a substrate. Raising the reaction temperature to 60 °C did not increase the conversion, but started to produce ring-opening byproducts due to over hydrogenation processes. Heterogeneous catalysts such as PtO<sub>2</sub> and Pd/C enabled the hydrogenation of one ketone group of phthalimides into an alcohol functionality but with very low selectivity since the aromatic ring of the phthalimide backbone was fully hydrogenated to some extent.<sup>15</sup>



Scheme 1.3 Ru-catalyzed monohydrogenation of *N*-substituted phthalimides.

Wan, Xie, and co-workers reported the selective reduction of phthalimides with  $(EtO)_3SiH$  or PMHS (PMHS = polymethylhydrosiloxane) by means of Zn(OAc)\_2•2H\_2O and TMEDA as the active catalyst at 70 °C (Scheme 1.4).<sup>16</sup> In this manner, different hydroxylactams were readily prepared in high yields after workup under basic conditions. The reaction was found to be compatible with different functional groups such as alkyl, benzyl, allyl, esters, amides, and bromides. Protected piperazine derivatives were also compatible. In the case of a pyridine-containing substrate, the reduction regioselectively took place at the carbonyl adjacent to the nitrogen atom, likely due to nitrogen-zinc coordination prior to the carbonyl reduction. When the aromatic ring of the phthalimide was substituted with an allyl fragment, a mixture of the two possible regioisomers was obtained (Scheme 1.4). This protocol was also applicable to other types of cyclic imides leading to the corresponding  $\omega$ -hydroxylactams. Zhang, Xie, and co-workers later accomplished the same transformation using KOH as catalyst at room temperature.<sup>17</sup>



**Scheme 1.4** Zn-catalyzed hydrosilane monoreduction of functionalized *N*-substituted phthalimides; silane = (EtO)<sub>3</sub>SiH or PMHS.

In 2016, Beller and co-workers described the first examples of transition metalcatalyzed reductive alkoxylation and amination reactions of phthalimides (Scheme 1.5).<sup>18</sup> They employed a catalytic system based on  $[Ru(acac)_3]$  (acac = acetylacetonate) with Triphos [Triphos = 1,1,1-tris(diphenylphosphinomethyl)-ethane] ligand and methanesulfonic acid (MeSO<sub>3</sub>H) in the presence of H<sub>2</sub> and an excess of alcohol or secondary amine. They provided a broad scope using methanol under rutheniumcatalyzed reductive conditions with a variety of N-substituted phthalimides. Alkyl, benzyl, aryl, ethers, primary amines, tertiary amines and halides (Br, Cl, F, CF<sub>3</sub>) were tolerated (Scheme 1.5, A). Under this reaction conditions, however, terminal and internal alkyne groups were hydrogenated into the corresponding alkyl groups. Similarly, a cyclic ketone was hydrogenated into the corresponding secondary alcohol. The reaction was also applicable to primary alcohols different from methanol. For instance, primary and secondary aliphatic alcohols gave the corresponding 2-alkoxylated isoindolinones in excellent yields. Phenethyl and benzylic alcohols, even polyfluorinated ones, reacted efficiently also. N-methylphthalimides substituted in the arene ring at the 4'-position with electron-donor groups, such as NH<sub>2</sub> and NMe<sub>2</sub> afforded one regioisomer as the major product (Scheme 1.5, B). However, when they were substituted with electron-withdrawing groups, mixtures of regioisomers were obtained (Scheme 1.5, B). The reactions could be carried out with the alcohol as solvent (neat) or in the presence of an excess of alcohol using THF as solvent. Interestingly, substrates containing primary aliphatic alcohols or carboxylic acids underwent subsequent intramolecular reductive methoxylation (Scheme 1.5, C). This route

constitutes an appealing access to original tricyclic compounds in a one-pot manner. It was also noted that the same ruthenium-based system was able to catalyze the reaction of *N*-substituted phthalimides with primary amines leading to selective reductive aminations when operating under 50 bar of  $H_2$ . The corresponding 2-aminated isoindolinones were obtained in good to moderate yields (Scheme 1.5, D).



**Scheme 1.5** Selective Ru-catalyzed reductive alkoxylation (A-B), one-pot intramolecular reductive cyclization (C) and reductive amination (D) of phthalimides.

Although the mechanism for the ruthenium-catalyzed alkoxylation and amination was not addressed, in 2017 Beller and co-workers showed that the same type of alkoxylation reactions was catalyzed by a non-noble metal-based catalytic system  $[Co(BF_4)_2 \bullet 6H_2O/Triphos]$  and they provided evidence for the mechanism in this case.<sup>19</sup> In contrast with the ruthenium-catalyzed transformation, the reactions with cobalt were carried out in the absence of acid and under milder reaction conditions  $[H_2$  (20 bar), 90 °C]. A mechanism based on kinetic studies and control experiments was proposed

(Scheme 1.6). The first step, which is claimed to be the rate-limiting one, is the cobaltcatalyzed hydrogenation of a carbonyl group leading to the hemiaminal intermediate **A**, which after protonation leads to intermediate **B**. The authors suggest that protons are generated from the complex [Co(BF<sub>4</sub>)<sub>2</sub>•6H<sub>2</sub>O]. Reductive alkoxylation of **B** in the presence of alcohols with elimination of water leads to the product. According to highresolution electrospray ionization mass spectrometry (ESI-HRMS) experiments, the Triphos ligand remained attached to the cobalt center during the hydrogenation step and the alkoxylation step as well.



Scheme 1.6 Postulated reaction mechanism for the Co-catalyzed selective reductive alkoxylation of phthalimides; solv = solvent.

The nucleophilic addition of Grignard, organozinc or lithium reagents to the carbonyl group of the phthalimide backbone constitutes a route to obtain the corresponding alcohol. However, most of the examples suffer from uncontrolled multiple additions that lead to a mixture of products.<sup>20</sup> In 2013, Johnson and co-workers reported the first successful example of a nickel-catalyzed addition of organozinc reagents (Et<sub>2</sub>Zn and Ar<sub>2</sub>Zn) to phthalimides leading to the corresponding 3-hydroxy- $\gamma$ -lactam products in good yields using a [Ni(COD)<sub>2</sub>] (COD = 1,5-cyclooctadiene) complex as pre-catalyst (Scheme 1.7).<sup>21</sup> The reaction is very sensitive to the electronic nature of the phthalimide substituents as no product was formed using *N*-alkyl and *N*-arylphthalimides containing electron-releasing functional groups (i.e., benzyl or 4-methoxyphenyl). Although no mechanistic data was provided, a catalytic cycle was proposed indicating that the reaction proceeded via a key nickelacycle intermediate

rather than a direct nucleophilic attack on the carbonyl bond (Scheme 1.7). Such plausible pathway is likely due to the relevance of PPh<sub>3</sub> as ligand. The authors also indicated the need to perform an acidic work up at the end of the reaction to recover the 3-hydroxy- $\gamma$ -lactam product. The non-catalyzed version was previously studied by the same group using stoichiometric amounts of [Ni(COD)<sub>2</sub>] and 2,2'-bipyridine as a ligand.<sup>22</sup>



Scheme 1.7 Ni-catalyzed addition of diorganozinc nucleophiles to *N*-substituted phthalimides and postulated mechanism.

#### 1.3 Full carbonyl reduction

The full reduction of one carbonyl group of the phthalimide backbone leads to valuable lactam building blocks. Most of the studies in this direction have been dominated by heterogeneous metal catalysts. In 1930, a pioneering study by Adkins and Cramer showed that *N*-H phthalimide was efficiently hydrogenated into the corresponding isoindolinone (phthalimidine) using a heterogeneous nickel catalyst under high pressures of H<sub>2</sub> (50-200 bar) at 200 °C (Scheme 1.8, A).<sup>23</sup> In 1988, Kreber, Hennige, and co-workers reported similar observations with Raney nickel as the catalyst (Scheme 1.8, A).<sup>24</sup> In 2013, Garcia and co-workers found that the hydrogenation of *N*-H phthalimide into isoindolinone was possible using 20 mol% of

[Ni(COD)<sub>2</sub>] as catalyst under 50 bar of H<sub>2</sub> and long reaction times (3-8 days) at 140-180 °C.<sup>25</sup> To overcome the harsh reaction conditions previously employed for nickel catalysis, in 1996 Milewska and co-workers developed a stepwise approach. They performed a selective monothionation with the Lawesson's reagent (LR) followed by desulfurization with Raney nickel in absolute ethanol leading to the corresponding lactam with no need for using autoclave reactors with H<sub>2</sub> (Scheme 1.8, B).<sup>26</sup>



Scheme 1.8 Ni-catalyzed hydrogenation of phthalimides into lactams.

Palladium catalysts, on the other hand, enabled the same transformation under relatively milder reaction conditions compared with nickel catalysts. McCrindle and co-workers reported that Pd/C efficiently hydrogenated some *N*-substituted phthalimides to give the corresponding isoindolinones (Scheme 1.9, A).<sup>27</sup> Interestingly, this methodology has been found suitable to carbohydrate-substituted phthalimides applying only 4.2 bar of H<sub>2</sub> (Scheme 1.9, B)<sup>28</sup> as well as pyridinone-substituted phthalimides applying 30 bar of H<sub>2</sub> (Scheme 1.9, C).<sup>29</sup> In the latter case, it is noteworthy to mention that the C=C bonds of the pyridinone moiety were also reduced. In other examples, it has been shown that trifluoroacetic acid was beneficial for the palladium-catalyzed hydrogenation of phthalimides.<sup>30</sup>


Scheme 1.9 Pd/C-catalyzed hydrogenation of phthalimides into lactams.

In 2011, Beller and co-workers described the selective monoreduction of phthalimides into the corresponding isoindolinones using 5 mol% of TBAF (TBAF = tetrabutylammonium fluoride) as catalyst in the presence of over-stoichiometric amounts of PMHS (typically 5 equiv.) at room temperature (Scheme 1.10).<sup>31</sup> Interestingly, this transformation was found to be compatible with a wide scope of substrates due to the fact that there was no need to use H<sub>2</sub> as reagent together with the very mild reaction conditions employed. As such, good yields were obtained for *N*-substituted phthalimides containing alkyl, benzyl, alkynes (terminal or internal), ethers, acetals, epoxides, and halides as functional groups. Combining in situ ATR-FTIR and UV-vis spectroscopic studies together with control experiments and deuteration experiments enabled the authors to propose a catalytic cycle, the fluoride anion is coordinated to the silicon center of Ph<sub>2</sub>SiH<sub>2</sub> leading to a very reactive pentacoordinated species, which subsequently attacks the C=O bond of the phthalimide

substrate. Since the silane reagent is in excess during the reaction, it forms additional pentacoordinated silicon species with fluoride anions enabling a second hydride transfer to take place prior to the release of the substrate and formation of Ph<sub>2</sub>HSiOSiHPh<sub>2</sub> as by-product. Overall, fluoride anions behave as the true catalyst in this transformation.



Scheme 1.10 Fluoride-catalyzed monoreduction of phthalimides and proposed mechanism.

In addition, the authors managed to perform a very appealing one-pot reduction of N-benzylphthalimide to N-benzylisoindoline in 55% yield combining the fluoridecatalyzed reduction with a subsequent iron-catalyzed reduction, using PMHS as reducing agent in both steps (Scheme 1.11).<sup>31</sup> This example shows the promising potential of performing cascade or domino sequences using phthalimides and homogeneous catalysts together. Alternatively, Garcia and co-workers reported the full hydrogenation of both carbonyl groups of N-trimethylsilylphthalimide leading to the corresponding isoindoline with a homogeneous nickel-based catalytic system, but with a very low yield of 30%.<sup>25</sup>



Scheme 1.11 One-pot reduction of phthalimides to isoindolines with two different homogeneous catalysts.

In 2016, Xie and co-workers reported a similar reaction to that described by Beller in 2011, but using KOH as catalyst and Ph<sub>2</sub>SiH<sub>2</sub> as reducing agent (Scheme 1.12).<sup>17</sup> Although the mechanism was not investigated, they showed the conversion of thirteen substituted phthalimides into the corresponding lactams, some of them including heterocyclic fragments. The reaction was found to be rather efficient lasting less than 3 hours.



Scheme 1.12 KOH-catalyzed monoreduction of phthalimides to lactams with Ph<sub>2</sub>SiH<sub>2</sub>.

#### 1.4 Aromatic ring reduction

In the 1960, McCrindle and co-workers reported a series of contributions dealing with the hydrogenation of the aromatic ring of the phthalimide backbone using Adams' platinum oxide (PtO<sub>2</sub>) as catalyst (Scheme 1.13).<sup>15,32</sup> The reactions with *N*-H and *N*-Me substituted phthalimides led to the corresponding hexahydrophthalimides in excellent yields under 1 bar of H<sub>2</sub> where the carbonyl groups remained unreacted. As the reaction follows a standard heterogeneous pathway, the conformation of the resulting product

was found to be *cis*. However, with other different substituents (acetyl, ester, amide, etc.) at the nitrogen side, partial reduction of carbonyl groups into alcohols was observed as a competitive side reaction.



Scheme 1.13 PtO<sub>2</sub>-catalyzed selective hydrogenation of the phthalimide aromatic ring.

The heterogeneously catalyzed hydrogenations of phthalimides have shown their importance as the corresponding hexahydrophthalimide products provide better chromatographic separation than the phthalimide partners. For example, Scheuer and co-workers reported the synthesis of chiral unusual aminoacids for a natural product structural determination, in which the key step was the hydrogenation of the aromatic ring of the phthalimide.<sup>33</sup> They realized that the hexahydrophthalimide molecules were better separated by preparative chiral HPLC than the phthalimide ones, thus enabling a more efficient synthesis of chiral amino acids (Scheme 1.14).



Scheme 1.14 PtO<sub>2</sub>-catalyzed hydrogenation of the phthalimide aromatic ring leading to mixture of easily separated hexahydrophthalimides.

With the aim of replacing the highly expensive platinum catalysts, ruthenium complexes have also been employed as catalysts for the hydrogenation of the aromatic ring of the phthalimide backbone. In 2005, Bruneau and co-workers reported the use of  $[Ru_4H_6(p-cymene)_4]Cl_2$  and  $[RuCl_2(p-cymene)]_2$  as efficient catalysts for the reduction of cyclic imides into the corresponding lactams with concomitant reduction of C=C bonds from the aromatic ring as well (Scheme 1.15).<sup>34</sup> In the case of *N*-H phthalimide, [Ru<sub>4</sub>H<sub>6</sub>(*p*-cymene)<sub>4</sub>]Cl<sub>2</sub> led exclusively to the corresponding *cis*-disposed lactam with full hydrogenation of the aromatic ring and one carbonyl group. On the other hand,  $[RuCl_2(p-cymene)]_2$  was less efficient because the reduction of the C=O bonds was not fully accomplished. N-Substituted phthalimides where only hydrogenated in the aromatic ring, leaving the carbonyl bonds unreacted. This fact highlights the relevance of the N-H functionality for assistance in the reduction of the carbonyl groups and that the reduction of the aromatic ring is easier than the reduction of carbonyl groups with this catalytic system. The reactions were performed in water as solvent and with 10-60 bar of H<sub>2</sub> gas at 50-90 °C using as low as 1-2 mol% of ruthenium pre-catalyst. Mercury test experiments indicated that the system operated under a homogeneous regime.



Scheme 1.15 Ru-catalyzed hydrogenation of the phthalimide aromatic ring.

In 2016, Beller and co-workers reported an interesting approach to hydrogenate aromatic rings, which is based on ruthenium nanoparticles immobilized on a nitrogendoped carbon support (Ru@NDCs-800).<sup>35</sup> In this way, *N*-H phthalimide was hydrogenated to give the corresponding aliphatic imide in 94% isolated yield (Scheme 1.16). Although no examples of *N*-substituted phthalimides were reported, this strategy

is particularly appealing since the authors even managed to recycle and reuse the catalyst up to five times with no obvious deactivation observed.



Scheme 1.16 Ru-on-particles-catalyzed hydrogenation of the phthalimide aromatic ring.

A couple of examples have also proven that rhodium complexes can be used as efficient catalysts for the hydrogenation of the aromatic ring of the phthalimide backbone.<sup>36-38</sup> The first example was reported by Agbossou-Niedercorn and co-workers.<sup>36</sup> They managed to hydrogenate the aromatic ring as well as both carbonyl groups of the phthalimide skeleton with formation of the corresponding cyclic amine in 58% yield. Although the reaction gave full conversion, the low yield was associated to unknown degradation products. The hydrogenation reaction was accomplished by using a hybrid catalytic system based on rhodium and molybdenum carbonyl complexes (Scheme 1.17). Furthermore, the most promising reaction conditions were found to be with the green solvent cyclopentyl methyl ether (CPME) and it was possible to recycle the catalytic system at least three times without significant loss of activity. Notably, this type of cyclic amine is a prevalent motif in numerous drug candidates such as the Mitiglinide (Scheme 1.17).<sup>37</sup>



Scheme 1.17 Rh/Mo-catalyzed reduction of *N*-H phthalimide into a biologicallyrelevant cyclic amine.

Lee, Sohn, and co-workers reported a series of modified rhodium nanoparticles as catalysts for the aromatic reduction of the *N*-H phthalimide.<sup>38</sup> Depending on the

structural features of the nanocatalyst, different reactivities and product selectivities were observed for the hydrogenation reaction (Scheme 1.18). For instance, using coreshell Pt<sub>3</sub>Ni@Rh starfish (Star) as catalyst led to the selective reduction of the aromatic ring with no reduction of the carbonyl groups even for long reaction times (6-24 h). The outcome was different with core-shell Pt<sub>3</sub>Ni@Rh pentagons (Pent) as catalysts. After 6 hours these catalysts started to hydrogenate also one carbonyl bond, leading to a ratio of products of 28:72 after 24 hours. A rhodium-based paddlewheel (PW) nanocatalyst, made up from a Pt<sub>3</sub>Ni crankshaft and two Rh five-fold starfish wheels, started to reduce also one carbonyl group before 6 hours (Scheme 1.18).



Scheme 1.18 Selective reduction of the aromatic ring of *N*-H-phthalimide with different Rh-based nanoparticles as catalysts.

In 2013, Garcia and co-workers reported the sole example for the full hydrogenation of *N*-methylphthalimide using a nickel catalyst, namely [(dippe)Ni( $\mu$ -H)]<sub>2</sub> (dippe = 1,2-bis(diisopropylphosphino)ethane).<sup>25</sup> The reaction was carried out with 1 mol% of nickel catalyst under 60 bar of H<sub>2</sub> at 140 °C in THF. Under these harsh reaction conditions, a modest 33% yield of cyclic amine was obtained (Scheme 1.19). Mercury tests were carried out confirming the formation of nickel nanoparticles during the catalysis. These catalytically active nanoparticles were further characterized by transmission electron microscopy (TEM).



Scheme 1.19 Ni-catalyzed reduction of N-methylphthalimide.

#### 1.5 Five-membered ring opening

The cleavage of the five-membered ring of the phthalimide skeleton can constitute an interesting approach towards molecular scaffolds difficult to synthesize by other means. This approach has met with success in the last decade, in part, due to the pioneering discovery by Ikariya and co-workers on ruthenium-catalyzed hydrogenation reactions. In 2007, they showed that selective hydrogenation of the five-membered ring of *N*-benzyl and *N*-phenylphthalimide, respectively, led to the corresponding alcoholamide products in excellent yields using only 1 mol% of Cp\*RuCl[Ph<sub>2</sub>P(CH<sub>2</sub>)<sub>2</sub>NH<sub>2</sub>- $\kappa^2$ -P,N] as catalyst and 10-30 bar of H<sub>2</sub> in the presence of catalytic amounts of base (Scheme 1.20, A).<sup>39</sup> The reactions were found to be rather fast (2 h) at a relatively mild temperature (80 °C). Control experiments revealed the crucial role of the NH<sub>2</sub> functionality of the ligand coordinated to the ruthenium center, which may provide appropriate Brønsted acidity in the transition state. The authors stressed the relevance of this methodology by performing a deprotection of a *N*-phthaloyl amino acid derivative (Scheme 1.20, B).



Scheme 1.20 Ru-catalyzed hydrogenation of phthalimides leading to ring-opening products and their relevance in organic synthesis.

A similar reaction outcome was observed by Adolfsson and co-workers after treating *N*-methylphthalimide with PMHS in the presence of catalytic amounts of Et<sub>2</sub>Zn and LiCl albeit with full hydrogenation of one carbonyl bond (Scheme 1.21).<sup>40</sup> The corresponding amino alcohol product was obtained in 67% yield under mild reaction conditions (room temperature) besides the formation of 11% of 2-methylisoindole as

byproduct (Scheme 1.21). Although mechanistic data were not provided, the authors suggested the participation of zinc-hydride species with LiCl acting as Lewis acid for amide carbonyl activation.



Scheme 1.21 Et<sub>2</sub>Zn/LiCl-catalyzed reduction of *N*-methylphthalimide leading, mainly, to an amino-alcohol product.

The transformation of phthalimides into amides was first reported by Garcia and co-workers, who described a single example using 1 mol% of [(dippe)Ni( $\mu$ -H)]<sub>2</sub> as precatalyst (Scheme 1.22).<sup>25</sup> The reaction provided benzamide with 82% selectivity (11% of isoindoline was also observed) under high pressure of H<sub>2</sub> (50 bar) and a long reaction time (3 days). Interestingly, the authors managed to isolate and characterize some potential intermediates by <sup>1</sup>H and <sup>31</sup>P NMR spectrometry analysis as well as X-ray crystallographic studies. These findings together with mercury tests enabled to postulate a homogeneous catalytic pathway for the transformation of *N*-H phthalimide into benzamide (Scheme 1.22). This reactivity of *N*-H phthalimide contrasts with that of the *N*-Me substituted analogue which led to the fully hydrogenated *N*-methyloctahydroisoindole without ring opening under related experimental conditions (Scheme 1.19).



Scheme 1.22 Ni-catalyzed transformation of *N*-H phthalimide into benzamide and postulated mechanism.

In 2017, Zhang and co-workers reported a highly selective hydrogenation of phthalimides into diols and primary amines using a tetradentate ruthenium complex catalyst and catalytic amounts of base in the presence of 50 bar of H<sub>2</sub> at 100 °C (Scheme 1.23).<sup>41</sup> When applied to *N*-benzylphthalimide as substrate, five-membered ring opening products were observed in 95% yield for the diol and 87% yield for the benzylamine. This methodology provided high turnover numbers (TON up to 9500 for *N*-benzylphthalimide) with very low catalyst loading (0.01 mol%).



Scheme 1.23 Ru-catalyzed hydrogenation of *N*-benzylphthalimides into a diol and benzylamine.

In a similar fashion, Milstein and co-workers reported a general protocol for the ruthenium-catalyzed hydrogenation of *N*-substituted phthalimides into diols (Scheme 1.24).<sup>42</sup> They employed a tridentate-supported ruthenium pre-catalyst that tolerated a large substrate scope including alkyl, aryl, benzyl, halide (F, Cl, CF<sub>3</sub>), ether, and

pyridine functional groups. The *N*-substituted phthalimides gave rise to the corresponding diols and primary amines in excellent yields under 20 bar of hydrogen gas and catalytic amounts of base (*t*-BuOK). According to preliminary mechanistic studies, the authors suggested a catalytic cycle (Scheme 1.24) in which, initially, one carbonyl bond is reduced to alcohol followed by C-N hydrogenolysis leading to a hydroxyamide intermediate. Intramolecular cyclization can give rise to a hemiaminal intermediate that eliminates the primary amine leading to phthalide (lactone). The former intermediate was detected by <sup>1</sup>H NMR spectrometry and GC analysis during the catalysis. A last hydrogenation step of phthalide affords the corresponding diol. Overall, the ruthenium catalyst participated in the hydrogenation and hydrogenolysis steps.<sup>42</sup>



Scheme 1.24 Ru-catalyzed hydrogenation of *N*-substituted phthalimides into diols and primary amines, and postulated mechanism.

An extremely appealing strategy is to take advantage of the five-membered ring opening of the phthalimide backbone for further bond forming reactions that might lead to more structurally complex molecules. In 2008, Kurahashi, Matsubara, and co-workers studied the nickel-catalyzed decarbonylative addition of phthalimides to internal alkynes leading to the corresponding ring extended *N*-substituted isoquinolones (Scheme 1.25, A),<sup>43</sup> the latter being biologically-relevant frameworks.<sup>44</sup> The active catalytic system was generated combining [Ni(COD)<sub>2</sub>] complex and trimethylphosphine as ligand in a 1:4 ratio. As such, oct-4-yne reacted with different

*N*-arylphthalimides, the best results being observed with electron-deficient substrates (including heteroaryls). Other internal alkynes were also tolerated although mixtures of isomers were formed when using non-symmetrical ones. When the reaction was attempted with *N*-phenylquinolimides as substrates, it was found that one isomer led to the selective carbonyl activation with exclusive formation of a single product, whereas the other isomer led to mixture of products (Scheme 1.25, B). The authors provided a plausible mechanism in which, first, Ni(0) cleaves the N-CO bond followed by decarbonylation and alkyne insertion leading to an unstable seven-membered ring intermediate that releases the product and regenerates the nickel catalyst (Scheme 1.25, framed).<sup>43</sup> Unfortunately, no data regarding these assumptions were provided. This strategy is complementary to the carboxylate-assisted ruthenium-catalyzed alkyne annulations by C-H/N-H functionalizations.<sup>45</sup>



Scheme 1.25 Ni-catalyzed decarbonylative addition of phthalimides to alkynes and postulated mechanism.

In 2010, Kurahashi, Matsubara, and co-workers reported a similar reaction but using symmetrical and unsymmetrical 1,3-dienes instead of alkynes as coupling partners.<sup>46</sup> This reaction provided 3-vinyldihydroisoquinolones in a high chemo- and regioselective manner via a nickel-catalyzed decarbonylative cycloaddition of phthalimides (Scheme 1.26, A). The reaction was successful for electron-deficient N-substituted phthalimides and no reaction was observed with 1,1-disubstituted 1,3dienes or unconjugated olefins (oct-1-ene, norbornene, methyl acrylate). 3'-Substituted *N*-(pyrrol-1-yl)phthalimides provided exclusively one regioisomer cycloadduct product (Scheme 1.26, B). However, 4'-substituted N-(pyrrol-1-yl)phthalimides provided mixtures of products in variable ratios (Scheme 1.26, C). The origin of the regioselectivity likely arises from the stabilization of nickelacycle intermediates that follow further diene insertion leading to acyclic  $\pi$ -allylnickel intermediates. Nucleophilic addition of the nitrogen atom onto the more substituted carbon atom of the allyl fragment should afford the observed products and regenerate the nickel catalyst (Scheme 1.26). Additionally, the authors found that 3'-amino-N-(pyrrol-1yl)phthalimide led to the opposite regioisomer of that expected, which was rationalized by a keto-enol tautomerism which prevents decarbonylation of the carbonyl group nearby the amino group.

Chapter 1



Scheme 1.26 Ni-catalyzed decarbonylative cycloaddition of phthalimides with 1,3dienes and postulated mechanism.

In 2013, Sueda and co-workers reported a silver-catalyzed reaction of readily available alcohols with *N*-alkynyl-substituted phthalimides leading to valuable *ortho*-(oxazol-2-yl)benzoates.<sup>47</sup> The reaction was catalyzed by Ag<sub>2</sub>O at high catalyst loading (30 mol%) and only unfunctionalized alkyl and aryl substituents were found to be compatible under the studied reaction conditions (Scheme 1.27). Although the reaction

mechanism remains elusive, control experiments suggested that the reaction proceeds as depicted in Scheme 1.27 with silver cations behaving as  $\sigma$ -electrophilic Lewis acids. Consequently, silver salts enabled nucleophilic addition of alcohol to the carbonyl group of the phthalimide substrate followed by ring opening and further 5-*endo*-digcyclization to form the product.



Scheme 1.27 Ag-catalyzed addition of alcohols to *N*-alkynylphthalimides leading to oxazoles and postulated mechanism.

The decarbonylative cross-coupling of phthalimides with diorganozinc reagents leading to *ortho*-alkylated benzamides was described by Johnson and co-workers using a nickel catalyst.<sup>48</sup> They realized that the choice of solvent and ligand played a crucial role for the success of the transformation (Scheme 1.28). Besides a narrow scope of substrates, some kinetic studies suggested the formation of nickelacycle intermediates during the catalytic cycle.



Scheme 1.28 Ni-catalyzed decarbonylative cross-coupling of phthalimides with diorganozinc reagents.

In 2016, Sheppard, Hailes, and co-workers reported the interesting reactivity observed upon heterogeneous hydrogenation of appropriately functionalized phthalimides with Pd/C as catalyst.<sup>49</sup> Under hydrogenation conditions, phthalimides containing dimethylhydrazine functional groups at 3'-position were found to give a ring opening transformation followed by lactam formation in the backside (Scheme 1.29, A). The same reaction was found to lead to a seven-membered ring-containing lactam starting from a conveniently designed phthalimide (Scheme 1.29, B). The resulting products are structurally related to a well-known polymerase inhibitor that has potential as a cancer chemotherapeutic drug.



Scheme 1.29 Sequential Pd/C-catalyzed lactam formation reactions via fivemembered ring opening of phthalimides.

#### **1.6** Conclusion

It is evident from this literature survey that the phthalimide backbone can be regarded nowadays as an extremely useful platform that can lead efficiently to more sophisticated molecular structures (lactams, isoindolones, isoindolinones, amines, amides, alcohols, etc.). Particularly, transition metal catalysis enables the straightforward synthesis of biologically appealing scaffolds. Although efficient, heterogeneous catalysts lead to a low degree of reaction control and low functional group tolerance due to the harsh reaction conditions generally employed. On the other hand, homogeneous catalysis enables a more advanced and sophisticated fine-tuning of the active species. This leads to very selective bond functionalizations with wide substrate scopes under relatively mild reaction conditions. Nevertheless, most of the mechanisms associated with the above-described reactions have not been investigated in depth. Obviously, a better understanding of the mechanisms operating in those cases will be extremely useful for the advancement of this research field. Furthermore, since more research efforts are being devoted to activate and functionalize in a controlled manner very strained chemical bonds (i.e. carbon-hydrogen, carbon-carbon, ethers, amides, etc.),<sup>50</sup> phthalimide molecules can follow such modern trend and open up a myriad of possibilities in terms of re-thinking the way we think in chemical synthesis. Additionally, the use of phthalimides as directing groups for transition metal-catalyzed C-H bond functionalization remains completely under-explored: another interesting entry into chemical diversity.<sup>51</sup>

#### **1.7 References**

- New Strategies in Chemical Synthesis and Catalysis; B. Pignataro, Wiley-VCH: Weinheim, 2012.
- [2] New Avenues to Efficient Chemical Synthesis; P. H. Seeberger, T. Blume, Springer: Heidelberg, 2007.
- [3] S. J. Lippard, *Nature*, **2002**, *416*, 587.
- [4] (a) M. S. Gibson, R. W. Bradshaw, Angew. Chem. Int. Ed. 1968, 7, 919. (b) Greenes's Protective Groups in Organic Synthesis: Fifth Edition; P. G. M. Wuts, Wiley-VCH: Weinheim, 2014, pp. 895-1193. (c) U. Ragnarsson, L. Grehn, Acc. Chem. Res., 1991, 24, 285.
- [5] (a) J. O. Osby, M. G. Martin, B. Ganem, *Tetrahedron Lett.* 1984, 25, 2093. (b) J.
   S. Alford, H. M. L. Davies, *Org. Lett.* 2012, 14, 6020.
- [6] (a) U. Sharma, P. Kumar, N. Kumar, B. Singh, *Mini-Rev. Med. Chem.* 2010, *10*, 678. (b) G.-H. Kuo, C. Prouty, W. V. Murray, V. Pulito, L. Jolliffe, P. Cheung, S. Varga, M. Evangelisto, J. Wang, *J. Med. Chem.* 2000, *43*, 2183. (c) R. Caraballo, M. Larsson, S. K. Nilsson, M. Ericsson, W. Qian, N. P. Nguyen Tran, T. Kindahl, R. Svensson, V. Saar, P. Artursson, G. Olivecrona, P.-A. Enquist, M. Elofsson, *Eur. J. Med. Chem.* 2015, *103*, 191. (d) G. E. Winter, D. L. Buckley, J. Paulk, J. M. Roberts, A. Souza, S. Dhe-Paganon, J. E. Bradner, *Science* 2015, *348*, 1376.
- [7] (a) Y. Wu, W. Zhu, *Chem. Soc. Rev.* 2013, 42, 2039. (b) A. D. Hendsbee, J.-P. Sun,
  W. K. Law, H. Yan, I. G. Hill, D. M. Spasyuk, G. C. Welch, *Chem. Mater.* 2016, 28, 7098.
- [8] (a) A. D. Hendsbee, S. M. McAfee, J.-P. Sun, T. M. McCormick, I. G. Hill, G. C. Welch, *J. Mater. Chem. C* 2015, *3*, 8904. (b) P. Gautam, R. Sharma, R. Misra, M. L. Keshtov, S. A. Kuklin, G. D. Sharma, *Chem. Sci.* 2017, *8*, 2017.
- [9] A. Pulido, L. Chen, T. Kaczorowski, D. Holden, M. A. Little, S. Y. Chong, B. J. Slater, D. P. McMahon, B. Bonillo, C. J. Stackhouse, A. Stephenson, C. M. Kane, R. Clowes, T. Hasell, A. I. Cooper, G. M. Day, *Nature* 2017, 543, 657.

- [10] (a) N.-J. Lee, J.-C. Koo, S.-S. Ju, S.-B. Moon, W.-J. Cho, I.-C. Jeong, S.-J. Lee, M.-Y. Cho, E. A. Theodorakis, *Polym. Int.* 2002, *51*, 569. (b) A. Postma, T. P. Davis, G. Li, G. Moad, M. S. O'Shea, *Macromolecules* 2006, *39*, 5307. (c) X. Guo, F. S. Kim, S. A. Jenekhe, M. D. Watson, *J. Am. Chem. Soc.* 2009, *131*, 7206. (d) H. Xin, X. Guo, F. S. Kim, G. Ren, M. D. Watson, S. A. Jenekhe, *J. Mater. Chem.* 2009, *19*, 5303.
- [11] (a) K. Okada, K. Okamoto, M. Oda, J. Am. Chem. Soc. 1988, 110, 8736. (b) J. Cornella, J. T. Edwards, T. Qin, S. Kawamura, J. Wang, C.-M. Pan, R. Gianatassio, M. Schmidt, M. D. Eastgate, P. S. Baran, J. Am. Chem. Soc. 2016, 138, 2174. (c) L. Candish, M. Teders, F. Glorius, J. Am. Chem. Soc. 2017, 139, 7440.
- [12] (a) S.-R. Ban, H.-Y. Xie, X.-X. Zhu, Q.-S. Li, *Eur. J. Org. Chem.* 2011, 6413. (b)
  M. G. Dekamin, M. Eslami, A. Maleki, *Tetrahedron* 2013, 69, 1074. (c) M. G. Dekamin, S. Z. Peyman, *Monatsch. Chem.* 2016, 147, 445.
- [13] For selected examples, see: (a) L. M. Rice, E. E. Reid, C. H. Grogan, J. Org. Chem. 1954, 19, 884. (b) K. C. Schreiber, V. P. Fernandez, J. Org. Chem. 1961, 26, 1744.
  (c) Z.-I. Horii, C. Iwata, Y. Tamura, J. Org. Chem. 1961, 26, 2273. (d) J. H. Brewster, A. M. Fusco, L. E. Carosino, B. G. Corman, J. Org. Chem. 1963, 28, 498. (e) J. H. Brewster, A. M. Fusco, J. Org. Chem. 1963, 28, 501. (f) Y. Kondo, B. Witkop, J. Org. Chem. 1968, 33, 206. (g) P. S. Anderson, M. E. Christy, C. D. Colton, W. Halczenco, G. S. Ponticelli, K. L. Shepard, J. Org. Chem. 1979, 44, 1519. (h) R. E. Gawley, S. R. Chemburkar, A. L. Smith, T. V. Anklekar, J. Org. Chem. 1988, 53, 5381. (i) L. A. Carpino, R. E. Padykula, D. E. Barr, F. H. Hall, J. G. Krause, R. F. Dufresne, C. J. Thoman, J. Org. Chem. 1988, 53, 2565. (j) M. H. Norman, G. C. Rigdon, F. Navas III, B. R. Cooper, J. Med. Chem. 1994, 37, 2552. (k) T. Nishio, H. Yamamoto, J. Heterocycl. Chem. 1995, 32, 883. (l) P. Pigeon, B. Decroix, Tetrahedron Lett. 1996, 37, 7707. (m) M. H. Norman, D. J. Minick, G. C. Rigdon, J. Med. Chem. 1996, 39, 149. (n) M. I. Collado, I. Manteca, N. Sotomayor, M.-J. Villa, E. Lete, J. Org. Chem. 1997, 62, 2080. (o) S. Cacchi, G.

Fabrizi, L. Moro, *Synlett* 1998, 741. (p) H. Okamura, H. Shimizu, Y. Nakamura, T. Iwagawa, M. Nakatani, *Tetrahedron Lett.* 2000, 41, 4147. (q) R. L. Hudkins, N. W. Johnson, J. Heterocycl. Chem. 2001, 38, 591. (r) S. Feng, C. A. Panetta, D. E. Graves, J. Org. Chem. 2001, 66, 612. (s) X.-H. Yuan, M.-J. Zhang, C.-Q. Kang, H.-Q. Guo, X.-P. Qiu, L.-X. Gao, *Synth. Commun.* 2006, 36, 435. (t) B. Decroix, A. Daïch, Š. Marchalín, J. Sikoraiová, *Tetrahedron Lett.* 2002, 43, 4747. (u) B. Decroix, A. Daïch, N. Hucher, J. Org. Chem. 2001, 66, 4695. (v) B. Decroix, P. Pigeon, S. Marchalin, A. Daïch, *Tetrahedron Lett.* 1998, 39, 9187. (w) B. Decroix, P. Pigeon, *Tetrahedron Lett.* 1998, 54, 8737. (y) B. Decroix, P. Pigeon, *Tetrahedron Lett.* 1997, 38, 2985.

- [14] S. Takebayashi, J. M. John, S. H. Bergens, J. Am. Chem. Soc. 2010, 132, 12832.
- [15] A. J. McAlees, R. McCrindle, J. Chem. Soc. C 1969, 2425.
- [16] G. Ding, B. Lu, Y. Li, J. Wan, Z. Zhang, X. Xie, Adv. Synth. Catal. 2015, 357, 1013.
- [17] G. Ding, C. Li, Y. Shen, B. Lu, Z. Zhang, X. Xie, Adv. Synth. Catal. 2016, 358, 1241.
- [18] J. R. Cabrero-Antonino, I. Sorribes, K. Junge, M. Beller, *Angew. Chem. Int. Ed.***2016**, 55, 387.
- [19] J. R. Cabrero-Antonino, R. Adam, V. Papa, M. Holsten, K. Junge, M. Beller, *Chem. Sci.* 2017, 8, 5536.
- [20] For successful examples, see: (a) E.-C. Wang, H.-F. Chen, P.-K. Feng, Y.-L. Lin, M.-K. Hsu, *Tetrahedron Lett.* 2002, 43, 9163; (b) T. Bousquet, J.-F. Fleury, A. Daïch, P. Netchitaïlo, *Tetrahedron* 2006, 62, 706; (c) P. Pigeon, B. Decroix, *Tetrahedron Lett.* 1996, 37, 7707.
- [21] J. M. Dennis, C. M. Calyore, J. S. Sjoholm, J. P. Lutz, J. J. Gair, J. B. Johnson, Synlett 2013, 24, 2567.

- [22] S. E. Havlik, J. M. Simmons, V. J. Winton, J. B. Johnson, J. Org. Chem. 2011, 76, 3588.
- [23] H. Adkins, H. I. Cramer, J. Am. Chem. Soc. 1930, 52, 4349.
- [24] H. Hennige, R. P. Kreber, M. Konrad, F. Jelitto, Chem. Ber. 1988, 121, 243.
- [25] A. Arevalo, S. Ovando-Segovia, M. Flores-Alamo, J. J. Garcia, *Organometallics* 2013, *32*, 2939.
- [26] M. J. Milewska, T. Bytner, T. Polonski, Synthesis 1996, 1485.
- [27] A. J. McAlees, R. McCrindle D. W. Sneddon, J. Chem. Soc. Perkin Trans. 1 1977, 2038.
- [28] X.-B. Meng, H. Li, Q.-H. Lou, M.-S. Cai, Z.-J. Li, Carbohydr. Res. 2004, 339, 1497.
- [29] N. A. Tolmachova, V. G. Dolovanyuk, I. I. Gerus, I. S. Kondratov, V. V. Polovinko,K. Bergander, G. Haufe, *Synthesis* 2011, *7*, 1149.
- [30] (a) A. Muller, K. Polborn, K. T. Wanner, J. Heterocycl. Chem. 2007, 44, 575. (b)
  B. L. Chenard, F. S. Menniti, Curr. Pharm. Des. 1999, 5, 381. (c) G. Hofner, C. E. Hoesl, C. Parsons, G. Quack, K. T. Wanner, Bioorg. Med. Chem. Lett. 2005, 15, 2231.
- [31] S. Das, D. Addis, L. R. Knopke, U. Bentrup, K. Junge, A. Bruckner, M. Beller, Angew. Chem. Int. Ed. 2011, 50, 9180.
- [32] (a) R. McCrindle, K. H. Overton, R. A. Raphael, J. Chem. Soc. 1962, 4798. (b) A.
  J. McAlees, R. McCrindle, Chem. and Ind. 1965, 1869.
- [33] A. Kimura, Y. Takada, T. Inayoshi, Y. Nakao, G. Goetz, W. Y. Yoshida, P. J. Scheuer, J. Org. Chem. 2002, 67, 1760.
- [34] R. Aoun, J.-L. Renaud, P. H. Dixneuf, C. Bruneau, Angew. Chem. Int. Ed. 2005, 44, 2021.
- [35] X. Cui, A. E. Surkus, K. Junge, C. Topf, J. Radnik, C. Kreyenschulte, M. Beller, *Nature Commun.* 2016, 7, 11326.

- [36] A. M. Maj, I. Suisse, N. Pinault, N. Robert, F. Agbossou-Niedercorn, *ChemCatChem* 2014, 6, 2621.
- [37] (a) J.-C. Souvie, C. Fugier, J.-P. Lecouve, *EP1127876A1*, 2001. (b) F. Sato, A. Tsubaki, H. Hokari, N. Tanaka, M. Saito, K. Akahane, M. Kobayashi, *EP19920302786*, 1999. (c) J.-P. Lecouve, C. Fugier, J.-C. Souvie, *WO99/01430*, 1999. (d) R. Aoun, J.-L. Renaud, P. H. Dixneuf, C. Bruneau, J.-C. Souvie, C. Fugier, *FR20030011226*, 2003.
- [38] N. T. Khi, H. Baik, H. Lee, J. Yoon, J.-H. Sohn, K. Lee, Nanoscale 2014, 6, 11007.
- [39] M. Ito, A. Sakaguchi, C. Kobayashi, T. Ikariya, J. Am. Chem. Soc. 2007, 129, 290.
- [40] O. O. Kovalenko, A. Volkov, H. Adolfsson, Org. Lett. 2015, 17, 446.
- [41] L. Shi, X. Tan, J. Long, X. Xiong, S. Yang, P. Xue, H. Lv, X. Zhang, *Chem. Eur. J.* 2017, 23, 546.
- [42] A. Kumar, T. Janes, N. A. Espinosa-Jalap, D. Milstein, J. Am. Chem. Soc. 2018, 140, 7453.
- [43] Y. Kajita, S. Matsubara, T. Kurahashi, J. Am. Chem. Soc. 2008, 130, 6058.
- [44] (a) T. N. Le, S. G. Gang, W.-J. Cho, J. Org. Chem. 2004, 69, 2768. (b) A. L. Ruchelman, P. J. Houghton, N. Zhou, A. Liu, L. F. Liu, E. J. LaVoie, J. Med. Chem. 2005, 48, 792. (c) B. D. Krane, M. Shamma, J. Nat. Prod. 1982, 45, 377.
- [45] L. Ackermann, Acc. Chem. Res. 2014, 47, 281.
- [46] K. Fujiwara, T. Kurahashi, S. Matsubara, Org. Lett. 2010, 12, 4548.
- [47] T. Sueda, A. Kawada, Y. Urashi, N. Teno, Org. Lett. 2013, 15, 1560.
- [48] K. S. DeGlopper, S. K. Fodor, T. B. D. Endean, J. B. Johnson, *Polyhedron* 2016, 114, 393.
- [49] S. Higson, F. Subrizi, T. D. Sheppard, H. C. Hailes, Green Chem. 2016, 18, 1855.
- [50] (a) F. Chen, T. Wang, N. Jiao, *Chem. Rev.* 2014, *114*, 8613. (b) J. Yamaguchi, A.
  D. Yamaguchi, K. Itami, *Angew. Chem. Int. Ed.* 2012, *51*, 8960. (c) F. Wang, S.
  Yu, X. Li, *Chem. Soc. Rev.* 2016, *45*, 6462. (d) J. Cornella, C. Zarate, R. Martin,

*Chem. Soc. Rev.* **2014**, *43*, 8081. (e) C. Liu, M. Szostak, *Chem. Eur. J.* **2017**, *23*, 7157 and references herein.

[51] X. Yang, G. Shan, Y. Rao, Org. Lett. 2013, 15, 2334.

[Part of this chapter has been published in Org. Lett. 2017, 19, 6404-6407]

# Chapter 2: Ruthenium-catalyzed protodecarbonylation of N-substituted phthalimide derivatives

#### 2.1 Introduction

The phthalimide motif is one of the most widely used functional groups in chemical synthesis. It enables protection of primary amines and behaves as an excellent nucleophile to install primary amines at will after treatment with hydrazine.<sup>1</sup> Phthalimides have also been applied as dyes,<sup>2</sup> porous solids,<sup>3</sup> polymers,<sup>4</sup> organocatalysts,<sup>5</sup> and for different biological applications.<sup>6</sup> Recently, phthalimides were conceived as key building blocks leading to important chemical skeletons due to their unique molecular structure. They are traditionally reduced employing overstoichiometric amounts of strong reagents (LiAlH<sub>4</sub><sup>7</sup> or BH<sub>3</sub><sup>8</sup>), superacids<sup>9</sup> or metal salts derived from Al,<sup>10</sup> Sn,<sup>11</sup> and Zn<sup>12</sup> under harsh reaction conditions. From a sustainable point of view, homogeneous catalysis has been considered to account for the functionalization of phthalimides under milder reaction conditions. Pharmaceutically and agrochemically relevant heterocyclic compounds have been obtained starting from phthalimides via (i) transition metal-catalyzed hydrogenations,<sup>13</sup> (ii) F- and Zn-catalyzed reductions with silanes<sup>14</sup> and (iii) Ru- and Co-catalyzed reductive alkoxylations and aminations.<sup>15</sup> In these approaches, the bicyclic structure of the phthalimide skeleton remained unreacted after selective hydrogen or nucleophile incorporation.13-15

Examples leading to the selective cleavage of the phthalimide skeleton are extremely rare, which highlights the challenges associated with these types of transformations.<sup>16</sup> For instance, a ruthenium catalyst was reported to hydrogenate *N*-protected phthalimides, leading to valuable alcohol-amide products in the presence of *t*-BuOK as strong base and 30 bar of H<sub>2</sub> (Scheme 2.1, A).<sup>16a</sup> One year later, a nickel catalyst enabled the decarbonylative addition of *N*-arylphthalimides to alkynes,

providing isoquinolones (Scheme 2.1, B).<sup>16b</sup> Finally, a nickel catalyst was reported to hydrogenate phthalimide to benzamide (one example) in 82% selectivity under 50 bar of H<sub>2</sub> after 72 hours (Scheme 2.1, C).<sup>16c</sup>



Scheme 2.1 Relevant examples of transition metal-catalyzed cleavage of the bicyclic structure of the phthalimide skeleton.

Clearly, the possibilities in terms of molecular diversity arising from breaking the phthalimide backbone in a controlled manner and milder reaction conditions are underdeveloped, especially considering that they could lead to new shortcuts in multistep chemical synthesis. In this chapter, a general and efficient ruthenium-catalyzed protocol enabling the highly chemoselective protodecarbonylation of *N*-substituted phthalimide derivatives into amides is developed and presented. Preliminary mechanistic studies that suggest an unexpected decarboxylation pathway are discussed as well (Scheme 2.2). Amides are ubiquitous building blocks in the fine and bulk chemical industry, and disclosing new pathways toward their synthesis is always appealing.<sup>17</sup>



Scheme 2.2 Ru-catalyzed protodecarbonylation of *N*-substituted phthalimides.

#### 2.2 Results and discussion

## 2.2.1 Ruthenium-catalyzed protodecarbonylation of N-substituted phthalimide derivatives: search for optimal reaction conditions.

Based on previous contributions by Chatani and co-workers dealing with the formation of phthalimides from amides via ruthenium catalysis and the reversibility of some of the steps claimed in the catalytic cycle (Scheme 2.3),<sup>18a,b</sup> we anticipated that the formal opposite reaction might be possible with related reaction conditions. Rovis and co-workers reported a similar reaction as Chatani, but with a more expensive rhodium catalyst instead.<sup>18c</sup>



Scheme 2.3 Chatani's Ru-catalyzed carbonylation at *ortho* C-H bonds in aromatic amides leading to phthalimides and postulated mechanism.

A systematic study searching for the optimal reaction conditions enabling the protodecarbonylation of phthalimides to amides was pursued (Table 2.1). N-methylphthalimide (1a) was chosen as a model substrate for the optimization

reactions. First, the catalytic reaction was performed in the presence of [RuCl<sub>2</sub>(pcymene)]<sub>2</sub> (5 mol%) and K<sub>2</sub>CO<sub>3</sub> (3 equiv.) in *N*-methyl-2-pyrrolidone (NMP) at 150 °C for 24 hours affording the desired product 2a in 56% yield (Table 2.1, entry 1). KOAc (1.5 equiv.) as additive did not influence the catalysis (Table 2.1, entry 2). On the other hand, the presence of  $H_2O$  (1.5 equiv.) led to the desired product in an excellent 93% yield with full conversion of the substrate (Table 2.1, entries 3). The reactions performed with other ruthenium complexes such as [RuCl<sub>3</sub>•xH<sub>2</sub>O] and [Ru<sub>3</sub>(CO)<sub>12</sub>] were not as efficient as that performed with [RuCl<sub>2</sub>(*p*-cymene)]<sub>2</sub> (Table 2.1, entries 4-5). A variety of inorganic and organic bases such as Na<sub>2</sub>CO<sub>3</sub>, KHCO<sub>3</sub>, NEt<sub>3</sub>, and NaOH were tested giving rise to 2a in 17, 34, 12, and 82% yield, respectively (Table 2.1, entries 6-9). The catalytic outcome was not improved using DMF, t-AmOH, toluene, and H<sub>2</sub>O as solvents, respectively (Table 2.1, entries 10-13). The activity of the ruthenium catalyst was found to depend on the amount of base, with 43 and 74% yield of 2a obtained in the presence of one and two equivalents of K<sub>2</sub>CO<sub>3</sub>, respectively (Table 2.1, entries 14-15). Increasing the catalyst loading to 10 mol% led to 79% yield of 2a (Table 2.1, entry 16) and decreasing the catalyst loading to 2.5, 1, and 0.5 mol% led to 99, 99, and 74% yield of 2a, respectively (Table 2.1, entries 17-19). Consequently, 1 mol% of [RuCl<sub>2</sub>(p-cymene)]<sub>2</sub> complex as pre-catalyst was selected as the optimal catalyst loading. Full conversion and high yields (>99%) of product 2a were obtained when performing the reaction for 14 and 6 hours, respectively (Table 2.1, entries 20-21). However, decreasing the time of the reaction to 3 and 1 hour afforded 2a in 64 and 31% yields, respectively (Table 2.1, entries 22-23). Lowering the temperature of the reaction to 130 °C and 110 °C was detrimental for the catalysis (Table 2.1, entry 24-25). Control experiments indicated no conversion of 1a without the ruthenium complex or K<sub>2</sub>CO<sub>3</sub> as the base as well as the need of argon atmosphere and distilled NMP (Table 2.1, entries 26-29). The role of  $H_2O$  in the outcome of the reaction was evaluated too. A drop in the conversion of 1a (50%) was observed when performing the catalysis with overnight-dried K<sub>2</sub>CO<sub>3</sub> (Table 2.1, entry 30).

$ \begin{array}{c}                                     $						
		1a Basa	Additivo	Solvent	2a	Viold(%) <sup>b</sup>
			Additive	Solvent		
1	5	K <sub>2</sub> CO <sub>3</sub>	-		24	56
2	5	K <sub>2</sub> CO <sub>3</sub>	KUAC		24	56
3	5 F	K <sub>2</sub> CO <sub>3</sub>			24	99 (93) 25
4° 50	5	K <sub>2</sub> CO <sub>3</sub>	H <sub>2</sub> O	NMP	24	35
54	5	$K_2CO_3$	H <sub>2</sub> O	NMP	24	trace
6	5	Na <sub>2</sub> CO <sub>3</sub>	H <sub>2</sub> O	NMP	24	17
/	5		H <sub>2</sub> O	NMP	24	34
8	5	NEt <sub>3</sub>	H <sub>2</sub> O	NMP	24	12
9	5	NaOH	H <sub>2</sub> O	NMP	24	82
10	5	K <sub>2</sub> CO <sub>3</sub>	H <sub>2</sub> O	DMF	24	16
11	5	K <sub>2</sub> CO <sub>3</sub>	п <sub>2</sub> О	t-AmOH	24	47
12	5	K <sub>2</sub> CO <sub>3</sub>	H <sub>2</sub> O	loluene	24	0
13	5	K <sub>2</sub> CO <sub>3</sub>	-	H <sub>2</sub> O	24	trace
14 <sup>e</sup>	5	K <sub>2</sub> CO <sub>3</sub>	H <sub>2</sub> O	NMP	24	(4
15 <sup>7</sup>	5	K <sub>2</sub> CO <sub>3</sub>	H <sub>2</sub> O	NMP	24	43
16	10	K₂CO₃	H <sub>2</sub> O	NMP	24	79
17	2.5	K <sub>2</sub> CO <sub>3</sub>	H <sub>2</sub> O	NMP	24	99
18	1	K <sub>2</sub> CO <sub>3</sub>	H <sub>2</sub> O	NMP	24	99
19	0.5	K <sub>2</sub> CO <sub>3</sub>	H <sub>2</sub> O	NMP	24	74
20	1	K <sub>2</sub> CO <sub>3</sub>	H <sub>2</sub> O	NMP	14	99
21	1	K <sub>2</sub> CO <sub>3</sub>	H <sub>2</sub> O	NMP	6	<b>99 (93)</b>
22	1	K <sub>2</sub> CO <sub>3</sub>	H <sub>2</sub> O	NMP	3	64
23	1	K <sub>2</sub> CO <sub>3</sub>	H <sub>2</sub> O	NMP	1	31
24 <sup>g</sup>	1	K <sub>2</sub> CO <sub>3</sub>	H <sub>2</sub> O	NMP	6	69
25 <sup>h</sup>	1	K <sub>2</sub> CO <sub>3</sub>	H <sub>2</sub> O	NMP	6	0
26 <sup>i</sup>	1	K <sub>2</sub> CO <sub>3</sub>	H <sub>2</sub> O	NMP	6	18
27 <sup>j</sup>	1	K <sub>2</sub> CO <sub>3</sub>	H <sub>2</sub> O	NMP	6	10
28	0	K <sub>2</sub> CO <sub>3</sub>	H <sub>2</sub> O	NMP	6	0
29	1	_	H <sub>2</sub> O	NMP	6	0
30 <sup>k</sup>	1	K <sub>2</sub> CO <sub>3</sub>	H <sub>2</sub> O	NMP	6	50

Table 2.1 Optimization of the reaction conditions.<sup>a</sup>

0

<sup>a</sup>Reaction conditions: **1a** (0.2 mmol), catalysts (1 mol%), Base (300 mol%) and Additive (150 mol%) are stirred in 1 mL of solvents for 6 h under Ar. <sup>b</sup>Determined by <sup>1</sup>H NMR spectroscopy against an internal standard (1,3,5-trimethoxybenzene). The isolated yield is shown in parentheses. <sup>c</sup>RuCl<sub>3</sub>•xH<sub>2</sub>O as the pre-catalyst. <sup>d</sup>Ru<sub>3</sub>(CO)<sub>12</sub> as the pre-catalyst. With 2 equiv. K<sub>2</sub>CO<sub>3</sub> <sup>f</sup>With 1 equiv. K<sub>2</sub>CO<sub>3</sub> <sup>g</sup>At 130 °C <sup>h</sup>At 110 °C. <sup>j</sup>Undisitilited solvent. <sup>j</sup>Under air. <sup>k</sup>With overnight-dried K<sub>2</sub>CO<sub>3.</sub>

### 2.2.2 Scope and limitations of the ruthenium-catalyzed protodecarbonylation of N-substituted phthalimide derivatives

With the optimized reaction conditions in hand, this catalytic methodology was extended to a variety of N-substituted phthalimide derivatives (1) in order to explore the generality of this reaction (Table 2.2). Aliphatic chains in the N-side are well tolerated although their bulkiness has a direct impact in the conversion. *n*-Bu-substituted amide **2b** was obtained in 50% yield, and the bulkier *i*-Pr-substituted amide 2c in 24% yield. These yields were improved by increasing the reaction time to 24 hours (88% yield of **2b**) and the catalyst loading to 2.5 mol% (87% yield of **2c**). Sterically-congested adamantyl-substituted amide 2d was not formed. Aliphatic chains appended with a cyano group provided 2e in a good yield (63%), which was increased to 91% after 24 hours. Aliphatic chains containing other C-O bonds such as ethers, ketones, and esters were compatible under catalytic conditions, enabling formation of the corresponding amides **2f**, **2g** and **2h** in 98, 73, and 26% isolated yields, respectively. In the case of **2h**, a higher yield of 50% was obtained when performing the catalysis during 24 hours and 2.5 mol% catalyst loading. The ruthenium catalyst is site-selective by performing the protodecarbonylation in the phthalimide skeleton without interfering with other C–O and C=O bonds. A naphthalene group attached to the nitrogen atom of the cylic imide was also compatible affording 2i in 92% yield and the very coordinating quinoline-containing amide 2j was obtained in 33% yield after 48 hours of reaction time using 5 mol% of  $[RuCl_2(p-cymene)]_2$ , indicating that relevant heterocyclic motifs are compatible under the studied reaction conditions. Benzyl fragments bearing different functional groups such as methyl, cyano and trifluoromethyl were also tolerated, leading to 2k-2n in 90-99% yields. The structure of 2k was further confirmed by X-ray crystallographic analysis. The benzylpyridine-containing amide derivative 20 was isolated in 88% yield, and the thiophene-containing amide 2p in 60% yield after 48 hours of reaction time and 5 mol% of catalyst loading. The steric effects and the coordinating properties of the substituents may account for those very few cases where

the yields were low. Interestingly, by simply increasing the reaction time and the catalyst loading, high yields were obtained even for these reluctant substrates.



Table 2.2 Ru-catalyzed protodecarbonylation of some N-substituted phthalimides.<sup>*a,b*</sup>

<sup>a</sup>Reaction conditions: **1** (0.4 mmol), H<sub>2</sub>O (0.6 mmol), K<sub>2</sub>CO<sub>3</sub> (1.2 mmol), [RuCl<sub>2</sub>(*p*-cymene)]<sub>2</sub> (1 mol%) in NMP (2.0 mL) at 150 °C for 6 h under argon atmosphere. <sup>*b*</sup>Isolated yields. <sup>*c*</sup>24 h reaction time. <sup>*d*</sup>2.5 mol% of [RuCl<sub>2</sub>(*p*-cymene)]<sub>2</sub>. <sup>*e*</sup>48 h reaction time. <sup>*f*</sup>5 mol% of [RuCl<sub>2</sub>(*p*-cymene)]<sub>2</sub>.

When the *N*-substituent of phthalimide contains aromatic moieties with different functional groups at different positions, the catalysis efficiently afforded the corresponding arylbenzamide products (Table 2.3). For instance, phenylbenzamide 2q was obtained in an excellent 98% yield and *ortho*-tolyl derivative 2t in 89% yield. Compound 2q was also synthesized in big quantity (up to 1.05 g and 97% yield), indicating that the catalysis is compatible at large scale as well. A methoxy group incorporated at the *ortho* position of the *N*-substituted phenyl moiety yielded 34% of 2s, likely due to inhibition by chelation to the catalyst. Nevertheless, the yield was

increased to 78% by performing the catalysis during 48 hours using 5 mol% of [RuCl<sub>2</sub>(*p*-cymene)]<sub>2</sub>. Chloro-derivative **2t** was isolated in 63% yield (no dechlorination was observed). When the *N*-substituent of the phthalimide contains aromatic moieties with different functional groups at the *para*-position (methyl, methoxy, fluoro, ketone, ester, and nitro), isolated yields of 80%-98% of amides **2u-2z** were obtained. Bromide-and iodide-containing phthalimides were converted into amides **2aa** and **2ab**, although the dehalogenated **2q** was observed in 26% and 76% yields, respectively. *meta*-Substituted phenyl groups with a methoxy moiety were also compatible, leading to **2ac** in 97% yield.



**Table 2.3** Ru-catalyzed protodecarbonylation of some *N*-arylphthalimides.<sup>*a,b*</sup>

<sup>a</sup>Reaction conditions: **1** (0.4 mmol), H<sub>2</sub>O (0.6 mmol), K<sub>2</sub>CO<sub>3</sub> (1.2 mmol), [RuCl<sub>2</sub>(*p*-cymene)]<sub>2</sub> (1 mol%) in NMP (2 mL) at 150 <sup>o</sup>C for 6 h under argon atmosphere. <sup>*b*</sup>Isolated yields. <sup>*c*</sup>48 h reaction time. <sup>*d*</sup>5 mol% of [RuCl<sub>2</sub>(*p*-cymene)]<sub>2</sub>.

A double protodecarbonylation reaction was also evaluated with a substrate containing two phthalimide groups bridged by an aliphatic chain. The reaction occurred efficiently leading to the bis-benzamide product **2ad** in 93% yield (Scheme 2.4).



Scheme 2.4 Ru-catalyzed double protodecarbonylation reaction.

Selectivity of the catalysis with *N*-phenyl phthalimides containing substituents at the 3'-and 4'-positions was studied as two possible regioisomers could form. Phthalimides containing fluoro, chloro and nitro groups at the 3'-position led exclusively to the *meta*-isomers **2ae-2ag**, respectively, with no evidence by TLC, <sup>1</sup>H NMR spectroscopy, and GC-MS analysis for the formation of other isomers (Table 2.4). Halide-containing amides **2ae** and **2af** were obtained in 65% yield and the nitrocontaining amide **2ag** in 87% yield. Increasing the reaction time to 24 hours led to **2ae** in 93% yield. Phthalimide substituted at the 3'-position with a methyl group provided a 38:62 mixture of *ortho-* and *meta*-isomers **3ah** with an overall yield of 92%. This indicates that electron-withdrawing groups such as nitro at 3'-position enhance the cleavage of the carbonyl group at the *ortho*-position (with respect to 3'-position).



**Table 2.4** Ru-catalyzed protodecarbonylation of 3'-substituted phthalimides.<sup>*a,b*</sup>

<sup>a</sup>Reaction conditions: **1** (0.4 mmol), H<sub>2</sub>O (0.6 mmol), K<sub>2</sub>CO<sub>3</sub> (1.2 mmol), [RuCl<sub>2</sub>(*p*-cymene)]<sub>2</sub> (1 mol%) in NMP (2 mL) at 150 °C for 6 h under argon atmosphere. <sup>b</sup>Isolated yields. <sup>c</sup>24 h reaction time. <sup>d</sup>Ratio of isomers determined by NMR spectroscopy analysis.

Next, it was found that substituents at the 4'-position have little impact on the selectivity, and mixture of isomers of similar ratios (*ca* 60:40) were observed for **2ai-2ak** (Table 2.5). Conversions of the phthalimides were found to depend on the electronic properties of the substituents at the 4'-position. By decreasing the electron-donating capabilities of the substituents (Me > F > NO<sub>2</sub>), the yield of the corresponding amides (**2ak**, **2ai** and **2aj**) decreased from 98 to 82 to 49%, respectively.



**Table 2.5** Ru-catalyzed protodecarbonylation of 4'-substituted phthalimides.<sup>*a,b*</sup>

<sup>a</sup>Reaction conditions: **1** (0.4 mmol), H<sub>2</sub>O (0.6 mmol), K<sub>2</sub>CO<sub>3</sub> (1.2 mmol), [RuCl<sub>2</sub>(*p*-cymene)]<sub>2</sub> (1 mol%) in NMP (2 mL) at 150 °C for 6 h under argon atmosphere. <sup>*b*</sup>Isolated yields. <sup>*c*</sup>Ratio of isomers determined by NMR spectroscopy analysis.

In addition, *N*-H phthalimide and phthalic anhydride were found to be suitable for this protodecarbonylation reaction to some extent. However, the corresponding benzamide and benzoic acid products were obtained in modest 17 and 51% yields, respectively (Scheme 2.5).



Scheme 2.5 Ru-catalyzed protodecarbonylation of *N*-H phthalimide and phthalic anhydride

Phthalimide derivatives containing substituents such as allyl, bromomethyl, *n*-bromobutyl group did not undergo protodecarbonylation under the developed methodology. Indeed, they afforded different hydrolyzed side-products in variable yields as shown in Scheme 2.6.



Scheme 2.6 Attempts of Ru-catalyzed protodecarbonylation with some *N*-substituted phthalimides.

When the catalysis was attempted with a substrate containing a styrene moiety (1an), no protodecarbonylation took place and hydrogenation of the C=C double bond was observed in trace amounts. This strongly suggests formation of H<sub>2</sub> during the catalysis (Scheme 2.7). H<sub>2</sub> gas formation was observed also in gas phase GC analysis in the presence and absence of substrate under the reaction conditions used in the catalysis (see detailed discussion in Section 2.3). This lack of reactivity of 1an in protodecarbonylation contrasts with the high reactivity of the analog benzyl derivatives 1k-n leading to 2k-n in excellent yields (Table 2.2).



Scheme 2.7 Attempts of Ru-catalyzed protodecarbonylation with a phthalimide derivative containing a terminal C=C double bond.

Unfortunately, cholesterol-substituted and alkyne-substituted phthalimide derivatives were not compatible for the protodecarbonylation reaction (Figure 2.1, top).

Other type of cyclic imides did not follow protodecarbonylation neither (Figure 2.1, bottom). Attempts to couple the ruthenium-catalyzed five-membered ring opening of phthalimide with new C-C and C-heteroatom bond forming reactions failed using different alkenes, alkynes and nucleophiles (i.e. primary alcohols and amines) as coupling partners.



Figure 2.1 Reluctant substrates in Ru-catalyzed protodecarbonylation.

#### 2.3 Mechanistic studies

First mechanistic studies aimed at unravelling the role of water in the rutheniumcatalyzed protodecarbonylation reaction of phthalimides. For that, a deuterium labelling experiment was performed in the presence of D<sub>2</sub>O instead of water. Performing an experiment with a mixture of solvents NMP:D<sub>2</sub>O (v/v 9:1) indicated full incorporation of deuterium at the aromatic carbon previously linked to the carbonyl moiety (**2a**-*d*), suggesting that water is the source of protons of the reaction (Scheme 2.8). The fast proton exchange during the work-up might explain the non-deuterated N-H amide group in **2a**-*d*. Unfortunately, using water as solvent inhibited the catalysis as above discussed (Table 2.1, entry 13).



Scheme 2.8 Deuteration experiments with phthalimide 1a.

In order to gain further insights into the reaction mechanism, the gas phase of the reaction mixture was qualitatively analyzed by GC. It indicated the presence of H<sub>2</sub> and CO<sub>2</sub> as the major components (Figures 2.2-2.4). Note that air (O<sub>2</sub> and N<sub>2</sub>) was observed because this analysis could not be done under completely argon atmosphere. For the formation of CO<sub>2</sub>, control experiments indicated that CO<sub>2</sub> was formed during the decarbonylation of the phthalimide ring because, without the substrate, almost no CO<sub>2</sub> was detected. Regarding the formation of H<sub>2</sub>, similar amounts of H<sub>2</sub> were detected in the reaction vessel in the presence and in the absence of substrate **1a**. In addition, a catalytic reaction was attempted under 1 bar of H<sub>2</sub> that gave rise to only 8% yield of amide **2a** (Scheme 2.9). These observations precluded the involvement of H<sub>2</sub> in the catalytic cycle and ruled out a standard ruthenium-catalyzed hydrogenation mechanism.



Scheme 2.9 Attempts of Ru-catalyzed protodecarbonylation in the presence of H<sub>2</sub>.
Chapter 2





Sample S – Molecularsieve5A – H2: 2939; O2: 23321; N2:160013; CO: 227

Figure 2.2 GC-Gas traces (using two columns) of the reaction mixture with 1a.

Sample NOS - PoraplotQ - H2 : 3864 ; CH4: 98; CO2 : 73



Figure 2.3 GC-Gas traces (using two columns) of a reaction performed without 1a.

### Chapter 2

Atmospheric air - PoraplotQ column - CO2 400ppm - CO2 : 39,42



Figure 2.4 GC-Gas traces (using two columns) of a blank control.

To verify whether the reaction was initiated via hydrolysis of the phthalimide ring, 2-(phenylcarbamoyl)benzoic acid was submitted to the standard reaction conditions. Benzoic acid and aniline were the only products formed (Scheme 2.10), thereby excluding any hydrolysis of the phthalimide backbone previous to the decarboxylation process.

$$(CONHPh + H_2O) (1.5 \text{ equiv.}) \xrightarrow{[RuCl_2(p-cymene)]_2 (1 \text{ mol}\%)} (CO_2H + H_2NPh + H_2$$

Scheme 2.10 Attempt of Ru-catalyzed protodecarbonylation on a plausible ringopened intermediate.

To trap some potential intermediates, catalysis was performed in the presence of 1 equivalent of TEMPO [TEMPO = (2,2,6,6-tetramethylpiperidin-1-yl)oxyl]. Although the conversion of **1a** decreased to <30%, formation of ring-opened intermediates containing two fragments of TEMPO (m/z = 474) were detected by GC-MS analysis (Scheme 2.11).



Scheme 2.11 Trapping experiments with TEMPO and substrate 1a.

In addition, performing the catalytic reaction with an imide buildup on a sixmembered ring did not proceed (Scheme 2.12), indicating that the ring strain release in 1 is probably the driving force for the initial step of the catalytic cycle. Mercury tests indicated the homogeneous regime of the catalysis, and attempts to identify ruthenium intermediates by different spectroscopic analysis failed.



Scheme 2.12 Attempt of Ru-catalyzed protodecarbonylation of a substrate with a six-membered phthalimide type ring.

Considering the above findings and previous contributions,<sup>18-19</sup> a mechanism is tentatively postulated in Scheme 2.13. First, ruthenium chloride-free species formed after reaction of  $[RuCl_2(p-cymene)]_2$  with K<sub>2</sub>CO<sub>3</sub>.<sup>20</sup> *N*-Coordination (or *O*-coordination) of ruthenium species to **1** should lead to **A1** (or **A2**),<sup>21</sup> which, after ring opening, forms **B**. Hydroxylation followed by release of protons or dihydrogen would lead to **C**, which, after decarboxylation, forms ruthenacycle **D**.<sup>22</sup> Protonolysis leads to **E** which is equilibrium with **2**, and the ruthenium catalyst is regenerated.



Scheme 2.13 Proposed catalytic cycle.

# 2.4 Conclusion

In summary, a general, chemoselective ruthenium-catalyzed reaction enabling conversion of phthalimides into amides was developed. The mechanism, which does not follow a standard hydrogenation pathway,<sup>16a</sup> involves a key decarboxylation step, with water serving as the source of protons. However, additional kinetics and computational studies would be necessary to further support the postulated mechanism. As the reaction is operationally simple and proceeds without any pressure of H<sub>2</sub>, it can be carried out in conventional laboratories with minimal risks. This work represents a new entry for the activation and further functionalization of challenging C-C(O) and  $C-N(R_2)$  bonds. Because the synthesis of amides and phthalimides is appealing in many scenarios relevant to chemistry and biology,<sup>23</sup> we anticipate that the presented method will inspire new synthetic shortcuts.

# 2.5 Experimental details

General information. All reagents were obtained from commercial sources and used as supplied. All reactions were carried out in flame-dried glassware under argon atmosphere unless otherwise noted. Catalytic experiments were performed in Schlenktype flasks under argon atmosphere unless otherwise noted. Organic solutions were concentrated under reduced pressure using a rotary evaporator. Thin-layer chromatography (TLC) were carried out on 0.25 mm Merck silica gel (60-F254). Flash column chromatography was performed using silica gel Silica 60 M, 0.04-0.063 mm. N-methyl-2-pyrrolidone (NMP) was distilled under reduced pressure and stored under molecular sieves and argon atmosphere. Technical grade petroleum ether (40-60) and ethyl acetate were used for column chromatography. CDCl3 was stored under nitrogen over molecular sieves. NMR spectra were recorded on an AVANCE III 400 spectrometer. <sup>1</sup>H NMR spectra were referenced to residual protiated solvent ( $\delta = 7.26$ ppm for CDCl<sub>3</sub>) and <sup>13</sup>C chemical shifts are reported relative to deuterated solvents ( $\delta$ = 77.0 ppm for CDCl<sub>3</sub>). The peak patterns are indicated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet, and br. for broad. GC-MS analyses were performed with a GCMS-QP2010S (Shimadzu) instrument with a GC-2010 equipped with a 30 m capillary column (Supelco, SLBTM-5ms, fused silica capillary column, 30 m x 0.25 mm x 0.25 mm film thickness), which was used with helium as the vector gas. The following GC conditions were used: initial temperature 80 °C for 2 minutes, then rate 20 °C/min until 280 °C and 280 °C for 28 minutes. HRMS were recorded on a Waters Q-Tof 2 mass spectrometer at the corresponding facilities of the CRMPO, Centre Régional de Mesures Physiques de l'Ouest, Université de Rennes 1. Melting points were performed on a LEICA VMHB Kofler system.

# Synthesis of substrates 1.

Method A. Phthalic anhydride (5 mmol, 0.74 g, 1 equiv.) and the corresponding aniline (5 mmol, 1 equiv.) were refluxed in acetic acid (30 mL) for 2-5 hours. Once at room

### Chapter 2

temperature, water was added and the solid recovered by filtration. After drying under vacuum the desired phthalimide **1** was obtained.



<u>Method B.</u> *N*-H Phthalimide (7 mmol, 1.03 g, 1 equiv.), potassium carbonate (14 mmol, 2.59 g, 2 equiv.) and the corresponding alkyl or benzyl halide (14 mmol, 2 equiv.) were heated at 40 °C in *N*, *N*-dimethylformamide (6 mL) for 18 hours. After solvents evaporation under vacuum, the mixture was added with water and extracted with DCM. The combined organic phase was dried over  $Na_2SO_4$ , filtered, and concentrated in *vacuo*. The desired phthalimide **1** was purified by silica gel column chromatography with a mixture of petroleum ether and ethyl acetate as eluent.



<u>Method C.</u> Phthalic anhydride (10 mmol, 1.48 g, 1 equiv.) and the corresponding amine (5 mmol, 0.5 equiv.) were refluxed in acetic acid (15 mL) for 8 hours. Once at room temperature, water was added and the solid recovered by filtration. After drying under vacuum the desired phthalimide **1** was obtained.



<u>Method D.</u> Hexahydrophthalic anhydride (10 mmol, 1.54 g, 1 equiv.) and the aniline (10 mmol, 1 equiv.) and THF (15 mL) were added to a 100 mL round bottom flask. The solution was stirred for 30 min at 40 °C. Removal of the solvent using a rotary evaporator gave the corresponding carboxylic acid-amide as white solid. The white

### Chapter 2

solid was then heated at 190 °C under Ar for 4 h. The desired phthalimide was purified by silica gel column chromatography with a mixture of petroleum ether and ethyl acetate as eluent.

$$H = \begin{pmatrix} H & 0 \\ H & 0 \\ H & 0 \end{pmatrix} + H = \begin{pmatrix} NH_2 \\ 40 & ^\circC, 30 & \text{min} \\ h & 0 \end{pmatrix} + \begin{pmatrix} H & 0 \\ 40 & ^\circC, 30 & \text{min} \\ h & 0 \end{pmatrix} + \begin{pmatrix} H & 0 \\ H & 0 \\ h & 0 \end{pmatrix} + \begin{pmatrix} H & 0 \\ H & 0 \\ h & 0 \end{pmatrix} + \begin{pmatrix} H & 0 \\ H & 0 \\ h & 0 \end{pmatrix} + \begin{pmatrix} H & 0 \\ H & 0 \\ h & 0 \\ h & 0 \end{pmatrix} + \begin{pmatrix} H & 0 \\ h & 0 \\$$

<u>Method E.</u> To an oven-dried pressure tube with a magnetic stir bar were added the 2-(3-bromophenyl)isoindoline-1,3-dione (1.0 mmol, 1.0 equiv.), CuI (5 mol%) and PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (5 mol%) under a N<sub>2</sub> atmosphere. A solvent THF (2.5 mL) was added. Then base, NEt<sub>3</sub> (2.5 mL) was added. Finally, the terminal alkyne (1.1 mmol, 1.1 equiv.) was added and the reaction was heated at 90 °C overnight. Upon completion of the reaction, the reaction mixture was quenched with water. The organic layer was diluted with DCM and washed with a saturated solution of NH<sub>4</sub>CI. The combined aqueous layers were extracted with DCM. The combined organic layers were dried over MgSO<sub>4</sub> and the solvent removed in *vacuo*. The crude product was purified by column chromatography to give the desired product.



### Characterization of substrates 1.

*N*-Methylphthalimide (1a): Prepared according to Method B starting from iodomethane in 88% isolated yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$ = 7.78 (dd, *J* = 5.6, 3.2 Hz, 2H), 7.66 (dd, *J* = 5.6, 3.2 Hz, 2H), 3.13 (s, 3H) ppm. The spectral data match those previously reported.<sup>24</sup> *N*-Butylphthalimide (1b): Prepared according to Method B starting from 1bromobutane in 98% isolated yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$ = 7.82 (dd, *J* = 5.6, 2.8 Hz, 2H), 7.70-7.68 (m, 2H), 3.67 (t, *J* = 7.6 Hz, 2H), 1.68-1.61 (m, 2H), 1.40-1.31 (m, 2H), 0.93 (t, *J* = 7.6 Hz, 2H), 1.68-1.61 (m, 2H), 1.40-1.31 (m, 2H), 0.93 (t, *J* = 7.6 Hz, 2H), 1.68-1.61 (m, 2H), 1.40-1.31 (m, 2H), 0.93 (t, *J* = 7.6 Hz, 2H), 1.68-1.61 (m, 2H), 1.40-1.31 (m, 2H), 0.93 (t, *J* = 7.6 Hz, 2H), 1.68-1.61 (m, 2H), 1.40-1.31 (m, 2H), 0.93 (t, *J* = 7.6 Hz, 2H), 1.68-1.61 (m, 2H), 1.40-1.31 (m, 2H), 0.93 (t, *J* = 7.6 Hz, 2H), 1.68-1.61 (m, 2H), 1.40-1.31 (m, 2H), 0.93 (t, *J* = 7.6 Hz, 2H), 1.40-1.31 (m, 2H), 0.93 (t, *J* = 7.6 Hz, 2H), 1.40-1.31 (m, 2H), 0.93 (t, *J* = 7.6 Hz, 2H), 1.40-1.31 (m, 2H), 0.93 (t, *J* = 7.6 Hz, 2H), 1.40-1.31 (m, 2H), 0.93 (t, *J* = 7.6 Hz, 2H), 1.40-1.31 (m, 2H), 0.93 (t, *J* = 7.6 Hz, 2H), 1.40-1.31 (m, 2H), 0.93 (t, *J* = 7.6 Hz, 2H), 1.40-1.31 (m, 2H), 0.93 (t, *J* = 7.6 Hz, 2H), 1.40-1.31 (m, 2H), 0.93 (t, *J* = 7.6 Hz, 2H), 1.40-1.31 (m, 2H), 0.93 (t, *J* = 7.6 Hz, 2H), 1.40-1.31 (m, 2H), 0.93 (t, *J* = 7.6 Hz, 2H), 1.40-1.31 (m, 2H), 0.93 (t, *J* = 7.6 Hz, 2H), 1.40-1.31 (m, 2H), 0.93 (t, *J* = 7.6 Hz, 2H), 1.40-1.31 (m, 2H), 0.93 (t, *J* = 7.6 Hz, 2H), 1.40-1.31 (m, 2H), 0.93 (t, J = 7.6 Hz), 1.40-1.31 (m, 2H), 0.93 (t, J = 7.6 Hz), 1.40-1.40 (m, 2H), 0.93 (t, J = 7.6 Hz), 1.40-1.40 (m, 2H), 0.93 (t, J = 7.6 Hz), 1.40-1.40 (m, 2H), 1.40-1.40 (m

3H) ppm. The spectral data match those previously reported.<sup>25</sup>

*N*-Isopropylphthalimide (1c): Prepared according to Method B starting from 2bromopropane in 78% isolated yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$ = 7.79 (dd, J = 5.6, 3.2 Hz, 2H), 7.68 (dd, J = 5.6, 3.2 Hz, 2H), 4.57-4.47 (m, 1H), 1.48 (d, J = 7.2 Hz, 6H) ppm. The spectral data match those

previously reported.<sup>26</sup>

*N*-(1-Adamantyl)phthalimide (1d): Prepared according to Method A starting from amantadine in 35% isolated yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$ = 7.75 (dd, *J* = 5.2, 3.2 Hz, 2H), 7.66 (dd, *J* = 5.2, 3.2 Hz, 2H), 2.52 (d, *J* = 2.8 Hz, 6H), 2.17 (s, 3H), 1.81-1.70 (m, 6H) ppm. The spectral

data match those previously reported.<sup>27</sup>

5-Phthalimidovaleronitrile (1e): Prepared according to Method B starting from 5-



bromovaleronitrile in 87% isolated yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.83 (dd, *J* = 5.6, 2.8 Hz, 2H), 7.72 (dd, *J* = 5.6, 3.2 Hz, 2H), 3.72 (t, *J* = 7.2 Hz, 2H), 2.42 (t, *J* = 7.2 Hz, 2H),

1.88-1.81 (m, 2H), 1.74-1.66 (m, 2H) ppm. The spectral data match those previously reported.<sup>26</sup>

*N*-[2-Methoxyethyl]phthalimide (1f): Prepared according to Method A starting from Ome 2-methoxyethanamine in 75% isolated yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.84 (dd, *J* = 5.2, 2.8 Hz, 2H), 7.70 (dd, *J* = 5.2, 2.8 Hz, 2H), 3.89 (t, J = 6.0 Hz, 2H), 3.63 (t, J = 6.0 Hz, 2H), 3.34 (s, 3H) ppm. The spectral data match those previously reported.<sup>28</sup>

*N*-Acetonylphthalimide (1g): Prepared according to Method B starting from chloroacetone in 50% isolated yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$ = 7.86 (dd, *J* = 5.2, 2.8 Hz, 2H), 7.73 (dd, *J* = 5.2, 2.8 Hz, 2H), 4.49 (s, 2H), 2.26 (s, 3H) ppm. The spectral data match those previously

reported.29

Methyl phthalimidoacetate (1h): Prepared according to Method B starting from ethyl bromoacetate in 75% isolated yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta = 7.87$  (dd, J = 5.6, 3.2 Hz, 2H), 7.73 (dd, J = 5.6, 3.2 Hz, 2H), 4.42 (s, 2H), 4.22 (q, J = 7.2 Hz, 2H), 1.27 (t, J = 7.2 Hz, 3H)

ppm. The spectral data match those previously reported.<sup>30</sup>

*N*-1-Naphthylphthalimide (1i): Prepared according to Method A starting from 1aminonaphthalene in 79% isolated yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta = 8.02$ -7.99 (m, 3H), 7.95 (d, J = 7.2 Hz, 1H), 7.82 (dd, J = 5.6, 2.8 Hz, 2H), 7.66-7.59 (m, 2H), 7.56-7.48 (m, 3H) ppm. The

spectral data match those previously reported.<sup>31</sup>

*N*-8-Quinolyl-phthalimide (1j): Prepared according to Method A starting from 8aminoquinoline in 76% isolated yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta = 8.86$  (dd, J = 4.4, 1.6 Hz, 1H), 8.23 (dd, J = 8.4, 1.6 Hz, 1H), 8.02-7.96 (m, 3H), 7.81 (dd, J = 5.2, 3.2 Hz, 2H), 7.76 (dd, J = 7.6,

1.6 Hz, 1H), 7.68 (dd, J = 7.6, 7.6 Hz, 1H), 7.44 (dd, J = 8.0, 4.4 Hz, 1H) ppm. The spectral data match those previously reported.<sup>32</sup>

N-Benzylphthalimide (1k): Prepared according to Method B starting from benzyl



bromide in 63% isolated yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.84 (dd, J = 5.6, 3.2 Hz, 2H), 7.70 (dd, J = 5.2, 3.2 Hz, 2H), 7.43 (d, J = 7.2 Hz, 2H), 7.34-7.27 (m, 3H), 4.85 (s, 2H) ppm. The

spectral data match those previously reported.<sup>33</sup>

*N-[p-(Methyl)benzyl]phthalimide (11):* Prepared according to Method B starting from



*p*-methylbenzyl bromide in 86% isolated yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.83 (dd, *J* = 5.6, 3.2 Hz, 2H), 7.69 (dd, *J* = 5.6, 3.2 Hz, 2H), 7.33 (d, *J* = 8.4 Hz, 2H), 7.12 (d, *J* = 7.6 Hz, 2H), 4.81 (s, 2H),

2.30 (s, 3H) ppm. The spectral data match those previously reported.<sup>26</sup>

*N-[p-(Cyano)benzyl]phthalimide* (1m): Prepared according to Method B starting from *p*-cyanobenzyl bromide in 86% isolated yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$ = 7.86 (dd, *J* = 5.6, 3.2 Hz, 2H), 7.73 (dd, *J* = 5.6, 3.2 Hz, 2H), 7.61 (d, *J* = 8.0 Hz, 2H), 7.52 (d, *J* = 8.0 Hz, 2H),

4.88 (s, 2H) ppm. The spectral data match those previously reported.<sup>34</sup>

N-[p-(Trifluoromethyl)benzyl]phthalimide (1n): Prepared according to Method B



starting from *p*-(triflouromethyl)benzyl bromide in 77% isolated yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.85 (dd, *J* = 5.6, 3.2 Hz, 2H), 7.72 (dd, *J* = 5.6, 3.2 Hz, 2H), 7.58-7.52 (m, 4H), 4.89 (s, 2H)

ppm. The spectral data match those previously reported.<sup>26</sup>

2-Phthalimidomethylpyridine (10): Prepared according to Method A starting from 2-



(dd, J = 7.6, 4.8 Hz, 1H), 5.01 (s, 2H) ppm. The spectral data match those previously reported.<sup>35</sup>

2-Phthalimidomethylthiophene (1p): Prepared according to Method A starting from 2-thiophenemethylamine in 47% isolated yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta = 7.84$  (dd, J = 5.2, 2.8 Hz, 2H), 7.69 (dd, J = 5.2, 2.8 Hz, 2H), 7.20 (dd, J = 5.2, 1.2 Hz, 1H), 7.14 (dd, J = 3.2, 0.4 Hz, 1H),

6.92 (dd, J = 5.2, 3.6 Hz, 1H), 5.01 (s, 2H) ppm. The spectral data match those previously reported.<sup>36</sup>

N-Phenylphthalimide (1q): Prepared according to Method A starting from aniline in



80% isolated yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.96 (dd, *J* = 5.6, 3.2 Hz, 2H), 7.80 (dd, *J* = 5.2, 3.2 Hz, 2H), 7.52 (dd, *J* = 7.6, 7.6 Hz, 2H), 7.34-7.27 (m, 3H) ppm. The spectral data match those

previously reported.25

*N-o*-Tolylphthalimide (1r): Prepared according to Method A starting from *o*-toluidine



in 43% isolated yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.96 (dd, J = 5.6, 3.2 Hz, 2H), 7.80 (dd, J = 5.6, 2.8 Hz, 2H), 7.39-7.31 (m, 3H), 7.21 (d, J = 7.6 Hz, 1H), 2.21 (s, 3H) ppm. The spectral data match

those previously reported.<sup>27</sup>

*N-o*-Methoxyphenylphthalimide (1s): Prepared according to Method A starting from



*o*-anisidine in 85% isolated yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.94 (dd, J = 5.6, 3.2 Hz, 2H), 7.77 (dd, J = 5.6, 3.2 Hz, 2H), 7.46-7.42 (m, 1H), 7.27-7.25 (m, 1H), 7.10-7.04 (m, 2H), 3.80 (s, 3H)

ppm. The spectral data match those previously reported.<sup>34</sup>

N-(o-Chlorophenyl)phthalimide (1t): Prepared according to Method A starting from

*o*-chloroaniline in 70% isolated yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta = 7.96$  (dd, J = 5.6, 3.2 Hz, 2H), 7.80 (dd, J = 5.6, 3.2 Hz, 2H), 7.59-7.55 (m, 1H), 7.46-7.38 (m, 2H), 7.37-7.35 (m, 1H) ppm. The

spectral data match those previously reported.<sup>37</sup>

*N-(p-Tolyl)*phthalimide (1u): Prepared according to Method A starting from *p*-toluidine in 72% isolated yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$ = 7.94 (dd, *J* = 5.6, 3.2 Hz, 2H), 7.78 (dd, *J* = 5.6, 3.2 Hz, 2H), 7.31 (s, 4H), 2.41 (s, 3H) ppm. The spectral data match those

previously reported.25

*N-p*-Anisylphthalimide (1v): Prepared according to Method A starting from *p*anisidine in 80% isolated yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$ = 7.94 (dd, *J* = 5.2, 2.8 Hz, 2H), 7.78 (dd, *J* = 5.6, 3.2 Hz, 2H), 7.34 (d, *J* = 9.2 Hz, 2H), 7.02 (d, *J* = 9.2 Hz, 2H), 3.85 (s, 3H)

ppm. The spectral data match those previously reported.<sup>25</sup>

*p*-Phthalimidoacetophenone (1w): Prepared according to Method A starting from *p*-



aminoacetophenone in 79% isolated yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$ = 8.10 (dd, *J* = 6.8, 2.0 Hz, 2H), 7.97 (dd, *J* = 5.6, 3.2 Hz, 2H), 7.82 (dd, *J* = 5.6, 3.2 Hz, 2H), 7.63 (dd, *J* = 6.8, 2.0 Hz, 2H), 7.63 (dd, J = 6.8, 2.0 Hz, 2H), 7.64 (dd, J

Hz, 2H), 2.64 (s, 3H) ppm. The spectral data match those previously reported.<sup>25</sup>

*N-(p-Ethoxycarbonylphenyl)phthalimide* (1x): Prepared according to Method A starting from benzocaine in 50% isolated yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta = 8.19$  (dd, J = 6.8, 1.6 Hz, 2H), 7.97 (dd, J = 5.2, 2.8 Hz, 2H), 7.82 (dd, J = 5.2, 2.8 Hz, 2H), 7.59 (dd, J = 6.8, 1.6 Hz, 2H), 4.41 (q, J = 7.2 Hz, 2H), 1.41 (t, J = 7.2 Hz, 3H) ppm. The spectral data match those previously reported.<sup>38</sup>

N-(p-Nitrophenyl)phthalimide (1y): Prepared according to Method A starting from p-



nitroaniline in 63% isolated yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  
$$\delta = 8.38$$
 (dd,  $J = 7.2$ , 2.0 Hz, 2H), 8.00 (dd,  $J = 5.2$ , 2.8 Hz, 2H), 7.85 (dd,  $J = 5.6$ , 3.2 Hz, 2H), 7.78 (dd,  $J = 7.2$ , 2.0 Hz,

2H) ppm. The spectral data match those previously reported.<sup>25</sup>

N-(p-Fluorophenyl)phthalimide (1z): Prepared according to Method A starting from



*p*-fluoroaniline in 82% isolated yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.86 (dd, *J* = 5.2, 3.2 Hz, 2H), 7.71 (dd, *J* = 5.2, 3.2 Hz, 2H), 7.34 (dd, *J* = 9.2, 4.8 Hz, 2H), 7.11 (dd, *J* = 8.8, 8.8 Hz,

2H) ppm. <sup>19</sup>F{<sup>1</sup>H} NMR (376 MHz, CDCl<sub>3</sub>):  $\delta$  = -113.8 ppm. The spectral data match those previously reported.<sup>39</sup>

*N-p*-Bromophenylphthalimide (1aa): Prepared according to Method A starting from *p*-bromoaniline in 88% isolated yield. <sup>1</sup>H NMR (400 MHz, *p*-bromoaniline in 88% isolated yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$ = 7.96 (dd, *J* = 5.2, 2.8 Hz, 2H), 7.80 (dd, *J* = 5.2, 2.8 Hz, 2H), 7.63 (d, *J* = 8.4 Hz, 2H), 7.36 (d, *J* = 8.8 Hz, 2H) ppm.

The spectral data match those previously reported.<sup>40</sup>

*N-p-*Iodophenylphthalimide (1ab): Prepared according to Method A starting from *p*-



iodoaniline in 80% isolated yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$ = 7.96-7.94 (m, 2H), 7.84-7.79 (m, 4H), 7.23 (d, *J* = 8.4 Hz, 2H) ppm. The spectral data match those previously reported.<sup>41</sup> N-(m-Methoxyphenyl)phthalimide (1ac): Prepared according to Method A starting



from *m*-anisidine in 76% isolated yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$ = 7.95 (dd, J = 5.2, 3.2 Hz, 2H), 7.78 (dd, J = 5.2, 3.2 Hz, 2H), 7.41 (dd, J = 8.0, 8.0 Hz, 1H), 7.04-7.02 (m, 1H), 6.99-6.96

(m, 1H), 6.94 (dd, J = 2.4, 1.2 Hz, 1H), 3.84 (s, 3H) ppm. The spectral data match those previously reported.<sup>42</sup>

N,N-Diphthaloyl-1,3-propanediamine (1ad): Prepared according to Method C



starting from 1,3-diaminopropane in 86% isolated yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$ = 7.83-7.79 (m, 4H), 7.71-7.67 (m, 4H), 3.75 (t, *J* = 7.2 Hz, 4H), 2.12-2.05 (m, 2H) ppm. The spectral data match those previously reported.<sup>43</sup>

*N*-Phenyl-*m*-fluorophthalimide (1ae): Prepared according to Method A starting from *m*-fluorophthalic anhydride in 91% isolated yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.82-7.77 (m, 2H), 7.53-7.49 (m, 2H), 7.47-7.40 (m, 4H) ppm. <sup>19</sup>F{<sup>1</sup>H} NMR (376 MHz, CDCl<sub>3</sub>):  $\delta$  = -112.3 ppm.

The spectral data match those previously reported.44

*N*-Phenyl-*m*-chlorophthalimide (1af): Prepared according to Method A starting from *m*-chlorophthalic anhydride in 94% isolated yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$ = 7.87 (dd, *J* = 4.8, 3.6 Hz, 1H), 7.71-7.70 (m, 2H), 7.53-7.48 (m, 2H), 7.45-7.41 (m, 3H) ppm. The spectral data match

those previously reported.45

N-Phenyl-m-nitrophthalimide (1ag): Prepared according to Method A starting from



*m*-nitrophthalic anhydride in 78% isolated yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.21 (dd, *J* = 7.6, 0.8 Hz, 1H), 8.15 (dd, *J* = 8.0,

0.8 Hz, 1H), 7.98 (dd, J = 8.0, 8.0 Hz, 1H), 7.54-7.50 (m, 2H), 7.46-7.42 (m, 3H) ppm. The spectral data match those previously reported.<sup>46</sup>

*N*-Phenyl-*m*-methylphthalimide (1ah): Prepared according to Method A starting from *m*-methylphthalic anhydride in 95% isolated yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$ = 7.78 (d, *J* = 7.2 Hz, 1H), 7.63 (d, *J* = 7.6 Hz, 1H),

7.54-7.49 (m, 3H), 7.45-7.38 (m, 3H), 2.75 (s, 3H) ppm. The spectral

data match those previously reported.<sup>47</sup>

N-Phenyl-p-fluorophthalimide (1ai): Prepared according to Method A starting from



*p*-fluorophthalic anhydride in 89% isolated yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.96 (dd, *J* = 8.4, 4.4 Hz, 1H), 7.62 (dd, *J* = 7.2, 2.0 Hz, 1H), 7.54-7.47 (m, 2H), 7.46-7.39 (m, 4H) ppm.

<sup>19</sup>F{<sup>1</sup>H} NMR (376 MHz, CDCl<sub>3</sub>):  $\delta$  = -101.1 ppm. The spectral data match those previously reported.<sup>44</sup>

*N*-Phenyl-*p*-nitrophthalimide (1aj): Prepared according to Method A starting from *p*-nitrophthalic anhydride in 98% isolated yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$ = 8.77 (dd, *J* = 6.0, 0.8 Hz, 1H), 8.67 (dd, *J* = 8.0, 2.0 Hz, 1H), 8.16 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.56-7.52 (m,

2H), 7.48-7.43 (m, 3H) ppm. The spectral data match those previously reported.<sup>31</sup>

N-Phenyl-p-methylphthalimide (1ak): Prepared according to Method A starting from



*p*-methylphthalic anhydride in 97% isolated yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.83 (d, *J* = 7.6 Hz, 1H), 7.75 (dd, *J* = 0.8, 0.8 Hz, 1H), 7.59-7.56 (m, 1H), 7.52-7.48 (m, 2H), 7.45-7.37 (m, 3H),

2.55 (s, 3H) ppm. The spectral data match those previously reported.<sup>36</sup>

N-(p-Vinylbenzyl)phthalimide (1an): Prepared according to Method B starting from



*p*-vinylbenzyl chloride in 77% isolated yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.83 (dd, *J* = 5.6, 2.8 Hz, 2H), 7.68 (dd, *J* = 5.6, 2.8 Hz, 2H), 7.40-7.34 (m, 4H), 6.67 (dd, *J* = 17.6, 11.2 Hz, 1H), 5.70

(dd, J = 17.6, 0.8 Hz, 1H), 5.22 (dd, J = 10.8, 0.8 Hz, 1H), 4.82 (s, 2H) ppm. The spectral data match those previously reported.<sup>48</sup>

2-Allylisoindoline-1,3-dione (1ao): Prepared according to Method B starting from



iodomethane in 99% isolated yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$ = 7.85 (dd, J = 5.6, 2.8 Hz, 2H), 7.71 (dd, J = 5.6, 2.8 Hz, 2H), 5.93-5.83 (m, 2H), 5.27-5.17 (m, 2H), 4.30-4.28 (m, 2H) ppm. The spectral

data match those previously reported.49

# (3S,8S,9S,10R,13R,14S,17R)-10,13-Dimethyl-17-((R)-6-methylheptan-2-yl)-



dioxoisoindolin-2-yl)acetate (1ar):

Prepared according to Method B at 70 °C in

98% isolated yield. White solid. Mp: 168-170 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.88 (dd, J = 5.2, 3.2 Hz, 2H), 7.74 (dd, J = 5.2, 3.2 Hz, 2H), 5.37 (d, J = 5.2 Hz, 1H), 4.72-4.64 (m, 1H), 4.41 (s, 2H), 2.36-2.32 (m, 2H), 2.02-1.78 (m, 5H), 1.65-1.32 (m, 14H), 1.25-1.05 (m, 7H), 1.01 (s, 3H), 0.87 (d, J = 2.0 Hz, 3H), 0.85 (d, J = 1.6 Hz, 3H), 0.67 (s, 3H) ppm. <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 167.5, 166.6, 139.3, 134.2, 132.0, 123.6, 123.0, 75.8, 56.6, 56.1, 49.9, 42.3, 39.7, 39.5, 39.2, 37.9, 36.8, 36.5, 36.2, 35.8, 31.87, 31.81, 28.2, 28.0, 27.6, 24.2, 23.8, 22.8, 22.5, 21.0, 19.3, 18.7, 11.8 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>37</sub>H<sub>51</sub>NO<sub>4</sub>Na 596.3710, found 596.3709 (0 ppm).

*N*-Phenylphthalamic acid (1as): Prepared according to a literature report starting from CONHPh phthalic anhydride and aniline in quantitative yield.<sup>50</sup> <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta$ = 9.15 (br. s, 2H), 7.71-7.67 (m, 2H), 7.60-7.56 (m, 2H), 7.02 (dd, *J* = 7.3, 8.4 Hz, 2H), 6.59 (dd, *J* = 8.4, 1.0 Hz, 2H), 8.53 (m, 1H) ppm. The spectral data match those previously reported.<sup>51</sup>

2-Phenyl-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (1at): Prepared according to Method A starting from 1,8-naphthalic anhydride in 78% isolated yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.64 (dd, *J* = 7.2, 1.2 Hz, 2H), 8.26 (dd, *J* = 8.4, 0.8 Hz, 2H), 7.78 (dd, *J* = 8.0, 7.2 Hz, 2H),

7.59-7.54 (m, 2H), 7.51-7.47 (m, 1H), 7.34 (dd, J = 4.0, 1.2 Hz, 2H) ppm. The spectral data match those previously reported.<sup>31</sup>

**3-Methyl-1-phenylmaleimide (1au):** Prepared according to Method A starting from methylmaleic anhydride in 77% isolated yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.48-7.43 (m, 2H), 7.36-7.32 (m, 3H), 6.46 (q, *J* = 2.0 Hz, 1H), 2.15 (d, *J* = 2.0 Hz, 3H) ppm. The spectral data match those

previously reported.52

*N*-Phenylhomophthalimide (1av): Prepared according to Method A starting from homophthalic anhydride in 95% isolated yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.25 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.67-7.63 (m, 1H), 7.54-7.43 (m, 4H), 7.35 (d, *J* = 7.2 Hz, 1H), 7.23-7.20 (m, 2H), 4.23 (s,

2H) ppm. The spectral data match those previously reported.<sup>53</sup>

*N*-Phenylphthalimidine (1aw): Prepared according to a literature report<sup>54</sup> in 98% isolated yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.93 (d, *J* = 7.6 Hz, 1H), 7.89-7.86 (m, 2H), 7.62-7.58 (m, 1H), 7.53-7.49 (m, 2H), 7.43

(dd, J = 8.4, 7.2 Hz, 2H), 7.18 (dd, J = 7.2, 7.2 Hz, 1H), 4.87 (s, 2H) ppm. The spectral data match those previously reported.<sup>55</sup>

Hexahydro-*N*-phenylphthalimide (1ax): Prepared according to Method D in 86% isolated yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.48-7.44 (m, 2H), 7.39-7.35 (m, 1H), 7.30-7.27 (m, 2H), 3.06-3.00 (m, 2H), 1.95-1.85 (m, 4H), 1.53-1.50 (m, 4H) ppm. The spectral data match those

previously reported.<sup>56</sup>

2-(3-(Phenylethynyl)phenyl)isoindoline-1,3-dione (1ay): Prepared according to Ph Method E in 87% isolated yield. Yellow solid. Mp: 154-156 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.96 (dd, *J* = 5.6, 2.8 Hz, 2H), 7.80 (dd, *J* = 5.6, 2.8 Hz, 2H), 7.65 (dd, *J* = 1.6, 1.6 Hz, 1H), 7.58-7.53 (m, 3H), 7.51-7.47 (m, 1H), 7.45-7.42 (m, 1H), 7.37-

7.34 (m, 3H) ppm. <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 167.0. 134.5, 131.8, 131.6, 131.1, 129.5, 129.1, 128.4, 128.3, 126.3, 124.4, 123.8, 122.9, 90.4, 88.4 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>22</sub>H<sub>13</sub>NO<sub>2</sub>Na 346.0838, found 346.0839 (0 ppm).

General procedure for the ruthenium-catalyzed protodecarbonylation reaction. General procedure:  $[RuCl_2(p-cymene)]_2$  (0.004 mmol, 2.5 mg, 0.01 equiv.), potassium carbonate (1.2 mmol, 165.8 mg, 3 equiv.), distilled water (0.6 mmol, 10.8 mg, 10.8 µL, 1.5 equiv.), substrate **1** (0.4 mmol, 1 equiv.) and *N*-methyl-2-pyrrolidone (2.0 mL) were introduced in a flame-dried Schlenk tube under argon atmosphere. The reaction mixture was stirred at 150 °C during six hours. Then, the reaction mixture was cooled down to room temperature and added 20 mL water, and then added HCl (1.0 M) to the mixture until pH is 7. The aqueous phase was extracted with ethyl acetate and the combined organic phases were dried over anhydrous MgSO<sub>4</sub>, filtered, and concentrated in *vacuo*. After solvents evaporation under vacuum, the amide product **2** or **3** was purified by column chromatography with a mixture of petroleum ether and ethyl acetate as the eluent.

# Characterization of products (2).

*N*-Methylbenzamide (2a): Isolated by column chromatography (SiO<sub>2</sub>, petroleum ether/ethyl acetate, 5:1 to 2:1, v/v) in 93% yield (50.3 mg) as a colourless solid using petroleum ether. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$ = 7.77-7.74 (m, 2H), 7.49-7.45 (m, 1H), 7.42-7.38 (m, 2H), 6.42 (br. s, 1H), 2.98 (d, J= 4.8 Hz, 3H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$ = 168.3, 134.5, 131.2, 128.3, 126.8, 26.7 ppm. GC: t<sub>R</sub> = 8.7 min; MS (EI): m/z = 134 (M<sup>+</sup>, 48), 105 (100), 77 (91), 51 (34). The spectral data match those previously reported.<sup>57</sup>

*N*-Butylbenzamide (2b): Isolated by column chromatography (SiO<sub>2</sub>, petroleum ether/ethyl acetate, 10:1 to 2:1, v/v) in 88% yield (62.4 mg) as a yellow oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta = 7.76$  (d, J = 7.6 Hz, 2H), 7.46 (dd, J = 7.2, 7.2 Hz, 1H), 7.39 (dd, J = 7.6, 7.6Hz, 2H), 6.36 (br. s, 1H), 3.43 (td, J = 6.8, 6.4 Hz, 2H), 1.62-1.54 (m, 2H), 1.43-1.34 (m, 2H), 0.93 (t, J = 7.2 Hz, 3H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta = 167.5$ , 134.7, 131.0,

128.2, 126.8, 39.7, 31.6, 20.0, 13.6 ppm. GC:  $t_R = 9.9$  min; MS (EI): m/z = 177 (M<sup>+</sup>, 8), 105 (100), 77 (41). The spectral data match those previously reported.<sup>58</sup>

*N*-Isopropylbenzamide (2c): Isolated by column chromatography (SiO<sub>2</sub>, petroleum ether/ethyl acetate, 10:1 to 2:1, v/v) in 87% yield (56.8 mg) as a colourless solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.76-7.73 (m, 2H), 7.50-7.46 (m, 1H), 7.44-7.39 (m, 2H), 5.94 (br. s, 1H), 4.33-4.25 (m, 1H), 1.26 (d, *J* = 6.4 Hz, 6H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 166.7, 135.0, 131.2, 128.5, 126.8, 41.9, 22.8 ppm. GC: t<sub>R</sub> = 8.7 min; MS (EI): m/z = 163 (M<sup>+</sup>, 25),

105 (100), 77 (39). The spectral data match those previously reported.<sup>59</sup>

*N-(p-Cyanobutyl)benzamide* (2e): Isolated by column chromatography (SiO<sub>2</sub>, petroleum ether/ethyl acetate, 10:1 to 2:1, v/v) in 91% yield (73.6 mg) as a colourless solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta = 7.75$  (dd, J = 8.0, 1.2 Hz, 2H), 7.48-7.43 (m, 1H), 7.39-

7.35 (m, 2H), 6.80 (br. s, 1H), 3.45-3.40 (m, 2H), 2.35 (t, J = 6.8 Hz, 2H), 1.76-1.63 (m, 4H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta = 167.7$ , 134.2, 131.4, 128.4, 126.8, 119.5, 38.6, 28.6, 22.6, 16.6 ppm. HRMS (ESI) calcd. for [M+Na]<sup>+</sup> C<sub>12</sub>H<sub>14</sub>N<sub>2</sub>ONa 225.09983, found 225.0996 (1 ppm). The spectral data match those previously reported.<sup>60</sup>

*N*-(2-Methoxyethyl)benzamide (2f): Isolated by column chromatography (SiO<sub>2</sub>, petroleum ether/ethyl acetate, 10:1 to 2:1, *v/v*) in 98% yield (70.3 mg) as a colourless oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.76-7.74 (m, 2H), 7.46-7.42 (m, 1H), 7.39-7.34 (m, 2H), 6.76 (br. s, 1H), 3.62-3.58 (m, 2H), 3.52-3.50 (m, 2H), 3.33 (s, 3H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 167.4, 134.4, 131.2, 128.3, 126.8, 71.0, 58.6, 39.5 ppm. HRMS (ESI) calcd. for [M+Na]<sup>+</sup> C<sub>10</sub>H<sub>13</sub>NO<sub>2</sub>Na 202.08385, found 202.0837 (1 ppm). The spectral data match those previously reported.<sup>61</sup>

N-(2-Oxopropyl)benzamide (2g): Isolated by column chromatography (SiO<sub>2</sub>,



petroleum ether/ethyl acetate, 10:1 to 2:1, v/v) in 73% yield (51.2 mg) as a yellow solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.80 (d, J = 6.8 Hz, 2H), 7.50-7.47 (m, 1H), 7.41 (dd, J = 7.6, 7.6 Hz, 2H), 7.04 (br.

s, 1H), 4.31 (d, J = 4.4 Hz, 2H), 2.23 (s, 3H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta = 203.0, 167.2, 133.6, 131.7, 128.5, 127.0, 50.2, 27.3$  ppm. GC: t<sub>R</sub> = 11.2 min; MS (EI): m/z = 177 (M<sup>+</sup>, 10), 135 (45), 105 (100), 77 (55). The spectral data match those previously reported.<sup>62</sup> Ethyl benzamidoacetate (2h): Isolated by column chromatography (SiO<sub>2</sub>, petroleum



ether/ethyl acetate, 10:1 to 2:1, v/v) in 50% yield (41.4 mg) as a colourless solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.82-7.80 (m, 2H), 7.54-7.49 (m, 1H), 7.46-7.42 (m, 2H), 6.69 (br. s, 1H), 4.29-

4.23 (m, 4H), 1.31 (t, J = 7.2 Hz, 3H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta =$  170.1, 167.4, 133.7, 131.8, 128.6, 127.0, 61.6, 41.9, 14.1 ppm. GC: t<sub>R</sub> = 10.9 min; MS (EI): m/z = 207 (M<sup>+</sup>, 7), 105 (100), 77 (35). The spectral data match those previously reported.<sup>63</sup>

*N*-(1-Naphthalenyl)benzamide (2i): Isolated by column chromatography (SiO<sub>2</sub>, petroleum ether/ethyl acetate, 10:1 to 2:1, v/v) in 92% yield (90.7 mg) as a pink solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.33 (br. s, 1H), 7.96-7.93 (m, 3H), 7.89-7.87 (m, 2H), 7.73 (d, J = 8.4 Hz, 1H), 7.57 (dd, J = 7.6, 7.6 Hz, 1H), 7.51-7.45 (m, 5H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 166.3, 134.7, 134.1, 132.4, 131.8, 128.73, 128.70, 127.6, 127.2, 126.3, 126.1, 126.0, 125.6, 121.4, 120.8 ppm. GC: t<sub>R</sub> = 16.0 min; MS (EI): m/z = 247 (M<sup>+</sup>, 8), 105 (100), 77 (62). The spectral data match those previously reported.<sup>59</sup>

**N-8-Quinolinylbenzamide (2j):** Isolated by column chromatography (SiO<sub>2</sub>, petroleum



ether/ethyl acetate, 10:1 to 2:1, v/v) in 33% yield (32.7 mg) as a colourless solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$ = 10.75 (br. s, 1H), 8.95 (dd, J = 7.6, 1.6 Hz, 1H), 8.85 (dd, J = 4.0, 1.6 Hz, 1H), 8.18

(dd, J = 8.0, 1.6 Hz, 1H), 8.09 (dd, J = 8.0, 1.6 Hz, 2H), 7.62-7.53 (m, 5H), 7.47 (dd, J = 8.4, 4.0 Hz, 1H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta = 165.4, 148.2, 138.8, 136.4, 135.1, 134.6, 131.8, 128.8$  (x 2), 128.0, 127.4, 127.3, 121.6, 116.5 ppm. GC: t<sub>R</sub> = 15.6 min; MS (EI): m/z = 248 (M<sup>+</sup>, 15), 105 (100), 77 (72). The spectral data match those previously reported.<sup>35</sup>

*N*-Benzylbenzamide (2k): Isolated by column chromatography (SiO<sub>2</sub>, petroleum ether/ethyl acetate, 10:1 to 2:1,  $\nu/\nu$ ) in 90% yield (76.2 mg) as a colourless solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.81-7.78 (m, 2H), 7.52-7.48 (m, 1H), 7.44-7.40 (m, 2H), 7.57-7.46 (m, 4H), 7.32-7.27 (m, 1H), 6.52 (br. s, 1H), 4.64 (d, *J* = 5.6 Hz, 2H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 167.4, 138.3, 134.2, 131.2, 128.4, 128.2, 127.5, 127.1, 126.9, 43.7 ppm. GC: t<sub>R</sub> = 12.5 min; MS (EI): m/z = 211 (M<sup>+</sup>, 47), 105 (100), 77 (57). The spectral data match those previously reported.<sup>64</sup> Crystals suitable for X-ray diffraction studies were grown by slow diffusion of *n*-heptane into a concentrated solution of **2x** in dichloromethane at room temperature.

*N-p*-Methylbenzylbenzamide (21): Isolated by column chromatography (SiO<sub>2</sub>, petroleum ether/ethyl acetate, 10:1 to 2:1,  $\nu/\nu$ ) in 98% yield (88.4 mg) as a colourless solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$ = 7.68 (d, *J* = 7.2 Hz, 2H), 7.36 (dd, *J* = 7.2, 7.2 Hz, 1H), 7.28 (dd, *J* = 7.6, 7.6 Hz, 2H), 7.11 (d, *J* = 8.0 Hz, 2H), 7.03 (d, *J* = 8.0 Hz, 2H), 6.65 (br. s, 1H), 4.45 (d, *J* = 5.6 Hz, 2H), 2.23 (s, 3H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$ = 167.3, 137.1, 135.2, 134.4, 131.3, 129.3, 128.4, 127.8, 126.9, 43.7, 21.0 ppm. GC: t<sub>R</sub> = 12.9 min; MS (EI): *m/z* = 225 (M<sup>+</sup>, 24), 105 (100), 77 (60). The spectral data match those previously reported.<sup>65</sup>

*N*-[(*p*-Cyanophenyl)methyl]benzamide (2m): Isolated by column chromatography (SiO<sub>2</sub>, petroleum ether/ethyl acetate, 10:1 to 2:1, *v/v*) in 90% yield (58.2 mg) as a colourless solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$ = 7.79 (d, *J* = 7.2 Hz, 2H), 7.58 (dd, *J* = 6.8, 1.6 Hz,

2H), 7.54-7.49 (m, 1H), 7.44-7.40 (m, 4H), 6.89 (br. s, 1H), 4.66 (d, J = 6.0 Hz, 2H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta = 167.6$ , 143.9, 133.7, 132.4, 131.9, 128.6, 128.1, 127.0, 118.7, 111.2, 43.4 ppm. GC:  $t_R = 15.2 \text{ min}$ ; MS (EI):  $m/z = 236 \text{ (M}^+, 18)$ , 105 (100), 77 (72), 51 (30). The spectral data match those previously reported.<sup>66</sup>

*N*-[[*p*-(Trifluoromethyl)phenyl]methyl]benzamide (2n): Isolated by column chromatography (SiO<sub>2</sub>, petroleum ether/ethyl acetate, 10:1 to 2:1, *v/v*) in 99% yield (110.9 mg) as a colourless solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$ = 7.80-7.78 (m, 2H), 7.56 (d, *J* = 8.4 Hz, 2H), 7.53-7.48 (m, 1H), 7.43-7.39 (m, 4H), 6.84 (br. s, 1H), 4.65 (d, *J* = 6.0 Hz, 2H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$ = 167.6, 142.4, 134.0, 131.7, 129.7 (q, *J*<sub>C-F</sub> = 32.9 Hz), 128.6, 127.8, 127.0, 125.6 (q, *J*<sub>C-F</sub> = 3.8 Hz), 124.0 (q, *J*<sub>C-F</sub> = 270.4 Hz), 43.4 ppm. <sup>19</sup>F{<sup>1</sup>H} NMR (376 MHz, CDCl<sub>3</sub>):  $\delta$  = -62.5 ppm. GC: t<sub>R</sub> = 12.3 min; MS (EI): *m/z* = 279 (M<sup>+</sup>, 10), 105 (100), 77 (64). The spectral data match those previously reported.<sup>67</sup>

*N-o*-**Picolylbenzamide** (20): Isolated by column chromatography (SiO<sub>2</sub>, petroleum ether/ethyl acetate, 10:1 to 2:1, v/v) in 88% yield (74.7 mg) as a colourless solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$ = 8.54 (d, J = 4.4 Hz, 1H), 7.88-7.85 (m, 2H), 7.68-7.64 (m, 2H), 7.51-7.46 (m, 1H), 7.44-7.40 (m, 2H), 7.30 (dd, J = 7.6, 7.6 Hz, 1H), 7.19 (dd, J = 7.2, 1.2 Hz, 1H), 4.74 (d, J = 4.8 Hz, 2H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$ = 167.3, 156.2, 148.9, 136.8, 134.3, 131.4, 128.5, 127.0, 122.4, 122.1, 44.7 ppm. GC: t<sub>R</sub> = 12.7 min; MS (EI): m/z = 212 (M<sup>+</sup>, 4), 107 (100), 77 (76), 51 (44). The spectral data match those previously reported.<sup>68</sup>

*N*-(2-Thienylmethyl)benzamide (2p): Isolated by column chromatography (SiO<sub>2</sub>, petroleum ether/ethyl acetate, 10:1 to 2:1, v/v) in 60% yield (52.3 mg) as a colourless solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.79-7.77 (m, 2H), 7.51-7.47 (m, 1H), 7.41 (dd, J = 7.2, 7.2 Hz, 2H), 7.23 (dd, J = 5.2, 0.8 Hz, 1H), 7.03 (d, J = 6.8 Hz, 1H), 6.96 (dd, J = 5.2, 3.6 Hz, 1H), 6.62 (br. s, 1H), 4.80 (d, J = 5.6 Hz, 2H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta =$ 167.1, 140.8, 134.1, 131.6, 128.5, 127.0, 126.9, 126.2, 125.3, 38.8 ppm. GC: t<sub>R</sub> = 12.6 min; MS (EI): m/z = 217 (M<sup>+</sup>, 42), 105 (100), 77 (44). The spectral data match those previously reported.<sup>69</sup>

*N*-Phenylbenzamide (2q): Isolated by column chromatography (SiO<sub>2</sub>, petroleum ether/ethyl acetate, 10:1 to 2:1,  $\nu/\nu$ ) in 98% yield (77.1 mg) as a colourless solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$ = 7.89-7.85 (m, 3H), 7.65 (d, *J* = 7.6 Hz, 2H), 7.57-7.52 (m, 1H), 7.49-7.45 (m, 2H), 7.37 (dd, *J* = 7.6, 7.6 Hz, 2H), 7.18-7.13 (m, 1H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$ = 165.8, 137.9, 135.0, 131.8, 129.1, 128.8, 127.0, 124.6, 120.2 ppm. GC: t<sub>R</sub> = 12.0 min; MS (EI): m/z = 197 (M<sup>+</sup>, 28), 105 (100), 77 (55). The spectral data match those previously reported.<sup>70</sup>

*N-o*-Tolylbenzamide (2r): Isolated by column chromatography (SiO<sub>2</sub>, petroleum ether/ethyl acetate, 10:1 to 2:1, v/v) in 89% yield (75.1 mg) as a colourless solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$ = 7.93-7.87 (m, 3H), 7.74 (br. s, 1H), 7.58-7.54 (m, 1H), 7.51-7.47 (m, 2H), 7.27-7.22 (m,

2H), 7.14-7.10 (m, 1H), 2.33 (s, 3H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$ = 165.7, 135.7, 134.8, 131.7, 130.5, 129.7, 128.7, 127.0, 126.7, 125.4, 123.4, 17.7 ppm. GC: t<sub>R</sub> = 12.3 min; MS (EI): *m/z* = 211 (M<sup>+</sup>, 28), 105 (100), 77 (50). The spectral data match those previously reported.<sup>71</sup>

N-(o-Methoxyphenyl)benzamide (2s): Isolated by column chromatography (SiO<sub>2</sub>,



petroleum ether/ethyl acetate, 10:1 to 2:1, v/v) in 78% yield (70.9 mg) as a colourless solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$ = 8.55 (dd, J = 7.6, 1.6 Hz, 2H), 7.90 (dd, J = 6.8, 1.6 Hz, 2H), 7.57-7.48 (m,

#### Chapter 2

3H), 7.11-7.01 (m, 2H), 6.93 (dd, J = 8.0, 1.2 Hz, 1H), 3.93 (s, 3H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta = 165.2, 148.1, 135.3, 131.6, 128.7, 127.8, 127.0, 123.8, 121.2, 119.8, 109.9, 55.8$  ppm. GC: t<sub>R</sub> = 12.8 min; MS (EI): m/z = 227 (M<sup>+</sup>, 29), 105 (100), 77 (46). The spectral data match those previously reported.<sup>72</sup>

N-(o-Chlorophenyl)benzamide (2t): Isolated by column chromatography (SiO<sub>2</sub>,



petroleum ether/ethyl acetate, 10:1 to 2:1, v/v) in 63% yield (58.3 mg) as a colourless solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.48 (dd, J = 8.4, 0.8 Hz, 1H), 8.37 (br. s, 1H), 7.84 (d, J = 7.6 Hz, 2H), 7.50 (dd,

J = 7.6, 7.6 Hz, 1H), 7.45-7.41 (m, 2H), 7.33 (dd, J = 8.0, 0.8 Hz, 1H), 7.25 (dd, J = 7.6, 7.6 Hz, 1H), 7.02-6.97 (m, 1H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta = 165.2$ , 134.6, 134.5, 132.1, 128.9, 128.8, 127.8, 127.0, 124.7, 123.0, 121.5 ppm. GC: t<sub>R</sub> = 12.3 min; MS (EI): m/z = 231 (M<sup>+</sup>, 5), 196 (27), 105 (100), 77 (77), 51 (27). The spectral data match those previously reported.<sup>73</sup>

N-(p-Tolyl)benzamide (2u): Isolated by column chromatography (SiO<sub>2</sub>, petroleum



ether/ethyl acetate, 10:1 to 2:1, v/v) in 96% yield (81.4 mg) as a colourless solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.86 (d, J = 7.2 Hz, 3H), 7.52 (d, J = 8.4 Hz, 3H), 7.48-7.44 (m, 2H), 7.16 (d, J =

8.0 Hz, 2H), 2.34 (s, 3H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 165.6, 135.3, 135.1, 134.2, 131.7, 129.5, 128.7, 127.0, 120.3, 20.9 ppm. GC: t<sub>R</sub> = 12.7 min; MS (EI): m/z = 211 (M<sup>+</sup>, 20), 105 (100), 77 (79). The spectral data match those previously reported.<sup>74</sup>

N-(p-Methoxyphenyl)benzamide (2v): Isolated by column chromatography (SiO<sub>2</sub>,



petroleum ether/ethyl acetate, 10:1 to 2:1, v/v) in 96% yield (87.1 mg) as a colourless solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$ = 7.86 (d, *J* = 7.2 Hz, 2H), 7.80 (br. s, 1H), 7.55-7.52 (m, 3H), 7.47 (dd, J = 7.2, 7.2 Hz, 2H), 6.90 (dd, J = 6.8, 2.0 Hz, 2H), 3.81 (s, 3H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta = 165.6, 156.6, 135.0, 131.7, 131.0, 128.7, 127.0, 122.1, 114.2, 55.5$  ppm. GC: t<sub>R</sub> = 13.6 min; MS (EI): m/z = 227 (M<sup>+</sup>, 21), 105 (100), 77 (59). The spectral data match those previously reported.<sup>74</sup>

**4-Benzamidoacetophenone** (**2w**): Isolated by column chromatography (SiO<sub>2</sub>, petroleum ether/dichloromethane, 4:1 to 1:2, v/v) in 98% yield (93.4 mg) as a colourless solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$ = 8.00 (dd, J = 6.8, 2.0 Hz, 3H), 7.90-7.88 (m, 2H), 7.77 (dd, J= 6.8, 2.0 Hz, 2H), 7.59 (dd, J = 7.6, 7.6 Hz, 1H), 7.53-7.49 (m, 2H), 2.60 (s, 3H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$ = 196.9, 165.7, 142.2, 134.5, 133.2, 132.3, 129.8, 128.9, 127.1, 119.2, 26.4 ppm. GC: t<sub>R</sub> = 15.6 min; MS (EI): m/z = 239 (M<sup>+</sup>, 8), 105 (100), 77 (69). The spectral data match those previously reported.<sup>75</sup>

Ethyl *p*-[(phenylcarbonyl)amino]benzoate (2x): Isolated by column chromatography  $CO_2Et$  (SiO<sub>2</sub>, petroleum ether/ethyl acetate, 10:1 to 2:1, *v/v*) in 94% yield (100.9 mg) as a colourless solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta = 8.37$  (br. s, 1H), 8.01 (dd, J = 6.8, 6.8 Hz, 2H), 7.85 (dd, J = 7.2, 7.2 Hz, 2H), 7.75 (dd, J = 7.2, 7.2 Hz, 2H), 7.52 (dd, J = 7.2, 7.2 Hz, 1H), 7.43 (dd, J = 7.2, 7.2 Hz, 2H), 4.34 (q, J = 7.2 Hz, 2H), 1.38 (t, J = 7.2 Hz, 3H)

ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 166.2, 166.0, 142.2, 134.5, 132.1, 130.7, 128.7, 127.1, 126.0, 119.2, 60.9, 14.3 ppm. GC: t<sub>R</sub> = 15.8 min; MS (EI): *m/z* = 269 (M<sup>+</sup>, 19), 105 (100), 77 (38). The spectral data match those previously reported.<sup>76</sup>

*N*-(*p*-Nitrophenyl)benzamide (2y): Isolated by column chromatography (SiO<sub>2</sub>, petroleum ether/ethyl acetate, 10:1 to 2:1, v/v) in 80% yield (77.5 mg) as a colourless solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$ = 8.27 (d, J = 9.2 Hz, 2H), 8.05 (br. s, 1H), 7.87 (dd, J = 8.4, 7.6 Hz, 4H), 7.62 (dd, J = 7.6, 7.6 Hz, 1H), 7.54 (dd, J = 7.6, 7.6 Hz, 2H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, acetone- $d_6$ ):  $\delta = 167.0$ , 146.4, 144.1, 135.5, 133.0, 129.4, 128.6, 125.5, 120.6 ppm. GC:  $t_R = 16.3$  min; MS (EI): m/z = 242 (M<sup>+</sup>, 10), 105 (100), 77 (53). The spectral data match those previously reported.<sup>77</sup>

*N-(p-Fluorophenyl)benzamide* (2z): Isolated by column chromatography (SiO<sub>2</sub>, petroleum ether/ethyl acetate, 10:1 to 2:1, *v/v*) in 96% yield (82.3 mg) as a colourless solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.79 (d, *J* = 7.6 Hz, 2H), 7.72 (br. s, 1H), 7.55-7.51 (m, 2H), 7.48 (d, *J* = 7.2 Hz, 1H), 7.44-7.40 (m, 2H), 7.00 (dd, *J* = 8.4, 8.4 Hz, 2H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = 165.5, 158.3 (d, *J*<sub>C-F</sub> = 239.0 Hz), 135.5 (d, *J*<sub>C-F</sub> = 2.3 Hz), 134.8, 131.6, 128.4, 127.6, 122.2 (d, *J*<sub>C-F</sub> = 7.7 Hz), 115.2 (d, *J*<sub>C-F</sub> = 22.2 Hz) ppm. <sup>19</sup>F{<sup>1</sup>H} NMR (376 MHz, CDCl<sub>3</sub>):  $\delta$  = -117.6 ppm. GC: t<sub>R</sub> = 12.0 min; MS (EI): *m/z* = 215 (M<sup>+</sup>, 12), 105 (100), 77 (80), 51 (28). The spectral data match those previously reported.<sup>78</sup>

N-(p-Bromophenyl)benzamide (2aa): Isolated by column chromatography (SiO<sub>2</sub>,



petroleum ether/ethyl acetate, 10:1 to 2:1, v/v) as a mixture of **3a:2q** in a ratio 74:26 according to <sup>1</sup>H NMR spectroscopy analysis. GC: t<sub>R</sub> = 14.6 min; MS (EI): m/z = 275 (M<sup>+</sup>, 10), 105

(100), 77 (45), 51 (10). The spectral data of **3a** match those previously reported.<sup>79</sup>

N-(p-Iodophenyl)benzamide (2ab): Isolated by column chromatography (SiO2,



petroleum ether/ethyl acetate, 10:1 to 2:1, v/v) as a mixture of **3b**:2**q** in a ratio 24:76 according to <sup>1</sup>H NMR spectroscopy analysis. GC: t<sub>R</sub> = 14.6 min; MS (EI): m/z = 323 (M<sup>+</sup>, 30), 105 (100), 77

(50), 51 (10). The spectral data of **3b** match those previously reported.<sup>80</sup>

*N*-(*m*-Methoxyphenyl)benzamide (2ac): Isolated by column chromatography (SiO<sub>2</sub>,

petroleum ether/ethyl acetate, 10:1 to 2:1, v/v) in 97% yield (88.5 mg) as a brown solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$ = 8.22 (br. s, 1H), 7.83 (d, J = 7.6 Hz, 2H), 7.49 (dd, J = 7.6, 7.6

Hz, 1H), 7.43-7.38 (m, 3H), 7.21 (dd, J = 8.0, 8.0 Hz, 1H), 7.14 (d, J = 7.6 Hz, 1H), 6.69 (dd, J = 8.0, 2.0 Hz, 1H), 3.77 (s, 3H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 166.0, 160.1, 139.2, 134.8, 131.7, 129.6, 128.6, 127.0, 112.5, 110.4, 105.9, 55.2 ppm. GC: t<sub>R</sub> = 13.4 min; MS (EI): m/z = 227 (M<sup>+</sup>, 19), 105 (100), 77 (66). The spectral data match those previously reported.<sup>72</sup>

N,N'-Trimethylenebis(benzamide) (2ad): Isolated by column chromatography (SiO<sub>2</sub>,



petroleum ether/ethyl acetate, 10:1 to 2:1, v/v) in 93% yield (106.2 mg) as a colourless solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$ = 7.88-7.86 (m, 4H), 7.52-7.48 (m, 2H),

7.45-7.41 (m, 4H), 7.29 (br. s, 2H), 3.58-3.53 (m, 4H), 1.84-1.78 (m, 2H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = 166.2, 134.6, 131.0, 128.2, 127.1, 37.0, 29.3 ppm. GC: t<sub>R</sub> = 19.3 min; MS (EI): *m*/*z* = 282 (M<sup>+</sup>, 8), 134 (27), 105 (100), 77 (46). The spectral data match those previously reported.<sup>81</sup>

*m*-Fluoro-*N*-phenylbenzamide (2ae): Starting from 1ae and isolated by column chromatography (SiO<sub>2</sub>, petroleum ether/ethyl acetate, 10:1 to 2:1, v/v) in 93% yield (80.1 mg) as a colourless solid. <sup>1</sup>H NMR (400

MHz, CDCl<sub>3</sub>):  $\delta$  = 7.88 (br. s, 1H), 7.64-7.56 (m, 4H), 7.48-7.43

(m, 1H), 7.41-7.35 (m, 2H), 7.27-7.24 (m, 1H), 7.22-7.14 (m, 1H) ppm.  ${}^{13}C{}^{1}H$  NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 164.2 (d,  $J_{C-F}$  = 36.8 Hz), 161.6, 137.6, 137.2 (d,  $J_{C-F}$  = 6.9 Hz), 130.4 (d,  $J_{C-F}$  = 7.7 Hz), 129.1, 124.8, 122.4 (d,  $J_{C-F}$  = 3.0 Hz), 120.3, 118.8 (d,  $J_{C-F}$  = 21.4 Hz), 114.5 (d,  $J_{C-F}$  = 23.0 Hz) ppm.  ${}^{19}F{}^{1}H$  NMR (376 MHz, CDCl<sub>3</sub>):  $\delta$  = -111.3

ppm. GC:  $t_R = 12.6$  min; MS (EI): m/z = 215 (M<sup>+</sup>, 30), 123 (100), 95 (52), 75 (15). The spectral data match those previously reported.<sup>82</sup>

*m*-Chloro-*N*-phenylbenzamide (2af): Starting from 1af and isolated by column chromatography (SiO<sub>2</sub>, petroleum ether/ethyl acetate, 10:1 to 2:1, v/v) in 65% yield (59.9 mg) as a colourless solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta = 7.93$  (br. s, 1H), 7.83 (s, 1H), 7.72 (d, J = 7.6Hz, 1H), 7.62 (d, J = 7.6 Hz, 2H), 7.50 (d, J = 8.0 Hz, 1H), 7.41-7.34 (m, 3H), 7.16 (dd, J = 7.6, 7.6 Hz, 1H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta = 164.5, 137.6, 136.7,$ 134.9, 131.8, 130.0, 129.1, 127.4, 125.1, 124.9, 120.4 ppm. GC: t<sub>R</sub> = 13.6 min; MS (EI): m/z = 231 (M<sup>+</sup>, 15), 139 (100), 111 (48), 75 (27). The spectral data match those previously reported.<sup>83</sup>

*m*-Nitro-*N*-phenylbenzamide (2ag): Starting from 1ag and isolated by column chromatography (SiO<sub>2</sub>, petroleum ether/ethyl acetate, 10:1 to 2:1, v/v) in 87% yield (87.1 mg) as a colourless solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta = 8.69$  (s, 1H), 8.39 (d, J = 8.0 Hz, 1H), 8.25 (d, J = 7.6 Hz, 1H), 8.01 (br. s, 1H), 7.71-7.64 (m, 3H), 7.39 (dd, J = 7.6, 7.6 Hz,

2H), 7.20 (dd, J = 7.2, 7.2 Hz, 1H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta = 163.3$ , 148.2, 137.2, 136.6, 133.4, 130.1, 129.2, 126.4, 125.3, 121.8, 120.5 ppm. GC: t<sub>R</sub> = 15.2 min; MS (EI): m/z = 242 (M<sup>+</sup>, 43), 212 (26), 150 (100), 120 (79), 104 (45), 92 (51), 65 (30). The spectral data match those previously reported.<sup>84</sup>

38:62 ratio of *o*-2ah:*m*-2ah according to <sup>1</sup>H NMR spectroscopy analysis. GC:  $t_R = 12.9$ 

#### Chapter 2

min (both isomers appear together); MS (EI): m/z = 211 (M<sup>+</sup>, 10), 119 (100), 91 (50), 65 (30). The spectral data match those previously reported.<sup>85</sup>

75 (10). The spectral data match those previously reported.<sup>80, 86</sup>

*m*-Nitro-*N*-phenylbenzamide (*m*-2aj): Starting from 1aj and isolated by column chromatography (SiO<sub>2</sub>, petroleum ether/ethyl acetate, 10:1 to 2:1, v/v) in 22% yield (21.3 mg) as a colourless solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta = 8.69$  (s, 1H), 8.39 (d, J = 8.0 Hz, 1H), 8.25 (d, J = 7.6 Hz, 1H), 8.01 (br. s, 1H), 7.71-7.64 (m, 3H), 7.39 (dd, J = 7.6, 7.6 Hz, 2H), 7.20 (dd, J = 7.2, 7.2 Hz, 1H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta = 163.3$ ,

148.2, 137.2, 136.6, 133.4, 130.1, 129.2, 126.4, 125.3, 121.8, 120.5 ppm. GC:  $t_R = 15.2$  min; MS (EI): m/z = 242 (M<sup>+</sup>, 43), 212 (26), 150 (100), 120 (79), 104 (45), 92 (51), 65 (30). The spectral data match those previously reported.<sup>84</sup>

*p*-Nitro-*N*-phenylbenzamide (*p*-2aj): Starting from 1aj and isolated by column chromatography (SiO<sub>2</sub>, petroleum ether/ethyl acetate, 10:1 to 2:1, v/v) in 27% yield (25.7 mg) as a colourless solid. <sup>1</sup>H NMR (400 MHz, acetone-*d*<sub>6</sub>):  $\delta$ = 9.82 (br. s, 1H), 8.37 (d, *J* = 8.8 Hz,

2H), 8.24 (d, J = 8.8 Hz, 2H), 7.84 (d, J = 8.0 Hz, 2H), 7.38 (dd, J = 8.0, 8.0 Hz, 2H), 7.16 (dd, J = 7.6, 7.6 Hz, 1H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, acetone- $d_6$ ):  $\delta = 164.7$ , 150.6, 142.0, 139.9, 129.8, 129.6, 125.1, 124.4, 121.2 ppm. GC: t<sub>R</sub> = 15.2 min; MS (EI):

### Chapter 2

m/z = 242 (M<sup>+</sup>, 42), 212 (27), 150 (100), 120 (78), 104 (45), 92 (51), 65 (30). The spectral data match those previously reported.<sup>85</sup>

*m*- and *p*-Methyl-*N*-phenylbenzamide (2ak): Starting from 1ak and isolated by  $rac{1}{H}$  +  $rac{1}{H}$  +  $rac{1}{H}$  column chromatography (SiO<sub>2</sub>, petroleum ether/ethyl acetate, 10:1 to 2:1, *v/v*) in 98% yield (89.0 mg) as a mixture of isomers in a 57:43 ratio of *m*-2ak:*p*-2ak according to <sup>1</sup>H NMR spectroscopy analysis. GC: t<sub>R</sub> = 12.9

min (both isomers appear together); MS (EI): m/z = 211 (M<sup>+</sup>, 10), 119 (100), 91 (50), 65 (30). The spectral data match those previously reported.<sup>85, 87</sup>

Benzamide (2al): Starting from phthalimide and isolated by column chromatography (SiO<sub>2</sub>, petroleum ether/ethyl acetate, 5:1 to 1:1, *v/v*) in 17% yield (8.3 mg) as a colourless solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$ = 7.83-7.80 (m, 2H), 7.54-7.50 (m, 1H), 7.46-7.42 (m, 2H), 6.26 (br. s, 2H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$ = 169.7, 133.4, 131.9, 128.6, 127.3 ppm. GC: t<sub>R</sub> = 8.8 min; MS (EI): *m/z* =121 (M<sup>+</sup>, 46), 105 (62), 77 (100), 51 (51). The spectral data match those

previously reported.88

Benzoic acid (2am): Starting from phthalic anhydride and isolated by column chromatography (SiO<sub>2</sub>, petroleum ether/ethyl acetate, 4:1 to 1:2, v/v) in OH 51% yield (25.1 mg) as a colourless solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta = 12.08$  (br. s, 1H), 8.16-8.13 (m, 2H), 7.65-7.61 (m, 1H), 7.52-7.47 (m, 2H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta = 172.5$ , 133.8, 130.2, 129.3, 128.5 ppm.

GC:  $t_R = 7.0 \text{ min}$ ; MS (EI):  $m/z = 122 \text{ (M}^+, 71)$ , 105 (94), 77 (100), 51 (76). The spectral data match those previously reported.<sup>89</sup>

## 2-(4-Hydroxybutyl)isoindoline-1,3-dione (2aq): Isolated by column chromatography



(SiO<sub>2</sub>, petroleum ether/ethyl acetate, 10:1 to 2:1, v/v) in 17% yield (14.8 mg) as a yellow solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$ =7.82 (dd, *J* = 5.6, 3.2 Hz, 2H), 7.69 (dd, *J* = 5.6, 3.2 Hz, 2H),

3.72 (t, J = 7.2 Hz, 2H), 3.68 (t, J = 6.4 Hz, 2H), 1.83 (br. s, 1H), 1.80-1.73 (m, 2H), 1.64-1.57 (m, 2H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta = 168.6$ , 134.0, 132.2, 123.3, 62.4, 37.8, 29.9, 25.2 ppm. The spectral data match those previously reported.<sup>90</sup>

## General procedure for the GC-Gas analysis of the reaction mixture.

[RuCl<sub>2</sub>(*p*-cymene)]<sub>2</sub> (0.01 mmol, 6.1 mg, 0.01 equiv.), potassium carbonate (3 mmol, 414.6 mg, 3 equiv.), distilled water (1.5 mmol, 27 mg, 27  $\mu$ L, 1.5 equiv.), substrate **1a** (1 mmol, 161 mg, 1 equiv.) and *N*-methyl-2-pyrrolidone (5 mL) were introduced in a flame-dried Schlenk tube under argon atmosphere. The reaction mixture was stirred at 150 °C during six hours. Then, the reaction mixture was cooled down to room temperature and analysed by GC-gas analysis (see details below) indicating the major presence of H<sub>2</sub> and CO<sub>2</sub> besides traces of CH<sub>4</sub> and CO. Air (O<sub>2</sub> and N<sub>2</sub>) was observed because the analysis could not be done under completely argon atmosphere. TLC and <sup>1</sup>H NMR spectroscopy analysis of the reaction mixture indicated the full conversion of **1a** into **2a**.

The same study was performed in a reaction lacking the substrate 1a.

Analysis method: Gas phase chromatography apparatus μGC 3000 SRA. Column chromatography: Molecular sieves 5Å-30 m. Oven temperature: 100 °C. Vector gas: Helium. Detector: Catharometer.

### Deuteration experiments.

[RuCl<sub>2</sub>(*p*-cymene)]<sub>2</sub> (0.001 mmol, 0.6 mg, 0.01 equiv.), potassium carbonate (0.3 mmol, 41.5 mg, 3 equiv.), substrate **1a** (0.1 mmol, 16 mg, 1 equiv.), *N*-methyl-2-pyrrolidone (0.9 mL) and D<sub>2</sub>O (0.1 mL) were introduced in a flame-dried Schlenk tube under argon atmosphere. The reaction mixture was stirred at 150 °C during six hours. Then, the reaction mixture was cooled down to room temperature and water (10 mL) was added. Then, HCl (1 M) was added until pH reached *ca*. 7. The aqueous phase was extracted with ethyl acetate (3 x 10 mL) and the combined organic layer was dried over anhydrous MgSO<sub>4</sub>, filtered, and concentrated in *vacuo*. After solvents evaporation, the reaction mixture was analysed without any further purification by <sup>1</sup>H NMR spectroscopy (using 1,3,5-trimethoxybenzene as internal standard) indicating the exclusive presence of product **2a**-*d* in 63% yield.

# Hydrogenation experiments.

[RuCl<sub>2</sub>(*p*-cymene)]<sub>2</sub> (0.002 mmol, 1.2 mg, 0.01 equiv.), potassium carbonate (0.6 mmol, 83 mg, 3 equiv.), distilled water (0.3 mmol, 5.4 mg, 5.4 µL, 1.5 equiv.), substrate **1a** (0.2 mmol, 32 mg, 1 equiv.) and *N*-methyl-2-pyrrolidone (1 mL) were introduced in a flame-dried Schlenk tube under argon atmosphere. Then, the reaction mixture was flushed with vaccum/H<sub>2</sub> over 3 cycles. The Schlenk tube was connected to a balloon filled with H<sub>2</sub> and the reaction mixture was stirred at 150 °C during six hours. Then, the reaction mixture was cooled down to room temperature and water (10 mL) was added. Then HCl (1 M) was added until pH reached *ca*. 7. The aqueous phase was extracted with ethyl acetate (3 x 10 mL) and the combined organic phases were dried over anhydrous MgSO<sub>4</sub>, filtered, and concentrated in *vacuo*. After solvents evaporation, <sup>1</sup>H NMR spectroscopy analysis (using 1,3,5-trimethoxybenzene as internal standard) indicated <10% formation of **2a** and >90% presence of **1a**.

# Study on a plausible intermediate (1al).

[RuCl<sub>2</sub>(*p*-cymene)]<sub>2</sub> (0.002 mmol, 1.2 mg, 0.01 equiv.), potassium carbonate (0.6 mmol, 83 mg, 3 equiv.), distilled water (0.3 mmol, 5.4 mg, 5.4  $\mu$ L, 1.5 equiv.), substrate **1al** (0.2 mmol, 48.2 mg, 1 equiv.) and *N*-methyl-2-pyrrolidone (1.0 mL) were introduced in a flame-dried Schlenk tube under argon atmosphere. The reaction mixture was stirred at 150 °C during six hours. Then, the reaction mixture was cooled down to room temperature and diluted with water (10 mL). Then, HCl (1 M) was added until pH reached *ca*. 7. The aqueous phase was extracted with ethyl acetate (3 x 10 mL) and the combined organic layer was dried over anhydrous MgSO<sub>4</sub>, filtered, and concentrated in *vacuo*. After solvents evaporation, the crude mixture was analysed by <sup>1</sup>H NMR spectroscopy indicating the exclusive formation of benzoic acid together with aniline.

## Trapping experiments with TEMPO.

[RuCl<sub>2</sub>(*p*-cymene)]<sub>2</sub> (0.002 mmol, 1.2 mg, 0.01 equiv.), potassium carbonate (0.6 mmol, 83 mg, 3 equiv.), distilled water (0.3 mmol, 5.4 mg, 5.4 µL, 1.5 equiv.), substrate **1a** (0.2 mmol, 32 mg, 1 equiv.), TEMPO (0.2 mmol, 31 mg, 1 equiv.) and *N*-methyl-2-pyrrolidone (1 mL) were introduced in a flame-dried Schlenk tube under argon atmosphere and the reaction mixture was stirred at 150 °C during six hours. Then, the reaction mixture was cooled down to room temperature and analysed by GC-MS indicating the presence of [**1a** + (2 x TEMPO)] at m/z = 474 besides the main presence of **1a** (see spectra below). The reaction mixture was further diluted with water (10 mL) and HCl (1 M) was added until pH reached *ca*. 7. Then, the aqueous phase was extracted with ethyl acetate (3 x 10 mL) and the combined organic phases were dried over anhydrous MgSO<sub>4</sub>, filtered, and concentrated in *vacuo*. After solvents evaporation, the desired product **2a** (24% isolated yield) was purified by column chromatography with a mixture of petroleum ether and ethyl acetate as the eluent.

### Mercury tests.

<u>Test A:</u> [RuCl<sub>2</sub>(*p*-cymene)]<sub>2</sub> (0.002 mmol, 1.2 mg, 0.01 equiv.), potassium carbonate (0.6 mmol, 83 mg, 3 equiv.), distilled water (0.3 mmol, 5.4 mg, 5.4  $\mu$ L, 1.5 equiv.), substrate **1a** (0.2 mmol, 32 mg, 1 equiv.), 1 drop of mercury and *N*-methyl-2-pyrrolidone (1 mL) were introduced in a flame-dried Schlenk tube under argon atmosphere. The reaction mixture was stirred at 150 °C during six hours. Then, the reaction mixture was cooled down to room temperature and water (10 mL) was added. Then HCl (1 M) was added to the mixture until pH reached *ca*. 7. The aqueous phase was extracted with ethyl acetate (3 x 10 mL) and the combined organic layer was dried over anhydrous MgSO<sub>4</sub>, filtered, and concentrated in *vacuo*. After solvents evaporation, the desired product **2a** was obtained in 92% isolated yield by column chromatography with a mixture of petroleum ether and ethyl acetate as the eluent.

<u>Test B:</u> [RuCl<sub>2</sub>(*p*-cymene)]<sub>2</sub> (0.002 mmol, 1.2 mg, 0.01 equiv.), potassium carbonate (0.6 mmol, 83 mg, 3 equiv.), distilled water (0.3 mmol, 5.4 mg, 5.4  $\mu$ L, 1.5 equiv.), substrate **1a** (0.2 mmol, 32 mg, 1 equiv.), and *N*-methyl-2-pyrrolidone (1 mL) were introduced in a flame-dried Schlenk tube under argon atmosphere. The reaction mixture was stirred at 150 °C during during one hour. Then, at 150 °C and under argon atmosphere, a drop of mercury was added to the reaction mixture, which was further stirred at 150 °C during five hours (total reaction time was six hours). Then, the reaction mixture was cooled down to room temperature and water (10 mL) was added. Then HCl (1 M) was added to the mixture until pH reached *ca.* 7. The aqueous phase was extracted with ethyl acetate (3 x 10 mL) and the combined organic layer was dried over anhydrous MgSO<sub>4</sub>, filtered, and concentrated in *vacuo*. After solvents evaporation, the desired product **2a** was obtained in 88% isolated yield by column chromatography with a mixture of petroleum ether and ethyl acetate as the eluent.

*Crystallographic details:* CCDC 1577926 (**2k**) contains the supplementary crystallographic data for this chapter. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data\_request/cif, or by emailing data\_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

### 2.6 References

- [1] (a) M. S. Gibson, R. W. Bradshaw, Angew. Chem. Int. Ed. 1968, 7, 919. (b) P. G. M. Wuts, in *Greenes's Protective Groups in Organic Synthesis: Fifth Edition*; P. G. M. Wuts, Ed.; Wiley-VCH, Weinheim, 2014, pp. 895-1193.
- [2] Y. Wu, W. Zhu, Chem. Soc. Rev. 2013, 42, 2039.
- [3] A. Pulido, L. Chen, T. Kaczorowski, D. Holden, M. A. Little, S. Y. Chong, B. J. Slater, D. P. McMahon, B. Bonillo, C. J. Stackhouse, A. Stephenson, C. M. Kane, R. Clowes, T. Hasell, A. I. Cooper, G. M. Day, *Nature* 2017, *543*, 657.
- [4] X. Guo, F. S. Kim, S. A. Jenekhe, M. D. Watson, J. Am. Chem. Soc. 2009, 131, 7206.
- [5] S.-R. Ban, H.-Y. Xie, X.-X. Zhu, Q.-S. Li, Eur. J. Org. Chem. 2011, 6413.
- [6] G. E. Winter, D. L. Buckley, J. Paulk, J. M. Roberts, A. Souza, S. Dhe-Paganon, J. E. Bradner, *Science* 2015, *348*, 1376.
- [7] K. C. Schreiber, V. P. Fernandez, J. Org. Chem. 1961, 26, 1744.
- [8] R. E. Gawley, S. R. Chemburkar, A. L. Smith, T. V. Anklekar, J. Org. Chem. 1988, 53, 5381.
- [9] K. Y. Koltunov, G. K. S. Prakash, G. Rasul, G. A. Olah, *Eur. J. Org. Chem.* 2006, 4861.
- [10] A. Arizpe, F. J. Sayago, A. I. Jimenez, M. Ordonez, C. Cativiela, Eur. J. Org. Chem. 2011, 6732.
- [11] S. Cacchi, G. Fabrizi, L. Moro, Synlett 1998, 741.
- [12] P. S. Anderson, M. E. Christy, C. D. Colton, W. Halczenco, G. S. Ponticello, K. L. Shepard, J. Org. Chem. 1979, 44, 1519.
- [13] (a) D. E. Patton, R. S. Drago, J. Chem. Soc. Perkin Trans. 1, 1993, 1611. (b) R. Aoun, J.-L. Renaud, P. H. Dixneuf, C. Bruneau, Angew. Chem. Int. Ed. 2005, 44, 2021. (c) S. Takebayashi, J. M. John, S. H. Bergens, J. Am. Chem. Soc. 2010, 132, 12832. (d) A. M. Maj, I. Suisse, N. Pinault, N. Robert, F. Agbossou-Niedercorn, ChemCatChem 2014, 6, 2621.
- [14] (a) S. Das, D. Addis, L. R. Knoepke, U. Bentrup, K. Junge, A. Brueckner, M. Beller, *Angew. Chem. Int. Ed.* 2011, *50*, 9180. (b) G. Ding, B. Lu, Y. Li, J. Wan, Z. Zhang, X. Xie, *Adv. Synth. Catal.* 2015, *357*, 1013.
- [15] (a) J. R. Cabrero-Antonino, I. Sorribes, K. Junge, M. Beller, Angew. Chem. Int. Ed. 2016, 55, 387. (b) J. R. Cabrero-Antonino, R. Adam, V. Papa, M. Holsten, K. Junge, M. Beller, Chem. Sci. 2017, 8, 5536.
- [16] (a) M. Ito, A. Sakaguchi, C. Kobayashi, T. Ikariya, J. Am. Chem. Soc. 2007, 129, 290. (b) Y. Kajita, S. Matsubara, T. Kurahashi, J. Am. Chem. Soc. 2008, 130, 6058.
  (c) A. Arevalo, S. Ovando-Segovia, M. Flores-Alamo, J. J. Garcia, Organometallics 2013, 32, 2939.
- [17] (a) E. Valeur, M. Bradley, *Chem. Soc. Rev.* 2009, *38*, 606. (b) R. M. Lanigan, T. D. Sheppard, *Eur. J. Org. Chem.* 2013, 7453. (c) R. M. de Figuereido, J.-S. Suppo, J.-M. Campagne, *Chem. Rev.* 2016, *116*, 12029.
- [18] (a) S. Inoue, H. Shiota, Y. Fukumoto, N. Chatani, J. Am. Chem. Soc. 2009, 131, 6898. (b) N. Hasegawa, V. Charra, S. Inoue, Y. Fukumoto, N. Chatani, J. Am. Chem. Soc. 2011, 133, 8070. (c) Y. Du, T. K. Hyster, T. Rovis, Chem. Commun. 2011, 47, 12074.
- [19] For ruthenium-catalyzed decarboxylation of esters and carboxylic acids, see: (a)
  N. Chatani, H. Tatamidani, Y. Ie, F. Kakiuchi, S. Murai, *J. Am. Chem. Soc.* 2001, *123*, 4849. (b) N. Y. Phani Kumar, S. Bechtoldt, K. Raghuvanshi, L. Ackermann, *Angew. Chem. Int. Ed.* 2016, 55, 6929. (c) J. Zhang, R. Shrestha, J. F. Hartwig, P.

Zhao, Nature Chem. 2016, 8, 1144. (d) L. Huang, A. Biafora, G. Zhang, V.
Bragoni, L. J. Goossen, Angew. Chem. Int. Ed. 2016, 55, 6933. (e) J.-L. Yu, S.-Q.
Zhang, X. Hong, J. Am. Chem. Soc. 2017, 139, 7224.

- [20] (a) B. Demerseman, M. D. Mbaye, D. Semeril, L. Toupet, C. Bruneau, P. H. Dixneuf, *Eur. J. Inorg. Chem.* 2006, 1174. (b) A. Azua, E. Peris, M. Albrecht, *Organometallics* 2010, 29, 3661. (c) A. Prades, E. Peris, M. Albrecht, *Organometallics* 2011, 30, 1162. (d) J. L. Drake, C. M. Manna, J. A. Byers, *Organometallics*, 2013, 32, 6891.
- [21] J. N. Coalter III, J. C. Bollinger, J. C. Huffman, U. Werner-Zwanziger, K. G. Caulton, E. R. Davidson, H. Gerard, E. Clot, O. Eisenstein, *New J. Chem.* 2000, 24, 9.
- [22] (a) B. Li, H. Feng, N. Wang, J. Ma, H. Song, S. Xu, B. Wang, *Chem. Eur. J.* 2012, 18, 12873. (b) R. Manikandan, P. Madasamy, M. Jeganmohan, ACS Catal. 2016, 6, 230.
- [23] V. R. Pattabiraman, J. W. Bode, Nature 2011, 480, 471.
- [24] S. Takebayashi, J. M. John, S. H. Bergens, J. Am. Chem. Soc. 2010, 132, 12832.
- [25] J.-C. Hsieh, C.-H. Cheng, Chem. Commun. 2005, 36, 4554.
- [26] G. Ding, C. Li, Y. Shen, B. Lu, Z. Zhang, X. Xie, Adv. Synth. Catal. 2016, 358, 1241.
- [27] S. Liu, Q. Deng, W. Fang, J.-F. Gong, M.-P. Song, M. Xua, T. Tu, Org. Chem. Front. 2014, 1, 1261.
- [28] L. Zhang, Y. Li, L.-Y. Jin, F. Liang, RSC Adv. 2015, 5, 65600.
- [29] P. Gupta, B. A. Shah, R. Parshad, G. N. Qazi, S. C. Taneja, *Green Chem.* 2007, 9, 1120.
- [30] P. Dawar, M. B. Raju, R. A. Ramakrishna, Tetrahedron Lett. 2011, 52, 4262.
- [31] H. J. Kim, J. Kim, S. H. Cho, S. Chang, J. Am. Chem. Soc. 2011, 133, 16382.
- [32] B. Khan, A. A. Khan, R. Kant, D. Koley, Adv. Synth. Catal. 2016, 358, 3753.
- [33] M. A. Ali, S. K. Moromi, A. S. Touchy, K. Shimizu, ChemCatChem 2016, 8, 891.

- [34] S. L. Yedage, D. S. D'silva, B. M. Bhanage, RSC Adv. 2015, 5, 80441.
- [35] S. Inoue, H. Shiota, Y. Fukumoto, N. Chatani, J. Am. Chem. Soc. 2009, 131, 6898.
- [36] M. Wang, J. Lu, J. Ma, Z. Zhang, F. Wang, Angew. Chem. Int. Ed. 2015, 54, 14061.
- [37] C. D. Chu, Y. H. Qi, W. Hao, Catal. Commun. 2007, 8, 1527.
- [38] V. Kumar, G. S. Banker, Int. J. Pharm. 1992, 79, 61.
- [39] L. K. Rasmussen, M. Begtrup, T. Ruhland, J. Org. Chem. 2004, 69, 6890.
- [40] R. Shrestha, P. Mukherjee, Y. Tan, Z. C. Litman, J. F. Hartwig, J. Am. Chem. Soc. 2013, 135, 8480.
- [41] S. A. Worlikar, R. C. Larock, J. Org. Chem. 2008, 73, 7175.
- [42] B. Nammalwar, N. P. Muddala, F. M. Watts, R. A. Bunce, *Tetrahedron* 2015, *71*, 9101.
- [43] M. V. de Almeida, F. M. Teixeira, M. V. N. de Souza, G. W. Amarante, C. C. de S. Alves, S. H. Cardoso, A. M. Mattos, A. P. Ferreira, H. C. Teixeira, *Chem. Pharm. Bull.* 2007, 55, 223.
- [44] S. D. Sarkar, L. Ackermann, Chem. Eur. J. 2014, 20, 13932.
- [45] F. J. Williams, P. E. Donahue, J. Org. Chem. 1977, 42, 3414.
- [46] Y. Shibata, K. Sasaki, Y. Hashimoto, S. Iwasaki, *Chem. Pharm. Bull.* 1996, 44, 156.
- [47] X.-F. Dong, J. Fan, X.-Y. Shi, K.-Y. Liu, P.-M. Wang, J.-F. Wei, J. Organomet. Chem. 2015, 779, 55.
- [48] X. Sun, X. Li, S. Song, Y. Zhu, Y.-F. Liang, N. Jiao, J. Am. Chem. Soc. 2015, 137, 6059.
- [49] G. Ding, C. Li, Y. Shen, B. Lu, Z. Zhang, X. Xie, Adv. Synth. Catal. 2016, 358, 1241.
- [50] A. M. Al-Azzawi, M. S. A. Al-Razzak, Int. J. Res. Pharm. Chem. 2013, 3, 682.
- [51] W. S. Sun, Y. S. Park, J. Yoo, K. D. Park, S. H. Kim, J.-H. Kim, H.-J. Park, J. Med. Chem. 2003, 46, 5619.

- [52] N. Matuszak, G. G. Muccioli, G. Labar, D. M. Lambert, *J. Med. Chem.* 2009, 52, 7410.
- [53] C.-Y. Cheng, H.-B. Tsai, M.-S. Lin, J. Heterocyclic Chem. 1995, 32, 73.
- [54] S. Wang, H. Huang, C. Bruneau, C. Fischmeister, ChemSusChem 2017, 10, 4150.
- [55] V. Kumar, S. Sharma, U. Sharma, B. Singh, N. Kumar, *Green Chem.* 2012, 14, 3410.
- [56] K. Kaminski, B. Wiklik, J. Obniska, Arch. Pharm. Chem. Life Sci. 2014, 347, 840.
- [57] A. B. Charette, M. Grenon, A. Lemire, M. Pourashraf, J. Martel, J. Am. Chem. Soc.2001, 123, 11829.
- [58] L. Ackermann, A. V. Lygin, N. Hofmann, Angew. Chem. Int. Ed. 2011, 50, 6379.
- [59] L. Zhang, S. Su, H. Wu, S. Wang, *Tetrahedron*, 2009, 65, 10022.
- [60] F. Foubelo, F. Lloret, M. Yus, Anal. Quimica 1995, 91, 260.
- [61] T. Higuchi, R. Tagawa, A. Iimuro, S. Akiyama, H. Nagae, K. Mashima, *Chem. Eur. J.* 2017, 23, 12795.
- [62] (a) U. Bratusek, S. Recnik, J. Svete, L. Golic, B. Stanovnik *Heterocycles* 2002, *57*, 2045. (b) O. A. Egorova, H. Seo, Y. Kim, D. Moon, Y. M. Rhee, K. H. Ahn, *Angew. Chem. Int. Ed.* 2011, *50*, 11446.
- [63] W.-J. Yoo, C.-J. Li, J. Am. Chem. Soc. 2006, 128, 13064.
- [64] L. U. Nordstrøm, H. Vogt, R. Madsen, J. Am. Chem. Soc. 2008, 130, 17672.
- [65] X. Cui, Y. Zhang, F. Shi, Y. Deng, Chem. Eur. J. 2011, 17, 1021.
- [66] G. A. Molander, M.-A. Hiebel, Org. Lett. 2010, 12, 4876.
- [67] P. Biallas, A. P. Häring, S. F. Kirsch, Org. Biomol. Chem. 2017, 15, 3184.
- [68] H. Sheng, R. Zeng, W. Wang, S. Luo, Y. Feng, J. Liu, W. Chen, M. Zhu, Q. Guo, *Adv. Synth. Catal.* 2017, 359, 302.
- [69] V. Rajkumar, Naveen, S. A. Babu, ChemistrySelect 2016, 6, 1207.
- [70] T. B. Halima, J. K. Vandavasi, M. Shkoor, S. G. Newman, ACS Catal. 2017, 7, 2176.
- [71] T. Miura, Y. Takahashi, M. Murakami, Chem. Commun. 2007, 3577.

- [72] H. Xu, C. Wolf, Chem. Commun. 2009, 1715.
- [73] G. Evindar, R. A. Batey, J. Org. Chem. 2006, 71, 1802.
- [74] C. K. Lee, J. S. Yu, Y. R. Ji, J. Heterocyclic Chem. 2002, 39, 1219.
- [75] W.-T. Xu, B. Huang, J.-J. Dai, J. Xu, H.-J. Xu, Org. Lett. 2016, 18, 3114.
- [76] K. Inamoto, M. Shiraishi, K. Hiroya, T. Doi, Synthesis 2010, 18, 3087.
- [77] P. Wójcik, V. Rosar, A. Gniewek, B. Milani, A. M. Trzeciak, J. Mol. Catal. A: Chemical 2016, 425, 322.
- [78] S. Ueda, H. Nagasawa, J. Org. Chem. 2009, 74, 4272.
- [79] K. Sasaki, D. Crich, Org. Lett. 2011, 13, 2256.
- [80] Z. Wang, W. Fan, G.-J. Deng, W. Zhou, Tetrahedron Lett. 2015, 56, 5449.
- [81] Y. Zhu, C. Li, A. O. Biying, M. Sudarmadji, A. Chen, D. T. Tuan, A. M. Seayad, *Dalton Trans.* 2011, 40, 9320.
- [82] R. Sharma, R. A. Vishwakarma, S. B. Bharate, Adv. Synth. Catal. 2016, 358, 3027.
- [83] J. R. Martinelli, D. A. Watson, D. M. M. Freckmann, T. E. Barder, S. L. Buchwald, *J. Org. Chem.* 2008, 73, 7102.
- [84] M. A. Ali, P. Saha, T. Punniyamurthy, *Synthesis* **2010**, *6*, 908.
- [85] Y. Wang, D. Zhu, L. Tang, S. Wang, Z. Wang, Angew. Chem. Int. Ed. 2011, 50, 8917.
- [86] G. Hong, D. Mao, X. Zhu, S. Wu, L. Wang, Org. Chem. Front. 2015, 2, 985.
- [87] G. Meng, P. Lei, M. Szostak, Org. Lett. 2017, 19, 2158.
- [88] C. Wu, X. Xin, Z.-M. Fu, L.-Y. Xie, K.-J. Liu, Z. Wang, W. Li, Z.-H. Yuan, W.-M. He, *Green Chem.* 2017, 19, 1983.
- [89] T. Hattori, H. Okami, T. Ichikawa, S. Mori, Y. Sawama, Y. Monguchi, H. Sajiki, *Adv. Synth. Catal.* 2017, 359, 3490.
- [90] M. Spallarossa, Q. Wang, R. Riva, J. Zhu, Org. Lett. 2016, 18, 1622.

[Part of this chapter has been published in J. Org. Chem. 2019, 84, 1898-1907]

# Chapter 3: Ruthenium-catalyzed selective C-H bond hydroxylation of cyclic imides

## 3.1 Introduction

Catalytic oxidations have become increasingly important in the last decades with the aim of replacing toxic and hazardous reagents in industrial and academic laboratories.<sup>1</sup> Additionally, they provide a plethora of possibilities to achieve selectivity patterns that are *per se* difficult or impossible to tackle with non-catalyzed reactions that traditionally require harsher reaction conditions than the catalytic ones.<sup>2</sup>

In this context, particular focus has been devoted to catalytic oxidations such as hydroxylation, epoxidation, acetoxylation and benzoxylation of C-H bonds thought to be traditionally unreactive.<sup>3</sup> Bio-inspired iron, copper and manganese complexes are the prevalent catalysts for aliphatic and alkene C-H bond oxidations as they promote oxygen atom transfer mechanisms *via* key oxo species.<sup>4</sup> On the other hand, the aromatic C-H bond oxidations are usually accomplished with palladium and ruthenium catalysts that enable the key C-H bond activation step *via* formation of a metallacycle intermediate assisted by a directing group.<sup>5</sup> In the former case, most of the examples have been performed with substrates containing a single aromatic fragment, which significantly decreases and simplifies the number of products that can be formed.<sup>6</sup> For example, in 2014, Rao and co-workers reported an efficient ruthenium(II)-catalyzed  $C(sp^2)$ -H bond hydroxylation with aryl carbamates as weak coordinating groups (Scheme 3.1).<sup>6a</sup> This reaction provides an interesting entry to catechols and pyrogallols in a semi-one-pot manner after a last step treatment with hydrazine reagent.



Scheme 3.1 Ru-catalyzed aromatic C-H bond hydroxylation of aryl carbamates.

The same year, Ackermann and co-workers reported an example of ruthenium(II)catalyzed C-H bond oxygenation by the assistance of extremely weak coordinating aldehydes (Scheme 3.2).<sup>6b</sup> It was shown that the direct oxygenation occurred by a kinetically relevant C-H bond ruthenacycle.



Scheme 3.2 Ru-catalyzed aromatic C-H bond hydroxylation of aldehydes.

Importantly, in the case where two aromatic fragments are present around the same directing group, undesired regio-selectivity issues as well as over-oxidation reactions are encountered.<sup>7</sup> An interesting strategy to circumvent this problem was reported by Rao and co-workers who demonstrated the regio-divergent catalytic behavior of ruthenium and palladium catalysts toward flexible, acyclic tertiary amides containing two aromatic fragments (Scheme 3.3).<sup>8</sup> Whereas the ruthenium catalyst formed the 5-membered metallacycle intermediate enabling the hydroxylation at the *ortho* C-H<sub>a</sub> bond of the phenyl ring A attached to the carbonyl group, the palladium catalyst favored the 6-membered metallacycle intermediate that promoted the hydroxylation at the *ortho* C-H<sub>b</sub> bond of the phenyl ring B attached to the nitrogen atom. The carbonyl group behaved in both cases as a weak directing group for this type of flexible substrate.<sup>8</sup>



Scheme 3.3 Regiodivergent catalysis in C-H bond hydroxylation of amides.

With this in mind, we wondered what the hydroxylation reaction outcome could be by swapping the weak directing group into a more rigid, although synthetically useful, cyclic imides (Scheme 3.4). We reasoned that cyclic imides containing two aromatic moieties, such as phthalimide-like molecules, may have difficulties to accommodate a 5-membered ruthenacycle intermediate (activation of  $C-H_a$ ) due to important ring strain, and consequently, the 6-membered ring (activation of  $C-H_b$ ) could preferentially form due to the specific pre-disposed orientation of the carbonyl group within the cyclic imide backbone (Scheme 3.4). If so, the behavior of the ruthenium catalysts would be the same as the palladium ones for this type of synthetically appealing directing group in hydroxylation reactions. In this chapter, we report such strategy, which enables a straightforward access to *ortho*-hydroxylated cyclic imides together with preliminary mechanistic studies to understand the unexpected absence of di-hydroxylated products.



Scheme 3.4 Site-selective aromatic C-H bond hydroxylation of cyclic imides.

Furthermore, *N*-phenyl-substituted cyclic imides containing hydroxyl groups in the *ortho* position represent an important class of compounds for polymer sciences<sup>9</sup> as well as biology and pharmacology (Figure 3.1).<sup>10</sup> So far, the use of cyclic imides as weak directing groups<sup>11</sup> in transition metal-catalyzed C-H bond functionalizations has been exclusively limited to selected examples of carbon-carbon bond forming reactions.<sup>12</sup> Oxygenation reactions *via* six-membered ruthenacycle intermediates with 2-pyridyloxy and 2-amino-pyrimidine substituents as strong directing group have been reported, respectively.<sup>13</sup>



side-chain polymer

Inhibitor of Dynamin I and II

Figure 3.1 Important ortho-hydroxy-substituted cyclic imides.

#### 3.2 Results and discussion

## 3.2.1 Optimization of the Ru-catalyzed site-selective aromatic C-H bond hydroxylation using cyclic imides as weak directing groups

A systematic study searching for the optimal reaction conditions enabling the hydroxylation of cyclic imides to ortho-hydroxylated cyclic imides was pursued (Table 3.1). *N*-Phenylphthalimide (1a) was selected as the model substrate for the optimization of the hydroxylation reaction with ruthenium complexes as the pre-catalysts. First, the catalytic reaction was performed in the presence of  $[RuCl_2(p-cymene)]_2$  (2.5 mol%) and PhI(OAc)<sub>2</sub> (200 mol%) as oxidant in a TFA/TFAA (TFA = trifluoroacetic acid, TFAA = trifluoroacetic anhydride) mixture as solvent under air at 80 °C for 15 hours, giving the desired product 2a in 45% yield, without any di-hydroxylation product formed during the catalysis (Table 3.1, entry 1). Next, the reaction was conducted with different oxidants such as PhI(TFA)<sub>2</sub>, K<sub>2</sub>S<sub>2</sub>O<sub>8</sub>, (NH<sub>4</sub>)<sub>2</sub>S<sub>2</sub>O<sub>8</sub>, H<sub>2</sub>O<sub>2</sub>, *m*-CPBA, (*t*-BuO)<sub>2</sub>, oxone and Cu(OAc)<sub>2</sub> (Table 3.1, entries 2-9). Among them, K<sub>2</sub>S<sub>2</sub>O<sub>8</sub> and (NH<sub>4</sub>)<sub>2</sub>S<sub>2</sub>O<sub>8</sub> were effective for the reaction and provided 2a in 78 and 83% yield, respectively (Table 3.1, entries 3-4). Solvents such as AcOH/TFAA, TFA, AcOH, toluene and 1,4-dioxane were also screened for this reaction with almost no formation of product 2a (Table 3.1, entries 10-15). It is worth noting that in the absence of TFAA, almost no reaction took place (Table 3.1, entry 11) which indicated the key role of TFAA as a source of trifluoroacetate anions during the catalytic cycle.<sup>5-8</sup> A ratio of TFA/TFAA of 9:1 slightly decreased yield and a ratio of 6:1 was as suitable as the optimal one of 3:1 (Table 3.1, entries 16-17). Other metal catalysts such as [RuCl<sub>3</sub>], [RuCl<sub>3</sub>(H<sub>2</sub>O)<sub>n</sub>], [Ru(O<sub>2</sub>CMes)<sub>2</sub>(*p*-cymene)] and [Pd(OAc)<sub>2</sub>] were tested for the hydroxylation reaction (Table 3.1, entries 18-21) and we found that  $[Ru(O_2CMes)_2(p-cymene)]$  and  $[Pd(OAc)_2]$  were equally efficient as [RuCl<sub>2</sub>(*p*-cymene)]<sub>2</sub> as the pre-catalyst affording **2a** in 86 and 84% yield, respectively. This shows that the selectivity is exclusively controlled by the structure and coordinating properties of the directing group as it was anticipated (Scheme 3.4). From a sustainable and economic point of view, however, ruthenium seems more appealing

	$ \begin{array}{c} H_{a} & O & H_{b} \\ \hline \\ N & \hline \\ O \\ 1 \\ 0 \\ 1 \\ 0 \\ 1 \\ 0 \\ 1 \\ 0 \\ 0 \\ 0$	/letal complex (x m )xidant, solvent, T,	ol%) 15 h		
Entry	Metal complex (x mol%)	Oxidant	2a Solvent	T (°C)	Yield <sup>b</sup>
1	$[RuCl_{2}(p-cymene)]_{2}$ (2.5)	PhI(OAc) <sub>a</sub>	ΤΕΔ/ΤΕΔΔ	80	45
י ס	$[RuCl_{n-cymene}]_{2} (2.5)$	$PhI(TEA)_{a}$		80	40
2	$[RuCl_2(p-cymene)]_2 (2.5)$	$K_{a}S_{a}O_{a}$		80	49
3	$[RuCl_2(p-cymenc)]_2 (2.5)$	(NH .)=S=O=	TFA/TFAA	80	/0 02
4	$[RuCl_2(p-cymenc)]_2(2.5)$			80	00
5	$[RuCl_2(p-cymene)]_2 (2.5)$	$\Pi_2 O_2$		80	0
6	$[RuCl_2(p-cymene)]_2 (2.5)$			80	17
7	$[\operatorname{RuCl}_{2}(p-\operatorname{cymene})]_{2}(2.5)$			80	0
8	$[RuCl_2(p-cymene)]_2(2.5)$			80	0
9	$[\operatorname{RuCl}_2(p-\operatorname{cymere}_2)]_2(2.5)$			00	0
10	$[RuCl_2(p-cymene)]_2 (2.5)$	$(NH_4)_2S_2O_8$	AcOH/TEAA (3:1)	80	0
11	$[RuCl_2(p-cymene)]_2 (2.5)$	$(NH_4)_2S_2O_8$	IFA	80	trace
12	$[RuCl_2(p-cymene)]_2 (2.5)$	$(NH_4)_2S_2O_8$	AcOH	80	0
13	$[RuCl_2(p-cymene)]_2$ (2.5)	(NH <sub>4</sub> ) <sub>2</sub> S <sub>2</sub> O <sub>8</sub>	DCE	80	0
14	[RuCl <sub>2</sub> ( <i>p</i> -cymene)] <sub>2</sub> (2.5)	(NH <sub>4</sub> ) <sub>2</sub> S <sub>2</sub> O <sub>8</sub>	Toluene	80	0
15	$[RuCl_2(p-cymene)]_2$ (2.5)	(NH <sub>4</sub> ) <sub>2</sub> S <sub>2</sub> O <sub>8</sub>	1,4-dioxane	80	0
16	[RuCl <sub>2</sub> (p-cymene)] <sub>2</sub> (2.5)	(NH <sub>4</sub> ) <sub>2</sub> S <sub>2</sub> O <sub>8</sub>	TFA/TFAA (9:1)	80	72
17	$[RuCl_2(p-cymene)]_2$ (2.5)	(NH <sub>4</sub> ) <sub>2</sub> S <sub>2</sub> O <sub>8</sub>	TFA/TFAA (6:1)	80	82
18	[RuCl <sub>3</sub> ] (5.0)	(NH <sub>4</sub> ) <sub>2</sub> S <sub>2</sub> O <sub>8</sub>	TFA/TFAA	80	0
19	[RuCl <sub>3</sub> (H <sub>2</sub> O) <sub>n</sub> ] (5.0)	$(NH_4)_2S_2O_8$	TFA/TFAA	80	39
20	[Ru(O <sub>2</sub> CMes) <sub>2</sub> (p-cymene)] (2.5)	$(NH_4)_2S_2O_8$	TFA/TFAA	80	86
21	[Pd(OAc) <sub>2</sub> ] (5.0)	$(NH_4)_2S_2O_8$	TFA/TFAA	80	84
22	[RuCl <sub>2</sub> (p-cymene)] <sub>2</sub> (1.0)	$(NH_4)_2S_2O_8$	TFA/TFAA	80	85
23 <sup>c</sup>	[RuCl <sub>2</sub> (p-cymene)] <sub>2</sub> (1.0)	(NH <sub>4</sub> ) <sub>2</sub> S <sub>2</sub> O <sub>8</sub>	TFA/TFAA	80	85 (82)
24 <sup>c</sup>	[RuCl <sub>2</sub> (p-cymene)] <sub>2</sub> (1.0)	$(NH_4)_2S_2O_8$	TFA/TFAA	100	85
25 <sup>c</sup>	[RuCl <sub>2</sub> ( <i>p</i> -cymene)] <sub>2</sub> (1.0)	$(NH_4)_2S_2O_8$	TFA/TFAA	60	50
26 <sup>c,d</sup>	[RuCl <sub>2</sub> ( <i>p</i> -cymene)] <sub>2</sub> (1.0)	$(NH_4)_2S_2O_8$	TFA/TFAA	80	79
27 <sup>c</sup>	[RuCl <sub>2</sub> (p-cymene)] <sub>2</sub> (0)	$(NH_4)_2S_2O_8$	TFA/TFAA	80	0

Table 3.1 Optimization of the reaction conditions.<sup>a</sup>

<sup>*a*</sup>Reaction conditions: **1a** (0.1 mmol), oxidant (0.2 mmol), metal complex (2.5 mol%) in TFA/TFAA (0.5 mL, v/v 3:1) at 80 °C for 15 h under air. <sup>*b*</sup>Determined by <sup>1</sup>H NMR spectroscopy against an internal standard (dibromomethane). The isolated yield is shown in parentheses. <sup>*c*</sup>1.2 equivalent of (NH<sub>4</sub>)<sub>2</sub>S<sub>2</sub>O<sub>8</sub>. <sup>*d*</sup>8 h.

than palladium for this type of transformations. Decreasing the amount of  $[RuCl_2(p-cymene)]_2$  to 1 mol% and decreasing the amount of oxidant  $(NH_4)_2S_2O_8$  to 1.2

equivalent led to a yield of 85% of product **2a** (Table 3.1, entries 22-23). Raising the temperature of the reaction to 100 °C provided similar yields of **2a** as when conducted at 80 °C (Table 3.1, entry 24) and decreasing the temperature to 60 °C as well as shortening the time of the reaction to 8 h, respectively, led to lower yields of **2a** (Table 3.1, entries 25-26). In the absence of any ruthenium complex, compound **1a** was found unreactive for this reaction (Table 3.1, entry 27). Overall, the optimized reaction conditions consisted of 1 or 2.5 mol% of [RuCl<sub>2</sub>(*p*-cymene)]<sub>2</sub>, (NH<sub>4</sub>)<sub>2</sub>S<sub>2</sub>O<sub>8</sub> as oxidant in a mixture of TFA/TFAA as solvents at 80 °C under air during 15 h (Table 3.1, entries 4 and 23). In this way, the targeted phenol derivative **2a** was obtained exclusively, in which the C-H bond oxidation occurred in the hydrogen atom H<sub>b</sub> (*ortho* position with respect to the nitrogen atom), with no evidence of the C-H bond functionalization taking place at the other possible hydrogen atom H<sub>a</sub> (Scheme 3.4). We also conducted a large scale experiment and we found that the reaction also proceeded efficiently. For instance, performing the catalytic reaction with substrate **1a** (2.0 mmol), the desired product **2a** was obtained in 82% isolated yield (392 mg).

## 3.2.2 Scope and limitations of the Ru-catalyzed site-selective aromatic C-H bond hydroxylation of different substituted aryl cyclic imides

With the optimized reaction conditions in hand, the scope of the reaction was evaluated with different *N*-substituted cyclic imides (Table 3.2). *para*-Substituted *N*-phenylphthalimides containing different functional groups such as methyl, diethylamino, fluoro, chloro, bromo, iodo and ester followed the protocol, leading to the corresponding phenols **2a**-**2h** in 80-90% isolated yields, respectively. The molecular structure of **2b** and **2d** was further established by single crystal X-ray diffraction studies. The very electron withdrawing nitro group provided the corresponding phenol **2i** in a moderate yield of 53%. *N*-Phenylphthalimides substituted with bromo and iodo groups in the *meta* position selectively afforded the phenols **2j** and **2k** in 75 and 87%

yields, respectively. The reaction was sensitive to the *ortho* substitution pattern of the *N*-phenyl side of the substrates. For instance, *N*-phenylphthalimide containing the small fluoro substituent at the *ortho* position afforded the corresponding phenol **2l** in 42% yield, whereas a substrate with the methyl group afforded the phenol **2m** in only 28% yield. No reaction was observed for substrates containing the hydroxyl, chloro and phenyl substituents at the *ortho* position. The reaction of *ortho*-substituted phthalimides seem to be affected not only by the bulkiness of the substituents but also by the electrostatic repulsion between the substituents and the imide carbonyl group.

**Table 3.2** Scope of the Ru-catalyzed site-selective aromatic C-H bond hydroxylation of different *N*-aryl cyclic imides substituted at the *N*-aryl side.<sup>*a,b*</sup>



<sup>a</sup>Reaction conditions: **1** (0.3 mmol), (NH<sub>4</sub>)<sub>2</sub>S<sub>2</sub>O<sub>8</sub> (0.36 mmol), [RuCl<sub>2</sub>(p-cymene)]<sub>2</sub> (1.0 mol %) in TFA/TFAA (1 mL, v/v 3:1) at 80 °C for 15 h under air. <sup>b</sup>Isolated yields. <sup>c</sup>2.5 mol % of [RuCl<sub>2</sub>(p-cymene)]<sub>2</sub>.

In addition, there was no impact for the reactivity of *N*-phenylphthalimides substituted at 3' or 4' position with different functional groups such as alkyl (Me, 'Bu), halide (F, Cl), and nitro, and the corresponding phenols **2n-2u** were obtained in 71-93% yields (Table 3.3). Interestingly, other cyclic imides behaved as excellent directing groups as the phthalimides. A cyclohexane-containing cyclic imide afforded the corresponding phenol **2v** in 91% yield and, *N*-phenyl-substituted succinimide and 2-methylmaleimide gave rise to the corresponding phenols **2w** and **2x** in 89% yield in both cases. The catalysis was also applicable (85% yield) to *N*-phenylnaphthalimide (**2y**), which is an appealing motif for material sciences.<sup>14</sup> In all cases (**2a-2y**, Table 3.2 and Table 3.3), no di-hydroxylated products were observed.

**Table 3.3** Scope of the Ru-catalyzed site-selective aromatic C-H bond hydroxylation with different substitutions at the cyclic imide backbone.<sup>*a,b*</sup>



<sup>a</sup>Reaction conditions: **1** (0.3 mmol), (NH<sub>4</sub>)<sub>2</sub>S<sub>2</sub>O<sub>8</sub> (0.36 mmol), [RuCl<sub>2</sub>(p-cymene)]<sub>2</sub> (1 mol %) in TFA/TFAA (1 mL,  $\nu/\nu$  3:1) at 80 °C for 15 h under air. <sup>b</sup>Isolated yields. <sup>c</sup>2.5 mol % of [RuCl<sub>2</sub>(p-cymene)]<sub>2</sub>.

As shown above (Table 3.1, entry 21),  $[Pd(OAc)]_2$  seems an equally efficient precatalyst as  $[RuCl_2(p-cymene)]_2$ . As such, we tested the generality of the reaction with 2 mol% of  $[Pd(OAc)_2]$  instead of 1 mol% of  $[RuCl_2(p-cymene)]_2$  as the pre-catalyst. A similar reactivity was observed as well and it was exemplified in the synthesis of the phenols **2a**, **2f**, **2p**, and **2y** in 70-80% isolated yields (Table 3.4). Again, no dihydroxylated products were observed and no hydroxylation was observed in other aromatic ring.

**Table 3.4** Pd-catalyzed site-selective aromatic C-H bond hydroxylation using representative cylic imides as weak directing groups.<sup>*a,b*</sup>



<sup>a</sup>Reaction conditions: **1** (0.3 mmol),  $(NH_4)_2S_2O_8$  (0.36 mmol),  $[Pd(OAc)_2$  (2 mol %) in TFA/TFAA (1 mL, v/v 3:1) at 80 °C for 15 h under air. <sup>b</sup>Isolated yields.

A substrate containing an internal alkyne group in the *N*-aryl side (**1z**) did not afford any hydroxylated products so far. However, formation of the 1,3-dione product **2z** was obtained in 51% isolated yield (Scheme 3.5). Such type of ruthenium-catalyzed oxidation of internal alkynes to diones have been studied elsewhere under modified reaction conditions.<sup>15</sup> On the other hand, raising the ruthenium catalyst loading to 20 mol% led to a complicated mixture of products difficult to analyze.



Scheme 3.5 Ru-catalyzed selective C-H bond hydroxylation of alkynyl substituted *N*-arylphthalimide

Unfortunately, the ruthenium-catalyzed site-selective C-H bond hydroxylation reaction was not compatible with methoxy groups. For instance, N-(2-methoxyphenyl)phthalimide, N-(3-methoxyphenyl)phthalimide and N-(4-methoxyphenyl)phthalimide decomposed under the studied reaction conditions leading to an unidentified mixture of species (Figure 3.2). Furthermore, no reactivity was found for N-(4-acetylphenyl)phthalimide, N-(4-cyanophenyl)phthalimide and N-(4-pyridyl)phthalimide (Figure 3.2) neither for C(sp<sup>3</sup>)-H bond hydroxylation of N-alkylphthalimides.



Figure 3.2 Reluctant cyclic imides encountered during the studies on the rutheniumcatalyzed site-selective C-H bond hydroxylation reaction.

#### 3.3 Mechanistic studies

To gain further insights into the reaction mechanism, we performed the catalysis with substrates lacking one and two carbonyl groups, respectively. Under the standard reaction conditions, the site- and regioselective mono-hydroxylation reaction took place with a cyclic amide (81% yield of **3**, Scheme 3.6) with traces of the di-hydroxylated product **4** detected by TLC and GC-MS analysis. However, increasing the number of equivalents of oxidant to three afforded exclusively the di-hydroxylated product **4** in 82% yield (Scheme 3.6) whereas an excess of oxidant (2-10 equiv.) had no impact when the representative cyclic imide **1a** was used (Scheme 3.6). On the other hand, performing the catalytic reaction with a substrate lacking two carbonyl groups (**1ab**, cyclic amine), no reaction occurred (Scheme 3.6), which indicates the coordinating role of the carbonyl group throughout the catalytic cycle. Consequently, the selectivity

observed for di- *vs* monohydroxylation in the resulting products is likely controlled by an increase in the steric bulk when going from cyclic amides to cyclic imides as the weak directing groups.



Scheme 3.6 Ru-catalyzed site-selective aromatic C-H bond hydroxylation using cyclic amide *versus* cyclic imides and cyclic amines as weak directing groups.

The above described findings together with previous contributions<sup>5-8</sup> enabled to propose a catalytic cycle (Scheme 3.7). Initially, one of the carbonyl groups of the imide substrate coordinated to a chloride-free ruthenium species leading to **A** that followed C-H bond activation at the *ortho* position to form the six-membered ruthenacycle intermediate **B**. After oxidation and reductive elimination, the trifluoroacetate product **D** was formed followed by hydrolysis releasing the final product **2**. The nature of **D** was evidenced by GC-MS analysis of the crude reaction mixture using **1a** as a substrate, which showed a peak at m/z = 335, corresponding to the trifluoroacetate-containing *N*-phenylphthalimide. After hydrolysis, this peak disappeared and the peak corresponding to the phenol **2a** (m/z = 239) was observed.



Scheme 3.7 Proposed catalytic cycle.

The origin of the selectivity for the exclusive mono-hydroxylation and the fact that the catalysis was sensitive to the *ortho* substitution pattern were addressed as well (Scheme 3.8). The rotational barrier around the *N*-phenyl axis of nonsubstituted *N*-phenylphthalimide was estimated to be *ca.* 10 kJ/mol, which suggests a fast interconversion between the staggered and the eclipsed conformations. This translates into an accessible pathway (blue arrows) for the catalytically productive intermediate **A**<sub>E</sub> (where the C-H bond is in close proximity of the ruthenium center) and ruthenacycle **B**<sub>E</sub> (co-planar six-membered ring). On the other hand, a substitution pattern in the *ortho* position favors the staggered conformation at a higher extent with a rotational barrier around the *N*-phenyl axis estimated to be, at least, higher than 20 kJ/mol for R = OH or OC(O)CF<sub>3</sub>. Consequently, the catalytically unproductive intermediates **A**<sub>S</sub> (distorted six-membered ruthenacycle) dominate in this catalytically unproductive case (red arrows).



Scheme 3.8 Proposed stereochemical model explaining the selectivity for mono- and regio-hydroxylation.

## 3.4 Post-functionalization reactions

Finally, a brief applicability of the transformation was demonstrated (Scheme 3.9). The *ortho*-hydroxylated phthalimides were alkylated leading to the methoxy-containing product **5** in almost quantitative yield. They could be transformed into a benzoxazole upon thermal treatment<sup>16</sup> and into amide **6** *via* ruthenium catalysis.<sup>17</sup> Deprotection with hydrazine led to the corresponding 2-aminoanisole (**7**), highlighting the great potential of the phthalimide ring as a traceless directing group for the transition metal-catalyzed C-H bond functionalizations.



Scheme 3.9 Post-functionalization reactions of 2a. Reaction conditions: (i) MeI (1.5 equiv.),  $K_2CO_3$  (1.5 equiv.), DMF (0.2 M), 20 °C, 2 h; (ii) H<sub>2</sub>O (1.5 equiv.),  $K_2CO_3$  (3 equiv.),  $[RuCl_2(p-cymene)]_2$  (5 mol%), NMP (0.2 M), 150 °C, 48 h; (iii)N<sub>2</sub>H<sub>4</sub>·H<sub>2</sub>O (7.75 equiv.), EtOH (0.2 M), reflux, 2 h.

### 3.5 Conclusion

In summary, we have developed a site- and regioselective  $C(sp^2)$ -H bond hydroxylation reaction of a large variety of functionalized cyclic imides (phthalimides, succinimides, maleimides, naphthalimides) and cyclic amides. The reactions proceeded under relatively mild conditions with as low as 1 mol% of readily available ruthenium or palladium catalysts affording the corresponding monohydroxylated products at the *ortho* position with respect to the nitrogen atom of the directing group. As such, cyclic imides can now be further exploited as easily-removable, weak directing groups for other types of C-H bond functionalizations, leading to useful shortcuts in the synthesis of fine chemicals.

## 3.6 Experimental details

General information. All reagents were obtained from commercial sources and used as supplied. All reactions were carried out in flame-dried glassware under argon atmosphere unless otherwise noted. Catalytic experiments were performed in Schlenktype flasks under argon atmosphere unless otherwise noted. Organic solutions were concentrated under reduced pressure using a rotary evaporator. Thin-layer chromatography (TLC) were carried out on 0.25 mm Merck silica gel (60-F254). Flash column chromatography was performed using silica gel Silica 60 M, 0.04-0.063 mm. Technical grade petroleum ether (40-60), *n*-heptane and ethyl acetate were used for column chromatography. CDCl<sub>3</sub> was stored under nitrogen over molecular sieves. NMR spectra were recorded on an AVANCE III 400 spectrometer. <sup>1</sup>H NMR spectra were referenced to residual protiated solvent ( $\delta = 7.26$  ppm for CDCl<sub>3</sub>,  $\delta = 2.50$  ppm for DMSO-*d*<sub>6</sub> and  $\delta = 2.05$  ppm for acetone-*d*<sub>6</sub>) and <sup>13</sup>C chemical shifts are reported relative to deuterated solvents ( $\delta = 77.0$  ppm for CDCl<sub>3</sub>,  $\delta = 39.5$  ppm for DMSO-*d*<sub>6</sub> and  $\delta = 29.8$  ppm for acetone-*d*<sub>6</sub>) [Note: acetone-*d*<sub>6</sub> contains traces of water at *ca*. 3 ppm]. The peak patterns are indicated as follows: s, singlet; d, doublet; t, triplet; q,

quartet; m, multiplet, and br. for broad. GC-MS analyses were performed with a GCMS-QP2010S (Shimadzu) instrument with a GC-2010 equipped with a 30 m capillary column (Supelco, SLBTM-5ms, fused silica capillary column, 30 m x 0.25 mm x 0.25 mm film thickness), which was used with helium as the vector gas. The following GC conditions were used: initial temperature 80 °C for 2 minutes, then rate 20 °C/min until 280 °C and 280 °C for 28 minutes. HRMS were recorded on a Waters Q-Tof 2 mass spectrometer at the corresponding facilities of the CRMPO, Centre Régional de Mesures Physiques de l'Ouest, Université de Rennes 1. Melting points were performed on a LEICA VMHB Kofler system.

## Synthesis of substrates (1).

<u>Method A:</u> Phthalic anhydride (5 mmol, 0.74 g, 1 equiv.) and the corresponding aniline (5 mmol, 1 equiv.) were refluxed in acetic acid (30 mL) for 2-5 hours. Once at room temperature, water was added and the solid recovered by filtration. After drying under vacuum the desired phthalimide **1** was obtained.

$$R_{2} + H_{2} + H_{1} + R_{1} + R_{1} + R_{2} + R_{2} + R_{2} + R_{2} + R_{1} + R_{2} + R_{2} + R_{1} + R_{2} + R_{2} + R_{1} + R_{2} + R_{2} + R_{1} + R_{2} + R_{2$$

<u>Method B:</u> A mixture of 2-formylbenzoic acid (5.0 mmol, 1 equiv.), amine (6.0 mmol, 1.2 equiv.), DABCO (10.0 mmol, 2 equiv.), HCOOH (1.25 mL), Pd(OAc)<sub>2</sub> (0.25 mmol, 5 mol%) in 1,4-dioxane (5 mL) was heated to 80 °C for 3h. After completion of the reaction, the mixture was cooled to room temperature, and diluted with DCM (50 mL). The solid was removed by filter, and the filtrate was washed with water (50 mL) and brine (50 mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/acetone = 5/1, v/v) to afford the desired product.



<u>Method C:</u> 1,2-Bis(bromomethyl)benzene (5.0 mmol, 1 equiv.), DIPEA (12.5 mmol, 2.5 equiv.), and aniline (7.50 mmol, 1.5 equiv.) dissolved in toluene (25 mL) were added to a tube sealing before vigorously stirring at 110 °C under a N<sub>2</sub> atmosphere. The resulting mixture was cooled to room temperature and extracted with ethyl acetate (3 x 10 mL). The combined organic phase was washed with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated in vacuo. The crude product was purified by column chromatography (petroleum ether) to obtain the desired product as a light yellow solid.

<u>Method D:</u> Hexahydrophthalic anhydride (10 mmol, 1.54 g, 1 equiv.) and the aniline (10 mmol, 1 equiv.) and THF (15 mL) were added to a 100 mL round bottom flask. The solution was stirred for 30 min at 40 °C. Removal of the solvent using a rotary evaporator gave the corresponding carboxylic acid-amide as white solid. The white solid was then heated at 190 °C under Ar for 4 h. The desired phthalimide was purified by silica gel column chromatography with a mixture of petroleum ether and ethyl acetate as eluent.



<u>Method E:</u> A solution of succinic acid (10 mmol, 1 equiv.) and primary amine (10 mmol, 1 equiv.) were dissolved in water (5.0 mL) in a flask and stirred and maintained at boiling for 2 h. The reaction progress was monitored by TLC (1:1 *n*-hexane/acetone).

After the reaction mixture was cooled to room temperature, the product was filtered, washed with water and recrystallized from methanol.



## Characterization of substrates 1.

N-Phenylphthalimide (1a): Prepared according to Method A starting from aniline in



80% isolated yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.96 (dd, *J* = 5.6 Hz, 3.2 Hz, 2H), 7.80 (dd, *J* = 5.2 Hz, 3.2 Hz, 2H), 7.52 (dd, *J* = 7.6 Hz, 7.6 Hz, 2H), 7.34-7.27 (m, 3H) ppm. The spectral data

match those previously reported.<sup>18</sup>

*N-(p-Tolyl)*phthalimide (1b): Prepared according to Method A starting from *p*-toluidine in 72% isolated yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$ = 7.94 (dd, J = 5.6 Hz, 3.2 Hz, 2H), 7.78 (dd, J = 5.6 Hz, 3.2 Hz, 2H), 7.31 (s, 4H), 2.41 (s, 3H) ppm. The spectral data match those

previously reported.18

N-((p-Diethylamino)phenyl)phthalimide (1c): Prepared according to Method A



starting from *N*,*N*-diethyl-1,4-phenylenediamine in 90% -NEt<sub>2</sub> isolated yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.93 (dd, *J* = 5.6, 3.2 Hz, 2H), 7.75 (dd, *J* = 5.6, 3.2 Hz, 2H), 7.20 (dd, *J* =

6.8, 2.4 Hz, 2H), 6.73 (dd, J = 6.8, 2.4 Hz, 2H), 3.38 (q, J = 7.2 Hz, 4H), 1.19 (t, J = 7.2 Hz, 6H) ppm. The spectral data match those previously reported.<sup>19</sup>

*N*-(*p*-Fluorophenyl)phthalimide (1d): Prepared according to Method A starting from



*p*-fluoroaniline in 82% isolated yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.86 (dd, *J* = 5.2 Hz, 3.2 Hz, 2H), 7.71 (dd, *J* = 5.2 Hz, 3.2 Hz, 2H), 7.34 (dd, *J* = 9.2 Hz, 4.8 Hz, 2H), 7.11 (dd, *J* =

8.8 Hz, 8.8 Hz, 2H) ppm. <sup>19</sup>F{<sup>1</sup>H} NMR (376 MHz, CDCl<sub>3</sub>):  $\delta$  = -113.8 ppm. The spectral data match those previously reported.<sup>20</sup>

N-(p-Chlorophenyl)phthalimide (1e): Prepared according to Method A starting from



4-chloroaniline in 91% isolated yield. <sup>1</sup>H NMR (400 MHz, Cl CDCl<sub>3</sub>):  $\delta$  = 7.96 (dd, *J* = 5.6, 3.2 Hz, 2H), 7.81 (dd, *J* = 5.6, 3.2 Hz, 2H), 7.48 (dd, *J* = 6.4, 2.4 Hz, 2H), 7.42 (dd, *J* = 6.4, 2.4 Hz,

2H) ppm. The spectral data match those previously reported.<sup>21</sup>

N-(p-Bromophenyl)phthalimide (1f): Prepared according to Method A starting from



*p*-bromoaniline in 88% isolated yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.96 (dd, *J* = 5.2 Hz, 2.8 Hz, 2H), 7.80 (dd, *J* = 5.2 Hz, 2.8 Hz, 2H), 7.63 (d, *J* = 8.4 Hz, 2H), 7.36 (d, *J* = 8.8 Hz,

2H) ppm. The spectral data match those previously reported.<sup>22</sup>

*N-(p-Iodophenyl)phthalimide (1g):* Prepared according to Method A starting from *p*-iodoaniline in 80% isolated yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta = 7.96-7.94$  (m, 2H), 7.84-7.79 (m, 4H), 7.23 (d, J = 8.4 Hz, 2H) ppm. The spectral data match those previously reported.<sup>23</sup>

N-(p-Ethoxycarbonylphenyl)phthalimide (1h): Prepared according to Method A



starting from benzocaine in 50% isolated yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.19 (dd, *J* = 6.8 Hz, 1.6 Hz, 2H), 7.97 (dd, *J* = 5.2 Hz, 2.8 Hz, 2H), 7.82 (dd, *J* = 5.2 Hz, 2.8

Hz, 2H), 7.59 (dd, J = 6.8 Hz, 1.6 Hz, 2H), 4.41 (q, J = 7.2 Hz, 2H), 1.41 (t, J = 7.2 Hz, 3H) ppm. The spectral data match those previously reported.<sup>24</sup>

*N-(p-Nitrophenyl)phthalimide* (1i): Prepared according to Method A starting from *p*-nitroaniline in 63% isolated yield. <sup>1</sup>H NMR (400 MHz, *p-NO*<sub>2</sub> CDCl<sub>3</sub>):  $\delta = 8.38$  (dd, J = 7.2 Hz, 2.0 Hz, 2H), 8.00 (dd, J = 5.2 Hz, 2.8 Hz, 2H), 7.85 (dd, J = 5.6 Hz, 3.2 Hz, 2H), 7.78

(dd, J = 7.2 Hz, 2.0 Hz, 2H) ppm. The spectral data match those previously reported.<sup>18</sup>

N-(m-Bromophenyl)phthalimide (1j): Prepared according to Method A starting from



3-bromoaniline in 70% isolated yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta = 7.96$  (dd, J = 5.6, 3.2 Hz, 2H), 7.80 (dd, J = 5.6, 3.2 Hz, 2H), 7.65 (dd, J = 2.0, 2.0 Hz, 1H), 7.55-7.52 (m, 1H), 7.44-7.41 (m,

1H), 7.37 (dd, J = 8.0, 8.0 Hz, 1H) ppm. The spectral data match those previously reported.<sup>25</sup>

N-(m-Iodophenyl)phthalimide (1k): Prepared according to Method A starting from 3-



8.0 Hz, 1H) ppm. The spectral data match those previously reported.<sup>22</sup>

N-(o-Fluorophenyl)phthalimide (11): Prepared according to Method A starting from



2-fluoroaniline in 91% isolated yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta = 7.97$  (dd, J = 5.6, 3.2 Hz, 2H), 7.81 (dd, J = 5.2, 3.2 Hz, 2H), 7.48-7.43 (m, 1H), 7.39-7.35 (m, 1H), 7.31-7.25 (m, 2H) ppm.

<sup>19</sup>F{<sup>1</sup>H} NMR (376 MHz, CDCl<sub>3</sub>):  $\delta$  = -118.7 ppm. The spectral data match those previously reported.<sup>26</sup>

*N-o-***Tolylphthalimide (1m):** Prepared according to Method A starting from *o*-toluidine

in 43% isolated yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.96 (dd, J = 5.6 Hz, 3.2 Hz, 2H), 7.80 (dd, J = 5.6 Hz, 2.8 Hz, 2H), 7.39-7.31 (m, 3H), 7.21 (d, J = 7.6 Hz, 1H), 2.21 (s, 3H) ppm. The spectral

data match those previously reported.<sup>27</sup>

*N*-Phenyl-3-methylphthalimide (1n): Prepared according to Method A starting from



*m*-methylphthalic anhydride in 95% isolated yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$ = 7.78 (d, *J* = 7.2 Hz, 1H), 7.63 (d, *J* = 7.6 Hz, 1H), 7.54-7.49 (m, 3H), 7.45-7.38 (m, 3H), 2.75 (s, 3H) ppm. The

spectral data match those previously reported.<sup>28</sup>

**N-Phenyl-3-fluorophthalimide** (10): Prepared according to Method A starting from



*m*-fluorophthalic anhydride in 91% isolated yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$ = 7.82-7.77 (m, 2H), 7.53-7.49 (m, 2H), 7.47-7.40 (m, 4H) ppm. <sup>19</sup>F{<sup>1</sup>H} NMR (376 MHz, CDCl<sub>3</sub>):  $\delta$ = -112.3 ppm.

The spectral data match those previously reported.<sup>29</sup>

*N*-Phenyl-3-chlorophthalimide (1p): Prepared according to Method A starting from 3-chlorophthalic anhydride in 94% isolated yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$ = 7.87 (dd, *J* = 4.8, 3.6 Hz, 1H), 7.71-7.70 (m, 2H),

7.53-7.48 (m, 2H), 7.45-7.41 (m, 3H) ppm. The spectral data match

those previously reported.<sup>30</sup>

N-Phenyl-3-nitrophthalimide (1q): Prepared according to Method A starting from 3-



nitrophthalic anhydride in 78% isolated yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$ = 8.21 (dd, *J* = 7.6, 0.8 Hz, 1H), 8.15 (dd, *J* = 8.0, 0.8 Hz,

1H), 7.98 (dd, J = 8.0, 8.0 Hz, 1H), 7.54-7.50 (m, 2H), 7.46-7.42 (m, 3H) ppm. The spectral data match those previously reported.<sup>31</sup>

N-Phenyl-4-methylphthalimide (1r): Prepared according to Method A starting from



4-methylphthalic anhydride in 97% isolated yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$ = 7.83 (d, *J* = 7.6 Hz, 1H), 7.75 (dd, *J* = 0.8, 0.8 Hz, 1H), 7.59-7.56 (m, 1H), 7.52-7.48 (m, 2H), 7.45-7.37 (m, 3H),

2.55 (s, 3H) ppm. The spectral data match those previously reported.<sup>32</sup>

N-Phenyl-4-tert-butylphthalimide (1s): Prepared according to Method A starting



from 4-tert-butylphthalic anhydride in 93% isolated yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.99 (dd, *J* = 2.0, 0.8 Hz, 1H), 7.88 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.81 (dd, *J* = 8.0, 2.0 Hz, 1H),

7.53-7.48 (m, 2H), 7.44-7.38 (m, 3H), 1.41 (s, 9H) ppm. The spectral data match those previously reported.<sup>33</sup>

N-Phenyl-4-fluorophthalimide (1t): Prepared according to Method A starting from 4-



fluorophthalic anhydride in 89% isolated yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.96 (dd, *J* = 8.4, 4.4 Hz, 1H), 7.62 (dd, *J* = 7.2, 2.0 Hz, 1H), 7.54-7.47 (m, 2H), 7.46-7.39 (m, 4H) ppm.

<sup>19</sup>F{<sup>1</sup>H} NMR (376 MHz, CDCl<sub>3</sub>):  $\delta$  = -101.1 ppm. The spectral data match those previously reported.<sup>29</sup>

N-Phenyl-4-nitrophthalimide (1u): Prepared according to Method A starting from 4-



nitrophthalic anhydride in 98% isolated yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.77 (dd, *J* = 6.0, 0.8 Hz, 1H), 8.67 (dd, *J* = 8.0, 2.0 Hz, 1H), 8.16 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.56-7.52 (m,

2H), 7.48-7.43 (m, 3H) ppm. The spectral data match those previously reported.<sup>34</sup>

**2-Phenylhexahydro-1***H***-isoindole-1,3**(2*H*)**-dione** (1v): Prepared according to Method O D in 86% isolated yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$ = 7.48-7.44



D in 86% isolated yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$ = 7.48-7.44 (m, 2H), 7.39-7.35 (m, 1H), 7.30-7.27 (m, 2H), 3.06-3.00 (m, 2H), 1.95-1.85 (m, 4H), 1.53-1.50 (m, 4H) ppm. The spectral data match

those previously reported.35

*N*-Phenylsuccinimide (1w): Prepared according to Method E starting from succinic acid in 65% isolated yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$ = 7.50-7.45 (m, 2H), 7.41-7.37 (m, 1H), 7.29-7.26 (m, 2H), 2.87 (s, 4H) ppm. The spectral data match those previously reported.<sup>36</sup>

3-Methyl-1-phenyl-1*H*-pyrrole-2,5-dione (1x): Prepared according to Method A starting from citraconic anhydride in 77% isolated yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.48-7.43 (m, 2H), 7.36-7.32 (m, 3H), 6.46 (q, *J* = 2.0 Hz, 1H), 2.15 (d, *J* = 2.0 Hz, 3H) ppm. The spectral data match

those previously reported.37

2-Phenyl-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (1y): Prepared according to Method A starting from 1,8-naphthalic anhydride in 78% isolated yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.64 (dd, *J* = 7.2, 1.2 Hz, 2H), 8.26 (dd, *J* = 8.4, 0.8 Hz, 2H), 7.78 (dd, *J* = 8.0, 7.2 Hz, 2H),

7.59-7.54 (m, 2H), 7.51-7.47 (m, 1H), 7.34 (dd, J = 4.0, 1.2 Hz, 2H) ppm. The spectral data match those previously reported.<sup>34</sup>

**2-(3-(Phenylethynyl)phenyl)isoindoline-1,3-dione** (1z): Prepared according to  $\overset{\text{Ph}}{//}$  Method E in 87% isolated yield. Yellow solid. Mp: 154-156 °C.



<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$ = 7.96 (dd, *J* = 5.6, 2.8 Hz, 2H), 7.80 (dd, *J* = 5.6, 2.8 Hz, 2H), 7.65 (dd, *J* = 1.6, 1.6 Hz, 1H), 7.58-7.53 (m, 3H), 7.51-7.47 (m, 1H), 7.45-7.42 (m, 1H), 7.37-7.34 (m, 3H) ppm. <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 167.0. 134.5, 131.8, 131.6, 131.1, 129.5, 129.1, 128.4, 128.3, 126.3, 124.4, 123.8, 122.9, 90.4, 88.4 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>22</sub>H<sub>13</sub>NO<sub>2</sub>Na 346.0838, found 346.0839 (0 ppm).

**2-Phenylisoindolin-1-one (1aa):** Prepared according to the previous reference<sup>31</sup> in 98% isolated yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$ = 7.93 (d, *J* = 7.6 Hz, 1H), 7.89-7.86 (m, 2H), 7.62-7.58 (m, 1H), 7.53-7.49 (m, 2H), 7.43 (dd, *J* = 8.4, 7.2 Hz, 2H), 7.18 (dd, *J* = 7.2, 7.2 Hz, 1H), 4.87 (s, 2H) ppm. The spectral data match those previously reported.<sup>38</sup>

2-Phenyl-2,3-dihydro-1*H*-isoindole (1ab): Prepared according to Method C starting



from 1,2-bis(bromomethyl)benzene in 89% isolated yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$ = 7.38-7.31 (m, 6H), 6.78 (dd, *J* = 7.6, 7.6 Hz,

1H), 6.71 (d, J = 7.6 Hz, 2H), 4.68 (s, 4H) ppm. The spectral data match those previously reported.<sup>39</sup>

*N*-(*o*-Chlorophenyl)phthalimide: Prepared according to Method A starting from 2chloroaniline in 70% isolated yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$ = 7.96 (dd, *J* = 5.6, 3.2 Hz, 2H), 7.80 (dd, *J* = 5.6, 3.2 Hz, 2H), 7.59-7.55 (m, 1H), 7.46-7.38 (m, 2H), 7.37-7.35 (m, 1H) ppm. The

spectral data match those previously reported.<sup>40</sup>

*N*-(2-Biphenyl)phthalimide: Prepared according to Method A starting from 2chloroaniline in 70% isolated yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$ = 7.81 (dd, *J* = 5.6, 3.2 Hz, 2H), 7.70 (dd, *J* = 5.6, 3.2 Hz, 2H), 7.55-7.48 (m, 3H), 7.35-7.32 (m, 1H), 7.29-7.20 (m, 5H) ppm. The

spectral data match those previously reported.<sup>41</sup>

*N*-(*p*-Methoxyphenyl)phthalimide: Prepared according to Method A starting from *p*-

anisidine in 80% isolated yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  

$$\delta = 7.94$$
 (dd,  $J = 5.2$ , 2.8 Hz, 2H), 7.78 (dd,  $J = 5.6$ , 3.2 Hz,  
2H), 7.34 (d,  $J = 9.2$  Hz, 2H), 7.02 (d,  $J = 9.2$  Hz, 2H), 3.85

(s, 3H) ppm. The spectral data match those previously reported.<sup>18,25</sup>

N-o-Methoxyphenylphthalimide: Prepared according to Method A starting from o-



ppm. The spectral data match those previously reported.<sup>26</sup>

N-(m-Methoxyphenyl)phthalimide: Prepared according to Method A starting from m-



anisidine in 76% isolated yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$ = 7.95 (dd, J = 5.2, 3.2 Hz, 2H), 7.78 (dd, J = 5.2, 3.2 Hz, 2H), 7.41 (dd, J = 8.0, 8.0 Hz, 1H), 7.04-7.02 (m, 1H), 6.99-6.96 (m,

1H), 6.94 (dd, J = 2.4, 1.2 Hz, 1H), 3.84 (s, 3H) ppm. The spectral data match those previously reported.<sup>42</sup>

*p*-Phthalimidoacetophenone: Prepared according to Method A starting from 4-



aminoacetophenone in 79% isolated yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.10 (dd, *J* = 6.8, 2.0 Hz, 2H), 7.97 (dd, *J* = 5.6, 3.2 Hz, 2H), 7.82 (dd, *J* = 5.6, 3.2 Hz, 2H), 7.63 (dd, *J* = 6.8,

2.0 Hz, 2H), 2.64 (s, 3H) ppm. The spectral data match those previously reported.<sup>18</sup>

*N-(p-Cyanophenyl)phthalimide:* Prepared according to Method A starting from 4-Aminobenzonitrile in 93% isolated yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.99 (dd, *J* = 5.6, 3.2 Hz, 2H), 7.84 (dd, *J* = 5.6, 3.2 Hz, 2H), 7.80 (dd, J = 6.4, 2.0 Hz, 2H), 7.69 (dd, J = 6.4, 2.0 Hz, 2H) ppm. The spectral data match those previously reported.<sup>43</sup>

*N*-(4-Pyridyl)phthalimide: Prepared according to Method A starting from 4aminopyridine in 76% isolated yield (1.19 g). 1H NMR (400 MHz, CDC13):  $\Box$  = 8.75 (dd, J = 4.8, 1.6 Hz, 2H), 7.99 (dd, J = 5.6, 3.2 Hz, 2H), 7.84 (dd, J = 5.6, 3.2 Hz, 2H), 7.61 (dd, J = 4.8, 1.6 Hz,

2H) ppm. The spectral data match those previously reported.<sup>44</sup>

## General procedure for the ruthenium-catalysed hydroxylation reaction.

*General procedure:* [RuCl<sub>2</sub>(*p*-cymene)]<sub>2</sub> (0.003 mmol, 1.8 mg, 0.01 equiv.), ammonium persulfate (0.36 mmol, 82.2 mg, 1.2 equiv.), substrate **1** (0.3 mmol, 1 equiv.) and TFA/TFAA (1.0 mL, 3:1, v/v) were introduced in a flame-dried Schlenk tube under air atmosphere. The reaction mixture was stirred at 80 °C during 15 hours. Then, the reaction mixture was cooled down to room temperature and diluted with H<sub>2</sub>O (50 mL). followed by extraction with CH<sub>2</sub>Cl<sub>2</sub> (3 x 20 mL). The combined organic layers were washed with brine (30 mL) and dried over Na<sub>2</sub>SO<sub>4</sub>. After filtration and evaporation of the solvents in *vacuo*, the crude product was purified by column chromatography on silica gel (*n*-heptane/EtOAc: 5/2, v/v) to give product **2** as a solid.

## Characterization of products (2-4).

2-(2-Hydroxyphenyl)isoindoline-1,3-dione (2a): Yellow solid, yield = 82%, 60.9 mg. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$ = 7.97 (dd, J = 5.6, 3.2 Hz, 2H), 7.81 (dd, J = 5.6, 3.2 Hz, 2H), 7.36-7.30 (m, 2H), 7.11-7.07 (m, 2H), 5.80 (br, 1H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, acetone-d<sub>6</sub>):  $\delta$  = 167.9,

154.9, 135.2, 133.5, 131.3, 131.2, 124.0, 120.6, 120.4, 117.5 ppm. MS (EI): *m/z* = 239

(M<sup>+</sup>, 52), 195 (100), 104 (39), 76 (64). The spectral data match those previously reported.<sup>45</sup>

2-(2-Hydroxy-4-methylphenyl)isoindoline-1,3-dione (2b): Colorless solid, yield =

$$0 \text{ HO} \qquad 90\%, 68.4 \text{ mg. Mp} > 250 \text{ °C dec. }^{1}\text{H NMR (400 MHz, CDCl_3):}$$
  
$$\delta = 7.96 \text{ (dd, } J = 5.6, 3.2 \text{ Hz, 2H}\text{)}, 7.80 \text{ (dd, } J = 5.6, 3.2 \text{ Hz, 2H}\text{)}, 7.18 \text{ (d, } J = 7.6 \text{ Hz, 1H}\text{)}, 6.90 \text{ (d, } J = 8.0 \text{ Hz, 2H}\text{)}, 5.71 \text{ (br, 1H}\text{)}, 100 \text{$$

2.36 (s, 3H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, acetone- $d_6$ ):  $\delta$ = 168.1, 154.6, 141.4, 135.1, 133.5, 130.9, 124.0, 121.4, 118.0, 117.7, 21.3 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>15</sub>H<sub>11</sub>NO<sub>3</sub>Na 276.0631, found 276.0635 (1 ppm).

2-(4-Diethylamino-2-hydroxyphenyl)isoindoline-1,3-dione (2c): Brown oil, yield =

88%, 65.0 mg. <sup>1</sup>H NMR (400 MHz, acetone- $d_6$ ):  $\delta$  = 7.95-7.88 NEt<sub>2</sub> (m, 4H), 7.31 (d, J = 8.4 Hz, 1H), 7.05 (d, J = 2.4 Hz, 1H), 6.99 (dd, J = 8.4, 2.4 Hz, 1H), 3.02 (q, J = 7.2 Hz, 4H), 0.99

Hz, 1H), 6.85-6.75 (m, 2H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz,

(t, J = 7.2 Hz, 6H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, acetone- $d_6$ ):  $\delta = 167.8$ , 155.0, 137.2, 135.3, 132.8, 130.6, 124.1, 124.0, 119.1, 113.6, 49.8, 13.0 ppm. HRMS (ESI) calcd. for  $[M + Na]^+ C_{18}H_{18}N_2O_3Na$  333.1210, found 333.1213 (1 ppm).

**2-(4-Fluoro-2-hydroxyphenyl)isoindoline-1,3-dione (2d):** Colorless solid, yield = 0 HO 78%, 45.5 mg. Mp: 225-228 °C. <sup>1</sup>H NMR (400 MHz, acetone-M - F d<sub>6</sub>):  $\delta = 9.27$  (br, 1H), 7.95-7.89 (m, 4H), 7.37 (dd, J = 8.8, 6.4

acetone- $d_6$ ):  $\delta = 167.9$ , 164.4 (d,  $J_{C-F} = 243.9$  Hz), 156.3 (d,  $J_{C-F} = 12.5$  Hz), 135.2, 133.4, 132.6 (d,  $J_{C-F} = 10.8$  Hz), 124.1, 116.8 (d,  $J_{C-F} = 3.3$  Hz), 107.4 (d,  $J_{C-F} = 22.9$  Hz), 104.6 (d,  $J_{C-F} = 25.2$  Hz) ppm. <sup>19</sup>F{<sup>1</sup>H} NMR (376 MHz, acetone- $d_6$ ):  $\delta = -112.3$  ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>14</sub>H<sub>8</sub>NO<sub>3</sub>FNa 280.0380, found 280.0381 (0 ppm).





85%, 60.6 mg. <sup>1</sup>H NMR (400 MHz, acetone- $d_6$ ):  $\delta$  = 9.24 (br, 1H), 7.96-7.90 (m, 4H), 7.36 (d, J = 8.4 Hz, 1H), 7.11 (d, J = 2.0 Hz, 1H), 7.03 (dd, J = 8.4, 2.0 Hz, 1H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100

MHz, acetone-*d*<sub>6</sub>):  $\delta$  = 167.7, 155.7, 135.8, 135.2, 133.3, 132.5, 124.1, 120.7, 119.4, 117.6 ppm. MS (EI): *m*/*z* = 273 (M<sup>+</sup>, 44), 229 (100), 104 (46), 76 (78). The spectral data match those previously reported.<sup>45</sup>

2-(4-Bromo-2-hydroxyphenyl)isoindoline-1,3-dione (2f): Colorless solid, yield = 77%, 73.5 mg. <sup>1</sup>H NMR (400 MHz, acetone- $d_6$ ):  $\delta$  = 7.95-7.89 (m, 4H), 7.29 (d, J = 8.4 Hz, 1H), 7.26 (d, J = 2.0 Hz, 1H), 7.18 (dd, J = 8.4, 2.0 Hz, 1H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz,

acetone- $d_6$ ):  $\delta$  = 167.6, 155.9, 135.2, 133.3, 132.8, 124.1, 123.70, 123.69, 120.5, 119.9 ppm. MS (EI): m/z = 317 (M<sup>+</sup>, 52), 275 (94), 104 (61), 76 (100), 50 (35). The spectral data match those previously reported.<sup>45</sup>

2-(2-Hydroxy-4-iodophenyl)isoindoline-1,3-dione (2g): Yellow solid, yield = 88%,



96.3 mg. Mp: 184-187 °C. <sup>1</sup>H NMR (400 MHz, acetone-*d*<sub>6</sub>):  $\delta$  = 9.15 (br, 1H), 7.95-7.89 (m, 4H), 7.46 (d, *J* = 2.0 Hz, 1H), 7.37 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.13 (d, *J* = 8.0 Hz, 1H) ppm. <sup>13</sup>C{<sup>1</sup>H}

NMR (100 MHz, acetone- $d_6$ ):  $\delta$ = 167.6, 155.7, 135.2, 133.3, 133.0, 129.9, 126.6, 124.1, 120.6, 95.3 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>14</sub>H<sub>8</sub>NO<sub>3</sub>INa 387.9441, found 387.9445 (1 ppm).

2-(4-Ethoxycarbonyl-2-hydroxyphenyl)isoindoline-1,3-dione (2h): Colorless solid,



yield = 81%, 47.8 mg. Mp: 210-213 °C. <sup>1</sup>H NMR (400 MHz, acetone- $d_6$ ):  $\delta$  = 7.97-7.91 (m, 4H), 7.71 (d, J = 2.0 Hz, 1H), 7.64 (dd, J = 8.0, 2.0 Hz, 1H), 7.47 (d, J = 8.0 Hz, 1H), 4.37 (q, J = 7.2 Hz, 2H), 1.38 (t, J = 7.2 Hz, 3H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, acetoned<sub>6</sub>):  $\delta = 167.5$ , 166.1, 154.8, 135.3, 133.40, 133.37, 131.5, 124.7, 124.2, 121.4, 118.2, 61.7, 14.5 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>17</sub>H<sub>13</sub>NO<sub>5</sub>Na 334.0686, found 334.0686 (0 ppm).

2-(2-Hydroxy-4-nitrophenyl)isoindoline-1,3-dione (2i): Colorless solid, yield = 53%,



45.2 mg. <sup>1</sup>H NMR (400 MHz, DMSO- $d_6$ ):  $\delta$  = 11.01 (br, 1H), 8.01-7.92 (m, 4H), 7.82-7.78 (m, 2H), 7.62 (d, J = 8.0 Hz, 1H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, DMSO- $d_6$ ):  $\delta$  = 166.3, 154.7,

148.4, 134.8, 131.8, 131.5, 125.3, 123.5, 113.9, 111.1 ppm. MS (EI): m/z = 248 (M<sup>+</sup>, 100), 204 (85), 104 (30), 76 (85), 50 (31). The spectral data match those previously reported.<sup>46</sup>

**2-(5-Bromo-2-hydroxyphenyl)isoindoline-1,3-dione (2j):** Colorless solid, yield =  $0 \to 0$  87%, 71.5 mg. <sup>1</sup>H NMR (400 MHz, acetone-*d*<sub>6</sub>):  $\delta$  = 9.08 (br, 1H), 7.96-7.90 (m, 4H), 7.57 (d, *J* = 2.4 Hz, 1H), 7.50 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.05 (d, *J* = 8.8 Hz, 1H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz,

acetone- $d_6$ ):  $\delta = 167.6$ , 154.5, 135.3, 134.0, 133.8, 133.3, 124.1, 121.9, 119.4, 111.0 ppm. MS (EI): m/z = 317 (M<sup>+</sup>, 34), 273 (82), 104 (60), 76 (100), 50 (34). The spectral data match those previously reported. <sup>45</sup>

**2-(2-Hydroxy-5-iodophenyl)isoindoline-1,3-dione (2k):** Brown solid, yield = 85%, O HO 93.0 mg. Mp > 250 °C dec.<sup>1</sup>H NMR (400 MHz, acetone- $d_6$ ):  $\delta =$ 

9.10 (br, 1H), 7.96-7.90 (m, 4H), 7.71 (d, J = 2.4 Hz, 1H), 7.66 (dd, J = 8.8, 2.4 Hz, 1H), 6.92 (d, J = 8.8 Hz, 1H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR

(100 MHz, acetone- $d_6$ ):  $\delta$  = 167.6, 155.2, 140.0, 139.7, 135.3, 133.4, 124.1, 122.2, 119.9, 80.2 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>14</sub>H<sub>8</sub>NO<sub>3</sub>INa 387.9441, found 387.9443 (0 ppm).

2-(6-Fluoro-2-hydroxyphenyl)isoindoline-1,3-dione (2l): Yellow solid, yield = 42%,

O HO  
N  
O F  
O HO  
S2.4 mg. Mp: 204-207 °C. <sup>1</sup>H NMR (400 MHz, acetone-
$$d_6$$
):  $\delta$ = 9.31  
(br, 1H), 8.01-7.94 (m, 4H), 7.39 (dd,  $J$  = 8.4, 6.8 Hz, 1H), 6.92 (d,  
 $J$  = 8.4 Hz, 1H), 6.84 (dd,  $J$  = 8.4, 8.4 Hz, 1H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR

(100 MHz, acetone- $d_6$ ):  $\delta = 167.2$ , 160.6 (d,  $J_{C-F} = 246.5$  Hz), 156.9 (d,  $J_{C-F} = 3.6$  Hz), 135.6, 133.2, 131.9 (d,  $J_{C-F} = 10.5$  Hz), 124.4, 113.3 (d,  $J_{C-F} = 3.0$  Hz), 108.8 (d,  $J_{C-F} = 16.0$  Hz), 107.3 (d,  $J_{C-F} = 20.0$  Hz) ppm. <sup>19</sup>F{<sup>1</sup>H} NMR (376 MHz, acetone- $d_6$ ):  $\delta = -122.0$  ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>14</sub>H<sub>8</sub>NO<sub>3</sub>FNa 280.0380, found 280.0383 (1 ppm).

2-(2-Hydroxy-6-methylphenyl)isoindoline-1,3-dione (2m): Colorless solid, yield =



28%, 21.1 mg. Mp: 145-148 °C. <sup>1</sup>H NMR (400 MHz, acetone- $d_6$ ):  $\delta$ = 8.75 (br, 1H), 7.97-7.91 (m, 4H), 7.22 (dd, J = 8.0, 8.0 Hz, 1H), 6.88 (dd, J = 8.0, 8.0 Hz, 2H), 2.14 (s, 3H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100

MHz, acetone-d<sub>6</sub>):  $\delta$  = 167.9, 155.1, 139.4, 135.3, 133.4, 130.8, 124.1, 122.0, 119.7, 114.8, 17.9 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>15</sub>H<sub>11</sub>NO<sub>3</sub>Na 276.0631, found 276.0635 (1 ppm).

**2-(2-Hydroxyphenyl)-4-methylisoindoline-1,3-dione (2n):** Colorless solid, yield =  $\begin{array}{c} Me \\ O HO \\ N \end{array}$   $\begin{array}{c} 90\%, 68.3 \text{ mg. Mp: } 187-190 \ ^{\circ}\text{C. }^{1}\text{H NMR} (400 \text{ MHz, acetone-}d_{6}): \delta \\ = 8.77 (br, 1H), 7.74-7.72 (m, 2H), 7.65-7.63 (m, 1H), 7.35-7.29 (m, 2H), 7.07 (dd, <math>J = 8.0, 1.2 \text{ Hz}, 1H), 6.98 (ddd, J = 7.6, 7.6, 1.2 \text{ Hz}, 1H) \end{array}$ 

1H), 2.70 (s, 3H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, acetone- $d_6$ ):  $\delta$  = 168.7, 167.8, 154.9, 138.6, 137.2, 134.6, 133.8, 131.3, 131.1, 129.9, 121.6, 120.5, 120.4, 117.5, 17.6 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>15</sub>H<sub>11</sub>NO<sub>3</sub>Na 276.0631, found 276.0634 (1 ppm).

**4-Fluoro-2-(2-hydroxyphenyl)isoindoline-1,3-dione (20):** Colorless solid, yield =  $\begin{array}{c} \mathsf{F} \\ \mathsf{O} \\ \mathsf{HO} \\ \mathsf{O} \end{array}$   $\begin{array}{c} \mathsf{A4\%}, 64.7 \text{ mg. Mp: } 200-203 \ ^{\circ}\text{C.} \ ^{1}\text{H} \text{ NMR (400 MHz, acetone-}d_6): \\ \delta = 8.82 \ (\text{br, 1H}), 7.95 \ (\text{ddd, } J = 8.0, 8.0, 4.4 \ \text{Hz, 1H}), 7.79 \ (\text{d, } J = 7.2 \ \text{Hz, 1H}), 7.63 \ (\text{dd, } J = 8.8, 8.8 \ \text{Hz, 1H}), 7.37-7.32 \ (\text{m, 2H}), 7.07 \ (\text{dd, } J = 8.0, 1.2 \ \text{Hz, 1H}), 6.99 \ (\text{ddd, } J = 7.6, 7.6, 1.2 \ \text{Hz, 1H}) \ \text{ppm.} \ ^{13}\text{C}\{^{1}\text{H}\} \ \text{NMR (100 MHz, acetone-}d_6): \\ \delta = 166.8 \ (\text{d, } J_{C-F} = 3.1 \ \text{Hz}), 164.6 \ (\text{d, } J_{C-F} = 1.6 \ \text{Hz}), 158.4 \ (\text{d, } J_{C-F} = 261.1 \ \text{Hz}), 154.8, 138.1 \ (\text{d, } J_{C-F} = 7.7 \ \text{Hz}), 135.7 \ (\text{d, } J_{C-F} = 1.8 \ \text{Hz}), 131.3 \ (\text{d, } J_{C-F} = 18.7 \ \text{Hz}), 123.2 \ (\text{d, } J_{C-F} = 19.8 \ \text{Hz}), 120.6, 120.4 \ (\text{d, } J_{C-F} = 3.7 \ \text{Hz}), 120.0, 119.0 \ (\text{d, } J_{C-F} = 12.5 \ \text{Hz}), 117.6 \ \text{ppm.} \ ^{19}\text{F}\{^{1}\text{H}\} \ \text{NMR (376 MHz, acetone-}d_6): \\ \delta = -115.7 \ \text{ppm. HRMS} \ (\text{ESI) calcd. for } [\text{M} + \text{Na}]^{+} \ C_{14}\ \text{H}_8\ \text{NO}_3\ \text{FNa } 280.0380, \ \text{found } 280.0383 \ (1 \ \text{ppm}). \end{array}$ 

**4-Chloro-2-(2-hydroxyphenyl)isoindoline-1,3-dione (2p):** Colorless solid, yield = 71%, 58.1 mg. Mp: 209-212 °C. <sup>1</sup>H NMR (400 MHz, acetone-*d*<sub>6</sub>):  $\delta = 8.82$  (br, 1H), 7.91-7.84 (m, 3H), 7.37-7.32 (m, 2H), 7.07 (dd, J) = 8.0, 1.2 Hz, 1H), 6.99 (ddd, J = 7.6, 7.6, 1.2 Hz, 1H) ppm. <sup>13</sup>C{<sup>1</sup>H}

NMR (100 MHz, acetone- $d_6$ ):  $\delta = 166.5$ , 165.5, 154.9, 136.6, 136.5, 135.6, 131.39, 131.36, 131.2, 129.0, 122.8, 120.6, 120.0, 117.6 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>14</sub>H<sub>8</sub>NO<sub>3</sub>ClNa 296.0085, found 296.0086 (0 ppm).

2-(2-Hydroxyphenyl)-4-nitroisoindoline-1,3-dione (2q): Colorless solid, yield =



76%, 64.8 mg. Mp: 226-229 °C. <sup>1</sup>H NMR (400 MHz, acetone- $d_6$ ):  $\delta = 8.87$  (br, 1H), 8.30-8.25 (m, 2H), 8.18 (dd, J = 7.6, 7.6 Hz, 1H), 7.38-7.34 (m, 2H), 7.08 (ddd, J = 7.6, 1.2, 1.2 Hz, 1H), 6.99 (ddd, J

= 7.6, 7.6, 1.2 Hz, 1H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, acetone- $d_6$ ):  $\delta$  = 165.9, 163.3, 154.8, 146.1, 137.1, 135.2, 131.6, 131.1, 129.1, 127.6, 124.4, 120.7, 119.7, 117.7 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>14</sub>H<sub>8</sub>N<sub>2</sub>O<sub>5</sub>Na 307.0325, found 307.0327 (0 ppm).
2-(2-Hydroxyphenyl)-5-methylisoindoline-1,3-dione (2r): Colorless solid, yield =

Me 
$$N = 0$$
 HO  $N = 0$  93%, 70.6 mg. Mp: 216-219 °C. <sup>1</sup>H NMR (400 MHz, acetone-  
d<sub>6</sub>):  $\delta = 8.71$  (br, 1H), 7.81 (d,  $J = 7.6$  Hz, 1H), 7.75 (s, 1H),  
7.71 (d,  $J = 7.6$  Hz, 1H), 7.35-7.27 (m, 2H), 7.05 (dd,  $J = 8.0$ ,

1.2 Hz, 1H), 6.97 (ddd, J = 7.6, 7.6, 1.2 Hz, 1H), 2.56 (s, 3H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, acetone- $d_6$ ):  $\delta = 168.0, 167.9, 154.9, 146.5, 135.6, 133.8, 131.3, 131.1, 130.9, 124.4, 123.9, 120.6, 117.5, 21.8 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>15</sub>H<sub>11</sub>NO<sub>3</sub>Na 276.0631, found 276.0632 (0 ppm).$ 

5-(*tert*-Butyl)-2-(2-hydroxyphenyl)isoindoline-1,3-dione (2s): Colorless solid, yield <sup>\*</sup>Bu (N - N) = 87%, 77.0 mg. Mp: 116-119 °C. <sup>1</sup>H NMR (400 MHz, acetone  $d_6$ ):  $\delta$  = 7.96-7.95 (m, 2H), 7.86 (d, J = 8.4 Hz, 1H), 7.36-7.29 (m, 2H), 7.07 (dd, J = 8.4, 1.2 Hz, 1H), 6.98 (ddd, J = 8.4, 8.4,

1.2 Hz, 1H), 1.44 (s, 9H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, acetone- $d_6$ ):  $\delta$ = 168.2, 167.8, 159.4, 154.9, 133.6, 132.1, 131.2, 131.1, 130.8, 123.9, 121.0, 120.54, 120.47, 117.5, 36.3, 31.4 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>18</sub>H<sub>17</sub>NO<sub>3</sub>Na 318.1101, found 318.1104 (1 ppm).

5-Fuloro-2-(2-hydroxyphenyl)isoindoline-1,3-dione (2t): Colorless solid, yield = 91%, 70.2 mg. Mp: 190-193 °C. <sup>1</sup>H NMR (400 MHz, acetone- $d_6$ ):  $\delta = 8.00$  (dd, J = 8.4, 4.4 Hz, 1H), 7.71-7.63 (m, 2H), 7.36-7.30 (m, 2H), 7.07 (dd, J = 8.0, 1.2 Hz, 1H), 6.98 (ddd, J = 7.6, 7.6,

1.2 Hz, 1H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, acetone-*d*<sub>6</sub>):  $\delta$ = 167.2 (d, *J*<sub>*C*-*F*</sub> = 252.5 Hz), 166.9, 166.6 (d, *J*<sub>*C*-*F*</sub> = 2.9 Hz), 154.8, 136.3 (d, *J*<sub>*C*-*F*</sub> = 9.5 Hz), 131.3 (d, *J*<sub>*C*-*F*</sub> = 17.7 Hz), 129.4 (d, *J*<sub>*C*-*F*</sub> = 2.8 Hz), 126.8 (d, *J*<sub>*C*-*F*</sub> = 9.5 Hz), 122.0 (d, *J*<sub>*C*-*F*</sub> = 23.8 Hz), 120.6, 120.2, 117.5, 111.6 (d, *J*<sub>*C*-*F*</sub> = 25.0 Hz) ppm. <sup>19</sup>F{<sup>1</sup>H} NMR (376 MHz, acetone-*d*<sub>6</sub>):  $\delta$  = -104.5 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>14</sub>H<sub>8</sub>NO<sub>3</sub>FNa 280.0380, found 280.0382 (1 ppm).

# 2-(2-Hydroxyphenyl)-5-nitroisoindoline-1,3-dione (2u): Yellow solid, yield = 82%,

<sup>O</sup><sub>2</sub>N 
$$(dd, J = 8.4, 2.0 \text{ Hz}, 1\text{H}), 8.64 (d, J = 2.0 \text{ Hz}, 1\text{H}), 8.23 (d, J = 8.0 \text{ Hz}, 1\text{H}), 7.39-7.33 (m, 2\text{H}), 7.09 (dd, J = 8.0, 1.2 \text{ Hz}, 1\text{H})$$

1H), 7.00 (ddd, J = 8.0, 8.0, 1.2 Hz, 1H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, acetone- $d_6$ ):  $\delta = 166.2, 166.0, 154.7, 152.9, 137.8, 134.7, 131.6, 131.0, 130.4, 125.6, 120.7, 119.8, 119.0, 117.6$  ppm. MS (EI): m/z = 248 (M<sup>+</sup>, 100), 204 (85), 104 (30) 76 (84), 50 (31). The spectral data match those previously reported.<sup>47</sup>

2-(2-Hydroxyphenyl)hexahydro-1H-isoindole-1,3(2H)-dione (2v): Colorless solid,



yield = 91%, 66.9 mg. Mp: 232-235 °C. <sup>1</sup>H NMR (400 MHz, acetone- $d_6$ ):  $\delta$  = 8.62 (br, 1H), 7.25 (ddd, J = 8.0, 8.0, 1.6 Hz, 1H), 7.09 (dd, J = 8.0, 1.6 Hz, 1H), 6.99 (d, J = 8.0 Hz, 1H), 6.91 (dd, J

= 7.6, 7.6 Hz, 1H), 3.13-3.07 (m, 2H), 1.91-1.86 (m, 4H), 1.50-1.47 (m, 4H) ppm.  $^{13}C{^{1}H}$  NMR (100 MHz, acetone-*d*<sub>6</sub>):  $\delta$  = 179.1, 154.2, 130.8, 130.5, 121.5, 120.5, 117.3, 41.0, 24.6, 22.6 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>14</sub>H<sub>15</sub>NO<sub>3</sub>Na 268.0944, found 268.0947 (1 ppm).

**1-(2-Hydroxyphenyl)pyrrolidine-2,5-dione (2w):** Yellow solid, yield = 89%, 33.9 mg. O HO  $^{1}$ H NMR (400 MHz, acetone-*d*<sub>6</sub>):  $\delta$  = 8.47 (br, 1H), 7.28-7.24 (m, 1H), 7.08 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.98 (dd, *J* = 8.4, 1.2 Hz, 1H), 6.91 (ddd,

<sup>O</sup> J = 7.6, 7.6, 1.2 Hz, 1H), 2.84 (s, 4H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, acetone- $d_6$ ):  $\delta = 177.2, 154.2, 130.9, 130.5, 121.3, 120.5, 117.5, 29.4$  ppm. MS (EI): m/z = 191 (M<sup>+</sup>, 100), 146 (88), 136 (54), 109 (100), 55 (84). The spectral data match those previously reported.<sup>48</sup>



 $\begin{array}{c} \mathsf{O} \ \mathsf{HO} \\ \mathsf{N} \\ \mathsf{O} \end{array} \xrightarrow{\mathsf{N}} \mathbf{S}^{\mathsf{O}}, \ \mathsf{54.2 \ mg.} \ ^{1}\mathsf{H} \ \mathsf{NMR} \ (400 \ \mathsf{MHz}, \ \mathsf{acetone-}d_{6}): \ \mathcal{S} = 8.61 \ (\mathsf{br}, \ 1\mathsf{H}), \\ \mathsf{7.28} \ (\mathsf{ddd}, J = 8.0, \ 8.0, \ 2.0 \ \mathsf{Hz}, \ 1\mathsf{H}), \ \mathsf{7.15} \ (\mathsf{dd}, J = 8.0, \ 2.0 \ \mathsf{Hz}, \ 1\mathsf{H}), \ \mathsf{7.00} \\ (\mathsf{dd}, J = 8.0, \ 1.2 \ \mathsf{Hz}, \ 1\mathsf{H}), \ \mathsf{6.92} \ (\mathsf{ddd}, J = 7.6, \ \mathsf{7.6}, \ 1.2 \ \mathsf{Hz}, \ 1\mathsf{H}), \ \mathsf{6.62} \ (\mathsf{q}, \ J = 2.0 \ \mathsf{Hz}, \ 1\mathsf{H}), \ \mathsf{2.11} \ (\mathsf{d}, J = 2.0 \ \mathsf{Hz}, \ \mathsf{3H}) \ \mathsf{ppm.} \ ^{13}\mathsf{C}\{^{1}\mathsf{H}\} \ \mathsf{NMR} \ (100 \ \mathsf{MHz}, \ \mathsf{acetone-}d_{6}): \end{array}$ 

 $\delta$  = 171.5, 170.4, 154.9, 147.0, 131.2, 130.9, 128.7, 120.52, 120.47, 117.4, 11.0 ppm. MS (EI): m/z = 203 (M<sup>+</sup>, 94), 159 (100), 133 (44), 68 (80), 52 (40). The spectral data match those previously reported.<sup>49</sup>

2-(2-Hydroxyphenyl)-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (2y): Colorless solid, yield = 85%, 59.8 mg. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = 9.62 (br, 1H), 8.50 (d, *J* = 7.6 Hz, 4H), 7.90 (dd, *J* = 7.6, 7.6 Hz, 2H), 7.29 (ddd, *J* = 7.6, 7.6, 1.6 Hz, 1H), 7.24 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.99 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.92 (ddd, *J* = 7.6, 7.6, 1.6 Hz, 1H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = 163.3, 153.4, 134.3, 131.4, 130.6, 130.3, 129.5, 127.9, 127.1, 122.9, 122.7, 119.0, 116.4 ppm. MS (EI): *m/z* = 289 (M<sup>+</sup>, 72), 272 (74), 244

(100), 126 (66). The spectral data match those previously reported.<sup>50</sup>

**2-(2-Hydroxyphenyl)isoindolin-1-one (3):** Colorless solid, yield = 81%, 54.6 mg. <sup>1</sup>H NMR (400 MHz, acetone-d<sub>6</sub>):  $\delta$  = 9.00 (br, 1H), 7.28 (ddd, J = 7.6, 1.2, 1.2 Hz, 1H), 7.70-7.68 (m, 2H), 7.60-7.56 (m, 1H), 7.46 (dd, J= 8.0, 1.6 Hz, 1H), 7.22 (ddd, J = 7.6, 7.6, 1.6 Hz, 1H), 7.03 (dd, J = 8.0, 1.6 Hz, 1H), 6.98 (ddd, J = 8.0, 8.0, 1.6 Hz, 1H), 5.08 (s, 2H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, acetone- $d_6$ ):  $\delta$  = 169.2, 152.5, 143.8, 133.1, 132.8, 129.1, 128.8, 128.0, 125.9, 124.3, 124.1, 121.2, 120.0, 53.2 ppm. MS (EI): m/z = 225 (M<sup>+</sup>, 84), 196 (30), 132 (100), 120 (45). The spectral data match those previously reported.<sup>51</sup>



$$\begin{array}{c} \text{O HO} \\ \text{Mp} > 250 \ ^{\circ}\text{C} \ \text{dec.} \ ^{1}\text{H} \ \text{NMR} \ (400 \ \text{MHz}, \ \text{acetone-}d_{6}): \ \delta = 8.46 \ (\text{br}, \\ 2\text{H}), \ 7.79 \ (\text{d}, J = 7.6 \ \text{Hz}, 1\text{H}), \ 7.65 \ -7.62 \ (\text{m}, 2\text{H}), \ 7.55 \ -7.51 \ (\text{m}, 1\text{H}), \\ 7.05 \ (\text{dd}, J = 8.4, \ 8.4 \ \text{Hz}, 1\text{H}), \ 6.53 \ (\text{d}, J = 8.4 \ \text{Hz}, 2\text{H}), \ 4.83 \ (\text{s}, 2\text{H}) \end{array}$$

ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, acetone- $d_6$ ):  $\delta$  = 169.3, 155.8, 144.4, 133.6, 132.4, 129.7, 128.5, 124.15, 124.10, 114.8, 108.8, 51.9 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>14</sub>H<sub>11</sub>NO<sub>3</sub>Na 264.0631, found 264.0632 (0 ppm).

#### General procedures of derivatization reactions and characterization of 5, 6 and 7.

Synthesis and characterization of 5: A solution of 2a (0.4 mmol, 1 equiv.) and K<sub>2</sub>CO<sub>3</sub> (0.6 mmol, 1.5 equiv.) in DMF (2 mL) was stirred at room temperature, then iodomethane (0.6 mmol, 1.5 equiv.) was added. After 2 h, the reaction mixture was diluted with H<sub>2</sub>O (40 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic phase was washed with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated in vacuo. The crude product was purified by column chromatography (*n*-heptane/EtOAc: 5/1, *v*/*v*) to obtain product 5 in 96% yield as a white solid.

*N-o*-Methoxyphenylphthalimide (5): Colorless solid, yield = 96%, 48.6 mg. <sup>1</sup>H NMR

$$(400 \text{ MHz, CDCl}_3): \delta = 7.94 \text{ (dd, } J = 5.6, 3.2 \text{ Hz, 2H}\text{)}, 7.77 \text{ (dd, } J = 5.6, 3.2 \text{ Hz, 2H}\text{)}, 7.86 \text{ (dd, } J = 5.6, 3.2 \text{ Hz, 2H}\text{)}, 7.46 \text{ (dd, } J = 5.6, 3.2 \text{ Hz, 2H}\text{)}, 7.46 \text{ (dd, } J = 5.6, 3.2 \text{ Hz, 2H}\text{)}, 7.10 \text{ (dd, } J = 5.6, 3.2 \text{ Hz, 2H}\text{)}, 7.46 \text{ (dd, } J = 5.6, 3.2 \text{ Hz, 2H}\text{)}, 7.10 \text{ (dd, } J = 5.6, 3.2 \text{ Hz, 2H}\text{)}, 7.10 \text{ (dd, } J = 5.6, 3.2 \text{ Hz, 2H}\text{)}, 7.46 \text{ (dd, } J = 5.6, 3.2 \text{ Hz, 2H}\text{)}, 7.10 \text{ (dd, } J = 5.6, 3.2 \text{ Hz, 2H}\text{)}, 7.10 \text{ (dd, } J = 5.6, 3.2 \text{ Hz, 2H}\text{)}, 7.46 \text{ (dd, } J = 5.6, 3.2 \text{ Hz, 2H}\text{)}, 7.10 \text{ (dd, } J = 5.6, 3.2 \text{ Hz, 2H}\text{)}, 7.10 \text{ (dd, } J = 5.6, 3.2 \text{ Hz, 2H}\text{)}, 7.10 \text{ (dd, } J = 5.6, 3.2 \text{ Hz, 2H}\text{)}, 7.46 \text{ (dd, } J = 5.6, 3.2 \text{ Hz, 2H}\text{)}, 7.10 \text{ (dd, } J = 5.6, 3.2 \text{ Hz, 2H$$

167.3, 155.4, 134.1, 132.2, 130.6, 130.0, 123.6, 120.8, 120.2, 112.1, 55.8 ppm. The spectral data match those previously reported.<sup>25</sup>

*Synthesis and characterization of 6*: [RuCl<sub>2</sub>(p-cymene)]<sub>2</sub> (0.002 mmol, 1.2 mg, 0.01 equiv.), potassium carbonate (0.6 mmol, 82.9 mg, 3 equiv.), distilled water (0.3 mmol, 5.4 mg, 5.4 μL, 1.5 equiv.), substrate **5** (0.2 mmol, 1 equiv.) and N-methyl-2-pyrrolidine

(1.0 mL) were introduced in a flame-dried Schlenk tube under argon atmosphere. The reaction mixture was stirred at 150 °C during 6 hours. Then, the reaction mixture was cooled down to room temperature and diluted with water (10 mL) followed by addition of HCl (1.0 M) until pH reached 7. The aqueous phase was extracted with ethyl acetate and the combined organic phases were dried over anhydrous MgSO<sub>4</sub>, filtered, and concentrated in vacuo. After solvents evaporation under vacuum, product **6** was purified by column chromatography (petroleum ether/EtOAc: 5/1, v/v) in 78% yield.

N-(o-Methoxyphenyl)benzamide (6): Colorless solid, yield = 78%, 70.9 mg. <sup>1</sup>H NMR

(400 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.55 (dd, *J* = 7.6, 1.6 Hz, 2H), 7.90 (dd, *J* = 6.8, 1.6 Hz, 2H), 7.57-7.48 (m, 3H), 7.11-7.01 (m, 2H), 6.93 (dd, *J* = 8.0, 1.2 Hz, 1H), 3.93 (s, 3H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz,

CDCl<sub>3</sub>):  $\delta$ = 165.2, 148.1, 135.3, 131.6, 128.7, 127.8, 127.0, 123.8, 121.2, 119.8, 109.9, 55.8 ppm. MS (EI): m/z = 227 (M<sup>+</sup>, 29), 105 (100), 77 (46). The spectral data match those previously reported.<sup>52</sup>

Synthesis and characterization of 7: A solution of 5 (0.2 mmol) and NH<sub>2</sub>NH<sub>2</sub>·H<sub>2</sub>O (80  $\mu$ L) in ethanol (1 mL) was heated under reflux for 2 h. The reaction mixture was cooled to room temperature, and the mixture was filtered through Celite. The solvent was removed, and the crude product was purified using column chromatography (*n*-heptane/EtOAc: 10/1, *v*/*v*) to give a red oil 7 in 83% yield.

*o*-Anisidine (7): Red oil, yield = 83%, 20.4 mg. <sup>1</sup>H NMR (400 MHz, acetone- $d_6$ ):  $\delta$  = 6.79 (d, J = 7.6 Hz, 1H), 6.69 (dd, J = 5.2, 1.2 Hz, 2H), 6.57 (ddd, J = 8.0, 4.8, 4.8 Hz, 1H), 4.32 (br, 2H), 3.80 (s, 3H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, acetone- $d_6$ ):  $\delta$  = 147.9, 138.4, 121.8, 117.8, 115.0, 111.3, 55.7 ppm.

The spectral data match those previously reported.<sup>53</sup>

*Crystallographic details:* CCDC 187307-187308 (**2b**, **2d**) contains the supplementary crystallographic data for this chapter. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data\_request/cif, or by emailing data\_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

#### 3.7 References

- [1] (a) M. S. Chen, M. C. White, Science 2007, 318, 783. (b) P. L. Fuchs, Handbook of Reagents for Organic Synthesis: Catalytic Oxidation Reactions, Wiley-VCH: Weinheim, 2013. (c) S. S. Stahl, P. L. Alsters, Liquid Phase Aerobic Oxidation Catalysis: Industrial Applications and Academic Perspectives, Wiley-VCH: Weinheim, 2016. (d) K. Muniz, Science of Synthesis: Catalytic Oxidation in Organic Synthesis, Thieme: Germany, 2018.
- [2] N. Mizuno, Modern Heterogeneous Oxidation Catalysis: Design, Reactions and Characterization, Wiley-VCH: Weinheim, 2009.
- [3] (a) T. Newhouse, P. S. Baran, Angew. Chem. Int. Ed. 2011, 50, 3362. (b) L. Boisvert, K. I. Goldberg, Acc. Chem. Res. 2012, 45, 899. (c) Y. Qiu, S. Gao, Nat. Prod. Rep. 2016, 33, 562. (d) Y.-F. Liang, N. Jiao, Acc. Chem. Res. 2017, 50, 1640. (e) J. Dong, E. Fernandez-Fueyo, F. Hollmann, C. E. Paul, M. Pesic, S. Schmidt, Y. Wang, S. Younes, W. Zhang, Angew. Chem. Int. Ed. 2018, 57, 9238.
- [4] (a) K. Ray, F. F. Pfaff, B. Wang, W. Nam, J. Am. Chem. Soc. 2014, 136, 13942. (b)
  S. D. McCann, S. S. Stahl, Acc. Chem. Res. 2015, 48, 1756. (c) N. Gagnon, W. B.
  Tolman, Acc. Chem. Res. 2015, 48, 2126. (d) S. Itoh, Acc. Chem. Res. 2015, 48, 2066. (e) W. N. Oloo, L. Que Jr., Acc. Chem. Res. 2015, 48, 2612. (f) A. C.
  Lindhorst, S. Haslinger, F. E. Kuhn, Chem. Commun. 2015, 51, 17193. (g) X.
  Engelmann, I. Monte-Perez, K. Ray, Angew. Chem. Int. Ed. 2016, 55, 7632. (h) G.

Olivo, O. Cusso, M. Costas, *Chem. Asian J.* **2016**, *11*, 3148. (i) A. J. Jasniewski, L. Que Jr., *Chem. Rev.* **2018**, *118*, 2554.

- [5] (a) D. A. Alonso, C. Najera, I.M. Pastor, M. Yus, *Chem. Eur. J.* 2010, *16*, 5274. (b)
  T. W. Lyons, M. S. Sanford, *Chem. Rev.* 2010, *110*, 1147. (c) S. Enthaler, A. Company, *Chem. Soc. Rev.* 2011, *40*, 4912. (d) Y. Rao, *Synlett* 2013, *24*, 2472. (e)
  V. S. Thirunavukkarasu, S. I. Kozhushkov, L. Ackermann, *Chem. Commun.* 2014, 50, 29.
- [6] (a) X. Yang, Y. Sun, Z. Chen, Y. Rao, Adv. Synth. Catal. 2014, 356, 1625. (b) F. Yang, K. Rauch, K. Kettelhoit, L. Ackermann, Angew. Chem. Int. Ed. 2014, 53, 11285. (c) K. Kim, H. Choe, Y. Jeong, J. H. Lee, S. Hong, Org. Lett. 2015, 17, 2550. (d) Y.-Q. Li, Q.-L. Yang, P. Fang, T.-S. Mei, D. Zhang, Org. Lett. 2017, 19, 2905. (e) Y. Guo, K.-K. Yu, L.-H. Xing, H.-W. Liu, W. Wang, Y.-F. Ji, Adv. Synth. Catal. 2017, 359, 410. (f) K. Raghuvanshi, D. Zell, L. Ackermann, Org. Lett. 2017, 19, 1278. (g) G. G. Dias, T. Rogge, R. Kuniyil, C. Jacob, R. F. S. Menna-Barreto, E. N. da Silva Junior, L. Ackermann, Chem. Commun. 2018, 54, 12840 and references cited therein.
- [7] (a) V. S. Thirunavukkarasu, L. Ackermann, Org. Lett. 2012, 14, 6206. (b) G. Shan, X. Yang, L. Ma, Y. Rao, Angew. Chem. Int. Ed. 2012, 51, 13070. (c) F. Mo, L. J. Trzepkowski, G. Dong, Angew. Chem. Int. Ed. 2012, 51, 13075. (d) P. Y. Choy, F. Y. Kwong, Org. Lett. 2013, 15, 270. (e) X. Yang, G. Shan, Y. Rao, Org. Lett. 2013, 15, 2334. (f) H.-Y. Zhang, H.-M. Yi, G.-W. Wang, B. Yang, S.-D. Yang, Org. Lett. 2013, 15, 6186. (g) G. Shan, X. Han, Y. Lin, S. Yu, Y. Rao, Org. Biomol. Chem. 2013, 11, 2318.
- [8] Y.-H. Sun, T.-Y. Sun, Y.-D. Wu, X. Zhang, Y. Rao, Chem. Sci. 2016, 7, 2229.
- [9] (a) T.-A. Chen, A. K.-Y. Jen, Y. Cai, J. Am. Chem. Soc. 1995, 117, 7295. (b) D. Yu,
  A. Ghavari, L. Yu, J. Am. Chem. Soc. 1995, 117, 11680. (c) S. H. Han, N. Misdan,
  S. Kim, C. M. Doherty, A. J. Hill, Y. M. Lee, Macromolecules 2010, 43, 7657.

- [10] (a) L. R. Odell, D. Howan, C. P. Gordon, M. J. Robertson, N. Chau, A. Mariana, A. E. Whiting, R. Abagyan, J. A. Daniel, N. N. Gorgani, P. J. Robinson, A. McCluskey, *J. Med. Chem.* 2010, *53*, 5267. (b) S. Mangani, L. Cancian, R. Leone, C. Pozzi, S. Lazzari, R. Luciani, S. Ferrari, M. P. Costi, *J. Med. Chem.* 2011, *54*, 5454.
- [11] (a) K. M. Engle, T.-S. Mei, M. Wasa, J.-Q. Yu, Acc. Chem. Res. 2012, 45, 788. (b)
  S. de Sarkar, W. Liu, S. I. Kozhushkov, L. Ackermann, Adv. Synth. Catal. 2014, 356, 1461.
- [12] (a) S. Nakazono, Y. Imazaki, H. Yoo, J. Yang, T. Sasamori, N. Tokitoh, T. Cedric, H. Kageyama, D. Kim, H. Shinokubo, A. Osuka, *Chem. Eur. J.* 2009, *15*, 7530.
  (b) S. Nakazono, S. Easwaramoorthi, D. Kim, H. Shinokubo, A. Osuka, *Org. Lett.* 2009, *11*, 5426. (c) S. Sharma, I. A. Khan, A. K. Saxena, *Adv. Synth. Catal.* 2013, *355*, 673. (d) J. A. Leitch, H. P. Cook, Y. Bhonoah, C. G. Frost, *J. Org. Chem.* 2016, *81*, 10081. (e) L. Zhang, D. He, Y. Liu, K. Wang, Z. Guo, J. Lin, H.-J. Zhang, *Org. Lett.* 2016, *18*, 5908. (f) S. Hameury, S. Kunz, M. Sommer, *ACS Omega* 2017, *2*, 2483. (g) C. Zhang, Y. Song, Z. Sang, L. Zhan, Y. Rao, *J. Org. Chem.* 2018, *83*, 2582.
- [13] (a) K. Raghuvanshi, K. Rauch, L. Ackermann, *Chem. Eur. J.* 2015, *21*, 1790. (b)
   T. Sarkar, S. Pradhan, T. Punniyamurthy, *J. Org. Chem.* 2018, *83*, 6444.
- [14] (a) Y. Wu, W. Zhu, *Chem. Soc. Rev.* 2013, 42, 2039. (b) A. D. Hendsbee, J.-P. Sun,
  W. K. Law, H. Yan, I. G. Hill, D. M. Spasyuk, G. C. Welch, *Chem. Mater.* 2016, 28, 7098.
- [15] (a) E. S. Gore, *Platinum Metals Rev.* 1983, 27, 111. (b) T.-C. Hu, P.-I. Hsiao, T.-H. Wang, Y.-W. Yang, C.-Y. Chang, Y.-H. Wu, W.-C. Sun, M.-S. Yu, C.-Y. Lee, Y.-H. Lo, *Dalton Trans.* 2011, 40, 12663. (c) Y. Xu, W. Wan, *Tetrahedron Lett.* 2013, 54, 642. (d) P. Mueller, J. Gody, *Helv. Chim. Acta* 1981, 64, 2531. (e) W. Ren, J. Liu, L. Chen, X. Wan, *Adv. Synth. Catal.* 2010, 352, 1424.

- [16] G. L. Tullos, J. M. Powers, S. J. Jeskey, L. J. Mathias, *Macromolecules* 1999, 32, 3598.
- [17] (a) Y.-C. Yuan, R. Kamaraj, C. Bruneau, T. Labasque, T. Roisnel, R. Gramage-Doria, *Org. Lett.* 2017, 19, 6404. (b) Y.-C. Yuan, C. Bruneau, R. Gramage-Doria, *Synthesis* 2018, 50, 4216.
- [18] J.-C. Hsieh, C.-H. Cheng, Chem. Commun., 2005, 36, 4554.
- [19] N. A. Zakharova, N. V. Khromov-Borisov, *Zhurnal Organicheskoi Khimii*, **1970**, 6, 116.
- [20] L. K. Rasmussen, M. Begtrup, T. Ruhland, J. Org. Chem. 2004, 69, 6890.
- [21] X. Wang, W. Xiong, Y. Huang, J. Zhu, Q. Hu, W. Wu, H. Jiang, Org. Lett. 2017, 19, 5818.
- [22] R. Shrestha, P. Mukherjee, Y. Tan, Z. C. Litman, J. F. Hartwig, J. Am. Chem. Soc.2013, 135, 8480.
- [23] S. A. Worlikar, R. C. Larock, J. Org. Chem. 2008, 73, 7175.
- [24] V. Kumar, G. S. Banker, Int. J. Pharm. 1992, 79, 61.
- [25] N. Sharma, G. Sekar, Adv. Synth. Catal. 2016, 358, 314.
- [26] S. L. Yedage, D. S. D'silva, B. M. Bhanage, RSC Adv. 2015, 5, 80441.
- [27] S. Liu, Q. Deng, W. Fang, J.-F. Gong, M.-P. Song, M. Xua, T. Tu, Org. Chem. Front. 2014, 1, 1261.
- [28] X.-F. Dong, J. Fan, X.-Y. Shi, K.-Y. Liu, P.-M. Wang, J.-F. Wei, J. Organomet. Chem. 2015, 779, 55.
- [29] S. D. Sarkar, L. Ackermann, Chem. Eur. J. 2014, 20, 13932.
- [30] F. J. Williams, P. E. Donahue, J. Org. Chem. 1977, 42, 3415.
- [31] Y. Shibata, K. Sasaki, Y. Hashimoto, S. Iwasaki, Chem. Pharm. Bull. 1996, 44, 156.
- [32] M. Wang, J. Lu, J. Ma, Z. Zhang, F. Wang, Angew. Chem. Int. Ed. 2015, 54, 14061.
- [33] S. De Sarkar, L. Ackermann, Chem. Eur. J. 2014, 20, 13932.
- [34] H. J. Kim, J. Kim, S. H. Cho, S. Chang, J. Am. Chem. Soc. 2011, 133, 16382.
- [35] K. Kaminski, B. Wiklik, J. Obniska, Arch. Pharm. Chem. Life Sci. 2014, 347, 840.

- [36] M. Kobeissi, O. Yazbeck, Y. Chreim, Tetrahedron Lett. 2014, 55 2523.
- [37] N. Matuszak, G. G. Muccioli, G. Labar, D. M. Lambert, J. Med. Chem. 2009, 52, 7410.
- [38] (a) V. Kumar, S. Sharma, U. Sharma, B. Singh, N. Kumar, *Green Chem.* 2012, *14*, 3410. (b) S. Wang, H. Huang, C. Bruneau, C. Fischmeister, *ChemSusChem* 2017, *10*, 4150.
- [39] C. Lin, L. Zhen, Y. Cheng, H.-J. Du, H. Zhao, X. Wen, L.-Y. Kong, Q.-L. Xu, H. Sun, Org. Lett. 2015, 17, 2684.
- [40] C. D. Chu, Y. H. Qi, W. Hao, Catal. Commun. 2007, 8, 1527.
- [41] S. Sharma, I. A. Khan, A. K. Saxena, Adv. Synth. Catal. 2013, 355, 673.
- [42] B. Nammalwar, N. P. Muddala, F. M. Watts, R. A. Bunce, *Tetrahedron* 2015, *71*, 9101.
- [43] R. J. Perry, S. R. Turner, J. Org. Chem. 1991, 56, 6573.
- [44] P. Wójcik, A. M. Trzeciak, Appl. Catal. A 2018, 560, 73.
- [45] C. Yao, Y. Bao, T. Lu, Q. Zhou, Org. Lett. 2018, 20, 2152.
- [46] Y. Yamamoto, T. Hisa, J Arai, Y Saito, F Yamamoto, T Mukai, T Ohshima, M Maeda, Y Ohkubo, *Bioorg. Med. Chem.* 2015, 23, 6807.
- [47] S. Mansor, N. Zakaria, A. Ariffin, S. W. Ng, Acta Cryst. 2008, E64, o1770.
- [48] M. J. Caulfield, M. G. Looney, R. A. Pittard, D. H. Solomon, *Polymer* 1998, 39, 6541.
- [49] T. M. Pyriadi, A. M. Alazawi, J. Polym. Sci.: Part A: Polym. Chem. 1999, 37, 427.
- [50] J. Wang, L. Yang, C. Hou, H. Cao, Org. Biomol. Chem. 2012, 10, 6271.
- [51] M. A. Khadim, L. D. Colebrook, Magnet. Res. Chem. 1985, 23, 259.
- [52] H. Xu, C. Wolf, Chem. Commun. 2009, 1715.
- [53] Y. Duan, T. Song, X. Dong, Y. Yang, Green Chem. 2018, 20, 2821.

[Part of this chapter has been published in Org. Biomol. Chem. 2019, 17, 7517-7525]

# Chapter 4: Ruthenium-catalyzed selective C(sp<sup>2</sup>)-H bond benzoxylation of biologically appealing N-arylisoindolinones

# 4.1 Introduction

Since the pioneering contributions from Crabtree and Sanford on palladiumcatalyzed C-H bond acyloxylation reactions,<sup>1</sup> metal-catalysed C-H bond oxidations has represented an important entry to form new C-O bonds in valuable organic molecules.<sup>2</sup> Indeed, it enables to rapidly access molecular diversity using different transition metal catalysts derived from Pd, Rh, Ir, Ru, Fe, Cu, Co, etc.<sup>3</sup> The main advantage of the transition metal-catalyzed C-H bond acyloxylation reactions is that they traditionally operate under mild reaction conditions, thus avoiding the use of harsh oxidizing reagents which are not always compatible with many sensitive functional groups.<sup>4</sup> So far, most of the research in this area has been devoted to the use of nitrogen-containing directing groups that are capable to strongly coordinate to the metal catalyst leading to the formation of key metallacycle species.<sup>4</sup> Making these methodologies compatible with weak directing groups is rather attractive<sup>5</sup> as they can be further implemented in the late stage functionalization of chemicals relevant for medicine, pharmacology, agrochemistry and material sciences.<sup>6</sup>

Amides constitute a particular class of useful weak directing groups. They have been used in many transition metal-catalyzed C-H bond functionalization reactions,<sup>7</sup> although their use in C-O bond forming reactions is rare.<sup>8</sup> In addition, *N*-substituted phenylbenzamides (Ar<sup>1</sup>-CONR-Ar<sup>2</sup>) are a sub-family of amides that present two aromatic fragments with two types of C-H bonds that can *a priori* react in a similar manner.<sup>9-11</sup> In the case of C-O bond forming reactions via transition metal-catalysed C-H bond functionalizations, Rao et al. showed that ruthenium catalysts enabled the hydroxylation to take place in a C-H bond from the benzamide ring A (Scheme 4.1, top) whereas palladium catalysts hydroxylated the C-H bond from the acetanilide ring **B** 

(Scheme 4.1, middle) in TFA/TFAA medium (TFA = trifluoroacetic acid, TFAA = trifluoroacetic acid anhydride).<sup>9</sup> Additionally, Jeganmohan et al. described the difficulty to perform selective C-H bond benzoxylation reactions with *N*-substituted phenylbenzamides as both possible products are formed in a 1:1 ratio (Scheme 4.1, bottom).<sup>10</sup>



Scheme 4.1 State-of-the-art for the directed transition metal-catalyzed C-H bond (hydro/benzo)xylations of *N*-substituted phenylbenzamides.

In Chapter 3, we applied a modified Rao's methodology to one example of *N*-arylisoindolinone,<sup>11</sup> which is the simplest cyclic version of *N*-substituted phenylbenzamides and the skeleton of which is found in many biologically relevant compounds.<sup>12</sup> For *N*-phenylisoindolinone, the C-H bond hydroxylation exclusively occurred in the aromatic ring **B** either with palladium or ruthenium catalysts (Scheme 4.2, top).<sup>11</sup> These examples show the current limitations and challenges encountered in C-H bond acyloxylation reactions in order to discriminate between two aromatic C-H sites for tertiary amides as weak directing groups. It can be noted that ruthenium-catalyzed  $C(sp^2)$ -H bond benzoxylation reactions using strong directing groups have been studied recently.<sup>13</sup> In this chapter, we report the development and scope of ruthenium catalysis enabling C-H bond benzoxylation reactions exclusively in the acetanilide ring **B** from the biologically relevant *N*-arylisoindolinone (Scheme 4.2, bottom).



Scheme 4.2 Ru-catalyzed C-H bond (hydro/benzo)xylations of *N*-arylisoindolinones as weak directing groups.

# 4.2 Results and discussion

# 4.2.1 Optimization of ruthenium-catalyzed C-H bond benzoxylation of isoindolinone

Initially, we focused on the ruthenium-catalyzed benzoxylation of isoindolinone 1a in the presence of benchmark benzoic acid (1.5 equiv.) as coupling partner (Table 4.1). A systematic study was performed using the air and moisture stable [RuCl<sub>2</sub>(pcymene)]<sub>2</sub> complex as pre-catalyst (5 mol%) in combination with different additives and oxidants (Table 4.1). First, we tested the reaction conditions employed by Jeganmohan and co-workers for the benzoxylation of acyclic tertiary amides (Scheme 4.1, c),<sup>10</sup> namely, AgSbF<sub>6</sub> (20 mol%) as chloride scavenger and (NH<sub>4</sub>)<sub>2</sub>S<sub>2</sub>O<sub>8</sub> (2 equiv.) as oxidant in 1,2-dichloroethane (DCE) as solvent at 100 °C. After 24 h, only trace amounts of the product 2a were detected (Table 4.1, entry 1). Interestingly, raising the temperature of the reaction to 110 °C, afforded 2a in 66% yield (Table 4.1, entry 2), with no functionalization in the benzene ring A. A similar result (69% yield) was observed when the reaction was conducted with  $Ag_2CO_3$  as oxidant (Table 4.1, entry 3). However, the use of  $K_2S_2O_8$  as oxidant was detrimental to the formation of **2a** (Table 4.1, entry 4) as was also the use of KPF<sub>6</sub> and AgOTf as additives, respectively (Table 4.1, entries 5-6). The use of 2-MeTHF as solvent provided 2a in 66% yield (Table 4.1, entry 7) and other solvents such as 1,4-dioxane, N,N-dimethylformamide (DMF) and

toluene were not as high yielding as DCE (Table 4.1, entries 8-10). Decreasing the amount of benzoic acid to 1.2 equivalent afforded **2a** in 56% yield (Table 4.1, entry 11). Conversely, using a slight excess of substrate **1a** (1.1 equiv.) with respect to benzoic acid (1 equiv.) gave rise to **2a** in 74% yield of isolated product (Table 4.1, entry 12), which constituted the highest yielding reaction conditions so far obtained. Furthermore, no bis-functionalization was observed. The starting substrate **1a** was recovered unreacted when the reaction was carried out in the absence of [RuCl<sub>2</sub>(*p*-cymene)]<sub>2</sub>, AgSbF<sub>6</sub> and Ag<sub>2</sub>CO<sub>3</sub>, respectively (Table 4.1, entries 13-15), thus, supporting the need of all reagents for this transformation.

H	0 H N B +	CO <sub>2</sub> H [RuCl <sub>2</sub> ( <i>p</i> -c) addit solve	/mene)] <sub>2</sub> (5 mol%) ive, oxidant ent, T, 24 h		
Entry	Additive	Oxidant	Solvent	T (°C)	Yield <sup>b</sup>
1	AgSbF <sub>6</sub>	(NH <sub>4</sub> ) <sub>2</sub> S <sub>2</sub> O <sub>8</sub>	DCE	100	trace
2	AgSbF <sub>6</sub>	(NH <sub>4</sub> ) <sub>2</sub> S <sub>2</sub> O <sub>8</sub>	DCE	110	66
3	AgSbF <sub>6</sub>	Ag <sub>2</sub> CO <sub>3</sub>	DCE	110	69 (67)
4	AgSbF <sub>6</sub>	K <sub>2</sub> S <sub>2</sub> O <sub>8</sub>	DCE	110	trace
5	KPF <sub>6</sub>	Ag <sub>2</sub> CO <sub>3</sub>	DCE	110	trace
6	AgOTf	Ag <sub>2</sub> CO <sub>3</sub>	DCE	110	trace
7	AgSbF <sub>6</sub>	Ag <sub>2</sub> CO <sub>3</sub>	2-MeTHF	110	66
8	AgSbF <sub>6</sub>	Ag <sub>2</sub> CO <sub>3</sub>	1,4-dioxane	110	36
9	AgSbF <sub>6</sub>	Ag <sub>2</sub> CO <sub>3</sub>	DMF	110	0
10	AgSbF <sub>6</sub>	Ag <sub>2</sub> CO <sub>3</sub>	Toluene	110	49
11 <sup>c</sup>	AgSbF <sub>6</sub>	Ag <sub>2</sub> CO <sub>3</sub>	DCE	110	56
12 <sup>d</sup>	AgSbF <sub>6</sub>	Ag <sub>2</sub> CO <sub>3</sub>	DCE	110	77 (74)
13 <sup>e</sup>	AgSbF <sub>6</sub>	Ag <sub>2</sub> CO <sub>3</sub>	DCE	110	0
14		Ag <sub>2</sub> CO <sub>3</sub>	DCE	110	0
15	AgSbF <sub>6</sub>		DCE	110	0

Table 4.1 Optimization of the reaction conditions.<sup>a</sup>

<sup>a</sup>Reaction conditions: **1a** (0.1 mmol), benzoic acid (0.15 mmol), [RuCl<sub>2</sub>(*p*-cymene)]<sub>2</sub> (5 mol%), additive (20 mol%), oxidant (200 mol%) and solvent (0.5 mL), 24 h, Ar. <sup>*b*</sup>Determined by <sup>1</sup>H NMR spectroscopy against an internal standard (dibromomethane). The isolated yield is shown in parentheses. <sup>*c*</sup>1.2 equiv. of benzoic acid. <sup>*a*</sup>Benzoic acid (0.1 mmol, 1 equiv.), **1a** (0.11 mmol, 1.1 equiv.). <sup>*e*</sup>Without [RuCl<sub>2</sub>(*p*-cymene)]<sub>2</sub>.

# 4.2.2 Scope and limitations of the Ru(II)-catalyzed C-H bond benzoxylation of isoindolinones

With the developed reaction conditions in hand (Table 4.1, entry 12), we evaluated the scope for this transformation (Table 4.2-4.3). The catalysis was compatible with different *para*-substitution patterns in the phenyl ring **B** of the *N*-arylisoindolinone backbone. As such, benzoxylated products 2a-2d that contain methyl, methoxy and chloro functional groups were obtained in 35-67% yields (Table 4.2). During the purification of 2d, the debenzoylated alcohol product 2dd was isolated in 19% (Figure 4.1). The formation of debenzoylated product was also observed in other cases (vide *infra* for discussion). The isoindolinone core containing a nitrile group at the *para*position did not afford the corresponding product 2e (Table 4.2). Isoindolinone bearing an ortho-tolyl substituent attached to the nitrogen atom was unreactive under catalytic conditions (2f), indicating that the sterically hindered substrates are significantly less reactive than unhindered substrates (Table 4.2). meta-Substitution in the phenyl ring of 1 with electronically different methyl and methoxy substituents led to the less hindered regioisomers 2g and 2h in 62% and 58% isolated yields, respectively (Table 4.2). This indicates that the most sterically accessible C-H bond is preferentially functionalized for these substrates. In the case of 2i, which contains a dioxolane group, small amounts of the other regioisomer were obtained as well (Table 4.2). Additionally, the molecular structures of 2a, 2b and 2c were unambiguously confirmed by single-crystal X-ray diffraction studies, which further supported the regio- and site-selectivity of the reaction (Table 4.2).



 Table 4.2 Scope of Ru-catalyzed C-H bond benzoxylation of different isoindolinones

 substituted at the N-side.<sup>a,b</sup>

<sup>a</sup>Reaction conditions: **1** (0.33 mmol), benzoic acid derivative (0.3 mmol), [RuCl<sub>2</sub>(*p*-cymene)]<sub>2</sub> (5 mol%), AgSbF<sub>6</sub> (20 mol%) and Ag<sub>2</sub>CO<sub>3</sub> (200 mol%), DCE (1.5 mL) at 110 °C, 24 h, Ar. <sup>b</sup>Isolated yields. <sup>c</sup>19% of the hydroxylated product was isolated. <sup>d</sup>Ratio of regioisomers determined by <sup>1</sup>H NMR, the major one is depicted.



Figure 4.1 Molecular structure of the by-product 2dd obtained and isolated during the purification of product 2d.

Benzoic acids containing different *para*-substituted functional groups as useful as fluoride, chloride, bromide, iodide, trifluoromethyl and nitro were reactive, and they provided the corresponding products **2j-2n** in 50-71% isolated yields (Table 4.3). Benzoic acids containing different *meta*-substituted functional groups such as nitro, chloride and methoxy were also suitable for this catalytic reaction, giving the corresponding products **2o-2q** in 53-73% isolated yields (Table 4.3). Furthermore,

 Table 4.3 Scope of Ru-catalyzed C-H bond benzoxylation of different substituted isoindolinones.<sup>*a,b*</sup>



<sup>a</sup>Reaction conditions: **1** (0.33 mmol), benzoic acid derivative (0.3 mmol), [RuCl<sub>2</sub>(*p*-cymene)]<sub>2</sub> (5 mol%), AgSbF<sub>6</sub> (20 mol%) and Ag<sub>2</sub>CO<sub>3</sub> (200 mol%) in DCE (1.5 mL) at 110 °C for 24 h under Ar. <sup>*b*</sup>Isolated yields. <sup>*c*</sup>21% of the hydroxylated product **3** was isolated.

*ortho*-substituted benzoic acids afforded the corresponding products with yields depending on the steric bulk of the substituent as shown in the synthesis of the fluoro derivative **2r** in 63% yield and the chloro derivative **2s** in 36% yield (Table 4.3). Polycyclic aromatic hydrocarbon fragments such as naphthalene were also compatible with the catalysis leading to **2t** in 62% yield (Table 4.3). Gratifyingly, heteroaromatic-containing carboxylic acids were also suitable for the reaction. Thus, thiophene-containing **2u** and furan-containing **2v** were obtained in 38% and 77% yields, respectively (Table 4.3). In the latter case, 21% of debenzoylated alcohol product was also isolated (**3**, Scheme 4.3). Additionally, the molecular structures of **2o** and **2t** were unambiguously confirmed by single-crystal X-ray diffraction studies, which further supported the regio- and site-selectivity of the reaction (Table 4.3).

Unfortunately, carboxylic acids containing nitrile, dimethylamino, pyridine and pyrrole functional groups were not viable for this reaction, in analogy to reactions reported before for substrates containing strong nitrogen-containing directing groups (Figure 4.2).<sup>13</sup> Neither acrylic acid nor trifluoroacetic acid formed any product in our hands (Figure 4.2).



**Figure 4.2** Reluctant carboxylic acid coupling partners encountered in the Rucatalyzed benzoxylation reaction of *N*-arylisoindolinones.

In general, trace amounts of starting material remained once the reaction was stopped. However, during the purification of 2d and 2u, small amounts of debenzoylated product were observed (2dd in Figure 4.2 and 3 in Scheme 4.3). This feature was observed in another set of carboxylic acids as coupling partners in which no acyloxylated products 2 were detected so far and debenzoylated phenol 3 was the only product that was formed (Scheme 4.3, top). For example, *N*-phenylisoindolinone

**1a** reacted under the standard reaction conditions with *para*-toluic, *para*methoxybenzoic, *ortho*-toluic, phenylacetic and acetic acid, respectively, leading exclusively to phenol **3** in variable yields (Scheme 4.3, top). The same behavior was identified when using the ester-substituted isoindolinone **1w**, which afforded **4** in 23% yield besides unreacted starting material **1w** (Scheme 4.3, bottom). Although we do not have any clear explanation of such findings, it can be suggested that the corresponding benzoxylated products **2** that transiently form are rather unstable under the conditions used in the catalysis and they are readily hydrolyzed into **3** and **4** (Scheme 4.3).



Scheme 4.3 Unexpected Ru-catalyzed hydroxylation reactions using carboxylic acids.

Unfortunately, attempts to perform the ruthenium-catalyzed C-H bond benzoxylation reaction with biologically-relevant indoprofen (1x) failed and no desired benzoxylated product was obtained (Scheme 4.4).<sup>12c</sup>



Scheme 4.4 Attempt of Ru-catalyzed C-H bond benzoxylation of biologically relevant indoprofen 1x.

# 4.3 Mechanistic studies

In order to get more insights into the reaction mechanism, we evaluated whether the carbonyl group of the isoindolinone fragment **1** might behave as a weak coordinating group to ruthenium during the reaction. For that, we performed a control experiment with a substrate lacking any carbonyl group, isoindoline **5**. With this substrate no benzoxylated product was observed with the reaction conditions employed in the catalysis (Scheme 4.5, top). The same observations were made using cyclic imides **6** and **7** as substrates, respectively (Scheme 4.5, middle and bottom).<sup>14</sup> The lack of reactivity in the case of **6** and **7** likely arises from the rigidity and/or bulkiness of the directing groups that prevent the accommodation of catalytically productive ruthenacycle intermediates.



Scheme 4.5 Attempts of the Ru-catalyzed C-H bond benzoxylation of isoindoline 5 (top), and cyclic imides 6 (middle) and 7 (bottom).

To further verify that the carbonyl group in **1** plays a key role for the C-H bond activation step, we performed the ruthenium-based catalysis in the absence of benzoic acid using a mixture of solvents DCE:D<sub>2</sub>O (Scheme 4.6). Under these reaction

conditions, 89% deuterium was incorporated in both *ortho* C-H bonds of the phenyl ring **B**. This indicates the ease and reversibility of the C-H bond activation step in the presence of the ruthenium catalyst.



benzoxylation reaction with substrate 1a.

Based on the above-described data and previous reports,<sup>10,13,15</sup> a catalytic cycle is proposed in Scheme 4.7. First, chloride-free carboxylate-containing ruthenium species are formed, which coordinate to the carbonyl group of the isoindolinone core (**I**). Then, base-assisted C-H bond metalation gives rise to a six-membered ruthenacycle intermediate **II**. Due to the large amount of carboxylic acid in the reaction media, intermediate **III** can form, which undergoes reductive elimination towards product formation and oxidation of the metal center to regenerate a ruthenium(**II**) species.



Scheme 4.7 Proposed catalytic cycle for the Ru-catalyzed C-H benzoxylation of 1.

# 4.4 Conclusion

In summary, we have developed an efficient benzoxylation reaction to selectively form unprecedented C-O bonds within the isoindolinone core. The catalysis tolerates an important number of functional groups at different positions within both coupling partners. This ruthenium(II) catalysis constitutes an example of site-selective transformation where the combination of the weak directing group (cyclic amide) with the ruthenium catalyst enables to discriminate between two aromatic C-H bonds having comparable bond dissociation energies. Moreover, mono-functionalized products are exclusively obtained for this C-O bond-forming reaction. Overall, this methodology highlights the uniqueness of ruthenium catalysts enabling formation of six-membered ring intermediates throughout the catalysis even with very weak directing groups.

# 4.5 Experimental details

*General information.* All reagents were obtained from commercial sources and used as supplied. All reactions were carried out in flame-dried glassware under argon atmosphere unless otherwise noted. Catalytic experiments were performed in Schlenktype flasks under argon atmosphere unless otherwise noted. Organic solutions were concentrated under reduced pressure using a rotary evaporator. Thin-layer chromatography (TLC) was carried out on 0.25 mm Merck silica gel (60-F254). Flash column chromatography was performed using silica gel Silica 60 M, 0.04-0.063 mm. *N*-Methyl-2-pyrrolidone (NMP) was distilled under reduced pressure and stored under molecular sieves and argon atmosphere. Technical grade petroleum ether (40-60) and ethyl acetate were used for column chromatography. CDCl<sub>3</sub> was stored under nitrogen over molecular sieves. NMR spectra were recorded on an AVANCE III 400 spectrometer. <sup>1</sup>H NMR spectra were referenced to residual protiated solvent ( $\delta = 7.26$ ppm for CDCl<sub>3</sub>) and <sup>13</sup>C chemical shifts are reported relative to deuterated solvents ( $\delta$ = 77.0 ppm for CDCl<sub>3</sub>). The peak patterns are indicated as follows: s, singlet; d, doublet;

t, triplet; q, quartet; m, multiplet, and br. for broad. GC-MS analyses were performed with a GCMS-QP2010S (Shimadzu) instrument with a GC-2010 equipped with a 30 m capillary column (Supelco, SLBTM-5ms, fused silica capillary column, 30 m x 0.25 mm x 0.25 mm film thickness), which was used with helium as the vector gas. The following GC conditions were used: initial temperature 80 °C for 2 minutes, then 20 °C/min until 280 °C and 280 °C for 28 minutes. HRMS were recorded on a Waters Q-Tof 2 mass spectrometer at the corresponding facilities of the CRMPO, Centre Régional de Mesures Physiques de l'Ouest, Université de Rennes 1. Melting points were performed on a LEICA VMHB Kofler system.

# Synthesis of substrates (1).

<u>Method A:</u> A mixture of 2-formylbenzoic acid (5.0 mmol, 1 equiv.), amine (6.0 mmol, 1.2 equiv.), DABCO (10.0 mmol, 2 equiv.), HCOOH (1.25 mL), Pd(OAc)<sub>2</sub> (0.25 mmol, 5 mol%) in 1,4-dioxane (5 mL) was heated to 80 °C for 3 h. After completion of the reaction, the mixture was cooled to room temperature, and diluted with DCM (50 mL). The solid was removed by filter, and the filtrate was washed with water (50 mL) and brine (50 mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/acetone = 5/1, v/v) to afford the desired product.



<u>Method B:</u> Phthalic anhydride (5 mmol, 0.74 g, 1 equiv.) and the corresponding aniline (5 mmol, 1 equiv.) were refluxed in acetic acid (30 mL) for 2-5 hours. Once at room temperature, water was added and the solid recovered by filtration. After drying under vacuum the desired phthalimide was obtained.



<u>Method C:</u> 1,2-Bis(bromomethyl)benzene (5.0 mmol, 1 equiv.), DIPEA (12.5 mmol, 2.5 equiv.), and aniline (7.50 mmol, 1.5 equiv.) dissolved in toluene (25 mL) were added to a tube sealing before vigorously stirring at 110 °C under a N<sub>2</sub> atmosphere. The resulting mixture was cooled to room temperature and extracted with ethyl acetate (3 x 10 mL). The combined organic phase was washed with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo*. The crude product was purified by column chromatography (petroleum ether) to obtain the desired product as a light yellow solid.

<u>Method D:</u> Hexahydrophthalic anhydride (10 mmol, 1.54 g, 1 equiv.) and aniline (10 mmol, 1 equiv.) and THF (15 mL) were added to a 100 mL round bottom flask. The solution was stirred for 30 min at 40 °C. Removal of the solvent using a rotary evaporator gave the corresponding carboxylic acid-amide as a white solid. The white solid was then heated at 190 °C under Ar for 4 h. The desired phthalimide was purified by silica gel column chromatography with a mixture of petroleum ether and ethyl acetate as eluent.



# Characterization of substrates (1).

2-Phenylisoindolin-1-one (1a): Prepared according to Method A starting from aniline in 98% isolated yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.93 (d, J = 7.6 Hz, 1H), 7.89-7.86 (m, 2H), 7.62-7.58 (m, 1H), 7.53-7.49 (m, 2H), 7.43 (dd, J = 8.4, 7.2 Hz, 2H), 7.18 (dd, J = 7.2, 7.2 Hz, 1H), 4.87 (s, 2H) ppm. The spectral data match those previously reported.<sup>16</sup>

2-(p-Tolyl)isoindolin-1-one (1b): Prepared according to Method A starting from p-



toluidine in 80% isolated yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$ Me = 7.92 (d, J = 7.2 Hz, 1H), 7.74 (d, J = 8.4 Hz, 2H), 7.59 (dd, J = 7.6, 7.6 Hz, 1H), 7.50 (dd, J = 6.8, 6.8 Hz, 2H), 7.24 (d, J =

8.4 Hz, 2H), 4.84 (s, 2H), 2.36 (s, 3H) ppm. The spectral data match those previously reported.<sup>16</sup>

2-(p-Methoxyphenyl)isoindolin-1-one (1c): Prepared according to Method A starting



from *p*-anisidine in 62% isolated yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.92 (d, *J* = 7.6 Hz, 1H), 7.74 (d, *J* = 9.2 Hz, 2H), 7.58 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.52-7.48 (m, 2H), 6.97 (d, *J* =

9.2 Hz, 2H), 4.83 (s, 2H), 3.83 (s, 3H) ppm. The spectral data match those previously reported.<sup>16</sup>

2-(p-Chlorophenyl)isoindolin-1-one (1d): Prepared according to Method A starting



from 4-chloroaniline in 61% isolated yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.92 (d, *J* = 7.2 Hz, 1H), 7.74 (dd, *J* = 9.2, 2.4 Hz, 2H), 7.61 (ddd, *J* = 7.6, 7.6, 1.2 Hz, 1H), 7.54-7.50 (m, 2H), 7.39

(dd, J = 9.2, 2.4 Hz, 2H), 4.84 (s, 2H) ppm. The spectral data match those previously reported.<sup>16</sup>

4-(1-Oxoisoindolin-2-yl)benzonitrile (1e): Prepared according to Method A starting from 4-aminobenzonitrile in 64% isolated yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$ = 8.06 (d, J = 9.2 Hz, 2H), 7.94 (d, J = 7.2 Hz, 1H), 7.71 (d, J = 8.8 Hz, 2H), 7.65 (dd, J = 7.6, 7.2 Hz, 1H), 7.54 (dd, J = 7.6, 7.2 Hz, 2H), 4.89 (s, 2H) ppm. The spectral data match those previously reported.<sup>16</sup>

2-(o-Tolyl)isoindolin-1-one (1f): Prepared according to Method A starting from o-



toluidine in 68% isolated yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$ = 7.96 (d, J = 7.6 Hz, 1H), 7.61 (ddd, J = 7.2, 7.2, 1.2 Hz, 1H), 7.55-7.50 (m, 2H), 7.35-7.32 (m, 1H), 7.30-7.24 (m, 3H), 4.74 (s, 2H),

2.27 (s, 3H) ppm. The spectral data match those previously reported.<sup>16</sup>

2-(m-Tolyl)isoindolin-1-one (1g): Prepared according to Method A starting from m-



toluidine in 65% isolated yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.93 (d, *J* = 6.8 Hz, 1H), 7.73 (s, 1H), 7.65-7.58 (m, 2H), 7.51 (dd, *J* = 7.2, 6.8 Hz, 2H), 7.32 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.01 (d, *J* =

7.6 Hz, 1H), 4.86 (s, 2H), 2.41 (s, 3H) ppm. The spectral data match those previously reported.<sup>16</sup>

2-(*m*-Methoxyphenyl)isoindolin-1-one (1h): Prepared according to Method A starting



from *m*-anisidine in 80% isolated yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.93 (d, *J* = 7.2 Hz, 1H), 7.69 (dd, *J* = 2.0, 1.6 Hz, 1H), 7.62-7.58 (m, 1H), 7.51 (dd, *J* = 7.6, 7.6 Hz, 2H), 7.34-7.32

(m, 2H), 6.76-6.73 (m, 1H), 4.86 (s, 2H), 3.87 (s, 3H) ppm. The spectral data match those previously reported.<sup>16</sup>

2-(Benzo[d][1,3]dioxol-5-yl)isoindolin-1-one (1i): Prepared according to Method A



starting from 3,4-(methylenedioxy)aniline in 58% isolated yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$ = 7.92 (d, *J* = 8.0 Hz, 1H), 7.61-7.57 (m, 2H), 7.51 (dd, *J* = 6.4, 5.6 Hz, 2H), 7.11 (dd, *J* = 8.4,

2.0 Hz, 1H), 6.85 (d, J = 8.4 Hz, 1H), 5.99 (s, 2H), 4.81 (s, 2H) ppm. The spectral data match those previously reported.<sup>16</sup>

Ethyl 4-(1-oxoisoindolin-2-yl)benzoate (1w): Prepared according to Method A starting from ethyl 4-aminobenzoate in 96% isolated yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta = 8.11$  (d, J = 8.4 Hz, 2H), 7.99 (d, J = 8.8 Hz, 2H), 7.94 (d, J = 7.6 Hz, 1H), 7.63 (dd, J = 7.6, 7.6 Hz, 1H), 7.53 (dd, J = 7.6, 7.6 Hz, 2H), 4.90 (s, 2H), 4.39 (q, J = 7.2 Hz, 2H), 1.41 (t, J = 7.2 Hz, 3H) ppm. The spectral data match those previously reported.<sup>16</sup>

2-(4-(1-Oxoisoindolin-2-yl)phenyl)propanoic acid (indoprofen, 1x): Prepared according to Method A starting from 2-(4- $CO_2H$  aminophenyl)propanoic acid in 68% yield. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = 12.29 (s, 1H), 7.85 (d, *J* = 8.8 Hz, 2H), 7.78 (d, *J* = 7.6 Hz, 1H), 7.70-7.66 (m, 2H), 7.57-7.53 (m, 1H), 7.35 (d, *J* = 8.8 Hz, 2H), 5.02 (s, 2H), 3.69 (q, *J* = 7.2 Hz, 1H), 1.38 (d, *J* = 7.2 Hz, 3H) ppm. The spectral data match those previously reported.<sup>17</sup>

2-Phenyl-2,3-dihydro-1*H*-isoindole (5): Prepared according to Method C starting from 1,2-bis(bromomethyl)benzene in 89% isolated yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$ = 7.38-7.31 (m, 6H), 6.78 (dd, *J* = 7.6, 7.6 Hz,

1H), 6.71 (d, J = 7.6 Hz, 2H), 4.68 (s, 4H) ppm. The spectral data match those previously reported.<sup>18</sup>

N-Phenylphthalimide (6): Prepared according to Method B starting from aniline in 80%

o isolated yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 
$$\delta$$
 = 7.96 (dd,  $J$  = 5.6,  
3.2 Hz, 2H), 7.80 (dd,  $J$  = 5.2, 3.2 Hz, 2H), 7.52 (dd,  $J$  = 7.6, 7.6

Hz, 2H), 7.34-7.27 (m, 3H) ppm. The spectral data match those previously reported.<sup>19</sup>

2-Phenylhexahydro-1*H*-isoindole-1,3(2*H*)-dione (7): Prepared according to Method



D in 86% isolated yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$ = 7.48-7.44 (m, 2H), 7.39-7.35 (m, 1H), 7.30-7.27 (m, 2H), 3.06-3.00 (m, 2H), 1.95-1.85 (m, 4H), 1.53-1.50 (m, 4H) ppm. The spectral data match

those previously reported.<sup>20</sup>

#### General procedure for the ruthenium-catalyzed C-H bond benzoxylation reaction.

*General procedure:* [RuCl<sub>2</sub>(p-cymene)]<sub>2</sub> (5 mol%), AgSbF<sub>6</sub> (20 mol%), Ag<sub>2</sub>CO<sub>3</sub> (0.2 mmol, 2.0 equiv.), *N*-arylisoindolinone derivative **1** (0.11 mmol, 1.1 equiv.), and the corresponding benzoic acid derivative (0.1 mmol, 1.0 equiv.) were taken in a 15 mL pressure tube, which was equipped with a magnetic stirrer. Solvent 1,2-dichloroethane (0.5 mL) was added to the tube via syringe, and the reaction mixture was degassed with argon three times. The reaction mixture was allowed to stir at 110 °C for 24 h. After being cooled to ambient temperature, the reaction mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> and then filtered through Celite. After evaporation of the solvent *in vacuo*, the crude product was purified by column chromatography on silica gel (*n*-heptane/EtOAc: 10:1 to 5:1) to give the desired product **2** as a solid.

# Characterization of products (2).

**2-(1-Oxoisoindolin-2-yl)phenyl benzoate (2a):** White solid, yield = 74%, 73.1 mg. Mp: 139-141 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$ = 8.08 (d, *J* = 8.0 Hz, 2H), 7.85 (d, *J* = 7.6, Hz, 1H), 7.56-7.49 (m, 3H), 7.46-7.36 (m, 7H), 4.76 (s, 2H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz,

 $CDCl_3$ ):  $\delta = 167.7, 164.9, 146.8, 141.7, 133.8, 132.0, 131.9, 131.0, 130.3, 129.0, 128.73, 131.0, 130.3, 129.0, 128.73, 130.$ 

128.66, 128.33, 128.27, 126.9, 124.3, 124.0, 122.9, 52.5 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>21</sub>H<sub>15</sub>NO<sub>3</sub>Na 352.0944, found 352.0948 (1 ppm).

5-Methyl-2-(1-oxoisoindolin-2-yl)phenyl benzoate (2b): White solid, yield = 49%, 50.7 mg. Mp: 158-160 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.07 (d, J = 7.2 Hz, 2H), 7.84 (d, J = 7.6, Hz, 1H), 7.55-7.49 (m, 2H), 7.43-7.35 (m, 5H), 7.18 (d, J = 7.6, Hz, 2H), 4.72 (s, 2H), 2.42 (s, 3H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 167.8, 165.0, 146.6, 141.7, 139.2, 133.7, 132.0, 131.8, 130.3, 129.0, 128.6, 128.2, 128.0, 127.6, 124.3, 124.2, 122.8, 52.5, 21.3 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>22</sub>H<sub>17</sub>NO<sub>3</sub>Na 366.1101, found 366.1104 (1 ppm).

5-Methoxy-2-(1-oxoisoindolin-2-yl)phenyl benzoate (2c): White solid, yield = 56%,



60.4 mg. Mp: 111-113 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.06 (d, *J* = 8.0 Hz, 2H), 7.83 (d, *J* = 7.6, Hz, 1H), 7.54-7.48 (m, 2H), 7.43-7.34 (m, 5H), 6.91 (d, *J* = 7.6, Hz, 2H), 4.70 (s,

2H), 3.84 (s, 3H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 167.9, 164.8, 159.8, 147.8, 141.7, 133.8, 132.0, 131.7, 130.3, 129.0, 128.9, 128.6, 128.2, 124.2, 123.6, 122.8, 112.8, 109.2, 55.8, 52.7 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>22</sub>H<sub>17</sub>NO<sub>4</sub>Na 382.1050, found 382.1054 (1 ppm).

**5-Chloro-2-(1-oxoisoindolin-2-yl)phenyl benzoate (2d):** Yellow solid, yield = 35%, 38.1 mg. Mp: < 50 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.06 (d, *J* = 7.6 Hz, 2H), 7.84 (d, *J* = 7.6 Hz, 1H), 7.58-7.52 (m, 2H), 7.46-7.35 (m, 7H), 4.74 (s, 2H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz,

CDCl<sub>3</sub>):  $\delta$ = 167.8, 164.5, 147.1, 141.6, 134.1, 133.7, 132.1, 131.7, 130.4, 129.8, 129.0, 128.8, 128.6, 128.4, 127.1, 124.5, 124.4, 122.9, 52.4 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>21</sub>H<sub>14</sub>NO<sub>3</sub><sup>35</sup>ClNa 386.0554, found 386.0555 (0 ppm).



(s, 3H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$ = 167.5, 164.2, 144.3, 141.6, 140.2, 136.9, 131.9, 131.6, 130.4, 129.3, 128.9, 128.6, 128.2, 127.5, 124.2, 123.3, 122.8, 52.4, 21.0 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>22</sub>H<sub>16</sub>NO<sub>3</sub><sup>35</sup>ClNa 400.0711, found 400.0708 (1 ppm).

4-Methoxy-2-(1-oxoisoindolin-2-yl)phenyl 4-chlorobenzoate (2h): Yellow solid,



yield = 68%, 79.8 mg. Mp: < 50 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.00 (d, J = 8.4 Hz, 2H), 7.83 (d, J = 7.6 Hz, 1H), 7.54 (dd, J = 7.6, 7.2 Hz, 1H), 7.44 (dd, J = 8.8, 8.0 Hz, 2H), 7.35 (d, J = 8.4 Hz, 2H), 7.27 (d, J = 8.8 Hz, 1H), 7.02

(s, 1H), 6.96 (d, J = 8.4 Hz, 1H), 4.75 (s, 2H), 3.83 (s, 3H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta = 167.5$ , 164.3, 157.9, 141.6, 140.1, 139.9, 132.0, 131.8, 131.6, 131.4, 128.9, 128.3, 127.5, 124.22, 124.19, 122.9, 114.0, 113.2, 55.8, 52.4 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>22</sub>H<sub>16</sub>NO<sub>4</sub><sup>35</sup>ClNa 416.0660, found 416.0659 (0 ppm).

6-(1-Oxoisoindolin-2-yl)benzo[d][1,3]dioxol-5-yl 4-chlorobenzoate (2i): Yellow



solid, yield = 64%, 77.8 mg. Mp: < 50 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.95 (d, *J* = 8.4 Hz, 2H), 7.82 (d, *J* = 7.2 Hz, 1H), 7.51 (dd, *J* = 7.6, 7.2 Hz, 1H), 7.44-7.38 (m, 2H), 7.32 (d, *J* = 8.4 Hz, 2H), 6.88 (s, 1H), 6.84 (s, 1H), 6.04 (s,

2H), 4.65 (s, 2H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 167.8, 164.2, 147.6, 146.0, 141.6, 141.2, 140.3, 131.9, 131.6, 129.0, 128.3, 127.3, 124.2, 123.7, 122.9, 107.8,

104.6, 102.4, 52.6 ppm. HRMS (ESI) calcd. for  $[M + Na]^+ C_{22}H_{14}NO_5^{35}CINa 430.0453$ , found 430.0458 (1 ppm).

2-(1-Oxoisoindolin-2-yl)phenyl 4-fluorobenzoate (2j): White solid, yield = 56%,

58.7 mg. Mp: 125-127 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$ = 8.09 (m, 2H), 7.82 (d, J = 7.6 Hz, 1H), 7.54-7.34 (m, 7H),7.04 (dd, J = 8.4, 8.4 Hz, 2H), 4.74 (s, 2H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 167.5, 166.2 (d,  $J_{C-F}$  = 253.6 Hz), 163.8, 146.7, 141.7,

132.9 (d,  $J_{C-F}$  = 9.5 Hz), 131.9, 131.8, 130.9, 128.7, 128.3, 128.1, 126.9, 125.2 (d,  $J_{C-F}$ = 3.0 Hz), 124.2, 123.8, 122.9, 115.8 (d,  $J_{C-F}$  = 22.0 Hz), 52.4 ppm. <sup>19</sup>F{<sup>1</sup>H} NMR (376 MHz, CDCl<sub>3</sub>):  $\delta$  = -104.1 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>21</sub>H<sub>14</sub>NO<sub>3</sub>FNa 370.0850, found 370.0850 (0 ppm).

2-(1-Oxoisoindolin-2-yl)phenyl 4-chlorobenzoate (2k): Yellow solid, yield = 64%,



69.8 mg. Mp: 58-60 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.00 (d, J = 8.8 Hz, 2H), 7.83 (d, J = 7.6 Hz, 1H), 7.54 (dd, J = 7.6, 7.6 Hz, 1H), 7.49-7.35 (m, 8H), 4.75 (s, 2H) ppm.

<sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 167.6, 164.0, 146.7, 141.7, 140.3, 132.0, 131.9, 131.7, 130.9, 129.0, 128.8, 128.4, 128.2, 127.5, 127.0, 124.3, 123.8, 122.9, 52.5 ppm. HRMS (ESI) calcd. for  $[M + Na]^+ C_{21}H_{14}NO_3^{35}ClNa 386.0554$ , found 386.0553 (0 ppm).

2-(1-Oxoisoindolin-2-yl)phenyl 4-bromobenzoate (2l): Yellow solid, yield = 65%,



Br

79.9 mg. Mp: 54-56 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.92 (d, J = 8.4 Hz, 2H), 7.83 (d, J = 7.6 Hz, 1H), 7.55-7.51(m, 3H), 7.49-7.42 (m, 4H), 7.40-7.36 (m, 2H), 4.75 (s, 2H)

ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 167.5, 164.2, 146.6, 141.7, 132.00, 131.98, 131.86, 131.76, 130.9, 129.1, 128.7, 128.4, 128.1, 128.0, 127.0, 124.3, 123.8, 122.9,

52.4 ppm. HRMS (ESI) calcd. for  $[M + Na]^+ C_{21}H_{14}NO_3^{79}BrNa$  430.0049, found 430.0050 (0 ppm).

2-(1-Oxoisoindolin-2-yl)phenyl 4-iodobenzoate (2m): Yellow solid, yield = 50%,



68.5 mg. Mp: 61-63 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.83 (d, *J* = 7.6 Hz, 1H), 7.78-7.72 (m, 4H), 7.53 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.48-7.35 (m, 6H), 4.75 (s, 2H) ppm. <sup>13</sup>C{<sup>1</sup>H}

NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 167.5, 164.4, 146.6, 141.6, 138.0, 132.0, 131.8, 131.6, 130.9, 128.7, 128.5, 128.3, 128.1, 127.0, 124.3, 123.8, 122.9, 101.9, 52.4 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>21</sub>H<sub>14</sub>NO<sub>3</sub>INa 477.9911, found 477.9913 (0 ppm).

**2-(1-Oxoisoindolin-2-yl)phenyl 4-(trifluoromethyl)benzoate (2n):** Yellow solid, yield = 71%, 84.6 mg. Mp: < 50 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.18 (d, J = 8.0 Hz, 2H), 7.81 (d, J = 8.0 Hz, 1H), 7.65 (d, J = 8.0 Hz, 2H), 7.54 (ddd, J = 7.6, 7.6, 1.2)

Hz, 1H), 7.49-7.37 (m, 6H), 4.77 (s, 2H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 167.4, 163.7, 146.5, 141.7, 135.0 (q, *J*<sub>*C-F*</sub> = 32.5 Hz), 132.3, 132.0, 131.8, 130.9, 130.7, 128.7, 128.4, 128.0, 127.1, 125.6 (q, *J*<sub>*C-F*</sub> = 3.7 Hz), 124.2, 123.8, 123.6 (q, *J*<sub>*C-F*</sub> = 270.1 Hz), 122.9, 52.4 ppm. <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>): δ -63.2 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>22</sub>H<sub>14</sub>NO<sub>3</sub>F<sub>3</sub>Na 420.0818, found 420.0820 (0 ppm).

2-(1-Oxoisoindolin-2-yl)phenyl 3-nitrobenzoate (20): Yellow solid, yield = 73%, 82.4 mg. Mp: 111-113 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$ = 8.82 (s, 1H), 8.40 (d, J = 8.0 Hz, 1H), 8.36 (dd, J = 8.0, 8.0 Hz, Hz, 1H), 7.76 (d, J = 7.6 Hz, 1H), 7.60 (dd, J = 8.0, 8.0 Hz,

1H), 7.53 (dd, J = 7.6, 7.6 Hz, 1H), 7.48-7.37 (m, 6H), 4.80 (s, 2H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta = 167.3$ , 162.7, 148.3, 146.2, 141.6, 135.8, 132.0, 131.7, 130.9, 130.8, 130.0, 128.6, 128.3, 128.0, 127.8, 127.2, 125.1, 124.1, 123.7, 123.0, 52.4 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>21</sub>H<sub>14</sub>N<sub>2</sub>O<sub>5</sub>Na 397.0795, found 397.0799 (1 ppm).

**2-(1-Oxoisoindolin-2-yl)phenyl 3-chlorobenzoate (2p):** Yellow solid, yield = 64%, 70.3 mg. Mp: < 50 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$ = 8.02 (s, 1H), 7.96 (d, *J* = 7.6 Hz, 1H), 7.83 (d, *J* = 7.2 Hz, 1H), 7.55-7.35 (m, 8H), 7.32 (dd, *J* = 7.6, 7.6 Hz, 1H), 4.76 (s, 2H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$ = 167.5, 163.6, 146.5, 141.6, 134.7, 133.7, 131.9, 131.8, 130.9, 130.8, 130.2, 129.9, 128.6, 128.33, 128.28, 128.1, 127.0, 124.2, 123.7,

122.9, 52.4 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>21</sub>H<sub>14</sub>NO<sub>3</sub><sup>35</sup>ClNa 386.0554, found 386.0555 (0 ppm).

2-(1-Oxoisoindolin-2-yl)phenyl 3-methoxybenzoate (2q): White solid, yield = 53%,



8.0 Hz, 1H), 7.08 (dd, J = 8.0, 2.4 Hz, 1H), 4.76 (s, 2H), 3.76 (s, 3H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta = 167.6$ , 164.7, 159.7, 146.8, 141.7, 132.0, 131.9, 130.9, 130.3, 129.6, 128.7, 128.3, 128.2, 126.8, 124.2, 123.9, 122.9, 122.7, 120.8, 114.2, 55.5, 52.5 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>22</sub>H<sub>17</sub>NO<sub>4</sub>Na 382.1050, found 382.1051 (0 ppm).

2-(1-Oxoisoindolin-2-yl)phenyl 2-fluorobenzoate (2r): White solid, yield = 63%,



65.6 mg. Mp: 88-90 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.01 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.85 (d, *J* = 7.6 Hz, 1H), 7.56-7.35 (m, 8H), 7.15 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.06 (dd, *J* = 8.4, 8.4 Hz, 1H), 4.80 (s, 2H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  =

167.6, 166.2 (d,  $J_{C-F}$  = 259.9 Hz), 162.0 (d,  $J_{C-F}$  = 3.9 Hz), 146.5, 141.8, 135.3 (d,  $J_{C-F}$ 

= 9.0 Hz), 132.6, 132.0, 131.9, 130.9, 128.6, 128.3, 128.2, 127.0, 124.24 (d,  $J_{C-F} = 4.1$  Hz), 124.22, 123.9, 122.9, 117.6 (d,  $J_{C-F} = 9.2$  Hz), 117.1 (d,  $J_{C-F} = 21.8$  Hz), 52.4 ppm. <sup>19</sup>F{<sup>1</sup>H} NMR (376 MHz, CDCl<sub>3</sub>):  $\delta$  = -108.8 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>21</sub>H<sub>14</sub>NO<sub>3</sub>FNa 370.0850, found 370.0852 (1 ppm).

2-(1-Oxoisoindolin-2-yl)phenyl 2-chlorobenzoate (2s): Yellow solid, yield = 36%,



38.9 mg. Mp: 110-112 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$ = 7.95 (d, *J* = 7.6 Hz, 1H), 7.87 (d, *J* = 7.6 Hz, 1H), 7.55 (dd, *J* = 7.6, 7.2 Hz, 1H), 7.48-7.37 (m, 8H), 7.29-7.23 (m, 1H), 4.80 (s, 2H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$ = 167.6, 163.4, 146.7,

141.9, 134.3, 133.3, 133.2, 132.1, 132.04, 131.96, 131.2, 131.0, 128.89, 128.86, 128.3, 127.1, 126.9, 124.3, 123.8, 123.0, 52.5 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>21</sub>H<sub>14</sub>NO<sub>3</sub><sup>35</sup>ClNa 386.0554, found 386.0555 (0 ppm).

2-(1-Oxoisoindolin-2-yl)phenyl 2-naphthoate (2t): Yellow solid, yield = 62%, 70.3



mg. Mp: < 50 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$ = 8.67 (s, 1H), 8.07 (d, *J* = 8.4 Hz, 1H), 7.88-7.82 (m, 4H), 7.60-7.37 (m, 9H), 4.80 (s, 2H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$ = 167.8, 165.0, 146.9, 141.7, 135.9, 132.5, 132.2,

131.94, 131.89, 131.0, 129.6, 128.8, 128.5, 128.4, 128.2, 127.8, 126.8, 126.2, 125.4, 124.3, 124.0, 122.9, 52.5 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>25</sub>H<sub>17</sub>NO<sub>3</sub>Na 402.1101, found 402.1099 (0 ppm).

2-(1-Oxoisoindolin-2-yl)phenyl thiophene-2-carboxylate (2u): Red solid, yield =



38%, 38.7 mg. Mp: < 50 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.88-7.85 (m, 2H), 7.56-7.50 (m, 3H), 7.46-7.34 (m, 5H), 7.06 (dd, *J* = 4.4, 4.4 Hz, 1H), 4.79 (s, 2H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100

MHz, CDCl<sub>3</sub>): *δ* = 167.7, 160.1, 146.3, 141.8, 135.2, 133.9, 132.2, 132.0, 131.9, 130.9,

128.6, 128.4, 128.3, 128.2, 126.9, 124.4, 123.9, 122.9, 52.5 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>19</sub>H<sub>13</sub>NO<sub>3</sub>SNa 358.0508, found 358.0510 (0 ppm).

**2-(1-Oxoisoindolin-2-yl)phenyl furan-2-carboxylate (2v):** Yellow solid, yield = 77%, 73.8 mg. Mp: < 50 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$ = 7.86 (d, J = 7.6 Hz, 1H), 7.57-7.36 (m, 8H), 7.29 (d, J = 7.6 Hz, 1H), 6.47 (dd, J = 2.8, 2.0 Hz, 1H), 4.79 (s, 2H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$ = 167.6, 156.3, 147.5, 145.9, 143.4, 141.8, 131.9, 130.9, 128.5, 128.24, 128.20, 126.9, 124.2, 123.7, 122.9, 120.1, 112.2, 52.4 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>19</sub>H<sub>13</sub>NO<sub>4</sub>Na 392.0737, found 392.0740 (1 ppm).

2-(4-Chloro-2-hydroxyphenyl)isoindolin-1-one (2dd): White solid, yield = 19%,



14.8 mg. Mp: 243-245 °C. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta$ = 10.31 (br, 1H), 7.77 (d, *J* = 7.6 Hz, 1H), 7.69-7.63 (m, 2H), 7.54 (ddd, *J* = 7.6, 7.6, 1.6 Hz, 1H), 7.36 (d, *J* = 8.4 Hz, 1H), 7.01 (d,

J = 2.4 Hz, 1H), 6.95 (dd, J = 8.4, 2.4 Hz, 1H), 4.82 (s, 2H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, DMSO-*d*<sub>6</sub>):  $\delta = 167.1$ , 154.0, 142.4, 132.0, 131.8, 130.2, 127.9, 124.6, 123.4, 123.2, 119.1, 116.4, 51.5 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>14</sub>H<sub>10</sub>NO<sub>2</sub><sup>35</sup>ClNa 282.0292, found 282.0291 (0 ppm).

**2-(2-Hydroxyphenyl)isoindolin-1-one (3):** Colorless solid, yield = 63%, 40.9 mg. <sup>1</sup>H



NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$ = 8.82 (br, 1H), 7.93 (d, *J* = 7.6 Hz, 1H), 7.64 (dd, *J* = 7.6, 7.2 Hz, 1H), 7.56-7.52 (m, 2H), 7.25-7.21 (m, 2H), 7.14 (dd, *J* = 8.4, 1.6 Hz, 1H), 6.99 (ddd, *J* = 8.0, 8.0, 1.6 Hz, 1H),

4.96 (s, 2H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 169.1, 150.9, 141.9, 132.6, 131.8, 128.8, 128.1, 127.5, 124.4, 122.8, 122.5, 121.3, 121.1, 52.7 ppm. MS (EI): *m/z* = 225 (M<sup>+</sup>, 84), 196 (30), 132 (100), 120 (45). The spectral data match those previously reported.<sup>11</sup>
Ethyl 3-hydroxy-4-(1-oxoisoindolin-2-yl)benzoate (4): White solid, yield = 23%, 20.1 mg. Mp: 205-207 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$ = 9.09 (br, 1H), 7.94 (d, J = 7.6 Hz, 1H), 7.79 (d, J = 1.6 Hz,

1H), 7.68-7.64 (m, 2H), 7.58-7.54 (m, 2H), 7.27 (d, *J* = 8.0

Hz, 1H), 5.00 (s, 2H), 4.37 (q, J = 7.2 Hz, 2H), 1.40 (t, J = 7.2 Hz, 3H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta = 169.4$ , 166.0, 150.5, 141.9, 133.0, 131.5, 130.0, 129.0, 124.6, 122.9, 122.6, 122.3, 122.0, 61.2, 52.8, 14.4 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>17</sub>H<sub>15</sub>NO<sub>4</sub>Na 320.0893, found 320.0888 (2 ppm).

# Deuteration experiments.

In an oven dried Schlenk tube, to a solution of isoindolinone **1a** (0.1 mmol, 1 equiv.) in DCE (0.45 mL) and D<sub>2</sub>O (0.05 mL) was added the combined solids: [RuCl<sub>2</sub>(*p*-cymene)]<sub>2</sub> (5 mol%), AgSbF<sub>6</sub> (20 mol%) and Ag<sub>2</sub>CO<sub>3</sub> (0.2 mmol, 2.0 equiv.). The reaction mixture was degassed with argon three times. The reaction mixture was allowed to stir at 110 °C for 24 h. After being cooled to ambient temperature, the reaction mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> and then filtered through Celite. The solvent was removed *in vacuo* and the crude mixture was purified by column chromatography (*n*-heptane/EtOAc, 4/1 to 1/1, *v*/*v*) to give the product as a white solid with 89% deuterium incorporation according to <sup>1</sup>H NMR spectroscopy studies.

*Crystallographic details:* CCDC 1910244-1910248 (**2a, 2b, 2c, 2o, 2t**) contains the supplementary crystallographic data for this chapter. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data\_request/cif, or by e-mailing data\_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

## 4.6 References

- [1] (a) T. Yoneyama, R. H. Crabtree, J. Mol. Catal. A 1996, 108, 35. (b) A. R.
   Dick, K. L. Hull, M. S. Sanford, J. Am. Chem. Soc. 2004, 126, 2300.
- [2] (a) S. Mukhopadhyay, A. T. Bell, Angew. Chem. Int. Ed. 2003, 42, 2990. (b)
  R. A. Periana, D. J. Taube, S. Gamble, H. Taube, T. Satoh, H. Fujii, Science
  1998, 280, 560. (c) R. E. Maleczka, F. Shi, D. Holmes, M. R. Smith, J. Am.
  Chem. Soc. 2003, 125, 7792. (d) T. Ishiyama, J. Takagi, K. Ishida, N. Miyaura,
  N. R. Anastasi, J. F. Hartwig, J. Am. Chem. Soc. 2002, 124, 390. (e) A.
  Hinman, J. Du Bois, J. Am. Chem. Soc. 2003, 125, 11510. (f) C. G. Espino, P.
  M. Wehn, J. Chow, J. Du Bois, J. Am. Chem. Soc. 2001, 123, 6935. (g) B. D.
  Dangel, J. A. Johnson, D. Sames, J. Am. Chem. Soc. 2001, 123, 8149.
- [3] (a) T. Newhouse, P. S. Baran, Angew. Chem. Int. Ed. 2011, 50, 3362. (b) L. Boisvert, K. I. Goldberg, Acc. Chem. Res. 2012, 45, 899. (c) Y. Qiu, S. Gao, Nat. Prod. Rep. 2016, 33, 562. (d) Y.-F. Liang, N. Jiao, Acc. Chem. Res. 2017, 50, 1640. (e) J. Dong, E. Fernandez-Fueyo, F. Hollmann, C. E. Paul, M. Pesic, S. Schmidt, Y. Wang, S. Younes, W. Zhang, Angew. Chem. Int. Ed. 2018, 57, 9238.
- [4] (a) K. Ray, F. F. Pfaff, B. Wang, W. Nam, J. Am. Chem. Soc. 2014, 136, 13942.
  (b) S. D. McCann, S. S. Stahl, Acc. Chem. Res. 2015, 48, 1756. (c) N. Gagnon, W. B. Tolman, Acc. Chem. Res. 2015, 48, 2126. (d) S. Itoh, Acc. Chem. Res. 2015, 48, 2066. (e) W. N. Oloo, L. Que, Jr., Acc. Chem. Res. 2015, 48, 2612.
  (f) A. C. Lindhorst, S. Haslinger, F. E. Kuhn, Chem. Commun. 2015, 51, 17193. (g) X. Engelmann, I. Monte-Perez, K. Ray, Angew. Chem. Int. Ed. 2016, 55, 7632. (h) G. Olivo, O. Cusso, M. Costas, Chem. Asian J. 2016, 11, 3148. (i) A. J. Jasniewski, L. Que, Jr., Chem. Rev. 2018, 118, 2554. (j) D. A. Alonso, C. Najera, I. M. Pastor, M. Yus, Chem. Eur. J. 2010, 16, 5274. (k) T. W. Lyons, M. S. Sanford, Chem. Rev. 2010, 110, 1147. (l) S. Enthaler, A. Company, Chem. Soc. Rev. 2011, 40, 4912. (m) Y. Rao, Synlett 2013, 24, 2472.

(n) V. S. Thirunavukkarasu, S. I. Kozhushkov, L. Ackermann, *Chem. Commun.* **2014**, *50*, 29.

- [5] (a) K. M. Engle, T.-S. Mei, M. Wasa, J.-Q. Yu, Acc. Chem. Res. 2012, 45, 788.
  (b) S. De Sarkar, W. Liu, S. I. Kozhushkov, L. Ackermann, Adv. Synth. Catal.
  2014, 356, 1461. (c) Y. Yang, K. Li, Y. Cheng, D. Wan, M. Li, J. You, Chem. Commun. 2016, 52, 2872. (d) C. Sambiagio, D. Schoenbauer, R. Blieck, T. Dao-Huy, G. Pototschnig, P. Schaaf, T. Wiesinger, M. F. Zia, J. Wencel-Delord, T. Besset, B. U. W. Maes, M. Schnuerch, Chem. Soc. Rev. 2018, 47, 6603.
- [6] (a) J. Yamaguchi, A. D. Yamaguchi, K. Itami, *Angew. Chem. Int. Ed.* 2012, *51*, 8960. (b) T. Brueckl, R. D. Baxter, Y. Ishihara, P. S. Baran, *Acc. Chem. Res.* 2012, *45*, 826. (c) J. F. Hartwig, *J. Am. Chem. Soc.* 2016, *138*, 2. (d) D. J. Abrams, P. A. Provencher, E. J. Sorensen, *Chem. Soc. Rev.* 2018, *47*, 8925.
- [7] (a) R.-Y. Zhu, M. E. Farmer, Y.-Q. Chen, J.-Q. Yu, Angew. Chem. Int. Ed. **2016**, 55, 10578. (b) Q.-Z. Zheng, N. Jiao, Tetrahedron Lett. **2014**, 55, 1121.
  (c) R. Das, G. S. Kumar, M. Kapur, Eur. J. Org. Chem. **2017**, 5439.
- [8] (a) V. S. Thirunavukkarasu, J. Hubrich, L. Ackermann, Org. Lett. 2012, 14, 4210. (b) D. Kalyani, M. S. Sanford, Org. Lett. 2005, 7, 4149. (c) L. V. Desai, K. J. Stowers, M. S. Sanford, J. Am. Chem. Soc. 2008, 130, 13285. (d) G. Shan, X. Yang, L. Ma, Y. Rao, Angew. Chem. Int. Ed. 2012, 51, 13070. (e) G. Shan, X. Han, Y. Lin, Y. Rao, Org. Biomol. Chem. 2013, 11, 2318.
- [9] Y.-H. Sun, T.-Y. Sun, Y.-D. Wu, X. Zhang, Y. Rao, Chem. Sci. 2016, 7, 2229.
- [10] N. Y. More, K. Padala, M. Jeganmohan, J. Org. Chem. 2017, 82, 12691.
- [11] Y.-C. Yuan, C. Bruneau, T. Roisnel, R. Gramage-Doria, J. Org. Chem. 2019, 84, 1898.
- [12] (a) K. Speck, T. Magauer, *Beilstein J. Org. Chem.* 2013, *9*, 2048. (b) R. K. Bhatia, *Curr. Top. Med. Chem.* 2017, *17*, 189. (c) M. R. Lunn, D. E. Root, A. M. Martino, S. P. Flaherty, B. P. Kelley, D. D. Coovert, A. H. Burghes, N. T.

Man, G. E. Morris, J. Zhou, E. J. Androphy, C. J. Sumner, B. R. Stockwell, *Chem. Biol.* 2004, *11*, 1489. (d) H. Miyachi, A. Azuma, E. Hioki, Y.
Kobayashi, S. Iwasaki, Y. Hashimoto, *Chem. Pharm. Bull.* 1996, *44*, 1980. (e)
J. S. Park, S. C. Moon, K. U. Baik, J. Y. Cho, E. S. Yoo, Y. S. Byun, M. H.
Park, *Arch. Pharm. Res.* 2002, *25*, 137. (f) D. Hamprecht, F. Micheli, G.
Tedesco, A. Checchia, D. Donati, M. Petrone, S. Terreni, M. Wood, *Bioorg. Med. Chem. Lett.* 2007, *17*, 428. (g) S. M. Allin, C. J. Northfield, M. I. Page,
A. M. Z. Slawin, *J. Chem. Soc. Perkin Trans.* 2000, 1715. (h) D. Enders, V.
Braig, G. Raabe, *Can. J. Chem.* 2001, *79*, 1528. (*i*) R. Hunter, P. Richards, *Org. Biomol. Chem.*, 2003, *1*, 2348. (j) F. Csende, G. Stajer, *Curr. Org. Chem.* 2005, *5*, 1261. (k) G. Stajer, F. Csende, *Curr. Org. Chem.* 2005, *5* 1277. (l) P.
Thapa, E. Corral, S. Sardar, B. S. Pierce, F. W. Foss, Jr. J. Org. Chem. 2019, 84, 1025.

- [13] (a) E. Kianmehr, S. B. Nasab, *Eur. J. Org. Chem.* 2019, 1038. (b)
  K. Raghuvanshi, K. Rauch, L. Ackermann, *Chem. Eur. J.* 2015, *21*, 1790. (c) T. Sarkar, S. Pradhan, T. Punniyamurthy, *J. Org. Chem.* 2018, *83*, 6444. (d) T. Okada, K. Nobushige, T. Satoh, M. Miura, *Org. Lett.* 2016, *18*, 1150. (e) K. Padala, M. Jeganmohan, *Chem. Commun.* 2013, *49*, 9651. (f) K. Raghuvanshi, D. Zell, L. Ackermann, *Org. Lett.* 2017, *19*, 1278.
- [14] Y.-C. Yuan, C. Bruneau, R. Gramage-Doria, Synthesis 2018, 50, 4216.
- [15] (a) L. Ackermann, *Chem. Rev.* 2011, *111*, 1315. (b) L. Ackermann, *Acc. Chem. Res.* 2014, *47*, 281. (c) L. Ackermann, R. Vicente, H. K. Potukuchi, V. Pirovano, *Org. Lett.* 2010, *12*, 5032. (d) I. Fabre, N. von Wolff, G. Le Duc, E. Ferrer Flegeau, C. Bruneau, P. H. Dixneuf, A. Jutand, *Chem. Eur. J.* 2013, *19*, 7595. (e) L. Ackermann, R. Vicente, A. Althammer, *Org. Lett.* 2008, *10*, 2299. (f) E. Ferrer Flegeau, C. Bruneau, P. H. Dixneuf, A. Jutand, *J. Am. Chem. Soc.* 2011, *133*, 10161. (g) P. B. Arockiam, C. Bruneau, P. H. Dixneuf, Chem. Rev.

**2012**, *112*, 5879. (h) C. Shan, L. Zhu, L.-B. Qu, R. Bai, Y. Lan, *Chem. Soc. Rev.* **2018**, *47*, 7552.

- [16] Y. Zhou, P. Chen, X. Lv, J. Niu, Y. Wang, M. Lei, L. Hu, *Tetrahedron Lett.* 2017, 58, 2232.
- [17] A. Verma, S. Patel, Meenakshi, A. Kumar, A. Yadav, S. Kumar, S. Jana, S. Sharma, C. D. Prasad, S. Kumar, *Chem. Commun.* 2015, *51*, 1371.
- [18] C. Lin, L. Zhen, Y. Cheng, H.-J. Du, H. Zhao, X. Wen, L.-Y. Kong, Q.-L. Xu, H. Sun, Org. Lett. 2015, 17, 2684.
- [19] J.-C. Hsieh, C.-H. Cheng, Chem. Commun. 2005, 36, 4554.
- [20] K. Kaminski, B. Wiklik, J. Obniska, Arch. Pharm. Chem. Life Sci. 2014, 347, 840.

[Part of this chapter has been published in Catal. Sci. Technol. 2019, 9, 4711-4717]

# Chapter 5: Site-selective Ruthenium-catalyzed C-H bond alkenylations with the biologically relevant isoindolinone core as a weak directing group

### 5.1 Introduction

Transition metal-catalyzed C-H bond functionalization using weak directing groups (WDG) has emerged in the last decade as a powerful approach in chemical synthesis.<sup>1</sup> Indeed, it allows an efficient and sustainable entry in the late-stage functionalization of molecules relevant for many fields, which is appealing from an industrial and academic point of view.<sup>2</sup> Carbonyl-containing moieties represent arguably the most important class of WDG and their use in bond forming reactions via transition metal-catalyzed C-H bond functionalizations is well established, especially when it is part of an acyclic WDG.<sup>3</sup> When this carbonyl group is part of a cyclic WDG a limited number of examples exist, most of them based on a six-membered ring.<sup>4</sup> On the other hand, the use of carbonyl-containing WDG based on a five-membered ring is synthetically appealing because these heterocycles are ubiquitous in multiple biologically relevant scaffolds.<sup>5</sup> For instance, they have been exploited in a limited number of C-H bond arylation, methylation and acylation reactions using expensive and scarce Pd, Rh and Ir catalysts (Scheme 5.1).<sup>6</sup>



Scheme 5.1 Transition metal-catalyzed C-H bond (aryl/methyl/acylation) reactions with five-membered ring weak directing groups.

For C-H bond alkenylation reactions, Frost and Ackermann, independently, reported on oxazolidinone, pyrrolidinone, thiazolidinone, hydantoin, succinimide and

pyrazolone as WDG using bench-stable ruthenium catalysts and electron deficient olefins such as acrylates (Scheme 5.2).<sup>7</sup> As such, the design of selective carbon-carbon and carbon-heteroatom bond forming reactions via transition metal-catalyzed C-H bond functionalization strategies using heterocyclic carbonyl-containing WDG is highly attractive.<sup>8</sup> It is important to remind that in the transition metal-catalyzed carbon-carbon bond forming reactions using five-membered ring weak directing groups shown in Scheme 5.1 and 5.2, only one aromatic C-H bond is available for functionalization, thus limiting selectivity issues.



Scheme 5.2 Ru-catalyzed C-H bond alkenylation with five-membered ring weak directing groups.

Considering the growing interest to develop transition metal-catalyzed C-H bond functionalizations applicable also to biologically appealing WDG, we turned our attention to isoindolinones.<sup>9</sup> The isoindolinone motif neighboring an *ortho*-substituted carbon-containing fragment is found in pharmacologically relevant structures.<sup>10-12</sup> For instance, **A** behaves as a liver X receptor modulator,<sup>10</sup> **B** is a IGF-1R (type-1 insulin-like growth factor receptor) inhibitor<sup>11</sup> and **C** is a microsomal triglyceride transfer protein inhibitor (Figure 5.1).<sup>12</sup>



**Figure 5.1** Selected biologically relevant molecules featuring the isoindolinone core with alkene and alkane substituents at the *ortho*-position of the *N*-phenyl ring.

In this chapter, a selective ruthenium-catalyzed C-H bond alkenylation of *N*-arylisoindolinones with a large scope of alkenes (beyond alkyl acrylates) and a high functional group tolerance is developed (Scheme 5.3). Despite the presence of two potentially reactive aromatic C-H sites (H<sub>a</sub> and H<sub>b</sub>), the C-H bond alkenylation reaction selectively occurred in the phenyl ring attached to the nitrogen atom (Scheme 5.3). The synthetic potential of the isoindolinone motif as WDG is demonstrated in several postfunctionalization reactions including the late-stage derivatization of the biologically relevant indoprofen. Preliminary mechanistic studies indicate the ease of the C-H bond activation step for this type of substrates and the identification of an unprecedented off-cycle ruthenium complex. Comparison of reactivity with related weak directing groups such as cyclic imides have been carried out as well.



Scheme 5.3 Ru-catalyzed C-H bond site-selective alkenylation with the isoindolinone core serving as a weak directing group.

#### 5.2 Results and discussion

# 5.2.1 Optimization of the site-selective ruthenium-catalyzed C-H bond alkenylation with the isoindolinone fragment serving as a weak directing group

Exhaustive reaction conditions were screened starting from substrate **1a** and using modified reaction conditions similar to those found in literature for structurally related substrates (Table 5.1).<sup>7</sup> First, the catalytic reaction was performed in the presence of  $[RuCl_2(p-cymene)]_2$  (5 mol%), AgSbF<sub>6</sub> (20 mol%) as halide scavenger, Cu(OAc)<sub>2</sub>•H<sub>2</sub>O (100 mol%) as oxidant and methyl acrylate (2.0 equiv.) as coupling partner in 2-MeTHF as solvent under air at 120 °C for 15 hours. These conditions gave rise to the product

		CO <sub>2</sub> Me		Э	
	0 H N + 1a	CO <sub>2</sub> Me [RuCl addir solver	2( <i>p</i> -cymene)] <sub>2</sub> 5 mol%) tive, oxidant tt, T, 15 h, Air		>
Entry	Additive	Oxidant	Solvent	T (°C)	Yield <sup>b</sup>
1 <sup>c</sup>	AgSbF <sub>6</sub>	Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O	2-MeTHF	120	77
2 <sup>c</sup>	AgSbF <sub>6</sub>	Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O	2-MeTHF	100	96
3 <sup>c</sup>	AgSbF <sub>6</sub>	Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O	2-MeTHF	80	50
4	AgSbF <sub>6</sub>	Cu(OAc)₂·H₂O	2-MeTHF	100	97(94)
5 <sup>d</sup>	AgSbF <sub>6</sub>	Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O	2-MeTHF	100	69
6 <sup>e</sup>	AgSbF <sub>6</sub>	Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O	2-MeTHF	100	46
7	AgSbF <sub>6</sub>	Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O	THF	100	96
8	AgSbF <sub>6</sub>	Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O	Dioxane	100	90
9	AgSbF <sub>6</sub>	Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O	DCE	100	90
10	AgSbF <sub>6</sub>	Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O	H <sub>2</sub> O	100	0
11	AgSbF <sub>6</sub>	Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O	GVL	100	41
12	AgSbF <sub>6</sub>	Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O	DEC	100	48
13	AgSbF <sub>6</sub>	Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O	1-Pentanol	100	39
14 <sup>f</sup>	AgSbF <sub>6</sub>	Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O	2-MeTHF	100	93
15	AgSbF <sub>6</sub>		2-MeTHF	100	trace
16		Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O	2-MeTHF	100	29
17 <sup>g</sup>	AgSbF <sub>6</sub>	Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O	2-MeTHF	100	0

Table 5.1 Optimization of the reaction conditions.<sup>a</sup>

<sup>*a*</sup>Reaction conditions: **1a** (0.1 mmol), methyl acrylate (0.2 mmol),  $[\text{RuCl}_2(p\text{-cymene})]_2$  (5 mol%), additive (20 mol%), oxidant (100 mol%) and solvent (0.5 mL), 15 h, air. <sup>*b*</sup>Determined by <sup>1</sup>H NMR spectroscopy against an internal standard (dibromomethane). The isolated yield is shown in parentheses. <sup>*c*</sup>3.0 equivalents of methyl acrylate. <sup>*d*</sup>1.5 equivalents of methyl acrylate. <sup>*e*</sup>1 mol% of [RuCl<sub>2</sub>(*p*-cymene)]<sub>2</sub>. <sup>*f*</sup>Under Ar. <sup>*g*</sup>Without [RuCl<sub>2</sub>(*p*-cymene)]<sub>2</sub>. Note: GVL =  $\gamma$ -valerolactone, DEC = diethyl carbonate.

**2a** in 77% yield (Table 5.1, entry 1). The resulting 1,2-disubstituted double bond in **2a** displayed *E*-configuration according to the high  $J_{\rm H,H}$  coupling constant (*ca.* 16 Hz) observed for the alkene protons by NMR spectroscopy studies. Next, the reaction was conducted at lower reaction temperatures such as 100 °C and 80 °C, and the product **2a** was obtained in 96% and 50% yield, respectively (Table 5.1, entries 2-3). Decreasing the amount of methyl acrylate to 2 equivalents or 1.5 equivalents led to **2a** in 97 and 69% yield, respectively (Table 5.1, entries 4-5). Performing the catalytic reaction with

1 mol% of [RuCl<sub>2</sub>(*p*-cymene)]<sub>2</sub> afforded **2a** in a modest 46% yield (Table 5.1, entry 6). Next, different solvents such as THF, dioxane, DCE, H<sub>2</sub>O,  $\gamma$ -valerolactone (GVL), diethyl carbonate (DEC) and 1-pentanol were employed instead of 2-MeTHF (Table 5.1, entries 7-13). Among them, THF, dioxane and DCE were rather effective for the catalysis, providing **2a** in 96, 90, and 90% yield, respectively. Under Argon atmosphere, the reaction also proceeded smoothly, giving the product **2a** in a 93% yield (Table 5.1, entry 14). In addition, control experiments indicated that all the reagents were necessary for the success of the reaction (Table 5.1, entries 15-17).

Gratifyingly, with the optimized reaction conditions (Scheme 5.4, top), the reaction was found to be regio- and site-selective as no C-H bond alkenylation was observed in the fused benzene ring ( $H_b$ ). This is consistent with the isoindolinone core accommodating a plausible six-membered ring ruthenacycle intermediate **I** rather than a five-membered ring **II** (Scheme 5.4, bottom).



Scheme 5.4 Optimal conditions found for the ruthenium-catalyzed C-H bond alkenylation of **1a**, and plausible intermediates controlling the site-selectivity.

# 5.2.2 Scope and limitations of the ruthenium-catalyzed site-selective C-H bond alkenylation with different terminal alkenes

Next, the scope of the reaction was evaluated and the catalysis was found efficient with other alkyl acrylates, such as ethyl, butyl, and benzyl, leading to the corresponding products **2b-2d** in 81-91% yield (Table 5.2). Interestingly, other electron deficient





<sup>a</sup>Reaction conditions: **1a** (0.2 mmol), alkene (0.4 mmol),  $[RuCl_2(p-cymene)]_2$  (5 mol%), AgSbF<sub>6</sub> (20 mol%) and Cu(OAc)<sub>2</sub>·H<sub>2</sub>O (100 mol%) in 2-MeTHF (1 mL) at 100 °C for 15 h under air. <sup>*b*</sup>Isolated yields (conversion in parentheses). <sup>*c*</sup>6% of alkylated product was present. <sup>*d*</sup>23% of alkylated product was present.

terminal alkenes containing synthetically useful functional groups such as nitrile, aldehyde, and ketone efficiently reacted with **1a** leading to **2e-2g** in 69-79% yields. In the case of **2f** and **2g**, small amounts of alkylated product were detected. Unexpectedly, the reaction was efficient with less electron deficient alkenes such as styrene and other styrene derivatives (4-fluorostyrene and 4-bromostyrene) leading to **2h-2j** in a decent 55-64% yield. It is important to emphasize that the alkene coupling partners leading to products **2e-2j** have been scarcely used in transition metal-catalyzed C-H bond alkenylation reactions,<sup>13</sup> despite their obvious synthetic potential. Additionally, the molecular structures of **2g** and **2h** were unambiguously established by single crystal X-

ray diffraction studies, which further supported the regio-, site- and stereo-selectivity of the alkenylation reaction (Table 5.2).

The catalysis also tolerated different *para*-substitution patterns in the *N*-phenyl side of 1 leading to 2k-2m in >90% yields (Table 5.3). The reaction was equally efficient at large scale starting from 3 mmol of isoindolinone 1k and the alkenylated product 2k was obtained in 91% yield (839 mg). Although nitrile and ester groups are known to behave as weak directing groups in similar ruthenium-catalyzed C-H bond alkenylation reactions,<sup>14</sup> we noticed that under our reaction conditions, the isoindolinone core exclusively dictates the selectivity of the reaction leading to 2n and **20** in 41 and 87% isolated yields, respectively, with no other regioisomers detected in the reaction mixture. *meta*-Substitution in the phenyl ring of 1 with electronically different methyl and methoxy substituents led to the same isomers 2p and 2q in 90 and 82% isolated yields, respectively. This indicates that the most sterically accessible C-H bond is preferentially functionalized for these substrates. In contrast, dioxolanecontaining isoindolinone reacted with methyl acrylate leading selectively to the most sterically hindered isomer (80:20 ratio) in 89% isolated yield (2r). When using acrylonitrile, which has been scarcely used as coupling partner, a single regioisomer (2s) was obtained in 90% isolated yield. The heterocyclic dioxolane group seems to behave as an additional WDG to some extent for ruthenium-catalyzed C-H bond alkenylations as it was reported before.<sup>15</sup> The *ortho*-substitution pattern in the phenyl ring slightly decreased the efficiency of the catalysis as shown in the formation of 2tand 2u in 42 and 56% isolated yields, respectively. Additionally, the molecular structures of **2l** and **2t** were also confirmed by single crystal X-ray diffraction studies.



 Table 5.3 Ru-catalyzed site-selective C-H bond alkenylation with isoindolinone derivatives.<sup>*a,b*</sup>

<sup>a</sup>Reaction conditions: **1** (0.3 mmol), alkene (0.6 mmol),  $[RuCl_2(p-cymene)]_2$  (5 mol%), AgSbF<sub>6</sub> (20 mol%) and Cu(OAc)<sub>2</sub>·H<sub>2</sub>O (100 mol%) in 2-MeTHF (1.5 mL) at 100 °C for 15 h under air. <sup>*b*</sup>Isolated yields (conversion in parentheses). <sup>*c*</sup>Ratio of isomers determined by NMR spectroscopy analysis.

Interestingly, ethyl phenylpropiolate as internal alkyne was reacted with **1a**, under our standard reaction conditions, leading to **2v** in 26% isolated yield (35% conversion). The molecular structures of **2v** was unambiguously established by single crystal X-ray

diffraction studies, which further supported the regio-, site- and stereoselectivity of the catalysis (Scheme 5.5).



Scheme 5.5 Ru-catalyzed site-selective C-H bond alkenylation of 1a with ethyl phenylpropiolate as coupling partner.

Unfortunately, very challenging alkynes, acrylamides, acrylic acid, aliphatic olefins (e.g. 1-octene) and sterically hindered alkenes were not reactive with isoindolinones **1** under the developed reaction conditions (Figure 5.2).



Figure 5.2 Reluctant coupling partners tested in the Ru-catalyzed C-H bond siteselective alkenylation of isoindolinones 1.

In some cases, trace amounts (<5%) of bis-functionalization was observed by NMR and GC-MS. In order to obtain some useful quantities of bis-functionalized product, the amounts of copper oxidant and methyl acrylate in the catalysis were doubled. Under these conditions, bis-alkenylated **2w** was obtained in 20% yield besides major formation of mono-alkenylated **2a** (Scheme 5.6, top). Bis-alkenylated **2w** was obtained in 29% yield starting from the mono-alkenylated **2a** under the standard

reaction conditions (Scheme 5.6, bottom). Similarly, submitting the mono-alkenylated 2k to the standard reaction conditions afforded bis-alkenylated 2x in 19% isolated yield (Scheme 5.6, bottom), confirming that the bis-alkenylation is difficult for this type of substrates. In these cases we noted formation of dienes derived from acrylate homocoupling as side products,<sup>16</sup> which indicates that this side-reaction competes with the ruthenium-catalyzed C-H bond functionalization to some extent under the studied reaction conditions.



Scheme 5.6 Ru-catalyzed twofold C-H bond site-selective alkenylation.

To demonstrate the practical utility of the methodology, we aimed at performing the late-stage functionalization of a biologically relevant compound. Indoprofen (**1y**) was selected as it displays anti-inflammatory activity (Scheme 5.7).<sup>17</sup> Interestingly, the ruthenium-catalyzed C-H bond alkenylation reaction exclusively led to the product **2y** as confirmed by multinuclear NMR studies in an excellent 92% isolated yield under our standard reaction conditions (Scheme 5.7). Despite the presence in the molecule of a carboxylic acid that could eventually act as a WDG for this transformation,<sup>18</sup> the isoindolinone core, again, dictates the selectivity of the catalysis even for this challenging substrate. In short, one out of four possible C-H bonds is selectively

alkenylated. Overall, this methodology is compatible with a large number of functional groups including alkyl, benzyl, phenyl, halide (F, Cl, Br), ester, nitrile, ketone, aldehyde, carboxylic acid and (a)cyclic ether.



**Scheme 5.7** Late-stage C-H bond site-selective alkenylation of biologically relevant indoprofen highlighting the four C-H bonds that could *a priori* be functionalized.

For comparison purposes, the catalysis was performed with phthalimide as WDG (**1z**), which is structurally related to isoindolinone but contains one additional carbonyl group (Scheme 5.8, top). In this manner, the mono-alkenylated product **2z** was obtained in a poor 20% yield with >70% of unreacted phthalimide starting material **1z** and formation of dienes derived from acrylate homocoupling as side products (Scheme 5.8, top).<sup>16</sup> Similar observations were made with other WDG containing two carbonyl groups such as succinimides, although the yields were slightly higher in those cases (ca. 50%).<sup>7b</sup> Intrigued by the difference of reactivity encountered between isoindolinones and phthalimides, we decided to attempt a C-H bond alkenylation with substrate **1zz**. This substrate is related to phthalimides but contain a fully hydrogenated benzene ring. Under our standard reaction conditions, 71% yield of the targeted product **2zz** was obtained. This clearly highlights that a certain degree of flexibility within the WDG is key to achieve decent levels of reactivity in ruthenium-catalyzed C-H bond alkenylations.



Scheme 5.8 Ru-catalyzed C-H bond alkenylation of cyclic imides 1z and 1zz.

# 5.3 Mechanistic studies

The high reactivity of the isoindolinone fragment versus the phthalimide one as WDG for alkenylation reactions was evidenced in deuteration experiments as well. With isoindolinone as WDG (**1a**), 90% deuterium incorporation was reached in the C-H bonds that can undergo alkenylation (Scheme 5.9, top). This shows the selectivity, ease and reversibility of the C-H bond activation step for *N*-arylisoindolinones. On the other hand, only 7.5% deuterium was incorporated in the case of phthalimide as WDG (**1z**, Scheme 5.9, bottom). It appears that, under the reactions conditions required for alkenylation, (i) the phthalimide fragment is too rigid to accommodate the ruthenacycle intermediate that enables the C-H activation step to occur and/or (ii) significant catalyst deactivation by substrate and/or product inhibition takes place. Nevertheless, we have shown in the ruthenium-catalyzed hydroxylation of phthalimide that the activation of the *ortho*-C-H bond is possible (Chapter 3). Probably the initial catalytically active ruthenium species that form in hydroxylation are chemically different than those formed in alkenylation, which explains the difference of reactivity between cyclic imides and cyclic amides in both set of reactions.



Scheme 5.9 Deuteration experiments with isoindolinone 1a and phthalimide 1z.

The catalysis performed with isoindoline, a substrate lacking both carbonyl groups, did not provide any alkenylated product (Scheme 5.10). These observations highlight the key role of the coordination of the carbonyl group belonging to the isoindolinone motif to ruthenium as a WDG throughout the catalytic cycle.



Scheme 5.10 Attempt of Ru-catalyzed C-H bond alkenylation with isoindoline.

Unfortunately, attempts to isolate ruthenium species belonging to the catalytic cycle failed so far. Interestingly, we managed to isolate in 86% yield the **Ru-1** complex in which the ruthenium(II) center is  $\eta^6$ -coordinated both to the *para*-cymene ligand and to the phenyl ring of **1a** (Scheme 5.11, top). The molecular structure of **Ru-1** was established by NMR and HRMS.<sup>19</sup> This ruthenium sandwich complex was used in catalytic amounts for the alkenylation of **1a**. In this case, only trace amounts of product **2a** were detected (Scheme 5.11, bottom). Consequently, **Ru-1** complex might be regarded as an off-cycle intermediate that leads to catalyst deactivation by substrate inhibition. Similar  $\eta^6$ -coordinated ruthenium species reported by Hartwig and Zhao

were unreactive for ruthenium-catalyzed decarboxylative alkyne hydroarylation reactions.<sup>20</sup>



Scheme 5.11 Synthesis of **Ru-1** complex and attempt of Ru-catalyzed C-H bond siteselective alkenylation of **1a** with **Ru-1** as pre-catalysts.

The above described combined data together with previous reports dealing with ruthenium-catalyzed C-H bond alkenylation reactions<sup>7,13</sup> enabled to propose a simplified reaction mechanism (Scheme 5.12). The *in situ* generated chloride-free ruthenium(II) species coordinates to the substrate **1** via the oxygen lone pair of the carbonyl group to form the intermediate **A**, which, after the C-H bond activation generates the metallacycle **B**. Coordination of the alkene coupling partner to the ruthenium *via* the C=C double bond leads to **C**, which, forms **D** after migratory insertion. Isomerization followed by  $\beta$ -hydride elimination forms **E** that leads to product **2** and regeneration of the ruthenium(II) catalyst by the copper salt oxidant. It can also be noted that the migratory insertion of the alkene, (**C** to **D**), might be more difficult with phthalimide than with isoindolinone due to the more rigid 5-membered ring of phthalimide [C(sp<sup>2</sup>)=O *versus* C(sp<sup>3</sup>)-H<sub>2</sub>]: a feature that could account as well to the difference of reactivity observed between cyclic amides and imides in the ruthenium-catalyzed alkenylation reaction.



Scheme 5.12 Proposed reaction mechanism.

# 5.4 Derivatization reactions

Finally, the potential of the presented methodology was studied by performing further derivatization reactions from compound 2k. The ester group in 2k was transformed into carboxylic acid (3) in quantitative yield, into primary amide (4) in 63% yield and secondary amide (5) in 77% yield, respectively (Scheme 5.13). These transformations overcome the few issues encountered in the lack of reactivity of acrylic acid and acrylamides as coupling partners, respectively, in the ruthenium-catalyzed alkenylation (Figure 5.2). Moreover, the alkene double bond of 2k was subsequently hydrogenated in the presence of catalytic amounts of Pd/C under 1 bar of H<sub>2</sub> affording the alkylated product **6** in quantitative yield (Scheme 5.13). Clearly, the C-H bond functionalization/hydrogenation sequence is a useful approach when direct C-H bond alkylations are not trivial as it is the case here for WDG.<sup>21</sup>



Scheme 5.13 Derivatizations of 2k. Reaction conditions: (i) KOH (1.1 equiv.), MeOH:H<sub>2</sub>O, 50 °C, 16 h, then HCl; (ii) NH<sub>3</sub> (10 equiv.), CaCl<sub>2</sub> (2 equiv.), MeOH, 80 °C, 24 h; (iii) Ethanolamine (5 equiv.), Na<sub>2</sub>CO<sub>3</sub> (1 equiv.), MeOH, reflux, 16 h; (iv) Pd/C, H<sub>2</sub> (1 atm), MeOH, 20 °C, 16 h.

# 5.5 Conclusion

In summary, we have shown the first use of biologically appealing isoindolinones as WDG in transition metal-catalyzed C-H bond functionalizations. This was disclosed for alkenylation reactions in the presence of a readily affordable ruthenium catalyst. The catalysis is efficient, selective and compatible with a broad scope of alkenes as coupling partners as well as with a large number of synthetically useful functional groups. Post-functionalizations and late-stage derivatization of a biologically relevant compound (indoprofen) account for the potential of this methodology. Although the **Ru-1** complex is not involved as intermediate in the reaction mechanism of this catalysis, its application in other C-H bond functionalization reactions remains to be addressed.

# 5.6 Experimental details

General information. All reagents were obtained from commercial sources and used as supplied. All reactions were carried out in flame-dried glassware under argon atmosphere unless otherwise noted. Catalytic experiments were performed in Schlenktype flasks under argon atmosphere unless otherwise noted. Organic solutions were concentrated under reduced pressure using a rotary evaporator. Thin-layer chromatography (TLC) were carried out on 0.25 mm Merck silica gel (60-F254). Flash column chromatography was performed using silica gel Silica 60 M, 0.04-0.063 mm. Technical grade petroleum ether (40-60), n-heptane and ethyl acetate were used for column chromatography. CDCl<sub>3</sub> was stored under nitrogen over molecular sieves. NMR spectra were recorded on an AVANCE III 400 spectrometer. <sup>1</sup>H NMR spectra were referenced to residual protiated solvent ( $\delta = 7.26$  ppm for CDCl<sub>3</sub>,  $\delta = 2.50$  ppm for DMSO- $d_6$  and  $\delta = 2.05$  ppm for acetone- $d_6$ ) and <sup>13</sup>C chemical shifts are reported relative to deuterated solvents ( $\delta$  = 77.0 ppm for CDCl<sub>3</sub>,  $\delta$  = 39.5 ppm for DMSO- $d_6$ and  $\delta = 29.8$  ppm for acetone- $d_6$  [Note: acetone- $d_6$  contains traces of water at *ca*. 3 ppm]. The peak patterns are indicated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet, and br. For broad. GC-MS analyses were performed with a GCMS-QP2010S (Shimadzu) instrument with a GC-2010 equipped with a 30 m capillary column (Supelco, SLBTM-5ms, fused silica capillary column, 30 m x 0.25 mm x 0.25 mm film thickness), which was used with helium as the vector gas. The following GC conditions were used: initial temperature 80 °C for 2 minutes, then rate 20 °C/min until 280 °C and 280 °C for 28 minutes. HRMS were recorded on a Waters Q-Tof 2 mass spectrometer at the corresponding facilities of the CRMPO, Centre Régional de Mesures Physiques de l'Ouest, Université de Rennes 1. Melting points were performed on a LEICA VMHB Kofler system.

### Synthesis of substrates 1.

<u>Method A:</u> A mixture of 2-formylbenzoic acid (5.0 mmol, 1 equiv.), amine (6.0 mmol, 1.2 equiv.), DABCO (10.0 mmol, 2 equiv.), HCOOH (1.25 mL), Pd(OAc)<sub>2</sub> (0.25 mmol, 5 mol%) in 1,4-dioxane (5 mL) was heated to 80 °C for 3h. After completion of the reaction, the mixture was cooled to room temperature, and diluted with DCM (50 mL). The solid was removed by filter, and the filtrate was washed with water (50 mL) and brine (50 mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/acetone = 5/1, v/v) to afford the desired product.



# Characterization of substrates 1.

**2-(2-Methoxyphenyl)isoindolin-1-one (1u):** Prepared according to Method A starting from *o*-anisidine in 61% isolated yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta = 7.94$  (d, J = 7.6 Hz, 1H), 7.58 (ddd, J = 7.2, 7.2, 1.2 Hz, 1H), 7.49 (dd, J = 7.6, 7.6 Hz, 2H), 7.43 (dd, J = 7.6, 2.0 Hz, 1H), 7.32 (ddd, J = 8.0, 8.0, 1.6 Hz, 1H), 7.06-7.00 (m, 2H), 4.80 (s, 2H), 3.82 (s, 3H) ppm. The spectral data match those previously reported.<sup>22</sup>

Synthesis and characterization of the other substrates 1 are described in the experimental details of Chapter 4.

# General procedure for the ruthenium-catalyzed C-H bond alkenylation reaction.

*General procedure:* In an oven dried carousel tube, to a solution of isoindolinone **1** (0.3 mmol, 1 equiv.) and the corresponding alkene (0.6 mmol, 2 equiv.) in 2-MeTHF (1.5 mL) was added the combined solids: [RuCl<sub>2</sub>(*p*-cymene)]<sub>2</sub> (5 mol%), AgSbF<sub>6</sub> (20 mol%)

and Cu(OAc)<sub>2</sub>·H<sub>2</sub>O (0.3 mmol, 1 equiv.). The carousel tube was sealed with a Teflon cap leaving the tap open and was heated to 100 °C for 15 h. The reaction mixture was diluted in EtOAc and filtered using a silica plug, eluting with EtOAc. The solvent was removed *in vacuo* and the crude mixture was purified using column chromatography (*n*-Heptane:EtOAc 4/1 to 1/1, *v*/*v*) to give the pure alkenylated product **2**.

# Characterization of products (2)

Methyl (*E*)-3-(2-(1-oxoisoindolin-2-yl)phenyl)acrylate (2a): White solid, yield =  $CO_2Me$  94%, 82.7 mg. Mp: 180-183 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.96 (d, *J* = 7.6 Hz, 1H), 7.73 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.67-7.61 (m, 2H), 7.56-7.46 (m, 3H), 7.40 (ddd, *J* = 7.6, 7.6, 1.2 Hz, 1H), 7.35 (dd, *J* = 7.6, 1.2 Hz, 1H), 6.46 (d, *J* = 16.0 Hz, 1H), 4.76 (s, 2H), 3.72 (s, 3H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 168.4, 167.1, 141.6, 140.3, 138.0, 132.7, 132.2, 132.0, 131.1, 128.6, 128.4, 128.2, 127.7, 124.7, 123.0, 120.2, 53.8, 51.8 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>18</sub>H<sub>15</sub>NO<sub>3</sub>Na 316.0944, found 316.0943 (0 ppm).

Ethyl (E)-3-(2-(1-oxoisoindolin-2-yl)phenyl)acrylate (2b): White solid, yield = 89%,

 $\int_{N} CO_{2}Et = 61.2 \text{ mg. Mp: } 148-151 \,^{\circ}\text{C. }^{1}\text{H NMR (400 MHz, CDCl_{3}): } \delta = 7.95 \,(\text{d}, J = 7.6 \text{ Hz}, 1\text{H}), 7.73 \,(\text{dd}, J = 7.6, 1.2 \text{ Hz}, 1\text{H}), 7.66-7.59 \,(\text{m}, 2\text{H}), 7.55-7.45 \,(\text{m}, 3\text{H}), 7.39 \,(\text{dd}, J = 7.6, 7.6 \text{ Hz}, 1\text{H}), 7.34 \,(\text{dd}, J = 7.6, 1.2 \text{ Hz}, 1\text{H}), 6.45 \,(\text{d}, J = 16.0 \text{ Hz}, 1\text{H}), 4.75 \,(\text{s}, 2\text{H}), 4.18 \,(\text{q}, J = 7.2 \text{ Hz}, 2\text{H}), 1.25 \,(\text{t}, J = 7.2 \text{ Hz}, 3\text{H}) \text{ ppm. }^{13}\text{C}\{^{1}\text{H}\} \text{ NMR (100 MHz, CDCl_{3}): } \delta = 168.4, 166.7, 141.6, 140.0, 138.0, 132.8, 132.1, 132.0, 131.0, 128.5, 128.4, 128.2, 127.6, 124.6, 123.0, 120.6, 60.6, 53.8, 14.3 \text{ ppm. HRMS (ESI) calcd. for [M + Na]^{+} C_{19}\text{H}_{17}\text{NO}_{3}\text{Na} 330.1101, found 330.1101 (0 \text{ ppm}).$ 

Butyl (E)-3-(2-(1-oxoisoindolin-2-yl)phenyl)acrylate (2c): White solid, yield = 91%,

 $\delta = 7.94$ (d, *J* = 7.6 Hz, 1H), 7.73 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.65-7.58 (m, 2H), 7.54-7.44 (m, 3H), 7.38 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.34 (dd, *J* = 7.6, 1.2 Hz, 1H), 6.44 (d, *J* = 16.0 Hz, 1H), 4.74 (s, 2H), 4.11 (t, *J* = 6.4 Hz, 2H), 1.58 (m, 2H), 1.32 (m, 2H), 0.86 (t, *J* = 7.2 Hz, 3H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta = 168.3, 166.7, 141.5, 139.9, 137.9, 132.7, 132.1, 131.9, 131.0, 128.5, 128.4, 128.2, 127.5, 124.5, 122.9, 120.5, 64.5, 53.7, 30.7, 19.2, 13.7 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>21</sub>H<sub>21</sub>NO<sub>3</sub>Na 358.1414, found 358.1412 (0 ppm).$ 

(*E*)-3-(2-(1-Oxoisoindolin-2-yl)phenyl)acrylonitrile (2e): White solid, yield = 79%,



41.0 mg. Mp: 140-142 °C. <sup>1</sup>H NMR (400 MHz, acetone- $d_6$ ):  $\delta$  = 7.90 (d, J = 8.0 Hz, 1H), 7.82 (d, J = 7.6 Hz, 1H), 7.71-7.65 (m, 2H), 7.62-7.55 (m, 4H), 7.49-7.45 (m, 1H), 6.28 (d, J = 16.4 Hz, 1H),

4.98 (s, 2H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, acetone- $d_6$ ):  $\delta$ = 168.2, 147.6, 143.4, 139.1, 132.81, 132.80, 132.76, 132.4, 129.0, 128.8, 128.7, 127.3, 124.4, 124.2, 119.0, 98.6, 53.9 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>17</sub>H<sub>12</sub>N<sub>2</sub>ONa 283.0842, found 283.0842 (0 ppm).



(E)-2-(2-(3-Oxobut-1-en-1-yl)phenyl)isoindolin-1-one (2g): White solid, yield =



92%, 49.8 mg. Mp: 152-154 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.93 (d, *J* = 7.6 Hz, 1H), 7.73 (d, *J* = 7.6 Hz, 1H), 7.61 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.57-7.45 (m, 4H), 7.38 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.33 (d, *J* = 8.8 Hz, 1H), 6.68 (d, *J* = 16.4 Hz, 1H), 4.76 (s, 2H), 2.22 (s,

3H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 198.2, 168.2, 141.4, 138.8, 138.1, 132.6, 132.2, 131.2, 129.8, 128.8, 128.5, 128.3, 127.9, 127.6, 124.4, 123.0, 53.6, 27.7 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>18</sub>H<sub>15</sub>NO<sub>2</sub>Na 300.0995, found 300.0993 (1 ppm).

(*E*)-2-(2-Styrylphenyl)isoindolin-1-one (2h): Yellow solid, yield = 64%, 39.9 mg. Mp:



169-171 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.03 (d, *J* = 7.6 Hz, 1H), 7.80 (d, *J* = 7.2 Hz, 1H), 7.64 (dd, *J* = 7.6, 7.2 Hz, 1H), 7.57 (dd, *J* = 7.6, 7.2 Hz, 1H), 7.51 (d, *J* = 7.2 Hz, 1H), 7.45-7.34 (m, 5H), 7.31 (dd, *J* = 7.6, 7.2 Hz, 2H), 7.24 (dd, *J* = 7.2, 7.2 Hz, 1H),

7.14 (d, J = 16.0 Hz, 1H), 7.09 (d, J = 16.0 Hz, 1H), 4.75 (s, 2H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta = 168.3$ , 141.7, 137.1, 136.4, 135.6, 132.3, 131.9, 131.5, 128.7, 128.6, 128.5, 128.39, 128.37, 128.0, 126.9, 126.8, 124.4, 124.1, 123.0, 53.7 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>22</sub>H<sub>17</sub>NONa 334.1202, found 334.1200 (1 ppm). (E)-2-(2-(4-Fluorostyryl)phenyl)isoindolin-1-one (2i): Yellow solid, yield = 63%,

41.2 mg. Mp: 49-51 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 
$$\delta$$
 = 8.01 (d, J  
= 7.2 Hz, 1H), 7.76 (dd, J = 7.2, 2.0 Hz, 1H), 7.63 (ddd, J = 7.2, 7.2,  
1.2 Hz, 1H), 7.56 (dd, J = 7.6, 7.2 Hz, 1H), 7.51 (d, J = 7.6 Hz, 1H),  
7.43-7.32 (m, 5H), 7.07 (d, J = 16.4 Hz, 1H), 7.00-6.95 (m, 3H),  
4.74 (s, 2H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 168.4,

162.6 (d,  $J_{C-F} = 246.2$  Hz), 141.7, 136.4, 135.5, 133.3 (d,  $J_{C-F} = 3.3$  Hz), 132.3, 132.0, 130.2, 128.7, 128.486 (d,  $J_{C-F} = 8.0$  Hz), 128.483, 128.4, 126.8, 124.5, 124.0 (d,  $J_{C-F} = 2.4$  Hz), 123.0, 115.7 (d,  $J_{C-F} = 21.5$  Hz), 53.8 ppm. <sup>19</sup>F{<sup>1</sup>H} NMR (376 MHz, CDCl<sub>3</sub>):  $\delta = -113.6$  ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>22</sub>H<sub>16</sub>NOFNa 352.1108, found 352.1108 (0 ppm).

(E)-2-(2-(4-Bromostyryl)phenyl)isoindolin-1-one (2j): Yellow solid, yield = 55%,



42.8 mg. Mp: 152-154 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$ = 8.00 (d, J = 7.6 Hz, 1H), 7.77-7.75 (m, 1H), 7.62 (ddd, J = 7.6, 7.6, 1.2 Hz, 1H), 7.56 (dd, J = 7.6, 7.2 Hz, 1H), 7.50 (d, J = 7.6 Hz, 1H), 7.42-7.36 (m, 4H), 7.35-7.32 (m, 1H), 7.25 (d, J = 8.4 Hz, 2H), 7.06 (d, J = 16.4 Hz, 1H), 7.02 (d, J = 16.4 Hz, 1H), 4.74 (s, 2H) ppm.

<sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$ = 168.3, 141.6, 136.5, 136.1, 135.3, 132.2, 132.0, 131.8, 130.1, 128.9, 128.51, 128.48, 128.34, 128.31, 126.8, 124.91, 124.89, 124.5, 123.0, 121.8, 53.8 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>22</sub>H<sub>16</sub>NOBrNa 412.0308, found 412.0309 (0 ppm).

Methyl (E)-3-(5-methyl-2-(1-oxoisoindolin-2-yl)phenyl)acrylate (2k): White solid,



Hz, 1H), 6.44 (d, J = 16.0 Hz, 1H), 4.72 (s, 2H), 3.71 (s, 3H), 2.41 (s, 3H) ppm. <sup>13</sup>C{<sup>1</sup>H}

NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 168.5, 167.1, 141.6, 140.3, 138.4, 135.4, 132.3, 132.1, 132.04, 131.98, 128.5, 128.0, 124.5, 122.9, 119.9, 53.8, 51.8, 21.3 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>19</sub>H<sub>17</sub>NO<sub>3</sub>Na 330.1101, found 330.1103 (1 ppm).

# Methyl (E)-3-(5-methoxy-2-(1-oxoisoindolin-2-yl)phenyl)acrylate (2l): White solid,

yield = 93%, 90.1 mg. Mp: 187-189 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.94 (d, J = 7.6 Hz, 1H), 7.63-7.49 (m, 4H), 7.26-7.20 (m, 2H), 7.02 (dd, J = 8.4, 2.8 Hz, 1H), 6.43 (d, J = 16.0 Hz, 1H), 4.70 (s, 2H), 3.86 (s, 3H), 3.72 (s, 3H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):

120.4, 117.2, 111.9, 55.7, 54.1, 51.8 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>19</sub>H<sub>17</sub>NO<sub>4</sub>Na 346.1049, found 346.1048 (0 ppm).

 $\delta = 168.7, 167.0, 159.3, 141.6, 140.1, 133.8, 132.0, 130.9, 129.5, 128.5, 124.5, 122.9, 129.5, 128.5, 124.5, 122.9, 129.5, 129$ 

Methyl (E)-3-(5-chloro-2-(1-oxoisoindolin-2-yl)phenyl)acrylate (2m): White solid,

yield = 92%, 90.5 mg. Mp: 201-203 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.95 (d, *J* = 7.6 Hz, 1H), 7.70 (s, 1H), 7.65 (dd, *J* = 7.6, 7.2 Hz, 1H), 7.60-7.52 (m, 3H), 7.44 (d, *J* = 8.0 Hz, 1H), 7.31 (d, *J* = 8.4 Hz, 1H), 6.46 (d, *J* = 16.0 Hz, 1H), 4.75 (s, 2H), 3.74 (s, 3H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 168.3, 166.7, 141.4, 139.0, 136.4, 134.2, 134.1, 132.3, 131.6, 130.9, 129.4, 128.6, 127.5, 124.6, 123.0, 121.2, 53.6, 51.9 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>18</sub>H<sub>14</sub>NO<sub>3</sub>ClNa 350.0554, found 350.0557 (1 ppm).

Methyl (E)-3-(5-cyano-2-(1-oxoisoindolin-2-yl)phenyl)acrylate (2n): White solid,

yield = 41%, 38.9 mg. Mp: 214-216 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.97-7.93 (m, 2H), 7.72 (d, J = 8.4 Hz, 1H), 7.66 (dd, J = 7.6, 7.2 Hz, 1H), 7.61-7.49 (m, 4H), 6.48 (d, J = 16.0 Hz, 1H), 4.80 (s, 2H), 3.75 (s, 3H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 168.1,

166.5, 141.8, 141.3, 138.6, 133.72, 133.69, 132.8, 131.8, 131.2, 128.9, 128.6, 124.8,

123.1, 122.0, 117.8, 112.0, 53.1, 52.1 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>19</sub>H<sub>14</sub>N<sub>2</sub>O<sub>3</sub>Na 341.0897, found 341.0898 (0 ppm).



131.63, 131.59, 130.1, 129.1, 128.6, 127.7, 124.6, 123.0, 120.9, 61.5, 53.3, 51.8, 14.4 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>21</sub>H<sub>19</sub>NO<sub>5</sub>Na 388.1155, found 388.1153 (1 ppm).

Methyl (E)-3-(4-methyl-2-(1-oxoisoindolin-2-yl)phenyl)acrylate (2p): White solid,



yield = 90%, 83.4 mg. Mp: 174-176 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$ = 7.93 (d, *J* = 7.6 Hz, 1H), 7.63-7.58 (m, 3H), 7.53-7.48 (m, 2H), 7.19 (d, *J* = 8.4 Hz, 1H), 7.14 (s, 1H), 6.40 (d, *J* = 16.0 Hz, 1H), 4.72 (s, 2H), 3.69 (s, 3H), 2.37 (s, 3H) ppm. <sup>13</sup>C{<sup>1</sup>H}

NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 168.4, 167.2, 141.8, 141.5, 140.0, 137.8, 132.0, 131.9, 129.7, 129.3, 128.7, 128.4, 127.4, 124.4, 122.9, 119.0, 53.8, 51.6, 21.3 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>19</sub>H<sub>17</sub>NO<sub>3</sub>Na 330.1101, found 330.1103 (1 ppm).





3.69 (s, 3H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 168.4, 167.4, 161.9, 141.5, 139.8, 139.4, 132.2, 131.9, 128.8, 128.5, 125.1, 124.6, 123.0, 117.6, 115.0, 113.2, 55.7, 53.9, 51.7 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>19</sub>H<sub>17</sub>NO<sub>4</sub>Na 346.1050, found 346.1052 (1 ppm).

Methyl (E)-3-(5-(1-oxoisoindolin-2-yl)benzo[d][1,3]dioxol-4-yl)acrylate (major)



and methyl (*E*)-3-(6-(1-oxoisoindolin-2-yl)benzo[*d*][1,3]dioxol-5-yl)acrylate (minor) (2r, 80:20): White solid, yield = 89%, 90.1 mg. Mp: 189-191 °C. NMR

data corresponding to the major regioisomer: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$ = 7.91 (d, J = 7.6 Hz, 1H), 7.59 (dd, J = 7.6, 7.2 Hz, 1H), 7.52-7.47 (m, 2H), 7.36 (d, J = 16.4 Hz, 1H), 6.86-6.75 (m, 3H), 6.10 (s, 2H), 4.69 (s, 2H), 3.68 (s, 3H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$ = 168.7, 167.5, 147.6, 147.5, 141.4, 134.9, 132.0, 131.8, 131.6, 128.4, 124.5, 123.2, 122.9, 121.5, 116.4, 109.5, 102.3, 54.2, 51.7 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>19</sub>H<sub>15</sub>NO<sub>5</sub>Na 360.0842, found 360.0844 (0 ppm).

(*E*)-3-(5-(1-Oxoisoindolin-2-yl)benzo[*d*][1,3]dioxol-4-yl)acrylonitrile (2s): White solid, yield = 90%, 82.0 mg. Mp: 188-190 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$ = 7.94 (d, *J* = 7.6 Hz, 1H), 7.64 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.57-7.51 (m, 2H), 7.06 (d, *J* = 16.4 Hz, 1H), 6.91 (d, *J* = 8.0 Hz, 1H), 6.82 (d, *J* = 8.0 Hz, 1H), 6.33 (d, *J* = 16.4 Hz, 1H), 6.15 (s, 2H), 4.70 (s, 2H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$ = 168.7, 147.8, 147.7, 141.3, 141.2, 132.4, 131.5, 131.1, 128.7, 124.6, 123.0, 121.6, 118.4, 115.7, 110.4, 102.7, 101.8, 54.2 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>18</sub>H<sub>12</sub>N<sub>2</sub>O<sub>3</sub>Na 327.0740, found 327.0745 (2 ppm). Methyl (E)-3-(3-methyl-2-(1-oxoisoindolin-2-yl)phenyl)acrylate (2t): White solid,

yield = 54%, 38.9 mg. Mp: 137-139 °C. <sup>1</sup>H NMR (400 MHz,  
CDCl<sub>3</sub>): 
$$\delta$$
 = 7.97 (d, J = 7.6 Hz, 1H), 7.64-7.50 (m, 5H), 7.38-7.32  
(m, 2H), 6.42 (d, J = 16.0 Hz, 1H), 4.64 (d, J = 17.2 Hz, 1H), 4.55  
(d, J = 17.2 Hz, 1H), 3.69 (s, 3H), 2.19 (s, 3H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR

(100 MHz, CDCl<sub>3</sub>):  $\delta$  = 168.3, 167.0, 141.7, 140.1, 137.9, 136.4, 133.7, 132.9, 132.1, 131.9, 128.9, 128.5, 125.2, 124.6, 123.1, 120.7, 52.6, 51.8, 18.1 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>19</sub>H<sub>17</sub>NO<sub>3</sub>Na 330.1101, found 330.1105 (1 ppm).

Methyl (E)-3-(3-methoxy-2-(1-oxoisoindolin-2-yl)phenyl)acrylate (2u): White solid,



yield = 56%, 54.3 mg. Mp: 173-175 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.92 (d, *J* = 7.6 Hz, 1H), 7.65-7.57 (m, 2H), 7.49 (dd, *J* = 7.2, 7.2 Hz, 2H), 7.38-7.29 (m, 2H), 7.01 (d, *J* = 8.0 Hz, 1H), 6.44 (d, *J* = 16.0 Hz, 1H), 4.83 (d, *J* = 16.8 Hz, 1H), 4.49 (d, *J* =

16.8 Hz, 1H), 3.74 (s, 3H), 3.67 (s, 3H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 168.8, 166.9, 156.3, 142.4, 139.8, 134.9, 132.0, 131.8, 129.4, 128.0, 126.3, 124.4, 122.9, 120.7, 118.8, 113.2, 55.9, 52.0, 51.6 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>19</sub>H<sub>17</sub>NO<sub>4</sub>Na 346.1050, found 346.1047 (1 ppm).

Ethyl (Z)-2-(2-(1-oxoisoindolin-2-yl)phenyl)-3-phenylacrylate (2v): Brown solid,



yield = 26%, 19.9 mg. Mp: 94-96 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.89 (d, *J* = 7.2 Hz, 1H), 7.58-7.40 (m, 7H), 7.36 (d, *J* = 7.2 Hz, 1H), 7.28-7.25 (m, 4H), 7.13 (s, 1H), 4.72 (s, 2H), 3.62 (q, *J* = 7.2 Hz, 2H), 0.68 (t, *J* = 7.2 Hz, 3H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz,

CDCl<sub>3</sub>):  $\delta$ = 168.8, 168.0, 142.0, 137.6, 136.9, 136.6, 135.8, 132.8, 132.0, 131.8, 130.9, 129.6, 128.6, 128.4, 128.3, 128.1, 124.2, 122.9, 61.2, 52.7, 13.2 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>25</sub>H<sub>21</sub>NO<sub>3</sub>Na 406.1414, found 406.1414 (0 ppm).





136.8, 134.7, 132.4, 131.3, 129.3, 129.1, 128.8, 125.0, 123.2, 121.8, 53.6, 51.9 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>22</sub>H<sub>19</sub>NO<sub>5</sub>Na 400.1155, found 400.1158 (1 ppm).

Dimethyl 3,3'-(5-methyl-2-(1-oxoisoindolin-2-yl)-1,3-phenylene)(2E,2'E)-diacryla



-te (2x): White solid, yield = 19%, 14.9 mg. Mp: 241-243 °C.
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 7.96 (d, J = 7.6 Hz, 1H), 7.62
(dd, J = 7.6, 7.2 Hz, 1H), 7.55-7.44 (m, 6H), 6.42 (d, J = 16.0 Hz, 2H), 4.59 (s, 2H), 3.67 (s, 6H), 2.42 (s, 3H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>): δ = 168.8, 166.7, 141.5, 139.2, 134.4,

134.2, 132.3, 131.3, 129.8, 128.6, 124.8, 123.2, 121.4, 53.6, 51.8, 21.3 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>23</sub>H<sub>21</sub>NO<sub>5</sub>Na 414.1312, found 414.1314 (0 ppm).

1-(2-Hydroxyphenyl)-3-methyl-1*H*-pyrrole-2,5-dione (2y): White solid, yield = 92%,



67.2 mg. Mp: 194-196 °C. <sup>1</sup>H NMR (400 MHz, acetone- $d_6$ ):  $\delta$  = 7.90 (s, 1H), 7.83 (d, J = 7.6 Hz, 1H), 7.71-7.50 (m, 6H), 6.56 (d, J = 16.0 Hz, 1H), 4.94 (s, 2H), 3.92 (q, J = 7.2 Hz,

1H), 3.66 (s, 3H), 1.54 (d, J = 7.2 Hz, 3H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, acetone- $d_6$ ):  $\delta = 175.2, 168.2, 167.3, 143.3, 142.2, 141.2, 138.2, 133.4, 132.9, 132.8, 131.0, 129.12, 129.07, 127.4, 124.5, 124.3, 120.3, 54.0, 51.8, 45.5, 19.0 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>21</sub>H<sub>19</sub>NO<sub>5</sub>Na 388.1155, found 388.1150 (1 ppm).$ 



139.3, 134.7, 133.2, 131.9, 131.2, 131.0, 129.8, 129.5, 127.5, 124.2, 120.7, 51.9 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>18</sub>H<sub>13</sub>NO<sub>4</sub>Na 330.0737, found 330.0737 (0 ppm).

Methyl (*E*)-3-(2-(1,3-dioxooctahydro-2*H*-isoindol-2-yl)phenyl)acrylate (2zz): CO<sub>2</sub>Me White solid, yield = 71%, 88.7 mg. Mp: 108-110 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$ = 7.72 (d, *J* = 7.2 Hz, 1H), 7.50-7.39 (m, 3H), 7.16-7.10 (m, 1H), 6.41 (d, *J* = 16.0 Hz, 1H), 3.74 (s, 3H), 3.14-3.05 (m, 2H), 1.99-1.88 (m, 4H), 1.63-1.50 (m, 4H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$ = 178.7, 166.7, 138.9, 132.5, 131.6, 131.0, 129.7, 128.8, 127.2, 120.6, 51.8, 40.4, 24.2, 21.0 mm, HDMS (ESI) colord for IM + Nol<sup>+</sup>C. H. NO. No. 226, 1206

51.8, 40.4, 24.2, 21.9 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>18</sub>H<sub>19</sub>NO<sub>4</sub>Na 336.1206, found 336.1206 (0 ppm).

# **Deuteration experiments**

<u>Deuteration experiments of 1a:</u> In an oven dried Schlenk tube, to a solution of isoindolinone **1a** (0.1 mmol, 1 equiv.) in 2-MeTHF (0.45 mL) and D<sub>2</sub>O (0.05 mL) was added the combined solids:  $[RuCl_2(p-cymene)]_2$  (5 mol%), AgSbF<sub>6</sub> (20 mol%) and Cu(OAc)<sub>2</sub> (1 equiv.). The Schlenk tube was sealed with a Teflon cap leaving the tap open to air and it was heated to 100 °C for 15 h. The reaction mixture was diluted in EtOAc and filtered using a silica plug eluting with EtOAc. The solvent was removed *in vacuo* and the crude mixture was purified by column chromatography (*n*-heptane/EtOAc, 4/1 to 1/1, *v/v*) to give the product as a white solid 90% deuterium incorporation according to <sup>1</sup>H NMR spectroscopy studies.

<u>Deuteration experiments of 1z</u>: In an oven dried Schlenk tube, to a solution of *N*-phenylphthalimide **1z** (0.1 mmol, 1 equiv.) in 2-MeTHF (0.45 mL) and D<sub>2</sub>O (0.05 mL) was added the combined solids: [RuCl<sub>2</sub>(*p*-cymene)]<sub>2</sub> (5 mol%), AgSbF<sub>6</sub> (20 mol%) and Cu(OAc)<sub>2</sub> (1 equiv.). The Schlenk tube was sealed with a Teflon cap leaving the tap open to air and it was heated to 100 °C for 15 h. The reaction mixture was diluted in EtOAc and filtered using a silica plug eluting with EtOAc. The solvent was removed *in vacuo* and the crude mixture was purified by column chromatography (*n*-heptane/EtOAc, 4/1 to 1/1, *v*/*v*) to give the product as a white solid with 7.5% deuterium incorporation according to <sup>1</sup>H NMR spectroscopy studies.

Synthesis of Ru-1:  $[RuCl_2(p-cymene)]_2$  (0.05 mmol, 0.5 equiv.), 1a (0.1 mmol, 1 equiv.) and AgSbF<sub>6</sub> (0.2 mmol, 2 equiv.) were mixed in THF (0.5 mL) and stirred at 55 °C over 3 days. Once at room temperature, the reaction mixture was filtered over celite to remove AgCl. After solvents evaporation, NMR analysis indicated the presence of Ru-1 and 1a in a 86:14 ratio.

*Characterization of Ru-1:* Brown solid, yield = 86%. Mp: >250 °C. <sup>1</sup>H NMR (400)



MHz, THF- $d_8$ ):  $\delta$  (assignment by COSY, HSQC and HMBC) = 7.94 (d, J = 7.7 Hz, 1H, H<sub>d</sub>), 7.82-7.85 (m, 3H, H<sub>f</sub> and H<sub>c</sub>,), 7.77 (d, J = 7.6 Hz, 1H, H<sub>g</sub>), 7.64 (t, J= 7.4 Hz, 1H, H<sub>e</sub>), 7.06 (t, J = 6.4 Hz, 2H, H<sub>b</sub>), 6.98 (s,

4H, H<sub>h</sub> and H<sub>i</sub>), 6.89 (t, J = 5.8 Hz, 1H, H<sub>a</sub>), 5.15 (s, 2H), 2.99 (sept, J = 6.8 Hz, 1H, CH), 2.46 (s, 3H, Me), 1.34 (d, J = 6.9 Hz, 6H, Me) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, THF- $d_8$ ):  $\delta$  (assignment by COSY, HSQC and HMBC) = 169.22 (C=O), 141.65 (*ipso*-C<sub>k</sub>), 135.03 (C-H<sub>f</sub>), 129.51 (*ipso*-C<sub>j</sub>), 129.09 (C-H<sub>e</sub>), 124.56 (C-H<sub>d</sub>), 123.93 (C-H<sub>g</sub>), 122.88 (*ipso*-C-N), 121.61 (*ipso*-C of *para*-cymene), 112.24 (*ipso*-C of *para*-cymene), 93.96 (2 x C-Hi or C-H<sub>h</sub>), 93.70 (2 x C-H<sub>b</sub>), 91.49 (2 x C-H<sub>h</sub> or C-H<sub>i</sub>), 90.79 (C-H<sub>a</sub>),

80.24 (2 x C-H<sub>c</sub>), 50.31 (CH<sub>2</sub>), 32.02 (CH), 21.65 (2 x CH<sub>3</sub>), 18.37 (CH<sub>3</sub>) ppm. <sup>19</sup>F{<sup>1</sup>H} NMR (376 MHz, THF- $d_8$ ):  $\delta$  = -126 (m) ppm. HRMS (ESI) calcd. for [M]<sup>2+</sup> C<sub>24</sub>H<sub>25</sub>NO<sup>102</sup>Ru 222.5484, found 222.5484 (0 ppm); calcd. for [M + SbF<sub>6</sub>]<sup>+</sup> C<sub>24</sub>H<sub>25</sub>NOF<sub>6</sub><sup>102</sup>Ru<sup>121</sup>Sb 679.9917, found 679.9918 (0 ppm); calcd. for [SbF<sub>6</sub>]<sup>-</sup> F<sub>6</sub><sup>121</sup>Sb 234.8948, found 234.8947 (0 ppm).

# General procedures of derivatization reactions and characterization of 3, 4, 5 and 6.

Synthesis and characterization of 3: To a solution of 2k (0.2 mmol, 1.0 equiv.) in H<sub>2</sub>O (0.5 mL) and MeOH (0.5 mL) was added KOH (0.22 mmol, 1.1 equiv.) and the reaction mixture was stirred at 50°C overnight. The mixture was brought to pH 1 with HCl 1 M and, then, it was extracted with CH<sub>2</sub>Cl<sub>2</sub>(3 x 10 mL). The organic phase was then washed with brine (30 mL) and it was dried over MgSO<sub>4</sub>. The resulting mixture was concentrated *in vacuo* to give the product **3** (58.7 mg, 99% yield).

(*E*)-3-(5-Methyl-2-(1-oxoisoindolin-2-yl)phenyl)acrylic acid (3): White solid, yield  $CO_2H$  = 99%, 58.7 mg. Mp > 260 °C dec. <sup>1</sup>H NMR (400 MHz, acetone-*d*<sub>6</sub>):  $\delta$  = 7.81 (d, *J* = 7.6 Hz, 1H), 7.76 (s, 1H), 7.70-7.55 (m, 4H), 7.42-7.35 (m, 2H), 6.51 (d, *J* = 16.0 Hz, 1H), 4.90 (s, 2H), 2.44 (s, 3H) ppm. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = 7.80-7.77 (m, 2H), 7.73-7.67 (m, 2H), 7.58 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.42-7.33 (m, 3H), 6.51 (d, *J* = 16.0 Hz, 1H), 4.88 (s, 2H), 2.39 (s, 3H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = 167.7, 167.1, 142.3, 139.3, 137.7, 135.4, 132.0, 131.7, 131.5, 131.3, 128.2, 127.9, 127.4, 123.6, 123.4, 120.6, 53.2, 20.6 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>18</sub>H<sub>15</sub>NO<sub>3</sub>Na 316.0944, found 316.0947 (1 ppm).

Synthesis and characterization of 4: A schlenk tube was charged with 2k (0.2 mmol, 1.0 equiv.) and anhydrous calcium chloride (0.4 mmol, 2.0 equiv.). The tube was

protected under argon and ammonia in methanol solution (7 N, 2 mmol, 10.0 equiv.) was added. The tube was sealed and heated at 80 °C overnight. The mixture was cooled to room temperature and the solvent was evaporated *in vacuo*. The residue was dissolved in water (30 mL) and it was extracted with dichloromethane (2 x 20 mL). The combined organic layer was dried over MgSO<sub>4</sub> and concentrated. The desired product **4** (36.9 mg, 63% yield) was obtained after purification by column chromatography.

(*E*)-3-(5-Methyl-2-(1-oxoisoindolin-2-yl)phenyl)acrylamide (4): White solid, yield  $= 63\%, 36.9 \text{ mg. Mp: } 171-173 \text{ °C. }^{1}\text{H NMR (400 MHz, DMSO-} d_6): \delta = 7.79 \text{ (d, } J = 7.6 \text{ Hz, } 1\text{H}), 7.72-7.66 \text{ (m, } 2\text{H}), 7.60-7.56 \text{ (m, } 2\text{H}), 7.52 \text{ (s, } 1\text{H}), 7.38 \text{ (d, } J = 8.0 \text{ Hz, } 1\text{H}), 7.31 \text{ (d, } J = 7.6 \text{ Hz, } 1\text{H}), 7.23 \text{ (d, } J = 16.0 \text{ Hz, } 1\text{H}), 7.11 \text{ (s, } 1\text{H}), 6.62 \text{ (d, } J = 16.0 \text{ Hz, } 1\text{H}), 4.83 \text{ (s, } 2\text{H}), 2.39 \text{ (s, } 3\text{H}) \text{ ppm. }^{13}\text{C}\{^{1}\text{H}\} \text{ NMR (100 MHz, DMSO-} d_6): \delta = 167.1, 166.5, 142.3, 137.6, 135.2, 134.6, 132.6, 132.0, 131.5, 130.8, 128.3, 128.2, 126.7, 123.8, 123.6, 123.3, 53.3, 20.7 \text{ ppm. HRMS (ESI) calcd. for [M + Na]^+ C_{18}\text{H}_{16}\text{N}_2\text{O}_2\text{Na } 315.1104, \text{ found } 315.1107 \text{ (1 ppm)}.$ 

Synthesis and characterization of 5: To a mixture of 2k (0.2 mmol, 1.0 equiv.) and Na<sub>2</sub>CO<sub>3</sub> (0.2 mmol, 1.0 equiv.) in MeOH (0.5 mL) was added ethanolamine (1 mmol, 5.0 equiv.). The reaction mixture was heated to reflux overnight before being allowed to return to room temperature. The reaction mixture was diluted in MeOH (10 mL) and the remaining solids were filtered. The filtrate was concentrated and the product **5** (54.6 mg, 77% yield) was purified by silica gel column chromatography (acetone/*n*-hexanes, 1/4 to 1/1, v/v).
#### (E)-N-(2-Hydroxyethyl)-3-(5-methyl-2-(1-oxoisoindolin-2-yl)phenyl)acrylamide

CONHCH<sub>2</sub>CH<sub>2</sub>OH (5): White solid, yield = 77%, 54.6 mg. Mp: 245-247 °C. <sup>1</sup>H NMR (400 MHz, DMSO- $d_6$ ):  $\delta$  = 8.12 (t, J = 6.0 Hz, 1H), 7.79 (d, J = 7.6 Hz, 1H), 7.72-7.66 (m, 2H), 7.60-7.55 (m, 2H), 7.38 (d, J = 8.0 Hz, 1H), 7.31 (d, J = 8.0 Hz, 1H), 7.23 (d, J = 15.6 Hz, 1H), 6.68

(d, J = 15.6 Hz, 1H), 4.83 (s, 2H), 4.71 (t, J = 5.2 Hz, 1H), 3.42 (td, J = 6.0, 5.2 Hz, 2H), 3.19 (td, J = 5.6, 6.0 Hz, 2H), 2.39 (s, 3H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, DMSOd<sub>6</sub>):  $\delta = 167.1, 164.8, 142.2, 137.6, 135.1, 134.0, 132.7, 132.0, 131.5, 130.8, 128.24, 128.22, 126.7, 123.8, 123.6, 123.3, 59.8, 53.2, 41.6, 20.8 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>20</sub>H<sub>20</sub>N<sub>2</sub>O<sub>3</sub>Na 359.1366, found 359.1367 (0 ppm).$ 

Synthesis and characterization of 6: To an oven dried Schlenk tube, 2k (0.2 mmol, 1.0 equiv.), palladium 10% on activated carbon (10 mg) and MeOH (1 mL) were added. Hydrogen gas was bubbled through the reaction mixture using a balloon. This was repeated twice before the Schlenk tube was sealed and a balloon of hydrogen gas was placed through the septum. The reaction was left to stir overnight at room temperature. Once TLC indicated completion of the reaction, the mixture was diluted in EtOAc and filtered through a plug of celite eluting with EtOAc. The filtrate was concentrate *in vacuo* to give the product **6** (61.9 mg, 99% yield).

Methyl 3-(5-methyl-2-(1-oxoisoindolin-2-yl)phenyl)propanoate (6): Colorless oil,



yield = 99%, 61.9 mg. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.93 (d, J = 7.2 Hz, 1H), 7.59 (ddd, J = 7.2, 7.2, 1.2 Hz, 1H), 7.51 (dd, J = 7.6, 7.6 Hz, 2H), 7.15 (s, 1H), 7.11 (d, J = 1.2 Hz, 2H),

4.73 (s, 2H), 3.58 (s, 3H), 2.87 (t, J = 8.0 Hz, 2H), 2.65 (t, J = 8.0 Hz, 2H), 2.36 (s, 3H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta = 173.4$ , 168.3, 141.7, 138.7, 138.5, 134.2, 132.4, 131.7, 130.4, 128.3, 127.9, 124.3, 122.9, 53.8, 51.6, 34.3, 26.4, 21.3 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>19</sub>H<sub>19</sub>NO<sub>3</sub>Na 332.1257, found 332.1257 (0 ppm). *Crystallographic details:* CCDC 1895843-1895847 (**2g, 2h, 2l, 2t, 2v**) contains the supplementary crystallographic data for this chapter. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data\_request/cif, or by emailing data\_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

#### 5.7 References

- (a) K. M. Engle, T.-S. Mei, M. Wasa, J.-Q. Yu, Acc. Chem. Res. 2012, 45, 788.
  (b) S. De Sarkar, W. Liu, S. I. Kozhushkov, L. Ackermann, Adv. Synth. Catal.
  2014, 356, 1461. (c) Y. Yang, K. Li, Y. Cheng, D. Wan, M. Li, J. You, Chem. Commun. 2016, 52, 2872. (d) C. Sambiagio, D. Schoenbauer, R. Blieck, T. Dao-Huy, G. Pototschnig, P. Schaaf, T. Wiesinger, M. F. Zia, J. Wencel-Delord, T. Besset, B. U. W. Maes, M. Schnuerch, Chem. Soc. Rev. 2018, 47, 6603. (e) P. B. Arockiam, C. Bruneau, P. H. Dixneuf, Chem. Rev. 2012, 112, 5879.
- [2] (a) J. Yamaguchi, A. D. Yamaguchi, K. Itami, *Angew. Chem. Int. Ed.* 2012, *51*, 8960. (b) J. Wencel-Delord, F. Glorius, *Nature Chem.* 2013, *5*, 369. (c) T. Cernak, K. D. Dykstra, S. Tyagarajan, P. Vachal, S. W. Krska, *Chem. Soc. Rev.* 2016, *45*, 546.
- [3] For reviews, see: (a) R.-Y. Zhu, M. E. Farmer, Y.-Q. Chen, J.-Q. Yu, Angew. Chem. Int. Ed. 2016, 55, 10578. (b) Q.-Z. Zheng, N. Jiao, Tetrahedron Lett. 2014, 55, 1121. (c) R. Das, G. S. Kumar, M. Kapur, Eur. J. Org. Chem. 2017, 5439.
- [4] For reviews, see: (a) E. N. da Silva Junior, G. A. M. Jardim, R. S. Gomes, Y.F. Liang, L. Ackermann, *Chem. Commun.* 2018, *54*, 7398. (b) D. Kang, K.
  Ahn, S. Hong, *Asian J. Org. Chem.* 2018, *7*, 1136.

- [5] Modern Heterocyclic Chemistry, Eds.: J. Alvarez-Builla, J. J. Vaquero, J. Barluenga, Wiley-CH, Weinheim, 2011.
- [6] (a) D. Kalyani, N. R. Deprez, L. V. Desai, M. S. Sanford, J. Am. Chem. Soc. 2005, 127, 7330. (b) C. S. Yeung, X. Zhao, N. Borduas, V. M. Dong, Chem. Sci. 2010, 1, 331. (c) D. Kalyani, K. B. McMurtrey, S. R. Neufeldt, M. S. Sanford, J. Am. Chem. Soc. 2011, 133, 18566. (d) S. R. Neufeldt, M. S. Sanford, Adv. Synth. Catal. 2012, 354, 3517. (e) S. R. Neufeldt, C. K. Seigerman, M. S. Sanford, Org. Lett. 2013, 15, 2302. (f) D. Li, N. Xu, Y. Zhang, L. Wang, Chem. Commun. 2014, 50, 14862. (g) Y. Huang, D. Wu, J. Huang, Q. Guo, J. Li, J. You, Angew. Chem. Int. Ed. 2014, 53, 12158. (h) P. Gao, W. Guo, J. Xue, Y. Zhao, Y. Yuan, Y. Xia, Z. Shi, J. Am. Chem. Soc. 2015, 137, 12231. (i) P. Gao, L. Liu, Z. Shi, Y. Yuan, Org. Biomol. Chem. 2016, 14, 7109. (j) G. Tan, Q. You, J. You, ACS Catal. 2018, 8, 8709.
- [7] (a) J. A. Leitch, P. B. Wilson, C. L. McMullin, M. F. Mahon, Y. Bhonoah, I. H. Williams, C. G. Frost, *ACS Catal.* 2016, *6*, 5520. (b) J. A. Leitch, H. P. Cook, Y. Bhonoah, G. C. Frost, *J. Org. Chem.* 2016, *81*, 10081. (c) W. Ma, H. Dong, D. Wang, L. Ackermann, *Adv. Synth. Catal.* 2017, *359*, 966.
- [8] (a) D. Kalyani, M. S. Sanford, Org. Lett. 2005, 7, 4149; (b) L. V. Desai, H. A. Malik, M. S. Sanford, Org. Lett. 2006, 8, 1141. (c) D. Kalyani, A. R. Dick, W. Q. Anani, M. S. Sanford, Tetrahedron 2006, 62, 11483. (d) K. H. Ng, A. S. C. Chan, W.-Y. Yu, J. Am. Chem. Soc. 2010, 132, 12862. (e) D. Lee, Y. Kim, S. Chang, J. Org. Chem. 2013, 78, 11102. (f) J. Ryu, J. Kwak, K. Shin, D. Lee, S. Chang, J. Am. Chem. Soc. 2013, 135, 12861. (g) V. Pascanu, F. Carson, M. V. Solano, J. Su, X. Zhou, M. J. Johansson, B. Martin-Matute, Chem. Eur. J. 2016, 22, 3729.
- [9] (a) M. H. Norman, D. J. Minick, G. C. Rigdon, *J. Med. Chem.* 1996, *39*, 149.
  (b) G. W. Muller, R. Chen, S.-Y. Huang, L. G. Corral, L. M. Wong, R. T.

Patterson, Y. Chen, G. Kaplan, D. I. Stirling, *Bioorg. Med. Chem. Lett.* **1999**, 9, 1625.

- [10] (a) S. Nomura, K. Endo-Umeda, A. Aoyama, M. Makishima, Y. Hashimoto, M. Ishikawa, ACS Med. Chem. Lett. 2015, 6, 902. (b) S. Nomura, K. Endo-Umeda, M. Makishima, Y. Hashimoto, M. Ishikawa, ChemMedChem 2016, 11, 2347. (c) S. Nomura, K. Endo-Umeda, S. Fujii, M. Makishima, Y. Hashimoto, M. Ishikawa, Bioorg. Med. Chem. Lett. 2018, 28, 796.
- [11] Y. Kanda, H. Ando, K. Kawashima, T. Sugita, M. Suzuki, H. Tagaya, T. Nakazato, Y. Yamashita, T. Takahashi, S. Nara, H. Nakamura, PCT Int. Appl. 2006, WO 2006080450 A1 20060803.
- [12] S. A. Biller, R. M. Lawrence, M. A. Pross, Statutory Invent. Regist. 1998, US 1729 H 19980505.
- [13] (a) T. Kitamura, Y. Fujiwara, Comp. Organomet. Chem. III, 2007, 10, 213. (b)
  F. Kakiuchi, Topics Organomet. Chem. 2007, 24, 1. (c) I. V. Seregin, V. Gevorgyan, Chem. Soc. Rev. 2007, 36, 1173. (d) E. M. Beck, M. J. Gaunt, Topics Curr. Chem. 2010, 292, 85. (e) S. Messaoudi, J.-D. Brion, M. Alami, Eur. J. Org. Chem. 2010, 6495. (f) S. I. Kozhushkov, L. Ackermann, Chem. Sci. 2013, 4, 886. (g) L. Zhou, W. Lu, Chem. Eur. J. 2014, 20, 634. (h) T. Satoh, M. Miura, Metal-Catalyzed Cross-Coupling Reactions and More, 2014, 3, 1389. (i) C. Bruneau, P. H. Dixneuf, Topics Organomet. Chem. 2016, 55, 137. (j) S. Bag, D. Maiti, Synthesis 2016, 48, 804. (k) W. Ma, P. Gandeepan, J. Li, L. Ackermann, Org. Chem. Front. 2017, 4, 1435. (l) M. Petrini, Chem. Eur. J. 2017, 23, 16115.
- [14] R. Manikandan, M. Jeganmohan, Chem. Commun. 2017, 53, 8931.
- [15] (a) M. Sonoda, F. Kakiuchi, N. Chatani, S. Murai, *Bull. Chem. Soc. Jpn.* 1997, 70, 3117. (b) K. Padala, M. Jeganmohan, *Org. Lett.* 2011, 13, 6144. (c) K. Padala, M. Jeganmohan, *Org. Lett.* 2012, 14, 1134. (d) K. Padala, S. Pimparkar, P. Madasamy, M. Jeganmohan, *Chem. Commun.* 2012, 48, 7140.

(e) J. Li, C. Kornhaass, L. Ackermann, *Chem. Commun.* 2012, 48, 11343. (f)
M. C. Reddy, M. Jeganmohan, *Eur. J. Org. Chem.* 2013, 1150. (g) W. Ma, L. Ackermann, *Chem. Eur. J.* 2013, 19, 13925. (h) M. C. Reddy, M. Jeganmohan, *Chem. Commun.* 2015, 51, 10738. (i) R. Manikandan, P. Madasamy, M. Jeganmohan, *ACS Catal.* 2016, 6, 230.

- [16] (a) X.-H. Hu, J. Zhang, X.-F. Yang, Y.-H. Xu, T.-P. Loh, J. Am. Chem. Soc.
  2015, 137, 3169. (b) J. Zhang, T.-P. Loh, Chem. Commun. 2012, 48, 11232.
- [17] M. R. Lunn, D. E. Root, A. M. Martino, S. P. Flaherty, B. P. Kelley, D. D. Coovert, A. H. Burghes, N. T. Man, G. E. Morris, J. Zhou, E. J. Androphy, C. J. Sumner, B. R. Stockwell, *Chem. Biol.* 2004, *11*, 1489.
- [18] (a) M. Pichette Drapeau, L. J. Goossen, *Chem. Eur. J.* 2016, 22, 18654. (b) G.
  Shi, Y. Zhang, *Adv. Synth. Catal.* 2014, 356, 1419.
- [19] For [Ru(*p*-cymene)(η<sup>6</sup>-arene)]<sup>2+</sup> complexes similar to Ru-1, see: (a) S. Suravajjala, J. R. Polam, L. C. Porter, *Organometallics* 1994, *13*, 37. (b) J. M. Wolff, W. S. Sheldrick, *J. Organomet. Chem.* 1997, *531*, 141. (c) A. J. Wiseman, R. G. Jones, M. J. Went, *J. Organomet. Chem.* 1997, *544*, 129. (d) J. R. Miura, J. B. Davidson, G. C. Hincapie, D. J. Burkey, *Organometallics* 2002, *21*, 584, (e) E. L. Velarde, R. A. Stephen, R. N. Mansour, L. T. Hoang, D. J. Burkey, *J. Am. Chem. Soc.* 2003, *125*, 1188. (f) H. S. Chae, D. J. Burkey, *Organometallics* 2003, *22*, 1761. (g) J. Dubarle-Offner, C. M. Clavel, G. Gontard, P. J. Dyson, H. Amouri, *Chem. Eur. J.* 2014, *20*, 5795.
- [20] J. Zhang, R. Shrestha, J. F. Hartwig, P. Zhao, Nature Chem. 2016, 8, 1144.
- [21] (a) C. Bruneau, R. Gramage-Doria, Adv. Synth. Catal. 2016, 358, 3847. (b) R.
  Gramage-Doria, S. Achelle, C. Bruneau, F. Robin-le Guen, V. Dorcet, T.
  Roisnel, J. Org. Chem. 2018, 83, 1462.
- [22] Y. Zhou, P. Chen, X. Lv, J. Niu, Y. Wang, M. Lei, L. Hu, *Tetrahedron Lett.* 2017, 58, 2232.

[Part of this chapter has been published in J. Org. Chem. 2019, 84, 12893-12903]

### Chapter 6: Selective Ruthenium-catalyzed C-H bond arylation with isoindolinone serving as a weak directing group

#### 6.1 Introduction

Isoindolinones are an important class of compounds which combine a benzene ring fused with a five-membered cyclic tertiary amide.<sup>1</sup> In particular, *N*-arylisoindolinones are present in many relevant pharmaceutical and medicinal compounds<sup>2</sup> as well as building blocks for pigments and other molecular materials.<sup>3</sup> For instance, indoprofen (**A**) displays anti-inflammatory activity,<sup>4</sup> DWP205190 (**B**) is known to be an inhibitor for the production of tumor necrosis factor TNF- $\alpha^5$  and **C** behaves as a potent and selective 5-HT<sub>2C</sub> antagonist (Figure 6.1).<sup>6</sup> Consequently, the synthesis to access molecular diversity arising from the isoindolinone motif is receiving increasing attention.<sup>7</sup>



Figure 6.1 Examples of important *N*-arylisoindolinones.

In particular, the use of weak directing groups in transition metal-catalyzed C-H bond functionalization<sup>8</sup> has emerged as a powerful strategy for implementation in the late-stage derivatizations of biologically active molecules in the last years.<sup>9</sup> In this context, C-C bond-forming reactions *via* transition metal-catalyzed C-H bond functionalization occupy a central place as they represent a sustainable approach compared to traditional Suzuki, Heck or Stille reaction that generate overstoichiometric amounts of organometallic species starting from highly pre-functionalized building blocks.<sup>10</sup>

#### Chapter 6

However, the use of N-substituted phenylbenzamides ( $Ar^1$ -CONR- $Ar^2$ ), the acyclic version of N-arylisoindolinones, as weak directing groups for the formation of new carbon-carbon bonds via transition metal-catalyzed C-H bond functionalization remains rare with limited examples reported to date (Scheme 6.1). For instance, Miura described а ruthenium-catalyzed hydroarylation of and co-workers N,N-diphenylbenzamide with diphenylacetylene in 2012 (Scheme 6.1, top).<sup>11</sup> Two years later, Glorius and co-workers reported a rhodium-catalyzed alkynylation of *N*-isopropyl **TIPS-EBX** (TIPS-EBX phenylbenzamide with = 1-[(triisopropylsilyl)ethynyl]-1,2-benziodoxol-3(1H)-one) as reagent (Scheme 6.1,  $(middle)^{12}$  and a ruthenium-catalyzed cyanation of N-methyl phenylbenzamide with NCTS (NCTS = N-cyano-N-phenyl-p-toluenesulfonamide) was developed by Ackermann and co-workers (Scheme 6.1, bottom).<sup>13</sup> In these three examples,<sup>11-13</sup> the C-H bond belonging to the benzamide aromatic ring A was the one that was functionalized (Scheme 6.1). These observations highlight the challenge to reverse the site-selectivity in order to discriminate between two similar aromatic C-H bonds where a carbon-carbon bond forming reaction can take place.<sup>11-14</sup> It is important to note that secondary amides (RCONH-R) behave differently than tertiary amides (RCONR<sub>2</sub>) when transiently coordinating to the metal catalyst throughout the catalytic cycle. Whereas in the former case the nitrogen atom strongly binds to the metal center due to amide tautomerization,<sup>15</sup> in the latter case it is the oxygen atom that weakly binds to the catalyst.<sup>16</sup> Furthermore, C-H bond arylation reactions occurring in the acetanilide aromatic ring **B** of tertiary phenylbenzamides are unknown to date, although transition metal-catalyzed C-H bond arylations with weak directing groups containing a single aromatic fragment have been reported.<sup>17</sup>

Chapter 6



Scheme 6.1 State-of-the-art for the site-selective transition metal-catalyzed carboncarbon bond forming reactions *via* C-H bond functionalizations of acyclic *N*substituted phenylbenzamides as weak directing groups.

In view of the need for methodologies available to target selective C-H bond functionalizations with biologically relevant molecules, site-selective rutheniumcatalyzed arylation reactions applied to the isoindolinone motif are herein reported in this chapter (Scheme 6.2). It was found that the carbonyl group of the cyclic tertiary amide turned out to act as an excellent weak directing group enforcing the catalysis to take place selectively at the *ortho* position of the acetanilide aromatic ring **B** employing readily available boronic acid derivatives and organotrifluoroborates as coupling partners (Scheme 6.2). The methodology was applied to the late-stage functionalization of a biologically relevant target: indoprofen **A** (Figure 6.1).



Scheme 6.2 Ru-catalyzed C-H bond arylations of *N*-arylisoindolinones with the cyclic amide behaving as weak directing group.

#### 6.2 Results and discussion

## 6.2.1 Optimization of the site-selective Ru-catalyzed C-H bond arylation with the isoindolinone serving as a weak directing group

Initially, and encouraged by the use of aryl boronic acids as coupling partners for ruthenium-catalyzed C-H bond arylation of tertiary benzamides containing a single aromatic fragment by Szostak and co-workers,<sup>16a</sup> N-phenylisoindolinone **1a** was reacted with phenylboronic acid as the aryl source under different reaction conditions in the presence of  $[RuCl_2(p-cymene)]_2$  as pre-catalyst to study the formation of arylated products (Table 6.1). First, the reaction conditions developed by Szostak were employed leading to 51% yield of the arylated product 2a, in which the C-H bond arylation occurred at the *ortho* position of the aromatic ring **B** (Table 6.1, entry 1). Gratifyingly, no C-H bond arylation occurred in the benzamide aromatic ring A according to the NMR, GC-MS and TLC analyses of the reaction mixture. Whereas the reaction conditions developed by Szostak are thought to proceed via a 5-membered ruthenacycle species,<sup>16a</sup> in our case, a 6-membered ruthenacycle species might form considering the outcome of the reaction. Unexpectedly, we noticed that the absence of water led to an increase of reactivity with 72% yield of targeted compound 2a (Table 6.1, entry 2). Changing THF as solvent for 2-MeTHF or NMP led to 2a in yields as low as 34% and 10%, respectively (Table 6.1, entries 3 and 4). The use of other solvents such as DMF, DCE, 1,4-dioxane, t-AmOH, toluene or acetonitrile completely inhibited the reaction (Table 6.1, entries 5-10). Reactions using different oxidants [Cu(OAc)<sub>2</sub>·H<sub>2</sub>O, (NH<sub>4</sub>)<sub>2</sub>S<sub>2</sub>O<sub>8</sub>, Ag<sub>2</sub>CO<sub>3</sub>, AgOAc] and triflate metal salts as additives [AgOTf, Zn(OTf)<sub>2</sub>] in place of Ag<sub>2</sub>O and Cu(OTf)<sub>2</sub> led to low yields of the product (Table 6.1, entries 11-16). In the presence of one equivalent of Cu(OTf)<sub>2</sub> instead of 20 mol%, the same reactivity was observed (Table 6.1, entry 17). Other ruthenium complexes such as  $[Ru(NC'Bu)_6](BF_4)_2$  and  $[Ru(p-cymene)(O_2CMes)_2]$  were catalytically unproductive (Table 6.1, entries 18 and 19). These observations suggest

	H O H A A A A A A A A A A A A A A A A A	B(OH) <sub>2</sub> [RuCl <sub>2</sub> AgSI solv	( <i>p</i> -cymene)] <sub>2</sub> (5 mol%) $pF_6$ , oxidant, additive vent, T, 20 h, Argon		
Entry	Oxidant	Additive	Solvent	T (°C)	Yield (%) <sup>b</sup>
1 <sup>c</sup>	Ag <sub>2</sub> O	Cu(OTf) <sub>2</sub>	THF	110	51
2	Ag <sub>2</sub> O	Cu(OTf) <sub>2</sub>	THF	110	72
3	Ag <sub>2</sub> O	Cu(OTf) <sub>2</sub>	2-MeTHF	110	34
4	Ag <sub>2</sub> O	Cu(OTf) <sub>2</sub>	NMP	110	10
5	Ag <sub>2</sub> O	Cu(OTf) <sub>2</sub>	DMF	110	trace
6	Ag <sub>2</sub> O	Cu(OTf) <sub>2</sub>	DCE	110	trace
7	Ag <sub>2</sub> O	Cu(OTf) <sub>2</sub>	1,4-dioxane	110	trace
8	Ag <sub>2</sub> O	Cu(OTf) <sub>2</sub>	<i>t</i> -AmOH	110	trace
9	Ag <sub>2</sub> O	Cu(OTf) <sub>2</sub>	Toluene	110	trace
10	Ag <sub>2</sub> O	Cu(OTf) <sub>2</sub>	CH₃CN	110	trace
11	Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O	Cu(OTf) <sub>2</sub>	THF	110	0
12	(NH <sub>4</sub> ) <sub>2</sub> S <sub>2</sub> O <sub>8</sub>	Cu(OTf) <sub>2</sub>	THF	110	0
13	Ag <sub>2</sub> CO <sub>3</sub>	Cu(OTf) <sub>2</sub>	THF	110	34
14	AgOAc	Cu(OTf) <sub>2</sub>	THF	110	9
15	Ag <sub>2</sub> O	AgOTf	THF	110	0
16	Ag <sub>2</sub> O	Zn(OTf) <sub>2</sub>	THF	110	0
179	d Ag <sub>2</sub> O	Cu(OTf) <sub>2</sub>	THF	110	75
18	⇒ Ag₂O	Cu(OTf) <sub>2</sub>	THF	110	0
19 <sup>/</sup>	Ag <sub>2</sub> O	Cu(OTf) <sub>2</sub>	THF	110	0
20	a Ag <sub>2</sub> O	Cu(OTf) <sub>2</sub>	THF	110	55
21	h Ag <sub>2</sub> O	Cu(OTf) <sub>2</sub>	THF	110	0
22	Ag <sub>2</sub> O	Cu(OTf) <sub>2</sub>	THF	110	trace
23		Cu(OTf) <sub>2</sub>	THF	110	trace
24	Ag <sub>2</sub> O		THF	110	13
25	Ag <sub>2</sub> O	Cu(OTf) <sub>2</sub>	THF	<del>9</del> 0	<b>74 (72)</b>
26	Ag <sub>2</sub> O	Cu(OTf) <sub>2</sub>	THF	70	66
27	Ag <sub>2</sub> O	Cu(OTf) <sub>2</sub>	THF	rt	59

Table 6.1	Optimization	of the	reaction	conditions. <sup>a</sup>
-----------	--------------	--------	----------	--------------------------

<sup>*a*</sup>Reaction conditions: **1a** (0.1 mmol), phenylboronic acid (0.25 mmol), catalysts (5 mol%), oxidant (100 mol%) and additive (20 mol%) are stirred in 0.5 mL of solvents for 20 h under Ar. <sup>*b*</sup>Determined by <sup>1</sup>H NMR spectroscopy against an internal standard (dibromomethane). The isolated yield is shown in parentheses. <sup>*c*</sup>3 equiv. of H<sub>2</sub>O. <sup>*d*</sup>1 equiv. of Cu(OTf)<sub>2</sub>. <sup>*e*</sup>[Ru(NC<sup>*t*</sup>Bu)<sub>6</sub>(BF<sub>4</sub>)<sub>2</sub>] as catalyst. <sup>*f*</sup>[Ru(*p*-cymene)(O<sub>2</sub>CMes)<sub>2</sub>] as catalyst. <sup>*g*</sup>Under air. <sup>*h*</sup>Without [RuCl<sub>2</sub>(*p*-cymene)]<sub>2</sub>. <sup>*k*</sup>Without AgSbF<sub>6</sub>.

that (i) the catalytically active species could involve *para*-cymene coordinated ruthenium complexes and (ii) the carboxylate anions inhibit the reactions to some extent (see also Table 6.1, entries 11 and 14). The reaction performed under air atmosphere

still afforded **2a** in 55% yield (Table 6.1, entry 20). Additionally, control experiments indicated the need of all reagents for the success of the reaction (Table 6.1, entries 21-24). We found that the reaction was also operating at temperatures lower than 110 °C. For instance, 74% yield of **2a** was obtained in a reaction conducted at 90 °C (Table 6.1, entry 25), 66% at 70 °C (Table 1, entry 26) and 59% at room temperature (Table 1, entry 27). This constitutes a unique example of ruthenium-catalyzed C-H bond arylation at room temperature and mild conditions using weak directing groups.<sup>18</sup>

# 6.2.2 Scope and limitations of the site-selective Ru-catalyzed C-H bond arylation with the isoindolinone serving as a weak directing group

Next, we applied the developed reaction conditions (Table 6.1, entry 2 and 25) to *N*-arylisoindolinones **1** and arylboronic acids containing both different substitution patterns in order to determine the scope and limitations for this transformation (Table 6.2). Isoindolinones para-substituted with methyl, methoxy and chloro groups were well tolerated leading to the corresponding arylated products 2b-2d in 60-86% yield. Notably, carboxylic acid ester groups were suitable for the ruthenium-catalyzed C-H bond arylation protocol affording 2e in 55% yield. Although ester groups are known to direct some ruthenium-catalyzed C-H bond functionalizations,<sup>19</sup> in the present case the isoindolinone core seems to be more appropriate for coordination to ruthenium and thus, it exclusively dictates the selectivity of the reaction. Unfortunately, nitrile-containing partners are not compatible with the catalysis (2f) as it appeared to be the case in other ruthenium-catalyzed C-H bond functionalizations as well.<sup>15-17</sup> Dioxolane-containing isoindolinone led to a single isomer 2g in 40% isolated yield. Methyl- and methoxysubstituted isoindolinones in meta position exclusively led to 2h and 2i in 55% and 59% yield, respectively. Moreover, the molecular structures of 2c, 2d and 2g were unambiguously established by single crystal X-ray diffraction studies (Table 6.2) which further supported the site- and regio-selectivity of the reaction.



**Table 6.2** Ru-catalyzed site-selective C-H bond arylation of differentN-arylisoindolinones 1 with phenylboronic acid.<sup>a,b</sup>

Furthermore, different substituted arylboronic acids were also investigated for this C-H bond arylation reaction (Table 6.3). *para*-Substituted phenylboronic acids were used in this protocol. Methyl- and methoxy-containing products 2j and 2k were formed in comparable yields of 77% and 79%. In the case of reactions with phenylboronic acids containing halides in the *para* position, a trend was observed following the order of reactivity F < Cl < Br with 2l, 2m and 2n obtained in 19, 55 and 81% yield, respectively. The reaction also took place using *ortho*-methoxyphenylboronic acid and *ortho*-fluorophenylboronic acid as coupling partners leading to 2o and 2p in 44% and 55% yield, respectively. *meta*-Substituted phenylboronic acids are overall well tolerated with the only exception of the chloride derivative, for which 2s was obtained in 15% yield.

<sup>&</sup>lt;sup>a</sup>Reaction conditions: **1** (0.3 mmol), phenylboronic acid (0.75 mmol), [RuCl<sub>2</sub>(*p*-cymene)]<sub>2</sub> (5 mol%), AgSbF<sub>6</sub> (20 mol%), Ag<sub>2</sub>O (100 mol%) and Cu(OTf)<sub>2</sub> (20 mol%) in THF (1.5 mL) at 110 °C for 20 h under Ar. <sup>*b*</sup>Isolated yields (conversion in parentheses).





<sup>a</sup>Reaction conditions: **1** (0.3 mmol), phenylboronic acid (0.75 mmol), [RuCl<sub>2</sub>(*p*-cymene)]<sub>2</sub> (5 mol%), AgSbF<sub>6</sub> (20 mol%), Ag<sub>2</sub>O (100 mol%) and Cu(OTf)<sub>2</sub> (20 mol%) in THF (1.5 mL) at 90 °C for 20 h under Ar. <sup>b</sup>Isolated yields (conversion in parentheses).

On the other hand, the reactions with methyl-, methoxy- and nitro-containing boronic acids afforded the corresponding products **2q**, **2r** and **2t** in 74%, 32% and 60% yields, respectively. As such, the reaction seems to be sensitive to the electronic effects imposed by the phenylboronic acids substituted in *meta* position. The reaction for 3,5-

#### Chapter 6

dimethylphenylboronic acid gave rise to the corresponding arylated product 2r in 62% yield. Naphthalene-containing boronic acids efficiently reacted leading to 2v and 2w in 83% and 70% yield, respectively. The reaction with very bulky 1-naphthaleneboronic acid still afforded the corresponding product 2x but in a low yield of 10%. Moreover, the molecular structures of 2o, 2q and 2s were unambiguously established by single crystal X-ray diffraction studies (Table 6.3) which further supported the site- and regio-selectivity of the reaction.

Unfortunately, the reactions were sensitive to the steric hindrance found in some substrates. For instance, *ortho*-substituted substrates did not react as shown in the lack of formation of **2ya-2yd** (Figure 6.2). Moreover, we noted that very challenging boronic acids such as alkyl boronic ones (e.g. 1-butylboronic acid potentially leading to **2ye**, Figure 6.2) and heteroaromatic-containing ones (e.g. 3-thiopheneboronic acid potentially leading to **2yf**, Figure 6.2) did not react under the studied reaction conditions illustrating the current limitations of the methodology as it has been shown before for ruthenium-catalyzed C-H bond arylation using other directing groups.<sup>16a,17</sup>



Figure 6.2 Limitations encountered in the Ru-catalyzed C-H bond arylation (2ya-2yd), and unsuccessful attempts of Ru-catalyzed C-H bond alkylation (2ye) and (hetero)arylation (2yf).

It is worthy to mention that the traditional synthetic route towards this types of products require the use of over-stoichiometric amounts of metal zinc and highly prefunctionalized starting materials, which require an important number of additional steps that significantly decreases the overall yield and generates significant chemical wastes.<sup>20a</sup> As such, the presented ruthenium-catalyzed arylation is appealing in terms of an atom- and step-economy methodology. Importantly, analogs to products **2** have been studied against the spinal muscular atrophy.<sup>20b</sup>

Interestingly, no C-H bond bis-arylation was observed for any of the cases presented in Table 6.2 and 6.3. In some cases, the product resulting from the homocoupling of the boronic acid derivative was detected as illustrated by the isolation of **3** during the purification of **2s** (Figure 6.3). This homocoupling reaction appears to be a side reaction that may explain the relatively low yields obtained in some of the cases in Table 6.2 and 6.3.



Figure 6.3 Molecular structure of the by-product 3 obtained and isolated during the purification of product 2s.

To further demonstrate the potential and utility of this methodology, we decided to apply it to the late-stage functionalization of biologically relevant indoprofen (Figure 6.1 and Scheme 6.1), which is known to display anti-inflammatory activity.<sup>4</sup> Indoprofen contains a carboxylic acid that, unfortunately, is not compatible under our standard reaction conditions. However, it can readily be transformed into an ester group, which in turn, is compatible with our methodology (see **2e** in Table 6.2). Consequently, we performed a reaction sequence involving (1) esterification, (2) ruthenium-catalyzed C-H bond arylation and (3) ester hydrolysis. In this manner, the corresponding *ortho*-phenylated indoprofen **4** was obtained in 76% overall yield starting from indoprofen in three steps (Scheme 6.1). The regio- and site-selectivity observed in the resulting product was determined by multinuclear NMR spectroscopy studies. During the sequence, only one column chromatography was performed in the second step as the first and third steps are almost quantitative and require a trivial acid/base workup for the isolation of the products. As such, this sequence can be considered as sustainable to some extent.



**Scheme 6.1** Application of the ruthenium-catalyzed C-H bond arylation to the latestage functionalization of indoprofen. Reaction conditions: (i) H<sub>2</sub>SO<sub>4</sub> (cat.), EtOH, reflux, 12 h, 99%; (ii) PhB(OH)<sub>2</sub> (2.5 equiv.), [RuCl<sub>2</sub>(*p*-cymene)]<sub>2</sub> (5 mol%), AgSbF<sub>6</sub> (20 mol%), Ag<sub>2</sub>O (1 equiv.), Cu(OTf)<sub>2</sub> (20 mol%), THF, 110 °C, 20 h, 85%; (iii) NaOH (2 M), MeOH:THF, r.t., 12 h, 90%.

#### 6.3 Preliminary mechanistic studies

In order to study the relevance of the carbonyl group from the isoindolinone core as a weak directing group in the catalysis, we performed a control reaction with a substrate lacking any carbonyl group. Under the studied reaction conditions, isoindoline **5** did no afford any arylated product (Scheme 6.2, top). The same observations were made using the cyclic imides **6** and **7** (Scheme 6.2, middle and bottom). These findings suggest that (i) the carbonyl group of the isoindolinone **1** acts as a weak directing group throughout the catalytic cycle and (ii) the flexibility and less steric hindrance of cyclic amides when compared to cyclic imides enable to accommodate key ruthenacycle species.



Scheme 6.2 Control experiments.

Deuteration experiments using N-phenylisoindolinone **1a** were performed and they were not conclusive at this stage.

These data, combined with previous observations,<sup>16a,17,21</sup> enabled us to suggest a plausible reaction mechanism for the C-H bond arylation of *N*-arylisoindolinones (Scheme 6.3). Initially, chloride-free ruthenium(II) species coordinate to substrate **1** *via* the oxygen lone pair of the ketone group to from species **I**. Then, base-assisted C-H bond activation enabled by triflate anions lead to a six-membered ruthenacycle species **II**. In the presence of boronic acids, intermediate **III** forms that undergoes reductive elimination giving product **2** and the resulting ruthenium(0) species are regenerated into active ruthenium(II) species upon oxidation with Ag<sub>2</sub>O.



Scheme 6.3 Proposed catalytic cycle.

#### 6.4 Additional experiments with other aryl sources

In addition, we reasoned that organotrifluoroborates, which are nowadays well recognized as efficient coupling partners in cross-coupling chemistry,<sup>22</sup> may eventually be used for ruthenium-catalyzed C-H bond arylation reactions as well. As a proof of concept, *N*-phenylisoindolinone **1a** was submitted to our standard reaction conditions

#### Chapter 6

but employing potassium phenyltrifluoroborate as the aryl source for the C-H bond functionalization instead of phenylboronic acid. Gratifyingly, the reaction was equally efficient leading to the mono-arylated product **2a** in 68% yield (Scheme 6.4).



Scheme 6.4 Ru-catalyzed C-H bond arylation of *N*-phenylisoindolinone 1a with potassium phenyltrifluoroborate as the aryl source

Finally, for comparison purposes, *N*-phenylisoindolinone **1a** was submitted to the reaction conditions traditionally used for ruthenium-catalyzed C-H bond arylation reactions using strong nitrogen-containing directing groups.<sup>23</sup> They consisted of  $[RuCl_2(p-cymene)]_2$  (5 mol%), KOAc (20 mol%), K<sub>2</sub>CO<sub>3</sub> as base, bromobenzene as aryl source in NMP as solvent at 150 °C (Scheme 6.5). Under these reaction conditions, the starting material **1a** was found completely unreactive. This shows the true potential of boronic acids and related derivatives<sup>17</sup> as an alternative to replace aryl halides and aryl pseudo-halides (e.g. triflates) as coupling partners for challenging transition metal-catalyzed C-H bond arylation reactions, as it is the case here for weak directing groups.



Scheme 6.5 Attempt of Ru-catalyzed C-H bond arylation of *N*-phenylisoindolinone 1a with bromobenzene as the aryl source.

Furthermore, the same reaction conditions applied to *N*-phenylphthalimide **6** did not produce any arylated product so far, but *N*-phenylbenzamide was formed to some extent (Scheme 6.6). In Chapter 2, we have reported improved reaction conditions, and substrate scope and limitations regarding this unexpected ruthenium-catalyzed protodecarbonylation reaction.



Scheme 6.6 Attempt of Ru-catalyzed C-H bond arylation of *N*-phenylphthalimide 6 with bromobenzene as the aryl source.

#### **6.5** Conclusion

In summary, we have developed an efficient ruthenium-catalyzed C-H bond arylation protocol to selectively form unprecedented aromatic  $C(sp^2)-C(sp^2)$  bonds within the biologically relevant isoindolinone core. The reactions tolerate an important number of useful functional groups [e.g. fluoro, chloro, bromo, nitro, alkyl, (a)cyclic ethers, esters, polycyclic aromatic hydrocarbons] at different positions (*ortho, meta, para*) within the different coupling partners due to the mild conditions used in the catalysis. This catalysis represents an example of general site-selective transformation where the combination of the weak directing group (cyclic amide) with the ruthenium catalyst enables to discriminate between two aromatic C-H bonds having comparable bond dissociation energies. Moreover, mono-functionalized products are exclusively obtained in the above-described catalysis.

The previously neglected homocoupling side-products observed during the C-H bond arylation reaction are likely originating from a simultaneous reaction that competes with the C-H bond arylation. In short, this methodology shows the relevance of ruthenium catalysts enabling formation of six-membered ruthenacycle intermediates throughout the catalysis even with very weak directing groups in the substrate. In addition, and considering the availability of the developed ruthenium-based catalytic systems, one could expect manifold implementations of this strategy in the late-stage functionalization of potential drug candidates (as it is shown here with indoprofen) and

#### Chapter 6

(supra)molecular materials that feature such relevant organic skeleton or similar chemical motifs.

#### 6.6 Experimental details

General information. All reagents were obtained from commercial sources and used as supplied. All reactions were carried out in flame-dried glassware under argon atmosphere unless otherwise noted. Catalytic experiments were performed in Schlenktype flasks under argon atmosphere unless otherwise noted. Organic solutions were concentrated under reduced pressure using a rotary evaporator. Thin-layer chromatography (TLC) were carried out on 0.25 mm Merck silica gel (60-F254). Flash column chromatography was performed using silica gel Silica 60 M, 0.04-0.063 mm. N-methyl-2-pyrrolidone (NMP) was distilled under reduced pressure and stored under molecular sieves and argon atmosphere. Technical grade petroleum ether (40-60) and ethyl acetate were used for column chromatography. CDCl<sub>3</sub> was stored under nitrogen over molecular sieves. NMR spectra were recorded on an AVANCE III 400 spectrometer. <sup>1</sup>H NMR spectra were referenced to residual protiated solvent ( $\delta = 7.26$ ppm for CDCl<sub>3</sub>) and <sup>13</sup>C chemical shifts are reported relative to deuterated solvents ( $\delta$ = 77.0 ppm for CDCl<sub>3</sub>). The peak patterns are indicated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet, and br. for broad. GC-MS analyses were performed with a GCMS-QP2010S (Shimadzu) instrument with a GC-2010 equipped with a 30 m capillary column (Supelco, SLBTM-5ms, fused silica capillary column, 30 m x 0.25 mm x 0.25 mm film thickness), which was used with helium as the vector gas. The following GC conditions were used: initial temperature 80 °C for 2 minutes, then rate 20 °C/min until 280 °C and 280 °C for 28 minutes. HRMS were recorded on a Waters Q-Tof 2 mass spectrometer at the corresponding facilities of the CRMPO, Centre Régional de Mesures Physiques de l'Ouest, Université de Rennes 1. Melting points were performed on a LEICA VMHB Kofler system.

#### Synthesis of substrates 1.

<u>Method A:</u> A mixture of 2-formylbenzoic acid (5.0 mmol, 1 equiv.), amine (6.0 mmol, 1.2 equiv.), DABCO (10.0 mmol, 2 equiv.), HCOOH (1.25 mL), Pd(OAc)<sub>2</sub> (0.25 mmol, 5 mol%) in 1,4-dioxane (5 mL) was heated to 80 °C for 3h. After completion of the reaction, the mixture was cooled to room temperature, and diluted with DCM (50 mL). The solid was removed by filter, and the filtrate was washed with water (50 mL) and brine (50 mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/acetone = 5/1, v/v) to afford the desired product.



#### Characterization of substrates 1.

**2-(2-Fluorophenyl)isoindolin-1-one (1yc):** Prepared according to Method A starting from *o*-fluoroaniline in 76% isolated yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta = 7.97$  (d, J = 7.4 Hz, 1H), 7.67-7.60 (m, 2H), 7.52 (t, J = 7.5 Hz, 2H), 7.33- 7.27 (m, 1H), 7.25-7.18 (m, 2H), 4.88 (s, 2H) ppm. <sup>19</sup>F{<sup>1</sup>H} NMR (376 MHz, CDCl<sub>3</sub>):  $\delta = -120.5$  ppm. The spectral data match those previously reported.<sup>24</sup>

Synthesis and characterization of the other substrates 1, 5, 6 and 7 are described in the experimental details of Chapter 4 and Chapter 5.

#### General procedure for the ruthenium-catalyzed C-H bond arylation reaction.

*General procedure:* [RuCl<sub>2</sub>(*p*-cymene)]<sub>2</sub> (5 mol%), AgSbF<sub>6</sub> (20 mol%), Ag<sub>2</sub>O (0.3 mmol, 1.0 equiv.), Cu(OTf)<sub>2</sub> (20 mol%), 2-Phenylisoindolin-*1*-one **1a** (0.3 mmol, 1.0 equiv.), and phenylboronic acid (0.75 mmol, 2.5 equiv.) were taken in a 15 mL pressure

tube, which was equipped with a magnetic stirring bar. Solvent THF (2.5 mL) was added to the tube via syringe, and the reaction mixture was degassed with argon three times. The reaction mixture was allowed to stir at 90 °C or 110 °C for 20 h. After being cooled to ambient temperature, the reaction mixture was diluted with DCM and then filtered through Celite. After evaporation of the solvent *in vacuo*, the crude product was purified by column chromatography on silica gel (*n*-heptane/EtOAc: 10:1 to 5:1) to give the desired product **2a** as a solid.

#### Characterization of products (2).

**2-([1,1'-Biphenyl]-2-yl)isoindolin-1-one (2a):** White oil, yield = 72%, 61.6 mg. <sup>1</sup>H

NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.93 (d, *J* = 7.2 Hz, 1H), 7.52-7.43 (m, 6H), 7.40-7.38 (m, 2H), 7.32-7.24 (m, 4H), 4.17 (s, 2H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 169.0, 141.7, 139.9, 139.2,

135.9, 132.2, 131.7, 131.1, 129.1, 128.7, 128.6, 128.4, 128.3, 128.1, 127.6, 124.3, 122.7, 52.3 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>20</sub>H<sub>15</sub>NONa 308.1046, found 308.1050 (1 ppm).

2-(5-Methyl-[1,1'-biphenyl]-2-yl)isoindolin-1-one (2b): White solid, yield = 60%,



54.3 mg. Mp: 167-169 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.93 (d, *J* = 7.2 Hz, 1H), 7.51-7.44 (m, 2H), 7.40-7.35 (m, 3H), 7.31-7.22 (m, 6H), 4.16 (s, 2H), 2.44 (s, 3H) ppm. <sup>13</sup>C{<sup>1</sup>H}

NMR (100 MHz, CDCl<sub>3</sub>): *δ* = 169.1, 141.7, 139.7, 139.2, 138.2, 133.3, 132.3, 131.7, 131.6, 129.4, 128.9, 128.6, 128.4, 128.1, 127.5, 124.3, 122.7, 52.4, 21.3 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>21</sub>H<sub>17</sub>NONa 322.1202, found 322.1202 (0 ppm).

2-(5-Methoxy-[1,1'-biphenyl]-2-yl)isoindolin-1-one (2c): White solid, yield = 84%,

79.1 mg. Mp: 162-164 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.92 (d, *J* = 7.2 Hz, 1H), 7.51-7.43 (m, 2H), 7.41-7.36 (m, 3H), 7.31-7.22 (m, 4H), 7.01-6.98 (m, 2H), 4.14 (s, 2H), 3.86 (s,

3H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 169.2, 159.2, 141.6, 141.2, 139.0, 132.2, 131.5, 130.2, 128.6, 128.3, 128.0, 127.7, 124.2, 122.6, 116.1, 114.1, 55.7, 52.6 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>21</sub>H<sub>17</sub>NO<sub>2</sub>Na 338.1152, found 338.1153 (0 ppm).

2-(5-Chloro-[1,1'-biphenyl]-2-yl)isoindolin-1-one (2d): White solid, yield = 86%,



82.8 mg. Mp: 121-123 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$ = 7.91 (d, *J* = 7.2 Hz, 1H), 7.53-7.42 (m, 5H), 7.37-7.34 (m, 2H), 7.33-7.26 (m, 4H), 4.14 (s, 2H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz,

CDCl<sub>3</sub>):  $\delta$  = 169.1, 141.6, 141.4, 137.9, 134.6, 133.8, 131.92, 131.90, 131.0, 130.4, 128.9, 128.7, 128.3, 128.24, 128.16, 124.4, 122.8, 52.1 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>20</sub>H<sub>14</sub>NO<sup>35</sup>ClNa 342.0656, found 342.0658 (1 ppm).

Ethyl 6-(1-oxoisoindolin-2-yl)-[1,1'-biphenyl]-3-carboxylate (2e): White oil, yield =



55%, 59.2 mg. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.15 (d, *J* = 2.0 Hz, 1H), 8.12 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.92 (d, *J* = 7.2 Hz, 1H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.54-7.45 (m, 2H), 7.40

(dd, J = 8.0, 1.6 Hz, 2H), 7.35-7.27 (m, 4H), 4.41 (q, J = 7.2 Hz, 2H), 4.17 (s, 2H), 1.40 (t, J = 7.2 Hz, 3H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta = 168.9, 166.0, 141.6, 140.2, 139.4, 138.5, 132.6, 132.0, 131.9, 130.0, 129.7, 129.0, 128.4, 128.3, 128.0, 124.4, 122.8, 61.3, 51.9, 14.5 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>23</sub>H<sub>19</sub>NO<sub>3</sub>Na 380.1257, found 380.1259 (0 ppm).$ 

2-(4-Phenylbenzo[d][1,3]dioxol-5-yl)isoindolin-1-one (2g): White solid, yield = 40%,

39.8 mg. Mp: 212-214 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$ = 7.90 (d, *J* = 7.2 Hz, 1H), 7.51-7.41 (m, 4H), 7.32-7.23 (m, 4H), 6.95 (d, *J* = 8.0 Hz, 1H), 6.89 (d, *J* = 8.0 Hz, 1H), 6.02 (s, 2H), 4.17

(s, 2H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$ = 169.4, 147.3, 146.2, 141.6, 132.7, 132.2, 131.7, 130.0, 129.1, 128.7, 128.2, 128.1, 124.4, 122.69, 122.65, 122.55, 108.0, 101.9, 52.9 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>21</sub>H<sub>15</sub>NO<sub>3</sub>Na 352.0944, found 352.0947 (1 ppm).

2-(4-Methyl-[1,1'-biphenyl]-2-yl)isoindolin-1-one (2h): White oil, yield = 55%, 49.8



mg. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.93 (d, *J* = 6.8 Hz, 1H), 7.52-7.44 (m, 2H), 7.38-7.35 (m, 3H), 7.30-7.23 (m, 6H), 4.16 (s, 2H), 2.43 (s, 3H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 169.2, 141.7, 139.2, 138.8, 137.0, 135.7, 132.3, 131.7, 131.0,

129.6, 129.3, 128.7, 128.5, 128.1, 127.4, 124.3, 122.7, 52.4, 21.2 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>21</sub>H<sub>17</sub>NONa 322.1202, found 322.1205 (1 ppm).

2-(4-Methoxy-[1,1'-biphenyl]-2-yl)isoindolin-1-one (2i): White solid, yield = 59%,



55.6 mg. Mp: 142-144 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$ = 7.93 (d, *J* = 7.2 Hz, 1H), 7.52-7.44 (m, 2H), 7.38-7.34 (m, 3H), 7.29-7.20 (m, 4H), 7.03-6.99 (m, 2H), 4.17 (s, 2H), 3.85 (s, 3H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 169.0, 159.7, 141.7,

139.0, 136.7, 132.22, 132.18, 131.9, 131.7, 128.7, 128.5, 128.1, 127.2, 124.3, 122.7, 114.7, 113.8, 55.6, 52.2 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>21</sub>H<sub>17</sub>NO<sub>2</sub>Na 338.1152, found 338.1155 (1 ppm).

2-(4'-Methyl-[1,1'-biphenyl]-2-yl)isoindolin-1-one (2j): White solid, yield = 77%,

Me O N

68.8 mg. Mp: 132-134 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$ = 7.94 (d, J = 7.6 Hz, 1H), 7.53-7.42 (m, 6H), 7.29-7.26 (m, 3H), 7.10 (d, J = 7.2 Hz, 2H), 4.20 (s, 2H), 2.30 (s, 3H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$ = 169.0, 141.7, 139.8, 137.3, 136.2, 135.9, 132.3,

131.6, 131.2, 129.5, 129.1, 128.4, 128.29, 128.28, 128.1, 124.3, 122.8, 52.2, 21.2 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>21</sub>H<sub>17</sub>NONa 322.1202, found 322.1201 (0 ppm).

2-(4'-Methoxy-[1,1'-biphenyl]-2-yl)isoindolin-1-one (2k): White oil, yield = 79%,



74.5 mg. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.93 (d, *J* = 6.8 Hz, 1H), 7.51-7.41 (m, 6H), 7.33-7.28 (m, 3H), 6.83 (dd, *J* = 6.8, 2.0 Hz, 2H), 4.20 (s, 2H), 3.75 (s, 3H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 169.0, 159.1, 141.7, 139.5, 135.9, 132.3, 131.6, 131.4, 131.1,

129.6, 129.1, 128.3, 128.2, 128.1, 124.2, 122.8, 114.2, 55.2, 52.2 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>21</sub>H<sub>17</sub>NO<sub>2</sub>Na 338.1152, found 338.1147 (1 ppm).

2-(4'-Fluoro-[1,1'-biphenyl]-2-yl)isoindolin-1-one (2l): Yellow solid, yield = 19%,



16.9 mg. Mp: 108-110 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$ = 7.92 (d, J = 7.6 Hz, 1H), 7.54-7.43 (m, 6H), 7.38-7.30 (m, 3H), 7.01-6.96 (m, 2H), 4.21 (s, 2H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$ = 169.1, 162.4 (d,  $J_{C-F}$  = 245.4 Hz), 141.6, 139.1, 136.0, 135.1 (d,  $J_{C-F}$ 

F = 3.5 Hz), 132.1, 131.8, 131.1, 130.1 (d,  $J_{C-F} = 8.0$  Hz), 129.2, 128.9, 128.5, 128.3, 124.4, 122.8, 115.7 (d,  $J_{C-F} = 21.3$  Hz), 52.4 ppm. <sup>19</sup>F{<sup>1</sup>H} NMR (376 MHz, CDCl<sub>3</sub>):  $\delta$  = -114.6 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>20</sub>H<sub>14</sub>NOFNa 326.0952, found 326.0951 (0 ppm).





52.4 mg. Mp: 141-143 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$ = 7.92 (d, *J* = 7.6 Hz, 1H), 7.55-7.42 (m, 6H), 7.34-7.31 (m, 3H), 7.26 (d, *J* = 8.4 Hz, 2H), 4.23 (s, 2H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 169.0, 141.5, 138.9, 137.6, 135.9, 133.7, 132.0, 131.9, 131.0,

129.8, 129.2, 129.1, 128.9, 128.5, 128.3, 124.3, 122.8, 52.4 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>20</sub>H<sub>14</sub>NO<sup>35</sup>ClNa 342.0656, found 342.0657 (0 ppm).

2-(4'-Bromo-[1,1'-biphenyl]-2-yl)isoindolin-1-one (2n): White solid, yield = 81%,



88.7 mg. Mp: 138-140 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$ = 7.91 (d, J = 7.2 Hz, 1H), 7.55-7.40 (m, 8H), 7.32 (d, J = 7.2 Hz, 1H), 7.27 (ddd, J = 8.0, 2.8, 1.6 Hz, 2H), 4.24 (s, 2H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 169.0, 141.5, 138.8, 138.1, 135.8, 132.0,

131.9, 131.8, 130.9, 130.1, 129.2, 129.1, 128.5, 128.2, 124.3, 122.8, 122.0, 52.4 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>20</sub>H<sub>14</sub>NO<sup>79</sup>BrNa 386.0151, found 386.0155 (1 ppm).





41.3 mg. Mp: 120-122 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$ = 7.88 (d, *J* = 7.6 Hz, 1H), 7.51-7.40 (m, 6H), 7.30-7.22 (m, 3H), 6.91 (dd, *J* = 7.6, 7.2 Hz, 1H), 6.84 (d, *J* = 8.0 Hz, 1H), 4.24 (s, 2H),

3.66 (s, 3H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 168.2, 156.4, 141.7, 137.0, 136.3, 132.5, 132.1, 131.5, 131.1, 129.3, 128.5, 128.4, 128.1, 128.0, 127.5, 124.2, 122.6, 120.9, 110.8, 55.6, 52.0 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>21</sub>H<sub>17</sub>NO<sub>2</sub>Na 338.1152, found 338.1150 (0 ppm).

2-(2'-Fluoro-[1,1'-biphenyl]-2-yl)isoindolin-1-one (2p): White solid, yield = 55%,

49.7 mg. Mp: 153-155 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$ = 7.85 (d, J = 7.6 Hz, 1H), 7.53-7.42 (m, 6H), 7.39-7.32 (m, 2H), 7.27-7.21 (m, 1H), 7.10-7.01 (m, 2H), 4.39 (s, 2H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$ = 168.2, 159.4 (d,  $J_{C-F}$  = 245.0 Hz), 141.6, 136.9, 133.9, 132.1, 131.8 (d,  $J_{C-F}$  = 1.4 Hz), 131.7, 131.5 (d,  $J_{C-F}$  = 3.1 Hz), 129.6 (d,  $J_{C-F}$  = 8.0 Hz), 129.3, 128.4, 128.1, 127.9, 126.7 (d,  $J_{C-F}$  = 15.4 Hz), 124.4 (d,  $J_{C-F}$  = 3.6 Hz), 124.3, 122.7, 115.7 (d,  $J_{C-F}$  = 22.1 Hz), 52.3 (d,  $J_{C-F}$  = 1.4 Hz) ppm. <sup>19</sup>F{<sup>1</sup>H} NMR (376 MHz, CDCl<sub>3</sub>):  $\delta$  = -116.4 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>20</sub>H<sub>14</sub>NOFNa 326.0952, found 326.0952 (0 ppm).

```
2-(3'-Methyl-[1,1'-biphenyl]-2-yl)isoindolin-1-one (2q): White solid, yield = 74%,
```



66.7 mg. Mp: 146-148 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$ = 7.94 (d, J = 6.4 Hz, 1H), 7.52-7.40 (m, 6H), 7.27 (d, J = 7.6 Hz, 1H), 7.22 (s, 1H), 7.20-7.14 (m, 2H), 7.06 (d, J = 7.2 Hz, 1H), 4.18 (s, 2H), 2.26 (s, 3H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 169.0,

141.7, 139.9, 139.0, 138.3, 135.9, 132.2, 131.6, 131.0, 129.1, 129.0, 128.52, 128.48, 128.3, 128.2, 128.0, 125.4, 124.2, 122.7, 52.2, 21.4 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>21</sub>H<sub>17</sub>NONa 322.1202, found 322.1203 (0 ppm).

2-(3'-Methoxy-[1,1'-biphenyl]-2-yl)isoindolin-1-one (2r): White oil, yield = 32%,



30.7 mg. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.93 (d, *J* = 7.2 Hz, 1H), 7.53-7.42 (m, 6H), 7.29 (d, *J* = 7.2 Hz, 1H), 7.20 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.00-6.94 (m, 2H), 6.82-6.79 (m, 1H), 4.19 (s, 2H), 3.65 (s, 3H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 169.1, 159.7,

141.8, 140.5, 139.8, 135.9, 132.2, 131.7, 131.0, 129.8, 129.2, 128.8, 128.4, 128.2, 124.3, 122.8, 120.9, 114.0, 113.3, 55.3, 52.3 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>21</sub>H<sub>17</sub>NO<sub>2</sub>Na 338.1152, found 338.1149 (1 ppm).



14.8 mg. Mp: 128-130 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.93 (d, J = 7.2 Hz, 1H), 7.55-7.44 (m, 6H), 7.40 (s, 1H), 7.32 (d, J = 7.2 Hz, 1H), 7.28-7.23 (m, 2H), 7.18 (dd, J = 7.6, 7.6 Hz, 1H), 4.23 (s, 2H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 169.1, 141.6, 141.0,

138.7, 136.1, 134.6, 132.1, 131.9, 131.0, 130.0, 129.3, 129.2, 128.6, 128.5, 128.3, 127.8, 126.8, 124.4, 122.8, 52.5 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>20</sub>H<sub>14</sub>NO<sup>35</sup>ClNa 342.0656, found 342.0654 (1 ppm).

2-(3'-Nitro-[1,1'-biphenyl]-2-yl)isoindolin-1-one (2t): Yellow solid, yield = 60%,



58.8 mg. Mp: 226-228 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.25 (dd, *J* = 2.0, 2.0 Hz, 1H), 8.10 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.85 (d, *J* = 7.6 Hz, 1H), 7.73 (d, *J* = 7.6 Hz, 1H), 7.55-7.41 (m, 7H), 7.35 (d, *J* = 7.6 Hz, 1H), 4.36 (s, 2H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz,

CDCl<sub>3</sub>):  $\delta$ = 168.7, 148.4, 141.3, 141.0, 138.0, 136.1, 134.7, 132.0, 131.8, 130.9, 129.8, 129.6, 129.0, 128.7, 128.4, 124.3, 123.3, 122.8, 122.5, 52.8 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>20</sub>H<sub>14</sub>N<sub>2</sub>O<sub>3</sub>Na 353.0897, found 353.0898 (0 ppm).

2-(3',5'-Dimethyl-[1,1'-biphenyl]-2-yl)isoindolin-1-one (2u): White solid, yield =



62%, 58.7 mg. Mp: 169-171 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.94 (d, *J* = 7.2 Hz, 1H), 7.52-7.41 (m, 6H), 7.29 (d, *J* = 6.8 Hz, 1H), 6.99 (s, 2H), 6.88 (s, 1H), 4.17 (s, 2H), 2.19 (s, 6H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 169.1, 141.8, 139.9, 139.1, 138.2,

135.9, 132.3, 131.6, 131.1, 129.3, 129.1, 128.4, 128.2, 128.1, 126.2, 124.3, 122.7, 52.2, 21.3 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>22</sub>H<sub>19</sub>NONa 336.1359, found 336.1363 (1 ppm).

2-(2-(Naphthalen-2-yl)phenyl)isoindolin-1-one (2v): White solid, yield = 83%, 83.1

mg. Mp: 204-206 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.97-7.95 (m, 1H), 7.92 (s, 1H), 7.83-7.77 (m, 2H), 7.73 (d, *J* = 8.4 Hz, 1H), 7.60-7.57 (m, 1H), 7.56-7.44 (m, 8H), 7.19-7.17 (m, 1H), 4.17 (s, 2H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 169.1, 141.6,

139.7, 136.8, 136.2, 133.5, 132.6, 132.1, 131.6, 131.4, 129.2, 128.8, 128.34, 128.31, 128.2, 128.1, 127.7, 127.4, 126.5, 126.3, 126.2, 124.2, 122.8, 52.3 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>24</sub>H<sub>17</sub>NONa 358.1202, found 358.1206 (1 ppm).

2-(2-(6-Methoxynaphthalen-2-yl)phenyl)isoindolin-1-one (2w): Brown solid, yield

= 70%, 76.7 mg. Mp: 176-178 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$ = 7.96-7.94 (m, 1H), 7.82 (s, 1H), 7.69 (d, J = 9.2 Hz, 1H), 7.61 (d, J = 8.4 Hz, 1H), 7.58-7.55 (m, 1H), 7.53-7.44 (m, 6H), 7.20-7.18 (m, 1H), 7.12 (dd, J = 9.2, 2.8 Hz, 1H), 7.07 (d, J = 2.8 Hz, 1H), 4.16 (s, 2H), 3.89 (s, 3H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):

 $\delta$  = 169.2, 158.1, 141.7, 139.8, 136.2, 134.6, 133.9, 132.2, 131.7, 131.4, 129.7, 129.2, 129.1, 128.6, 128.4, 128.1, 127.2, 127.1, 124.3, 122.8, 119.2, 105.7, 55.4, 52.3 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>25</sub>H<sub>19</sub>NO<sub>2</sub>Na 388.1308, found 388.1310 (0 ppm).

2-(2-(Naphthalen-1-yl)phenyl)isoindolin-1-one (2x): Brown oil, yield = 10%, 9.8 mg.



<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.83-7.75 (m, 4H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.58-7.35 (m, 9H), 7.09 (d, *J* = 8.0 Hz, 1H), 4.02 (d, *J* = 16.8 Hz, 1H), 3.87 (d, *J* = 16.8 Hz, 1H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 168.6, 141.5, 137.9, 137.4, 136.7, 133.7,

132.5, 132.1, 131.7, 131.5, 128.9, 128.34, 128.30, 128.0, 127.7, 127.3, 126.4, 126.1, 125.8, 125.6, 124.2, 122.6, 52.2 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>24</sub>H<sub>17</sub>NONa 358.1202, found 358.1202 (0 ppm).

**3,3'-Dichloro-1,1'-biphenyl (3):** Colorless oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.55 (s, 2H), 7.45-7.42 (m, 2H), 7.40-7.33 (m, 4H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR CI (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 141.7, 135.0, 130.2, 128.0, 127.4, 125.4 ppm. MS (EI): m/z: 222 (M<sup>+</sup>, 100), 152 (77), 93 (20), 75 (22). The spectral data match those previously reported.<sup>25</sup>

General procedure for the late-stage arylation of indoprofen (4a, 4b and 4):

Indoprofen A was synthesized according to a literature procedure.<sup>26</sup>

Esterification step: Indoprofen A (140.7 mg, 0.5 mmol, 1 equiv.) and concentrated  $H_2SO_4$  (1 drop) were stirred together in EtOH (2 mL) under reflux during 12 hours with a Dean-Stark condenser. Back at room temperature, solid sodium bicarbonate was added and the reaction mixture was filtered and concentrated under vacuum to afford the carboxylic acid ethyl ester indoprofen intermediate (4a) in quantitative yield and it was used without further purification for the next step.

**Ru-catalyzed C-H bond arylation:**  $[RuCl_2(p-cymene)]_2$  (5 mol%), AgSbF<sub>6</sub> (20 mol%), Ag<sub>2</sub>O (0.5 mmol, 1.0 equiv.), Cu(OTf)<sub>2</sub> (20 mol%), indoprofen derivative **4a** (0.5 mmol, 1.0 equiv.) and phenylboronic acid (1.25 mmol, 2.5 equiv.) were taken in a 15 mL Schlenk tube, which was equipped with a magnetic stirring bar. THF (2.5 mL) was added to the Schlenk tube via a syringe, and the reaction mixture was degassed with Argon three times. The reaction mixture was allowed to stir at 110 °C for 20 h. After being cooled to ambient temperature, the reaction mixture was diluted with DCM and then filtered through Celite. After evaporation of the solvent in vacuo, the crude product was purified by column chromatography on silica gel (*n*-heptane/EtOAc: 10:1 to 5:1) to give the arylated product **4b**.

**Ester hydrolysis: 4b** (0.27 mmol, 106 mg, 1 equiv.) and 2 M NaOH (1 mL) were stirred in a mixture of MeOH (1 mL) and THF (1 mL) at room temperature for 12 hours. Then,

the reaction mixture was basified to pH = 14 and washed with ethyl acetate three times. The aqueous layer was acidified to pH = 1 with concentrated HCl and the product 4 precipitated out. After washing with pentane and drying under vacuum, product 4 was isolated.

#### Characterization data of products 4a, 4b and 4:

Ethyl 2-(4-(1-oxoisoindolin-2-yl)phenyl)propanoate (4a): Yellow solid, yield = 99%, 153.0 mg. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.84 (d, J = 7.6 CO<sub>2</sub>Et Hz, 1H), 7.79-7.77 (m, 2H), 7.54-7.50 (m, 1H), 7.45-7.41 (m, 2H), 7.33-7.30 (m, 2H), 4.74 (s, 2H), 4.15-4.05 (m, 2H), 3.68 (q, J = 7.2 Hz, 1H), 1.47 (d, J = 7.2 Hz, 3H), 1.19 (t, J = 7.2 Hz, 3H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 174.4, 167.3, 140.1, 138.4, 136.6, 133.0, 132.0, 128.3, 128.1, 123.9, 122.6, 119.4, 60.7, 50.6, 44.9, 18.5, 14.1 ppm. The spectral data match those previously reported.<sup>27</sup>

#### Ethyl 2-(6-(1-oxoisoindolin-2-yl)-[1,1'-biphenyl]-3-yl)propanoate (4b): Colorless



oil, yield = 85%, 160.1 mg. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$ = 7.92 (d, J = 6.8 Hz, 1H), 7.52-7.39 (m, 7H), 7.32-7.23 (m,  $CO_{2}Et = 4H$ , 4.23-4.10 (m, 4H), 3.81 (q, J = 7.2 Hz, 1H), 1.56 (d, J= 7.2 Hz, 3H), 1.27 (t, J = 7.2 Hz, 3H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta =$ 174.2, 169.0, 141.6, 140.6, 139.8, 138.9, 134.7, 132.0, 131.6, 130.2, 129.1, 128.6, 128.3,

128.0, 127.7, 127.6, 124.2, 122.6, 60.9, 52.2, 45.3, 18.7, 14.2 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>25</sub>H<sub>23</sub>NO<sub>3</sub>Na 408.1570, found 408.1573 (1 ppm).

2-(6-(1-Oxoisoindolin-2-yl)-[1,1'-biphenyl]-3-yl)propanoic acid (4): White solid,



yield = 90%, 86.8 mg. Mp: 208-210 °C.  $^{1}$ H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.92 (d, J = 7.6 Hz, 1H), 7.52-7.41 (m, 5H), 7.39-7.35 (m, 2H), 7.31-7.24 (m, 4H), 4.16 (s, 2H), 3.83 (q,

J = 7.2 Hz, 1H), 1.57 (d, J = 7.2 Hz, 3H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta =$ 

179.2, 169.4, 141.7, 140.2, 140.0, 138.9, 134.9, 132.0, 131.8, 130.5, 129.3, 128.8, 128.5, 128.2, 128.0, 127.7, 124.4, 122.7, 52.4, 45.2, 18.4 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>23</sub>H<sub>19</sub>NO<sub>3</sub>Na 380.1257, found 380.1263 (2 ppm).

### General procedure for the attempt of ruthenium-catalyzed arylation reactions using bromobenzene as aryl source.

*General procedure:* A suspension of **1a** or **6** (0.1 mmol, 1.0 equiv.), bromobenzene (0.125 mmol, 1.25 equiv.),  $[RuCl_2(p-cymene)]_2$  (5 mol%), KOAc (20 mol%) and K<sub>2</sub>CO<sub>3</sub> (0.15 mmol, 1.5 equiv.) in NMP (0.5 mL) was stirred under Argon for 24 h at 150 °C. After being cooled to ambient temperature, the reaction mixture was diluted with DCM and then filtered through Celite. After evaporation of the solvent in vacuo, the crude product was analyzed by <sup>1</sup>H NMR spectroscopy studies.

*Crystallographic details:* CCDC 1910249-1910254 (**2c**, **2d**, **2g**, **2o**, **2s**, **2q**) contains the supplementary crystallographic data for this chapter. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data\_request/cif, or by emailing data\_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

#### 6.7 References

- [1] T. J. Donohoe, Science of Synthesis, 2001, 10, 653.
- [2] (a) K. Speck, T. Magauer, *Beilstein J. Org. Chem.* 2013, *9*, 2048. (b) R. K. Bhatia, *Curr. Top. Med. Chem.* 2017, *17*, 189.
- [3] A. Iqbal, F. Herren, O. Wallquist in *High Performance Pigments, 2nd ed.*,
   (Eds.: E. B. Faulkner, R. J. Schwartz), Wiley-VCH, Weinheim, 2009, pp. 243).

- [4] M. R. Lunn, D. E. Root, A. M. Martino, S. P. Flaherty, B. P. Kelley, D. D. Coovert, A. H. Burghes, N. T. Man, G. E. Morris, J. Zhou, E. J. Androphy, C. J. Sumner, B. R. Stockwell, *Chem. Biol.* 2004, *11*, 1489.
- [5] (a) H. Miyachi, A. Azuma, E. Hioki, Y. Kobayashi, S. Iwasaki, Y. Hashimoto, *Chem. Pharm. Bull.* **1996**, *44*, 1980. (b) J. S. Park, S. C. Moon, K. U. Baik, J. Y. Cho, E. S. Yoo, Y. S. Byun, M. H. Park, *Arch. Pharm. Res.* **2002**, *25*, 137.
- [6] D. Hamprecht, F. Micheli, G. Tedesco, A. Checchia, D. Donati, M. Petrone, S. Terreni, M. Wood, *Bioorg. Med. Chem. Lett.* 2007, 17, 428.
- [7] (a) S. M. Allin, C. J. Northfield, M. I. Page, A. M. Z. Slawin, J. Chem. Soc., Perkin Trans. 2000, 1715. (b) D. Enders, V. Braig, G. Raabe, Can. J. Chem. 2001, 79, 1528. (c) R. Hunter, P. Richards, Org. Biomol. Chem. 2003, 1, 2348.
  (d) F. Csende, G. Stajer, Curr. Org. Chem. 2005, 5, 1261. (e) G. Stajer, F. Csende, Curr. Org. Chem. 2005, 5, 1277. (f) P. Thapa, E. Corral, S. Sardar, B. S. Pierce, F. W. Foss, Jr. J. Org. Chem. 2019, 84, 1025. (g) Y.-C. Yuan, C. Bruneau, R. Gramage-Doria, Synthesis 2018, 50, 4216.
- [8] (a) K. M. Engle, T.-S. Mei, M. Wasa, J.-Q. Yu, Acc. Chem. Res. 2012, 45, 788.
  (b) S. De Sarkar, W. Liu, S. I. Kozhushkov, L. Ackermann, Adv. Synth. Catal.
  2014, 356, 1461. (c) Y. Yang, K. Li, Y. Cheng, D. Wan, M. Li, J. You, Chem. Commun. 2016, 52, 2872. (d) C. Sambiagio, D. Schoenbauer, R. Blieck, T. Dao-Huy, G. Pototschnig, P. Schaaf, T. Wiesinger, M. F. Zia, J. Wencel-Delord, T. Besset, B. U. W. Maes, M. Schnuerch, Chem. Soc. Rev. 2018, 47, 6603.
- [9] (a) J. Yamaguchi, A. D. Yamaguchi, K. Itami, *Angew. Chem. Int. Ed.* 2012, *51*, 8960. (b) T. Brueckl, R. D. Baxter, Y. Ishihara, P. S. Baran, *Acc. Chem. Res.* 2012, *45*, 826. (c) J. F. Hartwig, *J. Am. Chem. Soc.* 2016, *138*, 2. (d) D. J. Abrams, P. A. Provencher, E. J. Sorensen, *Chem. Soc. Rev.* 2018, *47*, 8925.
- [10] (a) M. Miura, T. Satoh, *Top. Organomet. Chem.* 2005, *14*, 55. (b) C. Jia, T. Kitamura, Y. Fujiwara, *Acc. Chem. Res.* 2001, *34*, 633. (c) J. Bouffard, K.

Itami, Top. Curr. Chem. 2010, 292, 231. (d) Y. Ping, L. Wang, Q. Ding, Y. Peng, Adv. Synth. Catal. 2017, 359, 3274. (e) H. Bohra, M. Wang, J. Mater. Chem. A, 2017, 5, 11550. (f) L. Theveau, C. Schneider, C. Fruit, C. Hoarau, ChemCatChem 2016, 8, 3183. (g) B. Li, P. H. Dixneuf, Top. Organomet. Chem. 2015, 48, 119. (h) G.-F. Zha, H.-L. Qin, E. A. B. Kantchev, RSC Adv. 2016, 6, 30875. (i) C. B. Bheeter, L. Chen, J.-F. Soule, H. Doucet, Catal. Sci. Technol. 2016, 6, 2005. (j) U. Sharma, A. Modak, S. Maity, A. Maji, D. Maiti in New Trends in Cross-Coupling: Theory and Applications (Eds.: T. Colacot), RSC, Cambridge, 2014, pp. 2251. (k) K. Yuan, J.-F. Soule, H. Doucet, ACS Catal. 2015, 2, 978. (1) Z. Huang, G. Dong, Tetrahedron Lett. 2014, 55, 5869. (m) L. Ackermann, J. Org. Chem. 2014, 79, 8948. (n) L. Djakovitch, F.-X. Felpin, ChemCatChem 2014, 6, 2175. (o) I. Hussain, T. Singh, Adv. Synth. Catal. 2014, 356, 1661. (p) R. Rossi, F. Bellina, M. Lessi, C. Manzini, Adv. Synth. Catal. 2014, 356, 17. (q) L. Zhou, W. Lu, Chem. Eur. J. 2014, 20, 634. (r) A. Sharma, D. Vacchani, E. Van der Eycken, Chem. Eur. J. 2013, 19, 1158. (s) O. Baudoin, Chem. Soc. Rev. 2011, 40, 4902.

- [11] (a) Y. Hashimoto, K. Hirano, T. Satoh, F. Kakiuchi, M. Miura, *Org. Lett.* 2012, 14, 2058. (b) Y. Hashimoto, K. Hirano, T. Satoh, F. Kakiuchi, M. Miura, *J. Org. Chem.* 2013, 78, 638.
- [12] K. D. Collins, F. Lied, F. Glorius, Chem. Commun. 2014, 50, 4459.
- [13] W. Liu, L. Ackermann, Chem. Commun. 2014, 50, 1878.
- [14] Examples of site-selective C-O bond forming reactions via aromatic C-H bond functionalizations are also rare, see: (a) Y.-H. Sun, T.-Y. Sun, Y.-D. Wu, X. Zhang, Y. Rao, *Chem. Sci.* 2016, *7*, 2229. (b) Y.-C. Yuan, C. Bruneau, T. Roisnel, R. Gramage-Doria, *J. Org. Chem.* 2019, *84*, 1898.
- [15] (a) L. Ackermann, L. Wang, R. Wolfram, A. V. Lygin, Org. Lett. 2012, 14, 728. (b) K. Padala, M. Jeganmohan, Chem. Eur. J. 2014, 20, 4092. (c) R. Manikandan, P. Madasamy, M. Jeganmohan, ACS Catal. 2016, 6, 230. (d) R.

Das, G. S. Kumar, M. Kapur, *Eur. J. Org. Chem.* 2017, 5439. (e) L. Ping, D.
S. Chung, J. Bouffard, S.-G. Lee, *Chem. Soc. Rev.* 2017, 46, 4299.

- [16] (a) P. Nareddy, F. Jordan, S. E. Brenner-Moyer, M. Szostak, ACS Catal. 2016, 6, 4755. (b) Y. Hashimoto, T. Ortloff, K. Hirano, T. Satoh, C. Bolm, M. Miura, Chem. Lett. 2012, 41, 151. (c) Das, R.; Kapur, M. Chem. Eur. J. 2016, 22, 16986. (d) R. Das, M. Kapur, Chem. Asian J. 2015, 10, 1505. (e) Z. Yang, F.-C. Qiu, J. Gao, Z.-W. Li, B.-T. Guan, Org. Lett. 2015, 17, 4316. (f) P. Nareddy, F. Jordan, M. Szostak, Chem. Sci. 2017, 8, 3204. (g) Z. Huang, H. N. Lim, F. Mo, M. C. Young, G. Dong, Chem. Soc. Rev. 2015, 44, 7764.
- [17] (a) F. Kakiuchi, S. Kan, K. Igi, N. Chatani, S. Murai, J. Am. Chem. Soc. 2003, 125, 1698. (b) F. Kakiuchi, Y. Matsuura, S. Kan, N. Chatani, J. Am. Chem. Soc. 2005, 127, 5936. (c) S. Hiroshima, D. Marsumura, T. Kochi, F. Kakiuchi, Org. Lett. 2010, 12, 5318. (d) M. Pucheault, S. Darses, J.-P. Genet, J. Am. Chem. Soc. 2004, 126, 15356. (e) Y. J. Park, E.-A. Jo, C.-H. Jun, Chem. Commun. 2005, 1185. (f) S. J. Pastine, D. V. Gribkov, D. Sames, J. Am. Chem. Soc. 2006, 128, 14220. (g) S. Ueno, N. Chatani, F. Kakiuchi, J. Org. Chem. 2007, 72, 3600. (h) K. Kitazawa, T. Kochi, M. Sato, F. Kakiuchi, Org. Lett. 2009, 11, 1951. (i) S. Nakazono, S. Easwaramoorthi, D. Kim, H. Shinokubo, A. Osuka, Org. Lett. 2009, 11, 5426. (j) H. Li, W. Wei, Y. Xu, C. Zhang, X. Wan, Chem. Commun. 2011, 47, 1497. (k) R. K. Chinnagolla, M. Jeganmohan, Org. Lett. 2012, 14, 5246. (1) R. K. Chinnagolla, M. Jeganmohan, Chem. Commun. 2014, 50, 2442. (m) Y. Zhao, V. Snieckus, Adv. Synth. Catal. 2014, 356, 1527. (n) J. Hubrich, T. Himmler, L. Rodefeld, L. Ackermann, Adv. Synth. Catal. 2015, 357, 474. (o) C. Sollert, K. Devaraj, A. Orthaber, P. J. Gates, L. T. Pilarski, Chem. Eur. J. 2015, 21, 5380. (p) R. K. Chinnagolla, A. Vijeta, M. Jeganmohan, Chem. Commun. 2015, 51, 12992. (q) D. J. Paymode, C. V. Ramana, J. Org. Chem. 2015, 80, 11551. (r) F. Hu, M. Szostak, Org. Lett. 2016, 18, 4186. (s) Y. Ogiwara, M. Miyake, T. Kochi, F. Kakiuchi,

Organometallics 2017, 36, 159. (t) Y. Koseki, K. Kitazawa, M. Miyake, T. Kochi, F. Kakiuchi, J. Org. Chem. 2017, 82, 6503. (u) F. Siopa, V.-A. R. Cladera, C. A. M. Alfonso, J. Oble, G. Poli, Eur. J. Org. Chem. 2018, 6101. (v) N. Dastbaravardeh, M. Schnuerch, M. D. Mihovilovic, Org. Lett. 2012, 14, 1930.

- [18] T. Gensch, M. N. Hopkinson, F. Glorius, J. Wencel-Delord, *Chem. Soc. Rev.* 2016, 45, 2900.
- [19] R. Manikandan, M. Jeganmohan, Chem. Commun. 2017, 53, 8931.
- [20] (a) For the only alternative synthesis of 2a reported to date, see: M. Ahmed, J. M. Vernon, J. Chem. Soc. Perkin Trans. 1, 1975, 2048. (b) J. Heemskerk, K. D. Barnes, J. M. McCall, G. Johnson, D. Fairfax, M. R. Johnson, PCT Int. Appl. 2007, WO2007 109211 A2 20070927.
- [21] (a) L. Ackermann, *Chem. Rev.* 2011, *111*, 1315. (b) L. Ackermann, *Acc. Chem. Res.* 2014, *47*, 281. (c) L. Ackermann, R. Vicente, H. K. Potukuchi, V. Pirovano, *Org. Lett.* 2010, *12*, 5032. (d) I. Fabre, N. von Wolff, G. Le Duc, E. Ferrer Flegeau, C. Bruneau, P. H. Dixneuf, A. Jutand, *Chem. Eur. J.* 2013, *19*, 7595. (e) L. Ackermann, R. Vicente, A. Althammer, *Org. Lett.* 2008, *10*, 2299. (f) E. Ferrer Flegeau, C. Bruneau, P. H. Dixneuf, A. Jutand, *J. Am. Chem. Soc.* 2011, *133*, 10161. (g) P. B. Arockiam, C. Bruneau, P. H. Dixneuf, *Chem. Rev.* 2012, *112*, 5879. (h) C. Shan, L. Zhu, L.-B. Qu, R. Bai, Y. Lan, *Chem. Soc. Rev.* 2018, *47*, 7552.
- [22] (a) G. A. Molander, N. Ellis, Acc. Chem. Res. 2007, 40, 275. (b) S. Darses, J.P. Genet, Chem. Rev. 2008, 108, 288.
- [23] (a) S. Oi, S. Fukita, N. Hirata, N. Watanuki, S. Miyano, Y. Inoue, *Org. Lett.* **2001**, *3*, 2579. (b) S. Oi, Y. Ogino, S. Fukita, Y. Inoue, *Org. Lett.* **2002**, *4*, 1783. (c) S. Oi, E. Aizawa, Y. Ogino, Y. Inoue, *J. Org. Chem.* **2005**, *70*, 3113. (d) S. Oi, K. Sakai, Y. Inoue, *Org. Lett.* **2005**, *7*, 4009. (e) S. Oi, R. Funayama, T. Hattori, Y. Inoue, *Tetrahedron* **2008**, *64*, 6051. (f) L. Ackermann, *Org. Lett.*
2005, 7, 3123. (g) L. Ackermann, A. Althammer, R. Born, Angew. Chem. Int. Ed. 2006, 45, 2619. (h) L. Ackermann, R. Born, P. Alvarez-Bercedo, Angew. Chem. Int. Ed. 2007, 46, 6364. (i) I. Ozdemir, S. Demir, B. Cetinkaya, C. Gourlaouen, F. Maseras, C. Bruneau, P. H. Dixneuf, J. Am. Chem. Soc. 2008, 130, 1156. (j) F. Pozgan, P. H. Dixneuf, Adv. Synth. Catal. 2009, 351, 1737. (k) A. Prades, M. Poyatos, E. Peris, Adv. Synth. Catal. 2010, 352, 1155. (l) B. Yu, X. Yan, S. Wang, N. Tang, C. Xi, Organometallics 2010, 29, 3222. (m) W. Li, P. B. Arockiam, C. Fischmeister, C. Bruneau, P. H. Dixneuf, Green Chem. **2011**, *13*, 2315. (n) B. Li, C. B. Bheeter, C. Darcel, P. H. Dixneuf, ACS Catal. 2011, 1, 1221. (o) S. Sersen, J. Kljun, F. Pozgan, B. Stefane, I. Turel, Organometallics 2013, 32, 609. (p) S. Gonell, E. Peris, ACS Catal. 2014, 4, 2811. (q) B. Li, C. Darcel, P. H. Dixneuf, *ChemCatChem* **2014**, *6*, 127. (r) M. Seki, ACS Catal. 2014, 4, 4047. (s) M. Seki, Org. Process Res. Dev. 2016, 20, 867. (t) C. Bruneau, R. Gramage-Doria, Adv. Synth. Catal. 2016, 358, 3847. (u) P. Nareddy, F. Jordan, M. Szostak, ACS Catal. 2017, 7, 5721. (v) R. Gramage-Doria, S. Achelle, C. Bruneau, F., Robin-le Guen, V. Dorcet, T. Roisnel, J. Org. Chem. 2018, 83, 1462. (w) R. Gramage-Doria, T. Roisnel, Eur. J. Org. Chem. 2018, 6083.

- [24] E. Kim, M. Jeong, B. M. Lee, B. H. Kim, *Heterocycles* 2018, 96, 1759.
- [25] T. Vogler, A. Studer, Adv. Synth. Catal. 2008, 350, 1963.
- [26] A. Verma, S. Patel, K. A. Meenakshi, A. Yadav, S. Kumar, S. Jana, S. Sharma,C. D. Prasad, S. Kumar, *Chem. Commun.* 2015, *51*, 1371.
- [27] T. Thatikonda, S. K. Deepake, U. Das, Org. Lett. 2019, 21, 2532.

[Part of this chapter has been submitted for publication]

# Chapter 7: C-H bond alkylation of cyclic amides with maleimides via a site-selective-determining six-membered ruthenacycle

# 7.1 Introduction

Carbon-carbon bond-forming reactions via transition metal-catalyzed C-H bond functionalization is an attractive methodology as it enables straightforward access to complex structures from low functionalized starting materials.<sup>1</sup> It represents a sustainable entry to atom- and step-economy transformations relevant for academic and industrial laboratories.<sup>2</sup> In this context, the use of directing groups to assist the C-H activation step prior to the carbon-carbon bond formation is well recognized since the pioneering contribution from Murai and co-workers.<sup>3</sup> As such, C-H bond arylations, alkenylations and alkylations are nowadays employed using a wide range of transition metal catalysts.<sup>4</sup>

Amongst the different useful coupling partners enabling C-H bond alkylations with transition metal catalysts, maleimides occupy a place of choice.<sup>5,6</sup> On one hand, their C=C double bond is highly electron deficient which is important for coordinating to the cationic metal center during the catalysis, and in the other hand, it is a useful motif which enables straightforward post-functionalizations into succinimides, pyrrolidines, lactams and lactims.<sup>7</sup> Importantly, maleimides are known to follow hydroarylation pathways instead of oxidative Heck ones during transition metal-catalyzed C-H bond functionalizations. The absence of a  $\beta$ -hydride elimination step results in a formal insertion of an alkyl fragment in the targeted C-H bond.<sup>8</sup> This feature has been explored in the C-H bond alkylation of arenes with transition metal catalysts. For instance, different strong and weak directing groups have been disclosed to promote aromatic C-H bond alkylations with maleimides in which five-membered metallacycle intermediates control the *ortho*-selectivity of the reaction as shown by Falck, Miura, Prabhu, Kim, Ackermann, Jeganmohan and others (Scheme 7.1).<sup>5</sup>



Scheme 7.1 C-H bond alkylations via 5-membered metallacycle intermediates.

Aromatic C-H bond alkylations with maleimides *via* larger six-membered metallacycle intermediates had met success only for Rh- and Co-based catalysts (Scheme 7.2).<sup>6</sup>



Scheme 7.2 C-H bond alkylations via 6-membered metallacycle intermediates.

Although ruthenium catalysts seem to accommodate six-membered ruthenacycle intermediates in aromatic C-H bond arylations and alkenylations,<sup>9</sup> the exploitation of such intermediates for C-H bond alkylation is elusive to date. In this chapter, we report aromatic C-H bond alkylations *via* six-membered ruthenacycles with maleimides as coupling partners. This is disclosed for the C-H bond functionalization of isoindolinones,<sup>10</sup> a type of biologically relevant cyclic amides that imposes selectivity issues as two aromatic C-H sites are a *priori* available (Scheme 7.3).



Scheme 7.3 Site-selective C-H bond alkylation *via* 6-membered ruthenacycle intermediates using cyclic amides as directing groups.

# 7.2 Results and discussion

# 7.2.1 Optimization of the site-selective Ru-catalyzed C-H bond alkylation of cyclic amides with maleimides

Initially, different reaction conditions were screened for the C-H bond alkylation of *N*-phenylisoindolinone **1a** with *N*-methylmaleimide in the presence of a ruthenium catalyst (Table 7.1). The best reaction conditions we found consisted in  $[RuCl_2(p$  $cymene)]_2$  (7.5 mol%) as pre-catalyst, AgSbF<sub>6</sub> (30 mol%) as halide scavenger, Cu(OAc)<sub>2</sub>·H<sub>2</sub>O (1.5 equiv.) as oxidant and AcOH (5 equiv.) in 1,2-dichloroethane (DCE) as solvent at 120 °C for 18 hours. With these reaction conditions, **2a** was obtained in 92% isolated yield with full conversion of **1a** (Table 7.1, entry 1). The compound arising from the C-H bond functionalization occurring in the aromatic ring B of **1a** was not observed, and the alkenylated version of **2a** formed only with trace amounts only detectable by GC-MS analysis. Control experiments indicated the need of all reagents (Table 7.1, entries 2-5). The presence of water and an excess of AcOH was detrimental for the catalysis (Table 7.1, entries 6-7). The reaction was finished after 6 hours (Table 7.1, entry 8), however, after 3 hours there was some starting material left (Table 7.1, entry 9). A recent aromatic C-H bond alkylation lasting two hours with a

very strong nitrogen-directing group (i.e. pyrimidine) *via* five-membered cobaltacycles has been reported.<sup>11</sup> We noted that the reaction was sensitive to temperature. For instance, at 100 °C **2a** was formed in 90% yield (Table 7.1, entry 10), whereas at 80 °C no reaction was observed (Table 7.1, entries 11). Lowering the loading of *N*-methylmaleimide to 1.5 equivalent and [RuCl<sub>2</sub>(*p*-cymene)]<sub>2</sub> to 5 mol%, still afforded the corresponding alkylated product **2a** in 89% and 80% yield, respectively (Table 7.1, entries 12-13). Replacing the pre-catalyst [RuCl<sub>2</sub>(*p*-cymene)]<sub>2</sub> by first-row metal complexes such as Mn<sub>2</sub>(CO)<sub>10</sub> and Co(OAc)<sub>2</sub>·4H<sub>2</sub>O afforded the starting materials completely unreacted (Table 7.1, entries 13-14).<sup>12</sup>

H	$H_{a}$ $H_{a$	Catalyst, A Cu(OAc) <u>;</u> Additir Solvent,	$r_{2}H_{2}O$ ve T, t	H <sub>b</sub> O B N-	
Entry	Catalyst (x mol%)	Additive	T ( <sup>o</sup> C)	t (h)	Yield (%) <sup>b</sup>
1	[RuCl <sub>2</sub> (p-cymene)] <sub>2</sub> (7.5)	AcOH	120	18	99 (92)
2	<u> </u>	AcOH	120	18	0
3 <sup>c</sup>	[RuCl <sub>2</sub> ( <i>p</i> -cymene)] <sub>2</sub> (7.5)	AcOH	120	18	0
4 <sup><i>d</i></sup>	[RuCl <sub>2</sub> ( <i>p</i> -cymene)] <sub>2</sub> (7.5)	AcOH	120	18	<10
5	[RuCl <sub>2</sub> ( <i>p</i> -cymene)] <sub>2</sub> (7.5)		120	18	55
6 <sup>e</sup>	[RuCl <sub>2</sub> ( <i>p</i> -cymene)] <sub>2</sub> (7.5)	AcOH	120	18	48
7 <sup>f</sup>	[RuCl <sub>2</sub> ( <i>p</i> -cymene)] <sub>2</sub> (7.5)	AcOH	120	18	59
8	[RuCl <sub>2</sub> ( <i>p</i> -cymene)] <sub>2</sub> (7.5)	AcOH	120	6	99
9	[RuCl <sub>2</sub> ( <i>p</i> -cymene)] <sub>2</sub> (7.5)	AcOH	120	3	71
10	[RuCl <sub>2</sub> ( <i>p</i> -cymene)] <sub>2</sub> (7.5)	AcOH	100	18	90
11	[RuCl <sub>2</sub> ( <i>p</i> -cymene)] <sub>2</sub> (7.5)	AcOH	80	18	0
12 <sup>g</sup>	[RuCl <sub>2</sub> ( <i>p</i> -cymene)] <sub>2</sub> (7.5)	AcOH	120	18	89
13	[RuCl <sub>2</sub> ( <i>p</i> -cymene)] <sub>2</sub> (5.0)	AcOH	120	18	80
14	Mn <sub>2</sub> (CO) <sub>10</sub> (7.5)	AcOH	120	18	0
15	Co(OAc) <sub>2</sub> :4H <sub>2</sub> O (7.5)	AcOH	120	18	0

Table 7.1 Optimization of the reaction conditions.<sup>a</sup>

<sup>a</sup>Reaction conditions: **1a** (0.1 mmol), *N*-methylmaleimide (0.2 mmol),  $[RuCl_2(p-cymene)]_2$  (7.5 mol%), AgSbF<sub>6</sub> (30 mol%), Cu(OAc)<sub>2</sub>·H<sub>2</sub>O (0.15 mmol), AcOH (0.5 mmol), DCE (0.5 mL), 120 °C, 18 h, argon. <sup>b</sup>Determined by <sup>1</sup>H NMR spectroscopy against an internal standard (dibromomethane). The isolated yield is shown in parentheses. <sup>o</sup>Without AgSbF<sub>6</sub>. <sup>d</sup>Without Cu(OAc)<sub>2</sub>·H<sub>2</sub>O. <sup>e</sup>With H<sub>2</sub>O (5 equiv). <sup>f</sup>With AcOH (10 equiv). <sup>g</sup>With N-methylmaleimide (1.5 equiv).

# 7.2.2 Evaluation of the scope for the site-selective Ru-catalyzed C-H bond alkylation of cyclic amides with maleimides

With the optimal reaction conditions in hand (Table 7.1, entry 1), we evaluated the scope of the catalysis with N-arylisoindolinones (1) bearing various functional groups at different positions (Table 7.2). Arylisoindolinones substituted in para position of the *N*-phenyl ring with electronically different methyl, methoxy, ester, and chloro groups were tolerated by the catalysis affording the corresponding alkylated products **2b-2e** in 70-96% isolated yields. The formation of 2e is a rare case in which the carboxylic acid ester group does not direct the transition metal-catalyzed C-H bond alkylation using maleimides.<sup>13</sup> Unfortunately, nitrile-containing partners are not compatible with the catalysis (2f). Dioxolane-containing isoindolinone 2g, where the alkylation takes place at the most hindered ortho position, was obtained in 85% yield. Methyl-substituted isoindolinone in *meta* position of the *N*-phenyl ring afforded the alkylated product **2h** in 66% yield. In the case of 2g and 2h, no formation of any other possible isomer was detected. On the other hand, the methoxy congener 2i was obtained in 76% yield with formation of traces of the other *ortho*-substituted isomer. The reaction was sensitive to the substitution pattern in the *ortho* position of the *N*-phenyl ring of the isoindolinones. For instance, the fluoro derivative 2j was obtained in an excellent 84% yield. However, swapping the fluoride group by a bulkier methyl group led to no reactivity. We assume that, as the bulkiness in the substitution at the *ortho* position increases, the *N*-phenyl axis rotation is restricted in such a way that it prevents formation of catalytically productive ruthenacycle intermediates.



 Table 7.2 Ru-catalyzed site-selective C-H bond alkylation of various

 N-arylisoindolinones 1 with N-methylmaleimide.<sup>a,b</sup>

<sup>a</sup>Reaction conditions: **1** (0.5 mmol), *N*-methylmaleimide (1.0 mmol), [RuCl<sub>2</sub>(*p*-cymene)]<sub>2</sub> (7.5 mol%), AgSbF<sub>6</sub> (30 mol%), Cu(OAc)<sub>2</sub>·H<sub>2</sub>O (0.75 mmol), HOAc (2.5 mmol), DCE (2.5 mL), 120 °C, 18 h, argon. <sup>*b*</sup>Isolated yield by column chromatography. <sup>*c*</sup>The minor regioisomer is not depicted.

Furthermore, different *N*-substituted maleimides were also investigated for this C-H bond alkylation reaction (Table 7.3). For instance, **1a** reacted with *N*-phenyl maleimide affording **2l** in 78% yield and its molecular structure was unambiguously established by single crystal X-ray diffraction studies, which further supported the regio- and site-selectivity of the reaction. Fluoro-, bromo-, and nitro-containing maleimides were tolerated during the catalysis leading to the corresponding alkylated products **2m**-**2o** in 64-76% yield. *N*-benzyl maleimide afforded the corresponding alkylated product **2p** in 88% isolated yield. Analogously, the trifluoro-containing

alkylated product 2q was obtained in a similar yield. Interestingly, heterocyclecontaining maleimides such as thiophene were tolerated affording the alkylated product 2r in 58% yield.

# Table 7.3 Ru-catalyzed site-selective C-H bond alkylation of isoindolinones 1a with different N-substituted maleimides.<sup>a,b</sup>



<sup>a</sup>Reaction conditions: **1** (0.5 mmol), *N*-substituted maleimide (1.0 mmol),  $[RuCl_2(p-cymene)]_2$  (7.5 mol%), AgSbF<sub>6</sub> (30 mol%), Cu(OAc)<sub>2</sub>·H<sub>2</sub>O (0.75 mmol), HOAc (2.5 mmol), DCE (2.5 mL), 120 °C, 18 h, argon. <sup>b</sup>Isolated yield by column chromatography.

Limitations appeared when using unsubstituted *N*-H maleimide as coupling partner (Scheme 7.4). In this case, the desired product **2s** was observed in 10% yield together with the presence of unreacted starting materials.



Scheme 7.4 N-H maleimide as coupling partner in Ru-catalyzed C-H bond alkylation.

We also noted that iodide substitution pattern, maleic anhydride and dimethyl maleate were not compatible for this alkylation reaction (Figure 7.1).



Figure 7.1 Reluctant coupling partners in Ru-catalyzed C-H bond alkylation.

# 7.3 Mechanistic studies

In order to gain some insights about the reaction mechanism, we performed a reaction with a substrate lacking any carbonyl group (**3**). Under the standard reaction conditions, no alkylated product was formed (Scheme 7.5), thus indicating the potential role of the carbonyl group in **1** as a weak directing group in the C-H bond activation step.<sup>14</sup>



Scheme 7.5 Control experiment with a substrate containing no carbonyl groups.

Additionally, deuteration experiments with **1a** afforded the product **1a**-*d* with 84% deuterium incorporation in the protons that underwent alkylation in the catalysis (Scheme 7.6, top), with no other deuterium exchange occurring in any other protons of

the molecule. When **1a**-*d* was used as substrate for the C-H bond alkylation with *N*-methylmaleimide under standard reaction conditions, the expected product **2a** was obtained with no deuterium on it (Scheme 7.6, bottom), suggesting the participation of acetic acid in the last step of the catalysis and the reversibility of the C-H bond activation step.



Scheme 7.6 Deuteration experiments.

Overall, these data together with precedents in the literature,<sup>5,15</sup> suggested the plausible, simplified mechanism displayed in Scheme 7.7. First, chloride-free ruthenium species may form, which, after a concerted metalation-deprotonation step with **1** leads to the six-membered ruthenacycle **A** with formation of acetic acid. Coordination of maleimide to ruthenium followed by alkene insertion leads to **B**, which, after protonolysis with acetic acid and oxidation of ruthenium with copper(II) enables the formation of **2** and regeneration of the catalytically active ruthenium species, respectively. It is noteworthy that with maleimide substrates, the formation of an intermediate of type **B** is not favorable for  $\beta$ -hydride elimination as observed in the case of alkenylation with acyclic olefins under related conditions,<sup>16b</sup> but prone to be cleaved by protonolysis even in the absence of added acetic acid (Table 1, entry 5).



Scheme 7.7 Proposed catalytic cycle.

# 7.4 Investigation of different directing groups in the Ru-catalyzed C-H bond alkylation with maleimides.

For comparison purposes, other directing groups potentially enabling sixmembered ruthenacycle intermediates were explored for this aromatic C-H bond alkylation. Cyclic imides such as **4** and **5**, which are known to enable rutheniumcatalyzed C-H bond hydroxylations and alkenylations to some extent,<sup>16</sup> did not react under the standard reaction conditions for C-H bond alkylation (Scheme 7.8).



Scheme 7.8 Evaluation of cyclic imides as directing groups in Ru-catalyzed C-H bond alkylation with *N*-methylmaleimide.

On the other hand, pyrrolidinone **6**, which promotes C-H bond alkenylations and benzoxylations,<sup>91,17</sup> smoothly reacted leading to the alkenylated product **6'** in 80% yield with the same regioselectivity as isoindolinones **1** and no evidences for bis-functionalization (Scheme 7.9, top). Unexpectedly, oxazolidinone **7**, which is structurally related to **6** and it is known to promote C-H bond alkenylations,<sup>91</sup> did not react under our standard reaction conditions for C-H bond alkylation (Scheme 7.9, bottom).



Scheme 7.9 Evaluation of pyrrolidinone and oxazolidinone as directing groups in Rucatalyzed C-H bond alkylation with *N*-methylmaleimide.

Nitrogen-containing directing groups such as benzylpyridine **8** and benzoylpyridine **9**, the latter being known to promote C-H bond arylations,<sup>9c,e</sup> did not afford any alkylated products in our hands (Scheme 7.10). Consequently, although nitrogen-containing directing groups are largely considered as better directing groups than ketones, the presented ruthenium-catalyzed C-H bond alkylation methodology highlights that it is not always the case and a balance between both coordination strength and stereo-electronic effects needs to be considered.



Scheme 7.10 Evaluation of pyridine-containing directing groups in Ru-catalyzed C-H bond alkylation with *N*-methylmaleimide.

# 7.5 Conclusion

In summary, we have shown that ruthenium catalysts enabled the regio-, mono-, and site-selective alkylation of *N*-arylisoindolinones with *N*-substituted maleimides in high yields and an excellent functional group tolerance [alkyl, benzyl, aryl, a(cyclic) ether, carboxylic ester, nitro, halides (i.e. F, Cl, Br, CF<sub>3</sub>), heteroaromatics (i.e. thiophene)]. A combination of control reactions and deuteration experiments support that the catalysis occurs via a reversible and large six-membered ruthenacycle in the key C-H bond activation step, which is unprecedented for ruthenium catalysts in alkylation reactions. The potential of isoindolinones enabling C-H bond functionalizations arises from the capability of the cyclic tertiary amide to behave as a weak directing group throughout the catalysis. It is also shown that isoindolinones and pyrrolidinones (cyclic amides) outperform cyclic imides, oxazolidinones and, also, pyridine-containing directing groups in ruthenium-catalyzed C-H bond alkylations when six-membered intermediates are formed.

# 7.6 Experimental details

General information. All reagents were obtained from commercial sources and used as supplied. All reactions were carried out in flame-dried glassware under argon atmosphere unless otherwise noted. Catalytic experiments were performed in Schlenktype flasks under argon atmosphere unless otherwise noted. Organic solutions were concentrated under reduced pressure using a rotary evaporator. Thin-layer chromatography (TLC) were carried out on 0.25 mm Merck silica gel (60-F254). Flash column chromatography was performed using silica gel Silica 60 M, 0.04-0.063 mm. N-methyl-2-pyrrolidone (NMP) was distilled under reduced pressure and stored under molecular sieves and argon atmosphere. Technical grade petroleum ether (40-60) and ethyl acetate were used for column chromatography. CDCl3 was stored under nitrogen over molecular sieves. NMR spectra were recorded on an AVANCE III 400 spectrometer. <sup>1</sup>H NMR spectra were referenced to residual protiated solvent ( $\delta = 7.26$ ppm for CDCl<sub>3</sub>) and <sup>13</sup>C chemical shifts are reported relative to deuterated solvents ( $\delta$ = 77.0 ppm for CDCl<sub>3</sub>). The peak patterns are indicated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet, and br. for broad. GC-MS analyses were performed with a GCMS-QP2010S (Shimadzu) instrument with a GC-2010 equipped with a 30 m capillary column (Supelco, SLBTM-5ms, fused silica capillary column, 30 m x 0.25 mm x 0.25 mm film thickness), which was used with helium as the vector gas. The following GC conditions were used: initial temperature 80 °C for 2 minutes, then rate 20 °C/min until 280 °C and 280 °C for 28 minutes. HRMS were recorded on a Waters Q-Tof 2 mass spectrometer at the corresponding facilities of the CRMPO, Centre Régional de Mesures Physiques de l'Ouest, Université de Rennes 1. Melting points were performed on a LEICA VMHB Kofler system.

Synthesis and characterization of substrates 1, 3, 4 and 5 are described in the experimental details of Chapter 4, Chapter 5 and Chapter 6.

# Synthesis of substrate 7.

<u>Method A:</u> In an oven dried carousel tube, to a solution of 2-oxazolidinone (2 mmol, 1 equiv.), ( $\pm$ )-trans-1,2-diaminocyclohexane (Ligand, 20 mol%) and aryl bromide (2 mmol, 1 equiv.) in 1,4-dioxane (2 mL) was added potassium carbonate (4 mmol, 2 equiv.) and copper iodide (10 mol%). The carousel tube was sealed with a Teflon cap and the tube was purged with Argon for 10 minutes before closing the tap. The reaction mixture was heated to 120 °C for 18 hours. Back at room temperature, the reaction mixture was diluted in EtOAc and filtered using a celite plug, eluting with EtOAc. The solvent was removed in *vacuo* and the crude mixture was purified using column chromatography (*n*-heptane/EtOAc: 4:1 to 1:1).



# Characterization of substrates 7.

**3-Phenyloxazolidin-2-one (7):** Prepared according to Method A in 86% isolated yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$ = 7.54 (d, *J* = 8.0 Hz, 2H), 7.38 (dd, *J* = 8.0, 8.0 Hz, 2H), 7.14 (dd, *J* = 7.6, 7.6 Hz, 1H), 4.50-4.46 (m, 2H), 4.08-4.04 (m, 2H) ppm. The spectral data match those previously reported.<sup>18</sup>

# Synthesis of N-substituted Maleimides.

<u>Method B:</u> Maleic anhydride (2 equiv.) and primary amine (1 equiv.) were stirred in acetic acid (1.5 mL per mmol of amine) until maleic anhydride dissolved completely. The reaction mixture was refluxed at 130 °C (oil bath temperature) under Argon over 18 hours. After completion of the reaction, the reaction mixture was then allowed to cool down to room temperature and it was transferred to a 500 mL beaker. Saturated sodium bicarbonate aqueous solution was added to the beaker containing the reaction mixture until pH reached *ca*. 7. The aqueous layer was extracted with ethyl acetate (3 x

20 mL) and the combined organic layers were further washed with brine solution (30 mL). The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (*n*-heptane/EtOAc: 10:1 to 2:1) to obtain the desired *N*-substituted maleimide.

$$\begin{array}{c}
0\\
0\\
0\\
0\\
\end{array} + R - NH_{2} \\
\begin{array}{c}
1) AcOH, 130 \ ^{\circ}C, overnight\\
2) H_{2}O\\
3) NaHCO_{3} (aq)
\end{array}$$

# Characterization of N-substituted Maleimides.

1-(2-Fluorophenyl)-1*H*-pyrrole-2,5-dione (1am): Prepared according to Method B starting from *o*-fluoroaniline in 82% isolated yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.46-7.39 (m, 1H), 7.30-7.21 (m, 3H), 6.90 (d, *J* = 1.6 Hz, 2H) ppm. <sup>19</sup>F{<sup>1</sup>H} NMR (376 MHz, CDCl<sub>3</sub>):  $\delta$  = -119.3 ppm. The

spectral data match those previously reported.<sup>19</sup>

1-(2-Bromophenyl)-1*H*-pyrrole-2,5-dione (1an): Prepared according to Method B starting from aniline in 97% isolated yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta = 7.71$  (dd, J = 8.0, 1.6 Hz, 1H), 7.43 (ddd, J = 7.6, 7.6, 1.6 Hz, 1H), 7.33 (ddd, J = 8.0, 8.0, 1.6 Hz, 1H), 7.26 (dd, J = 8.0, 1.6 Hz, 1H), 6.88

(s, 2H) ppm. The spectral data match those previously reported.<sup>20</sup>

1-(4-Nitrophenyl)-1*H*-pyrrole-2,5-dione (1ao): Prepared according to Method B starting from *p*-nitroaniline in 67% isolated yield. <sup>1</sup>H NMR (400  $N \rightarrow NO_2$  MHz, CDCl<sub>3</sub>):  $\delta = 8.33$  (d, J = 8.8 Hz, 2H), 7.68 (d, J = 8.4 Hz, 2H), 6.93 (s, 2H) ppm. The spectral data match those previously

reported.21



those previously reported.<sup>22</sup>

1-(Thiophen-2-ylmethyl)-1*H*-pyrrole-2,5-dione (1ar): Prepared according to Method B starting from 2-thiophenemethylamine in 78% isolated yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$ = 7.20 (d, *J* = 5.2 Hz, 1H), 7.06 (d, *J* = 3.6 Hz, 1H), 6.92 (dd, *J* = 5.2, 3.6 Hz, 1H), 6.70 (s, 2H), 4.84 (s, 2H) ppm. The spectral

data match those previously reported.<sup>22</sup>

1-(4-Iodophenyl)-1*H*-pyrrole-2,5-dione (1as): Prepared according to Method B starting from *p*-iodoaniline in 75% isolated yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.79 (d, *J* = 8.4 Hz, 2H), 7.13 (d, *J* = 8.0 Hz, 2H), 6.85 (s, 2H) ppm. The spectral data match those previously reported.<sup>23</sup>

# General procedure for the ruthenium-catalyzed C-H bond alkylation reaction.

*General procedure:*  $[RuCl_2(p-cymene)]_2$  (7.5 mol%), AgSbF<sub>6</sub> (30 mol%), Cu(OAc)<sub>2</sub>·H<sub>2</sub>O (0.75 mmol, 1.5 equiv.), *N*-arylisoindolinone **1** (0.5 mmol, 1 equiv.), and *N*-substituted maleimide (1.0 mmol, 2 equiv.) were taken in a 15 mL pressure tube, which was equipped with a magnetic stirrer. To this mixture was added AcOH (2.5 mmol, 5 eq) and 1,2-dichloroethane (2.5 mL) under Argon. Then, the reaction vial was sealed with the screw cap and allowed to stir at 120 °C for 18 h. After being cooled to ambient temperature, the reaction mixture was diluted with DCM and then filtered through Celite. After evaporation of the solvent *in vacuo*, the crude product was purified

by column chromatography on silica gel (*n*-heptane/EtOAc: 10:1 to 2:1) to give the desired product alkylated **2** as a solid.

# Characterization of products (2).

**1-Methyl-3-(2-(1-oxoisoindolin-2-yl)phenyl)pyrrolidine-2,5-dione** (2a): Brown solid, yield = 92%, 147.4 mg. Mp: 162-164 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$ = 7.84 (d, J = 7.6 Hz, 1H), 7.58 (dd, J = 7.6, 7.2 Hz, 1H), 7.50-7.46 (m, 2H), 7.40-7.34 (m, 2H), 7.28-7.25 (m, 1H), 7.22-7.20 (m, 1H), 4.85 (d, J = 17.2 Hz, 1H), 4.77 (d, J = 17.2 Hz, 1H), 4.10

(dd, J = 9.6, 5.2 Hz, 1H), 3.15 (dd, J = 18.8, 9.6 Hz, 1H), 2.97 (dd, J = 18.4, 5.2 Hz, 1H), 2.76 (s, 3H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta = 177.9, 176.3, 168.4, 141.9, 137.3, 136.7, 132.1, 131.4, 129.1, 129.0, 128.5, 128.4, 124.1, 122.9, 54.1, 42.4, 36.8, 24.8 ppm (one carbon peak overlaps with another one). HRMS (ESI) calcd. for <math>[M + Na]^+ C_{19}H_{16}N_2O_3Na 343.1053$ , found 343.1056 (1 ppm).

# 1-Methyl-3-(5-methyl-2-(1-oxoisoindolin-2-yl)phenyl)pyrrolidine-2,5-dione (2b):



Brown solid, yield = 88%, 148.0 mg. Mp: < 50 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$ = 7.83 (d, J = 8.0 Hz, 1H), 7.56 (ddd, J = 8.0, 8.0, 1.2 Hz, 1H), 7.47 (dd, J = 6.8, 6.0 Hz, 2H), 7.19-7.13 (m, 2H), 7.00 (s, 1H), 4.82 (d, J = 17.2 Hz, 1H), 4.73 (d, J =

17.2 Hz, 1H), 4.05 (dd, J = 9.2, 5.2 Hz, 1H), 3.13 (dd, J = 18.8, 9.6 Hz, 1H), 2.97 (dd, J = 18.8, 4.8 Hz, 1H), 2.77 (s, 3H), 2.34 (s, 3H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta = 178.0, 176.3, 168.5, 141.9, 139.1, 136.3, 134.5, 132.0, 131.5, 129.8, 128.7, 128.3, 128.2, 124.0, 122.9, 54.1, 42.3, 36.8, 24.8, 21.1 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>20</sub>H<sub>18</sub>N<sub>2</sub>O<sub>3</sub>Na 357.1209, found 357.1209 (0 ppm).$ 

# 3-(5-Methoxy-2-(1-oxoisoindolin-2-yl)phenyl)-1-methylpyrrolidine-2,5-dione (2c):



White solid, yield = 91%, 160.0 mg. Mp: 167-169 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.78 (d, J = 7.6 Hz, 1H), 7.53 (dd, J = 7.6, 7.2 Hz, 1H), 7.45-7.41 (m, 2H), 7.15 (d, J = 8.8 Hz, 1H), 6.86 (dd, J = 8.8, 2.8 Hz, 1H), 6.69 (s, 1H), 4.76 (d,

J = 17.6 Hz, 1H), 4.67 (d, J = 17.2 Hz, 1H), 4.00 (dd, J = 9.2, 5.6 Hz, 1H), 3.74 (s, 3H), 3.07 (dd, J = 18.8, 9.6 Hz, 1H), 2.94 (dd, J = 18.8, 4.8 Hz, 1H), 2.70 (s, 3H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta = 177.7$ , 176.1, 168.6, 159.6, 141.9, 137.8, 131.9, 131.4, 129.6, 128.2, 123.9, 122.8, 113.8, 55.5, 54.2, 42.5, 36.6, 24.7 ppm (two carbon peaks overlap with another ones). HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>20</sub>H<sub>18</sub>N<sub>2</sub>O<sub>4</sub>Na 373.1159, found 373.1158 (0 ppm).

# 3-(5-Chloro-2-(1-oxoisoindolin-2-yl)phenyl)-1-methylpyrrolidine-2,5-dione (2d):



White solid, yield = 96%, 170.0 mg. Mp: 192-194 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.87 (d, J = 7.2 Hz, 1H), 7.62 (ddd, J = 7.6, 7.6, 1.2 Hz, 1H), 7.52 (dd, J = 7.6, 7.2 Hz, 2H), 7.38 (dd, J = 8.4, 2.4 Hz, 1H), 7.24 (d, J = 8.4 Hz, 2H), 4.86 (d, J = 17.2

Hz, 1H), 4.78 (d, J = 16.8 Hz, 1H), 4.10 (dd, J = 9.6, 5.2 Hz, 1H), 3.20 (dd, J = 18.4, 9.6 Hz, 1H), 3.01 (dd, J = 18.4, 5.2 Hz, 1H), 2.82 (s, 3H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta = 177.4$ , 175.9, 168.6, 141.9, 138.5, 136.0, 134.8, 132.4, 131.2, 129.8, 129.4, 128.6, 124.4, 123.1, 54.1, 42.5, 36.6, 25.1 ppm (one carbon peak overlaps with another one). HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>19</sub>H<sub>15</sub>N<sub>2</sub>O<sub>3</sub><sup>35</sup>CINa 377.0663, found 377.0663 (0 ppm).

#### Ethyl 3-(1-methyl-2,5-dioxopyrrolidin-3-yl)-4-(1-oxoisoindolin-2-yl)benzoate (2e):



7.6, 6.8 Hz, 1H), 7.43 (dd, J = 7.6, 7.2 Hz, 2H), 7.32 (d, J = 8.4 Hz, 1H), 4.79 (d, J = 16.8 Hz, 2H), 4.31 (q, J = 7.2 Hz, 2H), 4.14 (dd, J = 9.6, 5.2 Hz, 1H), 3.15 (dd, J = 18.8, 9.6 Hz, 1H), 2.98 (dd, J = 18.4, 5.6 Hz, 1H), 2.71 (s, 3H), 1.32 (t, J = 7.2 Hz, 3H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta = 177.4$ , 175.9, 168.1, 165.1, 141.8, 141.4, 136.7, 132.2, 131.0, 130.7, 129.9, 129.7, 128.4, 128.2, 124.0, 122.9, 61.3, 53.7, 42.4, 36.4, 24.8, 14.2 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>22</sub>H<sub>20</sub>N<sub>2</sub>O<sub>5</sub>Na 415.1264, found 415.1260 (1 ppm).

# 1-Methyl-3-(5-(1-oxoisoindolin-2-yl)benzo[d][1,3]dioxol-4-yl)pyrrolidine-2,5-



dione (2g): Brown solid, yield = 85%, 155.0 mg. Mp > 260 °C
dec. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 7.88 (d, J = 7.6 Hz, 1H),
7.60 (dd, J = 7.6, 7.2 Hz, 1H), 7.51 (dd, J = 8.0, 8.0 Hz, 2H),
6.85-6.78 (m, 2H), 6.00 (s, 2H), 4.79 (d, J = 17.6 Hz, 2H), 3.95

(dd, J = 8.8, 7.2 Hz, 1H), 3.20-3.08 (m, 2H), 2.85 (s, 3H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta = 177.5, 176.5, 168.8, 147.5, 141.9, 132.2, 131.6, 131.2, 128.5, 124.4, 123.0, 121.5, 118.7, 108.4, 102.3, 54.6, 38.9, 35.1, 25.0 ppm (one carbon peak overlaps with another one). HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>20</sub>H<sub>16</sub>N<sub>2</sub>O<sub>5</sub>Na 387.0951, found 387.0949 (1 ppm).$ 

1-Methyl-3-(4-methyl-2-(1-oxoisoindolin-2-yl)phenyl)pyrrolidine-2,5-dione (2h):



White solid, yield = 66%, 109.9 mg. Mp: 153-155 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$ = 7.85 (d, *J* = 8.4 Hz, 1H), 7.58 (dd, *J* = 7.2, 7.2 Hz, 1H), 7.49 (dd, *J* = 6.8, 6.4 Hz, 2H), 7.18 (d, *J* = 7.6 Hz, 1H), 7.10 (d, *J* = 6.4 Hz, 2H), 4.86 (d, *J* = 17.2 Hz, 1H), 4.77 (d, *J* 

= 17.2 Hz, 1H), 4.06 (dd, J = 9.2, 5.2 Hz, 1H), 3.14 (dd, J = 18.8, 9.6 Hz, 1H), 2.98 (dd, J = 18.8, 5.2 Hz, 1H), 2.78 (s, 3H), 2.34 (s, 3H) ppm (one carbon peak overlaps with another one). <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$ = 178.2, 176.4, 168.5, 142.0, 139.2, 137.1, 133.5, 132.1, 131.6, 130.0, 129.0, 128.4, 124.2, 122.9, 54.2, 42.2, 36.8, 24.8,

20.9 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>20</sub>H<sub>18</sub>N<sub>2</sub>O<sub>3</sub>Na 357.1210, found 357.1212 (1 ppm).

#### 3-(4-Methoxy-2-(1-oxoisoindolin-2-yl)phenyl)-1-methylpyrrolidine-2,5-dione (2i):



White solid, yield = 76%, 132.9 mg. Mp: 154-156 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.87 (d, *J* = 7.6 Hz, 1H), 7.60 (dd, *J* = 7.2, 7.2 Hz, 1H), 7.50 (dd, *J* = 7.2, 6.4 Hz, 2H), 7.12 (d, *J* = 8.4 Hz, 1H), 6.93 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.81 (d, *J* = 2.8 Hz, 1H),

4.88 (d, J = 17.2 Hz, 1H), 4.79 (d, J = 16.8 Hz, 1H), 4.03 (dd, J = 9.6, 5.2 Hz, 1H), 3.78 (s, 3H), 3.15 (dd, J = 18.8, 9.6 Hz, 1H), 2.96 (dd, J = 18.8, 4.8 Hz, 1H), 2.79 (s, 3H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta = 178.4, 176.5, 168.5, 159.9, 142.0, 138.3, 132.2, 131.5, 129.2, 128.53, 128.50, 124.3, 123.0, 115.1, 113.9, 55.6, 54.2, 42.0, 36.9, 24.9 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>20</sub>H<sub>18</sub>N<sub>2</sub>O<sub>4</sub>Na 373.1159, found 373.1162 (1 ppm).$ 

# 3-(3-Fluoro-2-(1-oxoisoindolin-2-yl)phenyl)-1-methylpyrrolidine-2,5-dione (2j):



White solid, yield = 84%, 84.9 mg. Mp: 140-142 °C. This compound exists as a mixture (63:37) of two diastereo-atropoisomers due to the blocked rotation through the *N*-*C*(aryl) axis. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$ = 7.89 (d, *J* = 7.6 Hz, 1H, major), 7.83 (d, *J* = 7.6 Hz, 1H,

minor), 7.62-7.57 (m, 1H, major), 7.62-7.57 (m, 1H, minor), 7.52-7.45 (m, 2H, major), 7.52-7.45 (m, 2H, minor), 7.40-7.33 (m, 1H, major), 7.40-7.33 (m, 1H, minor), 7.18-7.13 (m, 1H, major), 7.18-7.13 (m, 2H, minor), 6.96 (d, J = 7.6 Hz, 1H, major), 4.93 (d, J = 16.8 Hz, 1H, major), 4.85 (d, J = 16.8 Hz, 1H, major), 4.70 (d, J = 16.8 Hz, 1H, minor), 4.50 (d, J = 16.8 Hz, 1H, minor), 4.14-4.09 (m, 1H, major), 4.14-4.09 (m, 1H, minor), 3.32-3.22 (m, 1H, major), 3.32-3.22 (m, 1H, major), 2.39 (s, 3H, minor) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta = 177.5$ , 177.4, 176.2, 175.5, 169.4, 168.6, 159.9 (d,  $J_{C-F} = 248.9$ 

Hz), 159.2 (d,  $J_{C-F} = 249.6$  Hz), 142.6, 142.5, 140.2, 139.3, 132.5, 132.3, 131.2, 130.5, 130.4 (d,  $J_{C-F} = 8.8$  Hz), 130.3 (d,  $J_{C-F} = 9.0$  Hz), 128.4, 128.3, 127.0 (d,  $J_{C-F} = 3.4$  Hz), 125.8 (d,  $J_{C-F} = 13.4$  Hz), 124.4, 124.3, 124.2, 123.1, 123.0, 122.1 (d,  $J_{C-F} = 3.5$  Hz), 116.3 (d,  $J_{C-F} = 20.5$  Hz), 116.1 (d,  $J_{C-F} = 20.3$  Hz), 52.9 (d,  $J_{C-F} = 3.4$  Hz), 51.9 (d,  $J_{C-F} = 3.6$  Hz), 44.7 (d,  $J_{C-F} = 2.6$  Hz), 41.3 (d,  $J_{C-F} = 2.3$  Hz), 36.9, 36.3, 25.2, 24.4 ppm. <sup>19</sup>F{<sup>1</sup>H} NMR (376 MHz, CDCl<sub>3</sub>):  $\delta = -118.8$  (major), -119.4 (minor) ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>19</sub>H<sub>15</sub>N<sub>2</sub>O<sub>3</sub>FNa 361.0959, found 361.0959 (0 ppm).

3-(2-(1-Oxoisoindolin-2-yl)phenyl)-1-phenylpyrrolidine-2,5-dione (2l): Brown

solid, yield = 78%, 149.0 mg. Mp: 246-248 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.93 (d, *J* = 7.6 Hz, 1H), 7.61 (dd, *J* = 7.6, 7.2 Hz, 1H), 7.54 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.45 (dd, *J* = 8.0, 5.2 Hz, 3H), 7.39-7.30 (m, 5H), 7.03 (s, 2H), 4.88 (d, *J* = 17.2 Hz, 1H), 4.79 (d, *J* = 16.8 Hz, 1H), 4.33 (dd, *J* = 7.6, 7.6 Hz, 1H), 3.39-3.23 (m, 2H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 177.0, 175.3, 168.8, 142.2, 137.6, 136.8, 132.2, 131.8, 131.6, 129.4, 129.3, 129.1, 128.8, 128.6, 128.5, 126.4, 124.4, 123.1, 54.3, 42.8, 36.9 ppm (one carbon peak overlaps with another one). HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>24</sub>H<sub>18</sub>N<sub>2</sub>O<sub>3</sub>Na 405.1210, found 405.1210 (0 ppm).

# 1-(2-Fluorophenyl)-3-(2-(1-oxoisoindolin-2-yl)phenyl)pyrrolidine-2,5-dione (2m):



White solid, yield = 76%, 60.9 mg. Mp: < 50 °C. This compound exists as a mixture (53:47) of two diastereo-atropoisomers due to the blocked rotation through the *N*-*C*(aryl) axis. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$ = 7.94 (d, *J* = 7.6 Hz, 1H), 7.62 (dd, *J* = 7.6, 7.2 Hz, 1H),

7.54 (dd, J = 7.6, 7.2 Hz, 1H), 7.49-7.30 (m, 6H), 7.18-7.00 (m, 3H), 4.94-4.81 (m, 2H), 4.39-4.36 (m, 1H), 3.46-3.13 (m, 2H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta =$ 176.2, 174.6 (d,  $J_{C-F} = 17.9$  Hz), 168.7 (d,  $J_{C-F} = 24.8$  Hz), 157.4 (d,  $J_{C-F} = 250.2$  Hz), 142.1, 137.6, 136.6, 132.2, 131.6, 131.0 (d,  $J_{C-F} = 7.8$  Hz), 129.4, 129.2, 128.5, 124.8, 124.7, 124.3, 123.1, 119.8 (d,  $J_{C-F} = 5.0 \text{ Hz}$ ), 116.7 (d,  $J_{C-F} = 19.2 \text{ Hz}$ ), 54.2, 42.3, 37.3 (d,  $J_{C-F} = 31.6 \text{ Hz}$ ) ppm (two carbon peaks overlap with another ones). <sup>19</sup>F{<sup>1</sup>H} NMR (376 MHz, CDCl<sub>3</sub>):  $\delta = -119.2$ , -119.7 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>24</sub>H<sub>17</sub>N<sub>2</sub>O<sub>3</sub>FNa 423.1115, found 423.1117 (0 ppm).

# 1-(2-Bromophenyl)-3-(2-(1-oxoisoindolin-2-yl)phenyl)pyrrolidine-2,5-dione (2n):

Brown solid, yield = 64%, 88.8 mg. Mp: 136-138 °C. This compound exists as a mixture (57:43) of two diastereoatropoisomers due to the blocked rotation through the *N*-*C*(aryl) axis. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.94 (dd, *J* = 7.2, 6.4 Hz, 1H), 7.68-7.13 (m, 11H), 4.96-4.76 (m, 2H), 4.43-4.37 (m, 1H), 3.48-3.11 (m, 2H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 176.10, 176.07, 174.5, 174.4, 168.9, 168.4, 142.3, 142.0, 137.8, 137.3, 136.5, 136.1, 133.52, 133.46, 132.25, 132.16, 131.70, 131.66, 131.61, 131.4, 131.1, 130.9, 129.9, 129.7, 129.4, 129.3, 129.24, 129.22, 128.8, 128.6, 128.5, 128.4, 128.3, 128.2, 127.9, 124.4, 124.2, 123.2, 123.1, 122.3, 122.2, 54.4, 54.2, 43.6, 42.2, 37.4, 37.0 ppm (one carbon peak overlaps with another one). HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>24</sub>H<sub>17</sub>N<sub>2</sub>O<sub>3</sub><sup>79</sup>BrNa 483.0315, found 483.0311 (1 ppm).

#### 1-(4-Nitrophenyl)-3-(2-(1-oxoisoindolin-2-yl)phenyl)pyrrolidine-2,5-dione (20):



Brown solid, yield = 70%, 59.7 mg. Mp: 126-128 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.13 (d, J = 8.4 Hz, 2H), 7.89 (d, J = 7.6 Hz, 1H), 7.61 (dd, J = 7.6, 7.2 Hz, 1H), 7.52 (dd, J = 7.6, 7.2 Hz, 1H), 7.46-7.25 (m, 7H), 4.79 (d, J = 17.2 Hz, 2H), 4.37 (dd, J = 8.0, 7.6 Hz, 1H), 3.36 (d, J = 8.4 Hz, 2H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz,

CDCl<sub>3</sub>):  $\delta$ = 176.3, 174.4, 168.8, 146.8, 142.1, 137.3, 136.3, 132.4, 131.3, 129.6, 129.3, 128.8, 128.6, 126.8, 124.3, 124.2, 123.1, 54.1, 43.3, 36.8 ppm (two carbon peaks overlap with another ones). HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>24</sub>H<sub>17</sub>N<sub>3</sub>O<sub>5</sub>Na 450.1060, found 450.1063 (1 ppm).

# 1-Benzyl-3-(2-(1-oxoisoindolin-2-yl)phenyl)pyrrolidine-2,5-dione (2p): Brown



solid, yield = 88%, 174.0 mg. Mp: < 50 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 7.90 (d, *J* = 7.6 Hz, 1H), 7.61 (dd, *J* = 7.6, 7.2 Hz, 1H), 7.54-7.49 (m, 2H), 7.42-7.23 (m, 8H), 7.13 (d, *J* = 7.2 Hz, 1H), 4.90 (d, *J* = 17.2 Hz, 1H), 4.81 (d, *J* = 17.2 Hz, 1H), 4.58 (d, *J* = 14.0 Hz, 1H), 4.50 (d, *J* = 14.0 Hz, 1H), 4.13 (dd, *J* = 9.6, 5.2 Hz, 1H), 3.22

(dd, J = 18.8, 9.6 Hz, 1H), 2.96 (dd, J = 18.8, 5.2 Hz, 1H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta = 177.6$ , 176.0, 168.5, 142.0, 137.5, 136.8, 135.7, 132.1, 131.6, 129.2, 129.1, 128.7, 128.6, 128.4, 128.3, 128.0, 124.2, 123.0, 54.2, 42.6, 42.1, 37.1 ppm (one carbon peak overlaps with another one). HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>25</sub>H<sub>20</sub>N<sub>2</sub>O<sub>3</sub>Na 419.1366, found 419.1368 (0 ppm).

# 3-(2-(1-Oxoisoindolin-2-yl)phenyl)-1-(4-(trifluoromethyl)benzyl)pyrrolidine-2,5-



**dione (2q):** White solid, yield = 88%, 81.3 mg. Mp: 78-80 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.89 (d, *J* = 7.6 Hz, 1H), 7.62 (dd, *J* = 7.6, 7.2 Hz, 1H), 7.54-7.50 (m, 4H), 7.43-7.35 (m, 4H), 7.29 (d, *J* = 7.6 Hz, 1H), 7.14 (d, *J* = 7.2 Hz, 1H), 4.88 (d, *J* = 16.8 Hz, 1H), 4.82 (d, *J* = 17.2 Hz, 1H), 4.62 (d, *J* = 14.0 Hz, 1H), 4.54 (d, *J* =

14.4 Hz, 1H), 4.17 (dd, J = 9.6, 5.2 Hz, 1H), 3.26 (dd, J = 18.8, 9.6 Hz, 1H), 3.02 (dd, J = 18.8, 5.2 Hz, 1H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta = 177.6$ , 175.9, 168.6, 142.0, 139.4 (q,  $J_{C-F} = 1.6$  Hz), 137.5, 136.5, 132.3, 131.6, 130.3 (q,  $J_{C-F} = 32.2$  Hz), 129.3 (q,  $J_{C-F} = 1.5$  Hz), 129.1, 128.6, 128.4, 127.9, 125.7 (q,  $J_{C-F} = 3.8$  Hz), 124.3, 124.0 (q,  $J_{C-F} = 270.4$  Hz), 123.1, 54.2, 42.3, 42.1, 37.1 ppm (one carbon peak overlaps with another one). <sup>19</sup>F{<sup>1</sup>H} NMR (376 MHz, CDCl<sub>3</sub>):  $\delta = -62.6$  ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>26</sub>H<sub>19</sub>N<sub>2</sub>O<sub>3</sub>F<sub>3</sub>Na 487.1240, found 487.1239 (0 ppm).

# 3-(2-(1-Oxoisoindolin-2-yl)phenyl)-1-(thiophen-2-ylmethyl)pyrrolidine-2,5-dione



(2r): White solid, yield = 58%, 70.1 mg. Mp: 216-218 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.89 (d, *J* = 7.6 Hz, 1H), 7.62 (dd, *J* = 7.6, 7.2 Hz, 1H), 7.52 (dd, *J* = 7.6, 7.2 Hz, 2H), 7.43-7.34 (m, 2H), 7.29 (dd, *J* = 7.2, 1.6 Hz, 1H), 7.18-7.12 (m, 2H), 7.04 (d, *J* = 3.6 Hz, 1H), 6.88 (dd, *J* = 5.2, 3.6 Hz, 1H), 4.90 (d, *J* = 17.2 Hz, 1H), 4.82

(d, J = 17.2 Hz, 1H), 4.76-4.66 (m, 2H), 4.13 (dd, J = 9.6, 5.2 Hz, 1H), 3.24 (dd, J = 18.8, 9.6 Hz, 1H), 2.97 (dd, J = 18.8, 4.8 Hz, 1H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta = 177.2$ , 175.6, 168.6, 142.0, 137.5, 137.2, 136.7, 132.2, 131.7, 129.3, 129.2, 128.6, 128.4, 128.1, 127.9, 126.9, 126.1, 124.4, 123.1, 54.3, 42.2, 37.2, 36.8 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>23</sub>H<sub>18</sub>N<sub>2</sub>O<sub>3</sub>SNa 425.0930, found 425.0931 (0 ppm).

3-(2-(1-Oxoisoindolin-2-yl)phenyl)pyrrolidine-2,5-dione (2s): Brown solid, yield =



10%, 14.8 mg. Mp: < 50 °C. <sup>1</sup>H NMR (400 MHz, acetone- $d_6$ ):  $\delta$  = 10.08 (s, br, 1H), 7.78 (d, J = 7.6 Hz, 1H), 7.69-7.64 (m, 2H), 7.55 (ddd, J = 7.6, 7.6, 2.0 Hz, 1H), 7.50-7.43 (m, 4H), 4.89 (d, J = 17.2 Hz, 2H), 4.36 (dd, J = 9.6, 5.6 Hz, 1H), 3.17 (dd, J = 18.4, 9.6 Hz,

1H), 2.95 (dd, J = 18.4, 5.6 Hz, 1H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, acetone- $d_6$ ):  $\delta = 178.7$ , 176.5, 168.0, 142.9, 138.2, 138.0, 131.9, 131.8, 128.7, 128.6, 128.5, 128.0, 124.5, 123.5, 123.3, 53.8, 44.0, 38.0 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>18</sub>H<sub>14</sub>N<sub>2</sub>O<sub>3</sub>Na 329.0897, found 329.0895 (0 ppm).

1-Methyl-3-(2-(2-oxopyrrolidin-1-yl)phenyl)pyrrolidine-2,5-dione (6'): White solid,

yield = 80%, 65.2 mg. Mp: 145-147 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$ = 7.34-7.26 (m, 2H), 7.17-7.12 (m, 2H), 4.07 (dd, J = 9.6, 5.2 Hz, 1H), 3.83-3.75 (m, 2H), 3.17 (dd, J = 18.8, 9.6 Hz, 1H), 3.01 (s, 3H), 2.87 (dd, J = 18.8, 4.8 Hz, 1H), 2.49 (t, J = 8.4 Hz, 2H), 2.23-2.10 (m, 2H) ppm.

<sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 177.9, 176.4, 175.4, 138.0, 135.8, 129.1, 128.7,

128.3, 127.2, 51.6, 42.4, 37.0, 31.2, 25.1, 19.0 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>15</sub>H<sub>16</sub>N<sub>2</sub>O<sub>3</sub>Na 295.1053, found 295.1053 (0 ppm).

# Deuteration experiments.

In an oven dried Schlenk tube, to a solution of isoindolinone **1a** (0.1 mmol, 1 equiv.) in DCE (0.45 mL) and D<sub>2</sub>O (0.05 mL) was added the combined reagents under argon:  $[RuCl_2(p-cymene)]_2$  (7.5 mol%), AgSbF<sub>6</sub> (30 mol%), HOAc (0.5 mmol, 5.0 equiv.) and Cu(OAc)<sub>2</sub>·H<sub>2</sub>O (0.15 mmol, 1.5 equiv.). The Schlenk tube was sealed with a Teflon cap and it was heated to 120 °C for 18 h. The reaction mixture was diluted in DCM and filtered using a silica plug eluting with DCM. The solvent was removed *in vacuo* and the crude mixture was purified by column chromatography (*n*-heptane/EtOAc, 4/1 to 1/1, *v*/*v*) to give the product **1a**-*d* as a white solid 84% deuterium incorporation according to <sup>1</sup>H NMR spectroscopy studies.

### 7.7 References

- [1] (a) G. Evano, C. Theunissen, Angew. Chem. Int. Ed. 2019, 58, 7202. (b) From C-H to C-C Bonds: Cross-Dehydrogenative-Coupling (Ed.: C.-J. Li), 2014, RSC, Cambridge, UK. (c) R. Narayan, K. Matcha, A. P. Antonchick, Chem. Eur. J. 2015, 21, 14678. (d) Y.-H. Zhang, G.-F. Shi, J.-Q. Yu, in Comprehensive Organic Synthesis 2<sup>nd</sup> Edition (Eds.: P. Knochel, G. A. Molander) 2014, Elsevier, Amsterdam, pp.1101.
- [2] (a) C. Sambiagio, D. Schoenbauer, R. Blieck, T. Dao-Huy, G. Pototschnig, P. Schaaf, T. Wiesinger, M. F. Zia, J. Wencel-Delord, T. Besset, B. U. W. Maes, M. Schnuerch, *Chem. Soc. Rev.* 2018, 47, 6603. (b) A. Dhakshinamoorthy, A. B. Asiri, H. Garcia, ACS Catal. 2019, 9, 1081. (c) S. Santoro, S. I. Kozhushkov, L. Ackermann, L. Vaccaro, *Green Chem.* 2016, 18, 3471. (d) J. Yamaguchi, A. D. Yamaguchi, K. Itami, Angew. Chem. Int. Ed. 2012, 51, 8960.

- [3] S. Murai, F. Kakiuchi, S. Sekine, Y. Tanako, A. Kamatani, M. Sonoda, N. Chatani, *Nature* 1993, 366, 529.
- [4] (a) Catalytic Hydroarylation of Carbon-Carbon Multiple Bonds (Ed.: L. Ackermann) 2018, Wiley-VCH, Weinheim, Germany. (b) I. Hussain, T. Singh, Adv. Synth. Catal. 2014, 356, 1661. (c) D. A. Colby, R. G. Bergman, J. A. Ellman, Chem. Rev. 2010, 110, 624. (d) I. V. Seregin, V. Gevorgyan, Chem. Soc. Rev. 2007, 36, 1173. (e) S. I. Kozhushkov, L. Ackermann, Chem. Sci. 2013, 4, 886. (f) F. Zhang, D. A. Spring, Chem. Soc. Rev. 2014, 43, 6906. (g) D. Alberico, M. E. Scott, M. Lautens, Chem. Rev. 2007, 107, 174. (h) O. Daugulis, H.-Q. Do, D. Shabashov, Acc. Chem. Res. 2009, 42, 1074. (i) Z. Dong, Z. Ren, S. J. Thompson, Y. Xu, G. Dong, Chem. Rev. 2017, 117, 9333.
- [5] (a) C. Zhu, J. R. Falck, *Chem. Commun.* **2012**, *48*, 1674. (b) C. Zhu, J. R. Falck, Tetrahedron 2012, 68, 9192. (c) W. Miura, K. Hirano, M. Miura, Org. Lett. 2015, 17, 4034. (d) K. R. Bettadapur, V. Lanke, K. R. Prabhu, Org. Lett. 2015, 17, 4658. (e) V. Lanke, K. R. Bettadapur, K. R. Prabhu, Org. Lett. 2015, 17, 4662. (g) Y. Moon, Y. Jeong, D. Kook, S. Hong, Org. Biomol. Chem. 2015, 13, 3918. (h) S. Sharma, S. H. Han, Y. Oh, N. K. Mishra, S. H. Lee, J. S. Oh, I. S. Kim, Org. Lett. 2016, 18, 2568. (i) S. Han, J. Park, S. Kim, S. H. Lee, S. Sharma, N. K. Mishra, Y. H. Jung, I. S. Kim, Org. Lett. 2016, 18, 4666. (j) P. Keshri, K. R. Bettadapur, V. Lanke, K. R. Prabhu, J. Org. Chem. 2016, 81, 6056. (k) S. H. Han, S. Kim, U. De, N. K. Mishra, J. Park, S. Sharma, J. H. Kwak, S. Han, H. S. Kim, I. S. Kim, J. Org. Chem. 2016, 81, 12416. (1) F. Jafarpour, M. Shamsianpour, RSC Adv. 2016, 6, 103567. (m) S. Sharma, Y. Oh, N. K. Mishra, U. De. H. Jo, R. Sachan, H. S. Kim, Y. H. Jung, I. S. Kim, J. Org. Chem. 2017, 82, 3359. (n) N. Muniraj, K. R. Prabhu, J. Org. Chem. 2017, 82, 6913. (o) R. Manoharan, M. Jeganmohan, Org. Lett. 2017, 19, 5884. (p) Z. Zhang, S. Han, M. Tang, L. Ackermann, J. Li, Org. Lett. 2017, 19, 3315. (q) S. L. Liu, Y. Li, J.-R. Guo, G.-C. Yang, X.-H. Li, J.-F. Gong, M.-P. Song, Org. Lett. 2017, 19, 4042 (r) A. Mandal, H. Sahoo, S. Dana, M. Baidya, Org. Lett.

2017, 19, 4138. (s) K. R. Bettadapur, V. Lanke, K. R. Prabhu, *Chem. Commun.*2017, 53, 6251. (t) S. H. Han, N. K. Mishra, H. Jo, Y. Oh, M. Jeon, S. Kim, W. J. Kim, J. S. Lee, H. S. Kim, I. S. Kim, *Adv. Synth. Catal.* 2017, 359, 2396. (u) S. H. Han, N. K. Mishra, M. Jeon, S. Kim, H. S. Kim, S.-Y. Jung, Y.-H. Jung, J.-M. Ku, I. S. Kim, *Adv. Synth. Catal.* 2017, 359, 3900. (v) M. Tamizmani, B. Ramesh, M. Jeganmohan, *J. Org. Chem.* 2018. 83, 3746. (w) J. Zhao, C. Pi, C. You, Y. Wang, X. Cui, Y. Wu, *Eur. J. Org. Chem.* 2018, 6919. (x) H. Zhao, X. Shao, T. Wang, S. Zhai, S. Qiu, C. Tao, H. Wang, H. Zhai, *Chem. Commun.* 2018, 54, 4927. (y) X. Chen, J. Ren, H. Xie, W. Sun, M. Sun, B. Wu, *Org. Chem. Front.* 2018, 5, 184.

- [6] (a) S. Sharma, S. H. Han, H. Jo, S. Han, N. K. Mishra, M. Choi, T. Jeong, J. Park,
  I. S. Kim, *Eur. J. Org. Chem.* 2016, 3611. (b) W. Yu, W. Zhang, Y. Liu, Z. Liu, Y.
  Zhang, *Org. Chem. Front.* 2017, *4*, 77. (c) M. S. Sherikar, R. Kapanaiah, V. Lanke,
  K. R. Prabhu, *Chem. Commun.* 2018, *54*, 11200. (d) M. Tamizmani, N. Gouranga,
  M. Jeganmohan, *ChemistrySelect* 2019, *4*, 2976. (e) C. Pan, Y. Wang, C. Wu, J.-T.
  Yu, *Org. Biomol. Chem.* 2018, *16*, 693. (f) S. K. Banjare, R. Chebolu, P. C.
  Ravikumar, *Org. Lett.* 2019, *21*, 4049.
- [7] (a) B.-B. Zhan, Y. Li, J.-W. Xu, X.-L. Nie, J. Fan, L. Jin, B.-F. Shi, *Angew. Chem. Int. Ed.* 2018, *57*, 5858. (b) A. R. Katritzky, J. Yao, M. Qi, Y. Chou, D. J. Sikora, S. Davis, *Heterocycles* 1998, *48*, 2677. (c) L. Shemchuk, V. Chernykh, P. Arzumanov, D. Levashov, L. Shemchuk, *Russ. J. Org. Chem.* 2007, *43*, 615. (d) H. Gali, K. R. Prabhu, S. R. Karra, K. V. Katti, *J. Org. Chem.* 2000, *65*, 676.
- [8] R. Manoharan, M. Jeganmohan, Asian J. Org. Chem. 2019, doi: 10.1002/ajoc.201900054.
- [9] (a) L. Ackermann, E. Diers, A. Manvar, Org. Lett. 2012, 14, 1154. (b) W. Ma, L. Ackermann, Chem. Eur. J. 2013, 19, 13925. (c) B. Li, C. Darcel, P. H. Dixneuf, ChemCatChem 2014, 6, 127. (d) S. Nakanowatari, L. Ackermann, Chem. Eur. J. 2015, 21, 16246. (e) C. Bruneau, R. Gramage-Doria, Adv. Synth. Catal. 2016, 358, 3847. (f) L. Ackermann, L. Wang, R. Wolfram, A. V. Lygin, Org. Lett. 2012, 14,

728. (g) J. Li, C. Kornhaass, L. Ackermann, *Chem. Commun.* 2012, *48*, 11343. (h)
M. C. Reddy, M. Jeganmohan, *Eur. J. Org. Chem.* 2013, 1150. (i) B. Li, J. Ma, Y.
Liang, N. Wang, S. Xu, H. Song, B. Wang, *Eur. J. Org. Chem.* 2013, 1950. (j) S.
R. Chidipudi, M. D. Wieczysty, I. Khan, H. W. Lam, *Org. Lett.* 2013, *15*, 570. (k)
R. Manikandan, M. Jeganmohan, *Org. Lett.* 2014, *16*, 3568. (l) J. A. Leitch, P. B.
Wilson, C. L. McMullin, M. F. Mahon, Y. Bhonoah, I. H. Williams, C. G. Frost, *ACS Catal.* 2016, *6*, 5520. (m) J. A. Leitch, H. P. Cook, Y. Bhonoah, C. G. Frost, *J. Org. Chem.* 2016, *81*, 10081. (n) W. Ma, H. Dong, D. Wang, L. Ackermann, *Adv. Synth. Catal.* 2017, *359*, 966. (o) D. C. Fabry, M. A. Ronge, J. Zoller, M.
Rueping, *Angew. Chem. Int. Ed.* 2015, *54*, 2801. (p) A. Bechtoldt, C. Tirler, K.
Raghuvanshi, S. Warratz, C. Kornhaass, L. Ackermann, *Angew. Chem. Int. Ed.* 2016, *55*, 264. (q) T. Li, J. Zhang, C. Yu, X. Lu, L. Xu, G. Zhong, *Chem. Commun.* 2017, *53*, 12926. (r) C. Suzuki, K. Hirano, T. Satoh, M. Miura, *Org. Lett.* 2013, *15*, 3990.

[10] (a) K. Speck, T. Magauer, *Beilstein J. Org. Chem.* 2013, *9*, 2048. (b) R. K. Bhatia, *Curr. Top. Med. Chem.* 2017, *17*, 189. (c) M. R. Lunn, D. E. Root, A. M. Martino, S. P. Flaherty, B. P. Kelley, D. D. Coovert, A. H. Burghes, N. T. Man, G. E. Morris, J. Zhou, E. J. Androphy, C. J. Sumner, B. R. Stockwell, *Chem. Biol.* 2004, *11*, 1489. (d) H. Miyachi, A. Azuma, E. Hioki, Y. Kobayashi, S. Iwasaki, Y. Hashimoto, *Chem. Pharm. Bull.* 1996, *44*, 1980. (e) J. S. Park, S. C. Moon, K. U. Baik, J. Y. Cho, E. S. Yoo, Y. S. Byun, M. H. Park, *Arch. Pharm. Res.* 2002, *25*, 137. (f) D. Hamprecht, F. Micheli, G. Tedesco, A. Checchia, D. Donati, M. Petrone, S. Terreni, M. Wood, *Bioorg. Med. Chem. Lett.* 2007, *17*, 428. (g) S. M. Allin, C. J. Northfield, M. I. Page, A. M. Z. Slawin, *J. Chem. Soc. Perkin Trans.* 2000, 1715. (h) D. Enders, V. Braig, G. Raabe, *Can. J. Chem.* 2001, *79*, 1528. (i) R. Hunter, P. Richards, *Org. Biomol. Chem.* 2003, *1*, 2348. (j) F. Csende, G. Stajer, *Curr. Org. Chem.* 2005, *9*, 1261. (k) G. Stajer, F. Csende, *Curr. Org. Chem.* 2005, *9*, 1277. (l) P.

Thapa, E. Corral, S. Sardar, B. S. Pierce, F. W. Foss Jr., J. Org. Chem. 2019, 84, 1025.

- [11] S. Muniraj, K. R. Prabhu, ACS Omega 2017, 2, 4470.
- [12] P. Gandeepan, T. Mueller, D. Zell, G. Cera, S. Warratz, L. Ackermann, *Chem. Rev.* 2019, *119*, 2192.
- [13] (a) K. N. Y. Phani, T. Rogge, Y. S. Reddy, A. Bech-toldt, E. Clot, L. Ackermann, *Chem. Eur. J.* 2017, 23, 17449. (b) J.-T. Yu, R. Chen, H. Jia, C. Pan, *J. Org. Chem.* 2018, 83, 12086. (c) F. Li, Y. Zhou, H. Yang, D. Liu, B. Sun, F.-L. Zhang, *Org. Lett.* 2018, 20, 146.
- [14] (a) K. M. Engle, T.-S. Mei, M. Wasa, J.-Q. Yu, Acc. Chem. Res. 2012, 45, 788.
  (b) S. De Sarkar, W. Liu, S. I. Kozhushkov, L. Ackermann, Adv. Synth. Catal.
  2014, 356, 1461. (c) Y. Yang, K. Li, Y. Cheng, D. Wan, M. Li, J. You, Chem. Commun. 2016, 52, 2872. (d) Q.-Z. Zheng, N. Jiao, Tetrahedron Lett. 2014, 55, 1121. (e) R. Das, G. S. Kumar, M. Kapur, Eur. J. Org. Chem. 2017, 5439.
  (f) E. N. da Silva Junior, G. A. M. Jardim, R. S. Gomes, Y.-F. Liang, L. Ackermann, Chem. Commun. 2018, 54, 7398. (g) D. Kang, K. Ahn, S. Hong, Asian J. Org. Chem. 2018, 7, 1136.
- [15] (a) C. Shan, L. Zhu, L.-B. Qu, R. Bai, Y. Lan, *Chem. Soc. Rev.* 2018, 47, 7552.
  (b) L. Ackermann, *Chem. Rev.* 2011, *111*, 1315. (c) E. Ferre Flegeau, C. Bruneau, P. H. Dixneuf, A. Jutand, *J. Am. Chem. Soc.* 2011, *133*, 10161. (d) D. L. Davies, S. A. MacGregor, C. L. McMullin, *Chem. Rev.* 2017, *117*, 8649.
  (e) I. Fabre, N. von Wolff, G. Le Duc, E. Ferrer Flegeau, C. Bruneau, P. H. Dixneuf, A. Jutand, *Chem. Eur. J.* 2013, *19*, 7595.
- [16] (a) Y.-C. Yuan, C. Bruneau, T. Roisnel, R. Gramage-Doria, *J. Org. Chem.* **2019**, *84*, 1898. (b) Y.-C. Yuan, C. Bruneau, T. Roisnel, R. Gramage-Doria, *Catal. Sci. Technol.* **2019**, *9*, 4711.
- [17] Y.-C. Yuan, C. Bruneau, T. Roisnel, R. Gramage-Doria, *Org. Biomol. Chem.***2019**, *17*, 7517.

- [18] J. A. Leitch, P. B. Wilson, C. L. McMullin, M. F. Mahon, Y. Bhonoah, I. H. Williams, C. G. Frost, ACS Catal. 2016, 6, 5520.
- [19]H. Sun, A. Horatscheck, V. Martos, M. Bartetzko, U. Uhrig, D. Lentz, P. Schmieder, M. Nazare, *Angew. Chem. Int. Ed.* 2017, 56, 6454.
- [20] N. Matuszak, G. G. Muccioli, G. Labar, D. M. Lambert, J. Med. Chem. 2009, 52, 7410.
- [21] K. P. Haval, S. B. Mhaske, N. P. Argade, Tetrahedron 2006, 62, 937.
- [22] X. Gao, L. Tang, L. Huang, Z.-S. Huang, Y. Ma, G. Wu, Org. Lett. 2019, 21, 745.
- [23] D. Lubriks, I. Sokolovs, E. Suna, Org. Lett., 2011, 13, 4324.

# **Conclusions and Perspectives**

In this PhD thesis, several ruthenium-catalyzed C-H bond functionalization reactions have been developed, especially, those including the scission of C-C and C-N bonds, as well as the formation of C-O bonds  $[C(sp^2)-H bond hydroxylation and benzoxylation]$  and the formation of C-C bonds  $[C(sp^2)-H bond alkenylation, arylation and alkylation]$ *via*C-H bond functionalization strategies. The most important contributions are pointed out here in the following general scheme:



In the **first chapter** of this thesis, a summary of the transition metal-catalyzed transformations of phthalimides, an important class of cyclic imides, has been surveyed.

In the **second chapter**, a highly chemo-selective and efficient (up to 99% yield) transformation of phthalimides into amides using an air- and moisture-stable ruthenium catalyst has been established. The reaction was found to be rather general (38 examples)

and the fact it requires no dihydrogen gas to occur, makes it appealing for real applications in industry and academia. A number of mechanistic studies (GC gas phase analysis, deuteration experiments, control experiments, trapping of intermediates) revealed a homogeneous pathway involving five-membered ring opening and  $CO_2$  release with water being the proton source.

**Chapter 3** is dedicated to the development of a regio- and site-selective  $C(sp^2)$ -H bond hydroxylation reaction of a large variety of functionalized phthalimides, succinimides, maleimides, naphthalimides, and cyclic amides (27 examples). The reactions proceeded under relatively mild conditions with as low as 1 mol% of readily-available ruthenium or palladium catalysts affording the corresponding mono-hydroxylated products at the *ortho* position with respect to the nitrogen atom of the directing group (up to 93% yield). In the case of cyclic imides, selective mono-hydroxylation occured even in the presence of large amounts of reagents. In contrast, with cyclic amides bis-hydroxylation took place.

The **chapter 4** shows the first use of the biologically-relevant isoindolinone (cyclic amide) as a weak coordinating group in transition metal-catalyzed C-H bond functionalization. In particular, this was applied to benzoxylation reactions in the presence of readily affordable (hetero)aromatic carboxylic acids. Selective mono-functionalizations in the *ortho* position with respect to the nitrogen atom were achieved smoothly with a simple ruthenium-based catalytic system. The successful reaction were efficient (up to 77% yield) with various functional groups (20 examples). Debenzoylated products were observed with a few functional groups. Cyclic imides and pyrrolidinones were found to be less efficient directing groups than isoindolinones.

In **chapter 5**, a general Ru-catalyzed C-H bond alkenylation with isoindolinone serving as a weak directing group is presented (30 examples with up to 99% yield). Selective mono-alkenylations in the *ortho* position with respect to the nitrogen atom were achieved in high yields with a ruthenium-based catalytic system under air

atmosphere. The reaction displayed one of the largest scope of alkenes (beyond acrylates) with multiple useful functional groups (including styrenes and alkynes). The versatility and high functional group tolerance of the catalysis enabled the late-stage functionalization of indoprofen and further derivatizations. Bis-alkenylation was reached in low yields (<20%) after increasing the stoichiometry of the reagents. Cyclic imides such as naphthalimides gave poor conversion, however, when the benzene is swapped by a cyclohexane ring, the carbonyl groups are likely out of plane and the alkenylation was observed in 71% yield. Therefore, subtle steroelectronic effects in very similar directing groups can lead to extremely different outcomes during the catalysis. A number of deuteration and control experiments suggested that the carbonyl group from the cyclic amide behaves as a weak directing group to assist the C-H bond activation step during the catalysis. In addition, we managed to isolate and characterize an unprecedented ruthenium-substrate complex which was found to be inactive in the catalysis.

The **sixth chapter** is devoted to the aromatic C–H bond arylation of *N*-arylisoindolinones (cyclic amides) with ruthenium catalysts in the presence of benchmark boronic acids and potassium aryltrifluoroborate derivatives, respectively. This reaction leading to biaryl formation tolerates an important number of functional groups (25 examples) due to the mild conditions used and it gives rise to mono-arylation compounds at the *ortho* position with respect to the nitrogen atom of the directing group (up to 86% yield). In these reactions, homo-coupling of the boronic acid partners was observed to some extent with specific substrates. This methodology was applied to the late-stage functionalization of indoprofen. Cyclic imides were unreactive under identical conditions and we noted that the reaction conditions required for C-H bond arylation with strong nitrogen-containing directing groups are not suitable for cyclic amides and imides.

The last chapter of the manuscript is focused on the very first examples of

258

aromatic C-H bond alkylation reactions with directing groups leading to six-membered ruthenacycle intermediates. The reactions with cyclic amides (i.e. *N*-arylisoindolinones and *N*-arylpyrrolidinones) and *N*-substituted maleimides gave rise to alkylated products in which the C-H bond functionalization took place in the *ortho* position of the benzene ring attached to the nitrogen atom. Again, as it is found in chapters 3-6, no C-H bond functionalization occurred in the other aromatic ring in which a five-membered intermediate might be formed. These systems appear to be very suitable to accommodate six-membered ruthenacycle intermediates, which drive the reaction to a unique site-selectivity.

The above-presented results highlight the importance to study synthetically useful and appealing directing groups in C-H bond functionalization together with a better understanding of the role of ruthenium in the different associated mechanisms. It was thus clearly evidenced that closely related directing groups such as cyclic imides and cyclic amides present different behaviors depending on the type of functionalization even though the activation of the same C-H bond is a common feature in all of them.

Future, short- and long-term, research efforts to follow-up the contributions reported in this PhD thesis could be the following:

- The study of the real intermediates formed during the catalytic events by means of (1) synthesis and isolation of ruthenium complexes, (2) kinetic studies to unravel the different orders of reagents as well as whether substrate/product inhibition or catalyst deactivation are at play, and (3) DFT calculations to identify the feasibility of the postulated and elusive ruthenium intermediates.

- The application of new strategies relying on green chemistry such as (1) the exploitation of solvent-free (or neat) reaction conditions, (2) the use of water as reaction media, and (3) the implementation of ruthenium-catalyzed C-H bond functionalization strategies in flow chemistry.

- The study of ruthenium catalysts with cyclic imides and amides in view to (1) form new carbon-heteroatom bonds (C-N, C-halide, C-Si,...) *via* C-H bond functionalization strategies and (2) tackle remote selectivity such as *meta* and *para* which are relatively scarce when compared to other noble transition metals such as Pd, for instance.

```
****
```
Dans cette thèse, différentes réactions de fonctionnalisation des liaisons C-H catalysées du ruthénium ont été développées. En particulier, ces transformations impliquent la coupure sélective des liaisons C-C et C-N, ainsi, que des nouvelles formations de liaisons C-O [hydroxylation et benzoxylation des liaisons C(sp<sup>2</sup>)-H] et de liaisons C-C [alcénylation, arylation et alkylation des liaisons C(sp<sup>2</sup>)-H] mettant en jeu des stratégies de fonctionnalisation des liaisons C-H. Les résultats les plus marquants et représentatifs sont rassemblés dans le schéma suivant :



Dans le **premier chapitre** de cette thèse, une revue bibliographique concernant les transformations chimiques de phthalimides, une famille d'amides cycliques importante dans différents domaines, par des catalyseurs homogènes à base de métaux de transition est présentée.

Dans le **deuxième chapitre**, une transformation très sélective et efficace (jusqu'à 99% de rendement) de phthalimides en amides secondaires en utilisant des catalyseurs robustes du ruthénium a été établie. Ce type de réaction s'est avéré très général (38 exemples) et dû au fait qu'elle n'a pas besoin du gaz dihydrogène pour avoir lieu, apparaît intéressant pour des applications directes dans l'industrie et d'un point de vue fondamental. Un certain nombre d'études mécanistiques (analyse de la phase gazeuse par GC, réactions de contrôle et de deutération, piégeage d'intermédiaires) permet de postuler un cycle catalytique impliquant l'ouverture du cycle à cinq chaînons et formation du CO2 avec l'eau comme source de protons.

Le **chapitre 3** est dédié au développement d'une réaction régio- et site-sélective d'hydroxylation the liaisons  $C(sp^2)$ -H d'une variété de phthalimides, succinimides, maleimides, naphtalimides et amides cycliques (27 exemples). Ces réactions ont lieu dans des conditions douces avec une charge en catalyseur de ruthénium ou de palladium aussi faible qu'1 mol%. Les produits correspondants mono-hydroxylés ont été fonctionnalisés en position ortho par rapport à l'atome d'azote du groupement directeur (jusqu'à 93% de rendement). Dans le cas des imides cycliques, la mono-hydroxylation sélective a lieu même en présence d'un large excès des réactifs. En revanche, dans les mêmes conditions réactionnelles, les amides cycliques donnent lieu à des produits bis-hydroxylés.

Le chapitre 4 montre la première utilisation d'une famille d'amides cycliques importante dans le domaine de la biologie, les isoindolinones, comme des groupements directeurs pour la fonctionnalisation des liaisons C-H par les métaux de transition. Plus précisément, l'application à des réactions de benzoxylation en présence d'acides carboxyliques (hétéro)aromatiques qui sont, en général, très disponibles. Avec un catalyseur de ruthénium très accessible, des mono-fonctionnalisations sélectives en position *ortho* par rapport à l'atome d'azote ont été réalisées. Les réactions sont efficaces (à hauteur de 77% de rendement) avec différents groupements fonctionnels

portés par les partenaires de couplage (20 exemples). Avec certains groupements fonctionnels des produits hydroxylés ont été observés. Les imides cycliques et des pyrrolidinones apparaissaient moins efficaces en tant que groupements directeurs que les isoindolinones (amides cycliques).

Dans le chapitre 5, une réaction générale d'alcénylation des liaisons C-H catalysée par des complexes du ruthénium avec des isoindolinones comme groupement directeur est présentée (30 exemples à hauteur de 99% de rendement). Des monoalcénylations sélectives en position ortho par rapport à l'atome d'azote ont été obtenues avec des rendements élevés avec un catalyseur au ruthénium qui fonctionne en présence d'air. Les réactions se sont avérées compatibles avec un nombre très important d'alcènes en tant que partenaire de couplage avec divers groupements chimiques facile à post-fonctionnaliser. La polyvalence et tolérance de la réaction catalytique à différents groupements fonctionnels chimiques a permis une post-dérivatisation de l'indoprofen. Des réactions de bis-alcénylation ont lieu à hauteur de <20% de rendement en utilisant un large excès de réactifs. Des imides cycliques comme les phthalimides conduisent à des conversions très faibles, mais quand le cycle benzénique est complètement hydrogéné en cyclohexane, des rendements supérieurs à 70% en alcénylation sont obtenus en raison de la non-coplanéarité des groupements carbonyles dans ce substrat. Ainsi, des effets stéréo-électroniques subtils dans des groupements directeurs voisins peuvent occasionner des résultats très différents lors de la catalyse. Des tests de contrôle et de deutération suggèrent que le groupement carbonyle des amides cycliques joue le rôle de groupement directeur faible dans l'étape élémentaire d'activation C-H pendant la catalyse. De plus, il a été possible d'isoler et de caractériser un complexe sans précèdent du type ruthénium-substrat qui est inactif dans cette catalyse.

Le **sixième chapitre** est consacré à l'arylation des liaisons aromatiques C-H des *N*-arylisoindolinones (amides cycliques) avec des catalyseurs au ruthénium en présence des acides boroniques très accessibles et des dérives d'aryltrifluoroborate de potassium,

respectivement. Ces réactions forment de nouveaux motifs biaryliques avec une grande tolérance à différents groupements fonctionnels (25 exemples) en raison des conditions réactionnelles très douces employées. En plus, seul le composé mono-arylé sélectivement en position *ortho* par rapport à l'atome d'azote du groupement directeur se forme (à hauteur de 86% de rendement). Dans certains cas, des sous-produits issus de l'homocouplage de l'acide boronique sont observés. Cette méthodologie a été appliquée à la post-fonctionnalisation de l'indoprofen. Contrairement aux amides cycliques, les imides cycliques ne sont pas réactifs dans ces conditions. Il a aussi été constaté que les conditions réactionnelles classiquement utilisées pour l'arylation des liaisons C-H avec des groupements directeurs à base d'azote (groupement directeur fort) ne sont pas compatibles avec des groupements directeurs à base d'amides ou imides cycliques (groupement directeur faible).

Le **dernier chapitre** du manuscrit est axé sur les tout premiers exemples d'alkylation des liaisons C-H avec des groupements directeurs menant à des intermédiaires ruthénacycles à 6 chaînons. Les réactions des amides cycliques telles que les *N*-arylisoindolinones ou les *N*-arylpyrrolidinones avec les maleimides comme partenaires de couplage donnent lieu à des produits issus de l'alkylation avec fonctionnalisation C-H en position *ortho* du groupement phényle directement relié à l'atome d'azote. A nouveau, comme c'était le cas dans les chapitres 3-6, aucune fonctionnalisation des liaisons C-H a lieu sur l'autre cycle benzénique où des intermédiaires ruthénacycles à 5 chaînons peuvent se former. Ces systèmes semblent être très appropriés pour s'adapter à des intermédiaires ruthénacycles à 6 chaînons, lesquels contrôlent la sélectivité de site pour cette réaction.

Les travaux issus de cette thèse soulignent l'importance d'étudier des groupements directeurs synthétiquement important dans des réactions de fonctionnalisations des liaisons C-H, ainsi que de rechercher une meilleure compréhension du rôle du ruthénium dans les différents mécanismes réactionnelles. Il paraît clairement établi que

des groupements directeurs voisins tels que les imides et les amides cycliques présentent différents comportements en fonction du type de fonctionnalisation bien que l'activation de la même liaison C-H soit commune dans tous les cas.

Des travaux futurs à moyen et long terme pouvant découler des résultats issus de cette thèse pourraient être les suivants :

- L'étude des intermédiaires réels qui se forment pendant la catalyse par différents moyens tels que (1) la synthèse et la caractérisation des nouveaux complexes de ruthénium, (2) des études cinétiques approfondies pour établir l'ordre en réactifs et catalyseurs ainsi que pour déterminer s'il y a lieu l'inhibition par les substrats et/ou le produit et quelle est la cause de la désactivation du catalyseur, et (3) des calculs théoriques (type DFT) pour identifier la faisabilité des intermédiaires supposés du ruthénium.

- L'application des nouvelles stratégies basées sur les principes de la chimie verte tels que (1) l'utilisation des conditions réactionnelles sans solvant, (2) l'utilisation de l'eau comme réactif ou solvant, et (3) la mise en œuvre de stratégies de fonctionnalisation de liaisons C-H catalysées par le ruthénium en chimie en flux continu.

- L'étude des catalyseurs à base de ruthénium avec des amides et des imides cycliques de manière à (1) former des nouvelles liaisons carbone-hétéroatome (C-N, C-halogénure, C-Si,...) par des stratégies des fonctionnalisations des liaisons C-H, et (2) aborder des sélectivités dites *remote* telles que *meta* et *para* lesquelles sont relativement rares comparées avec d'autres métaux de transitions nobles comme le palladium, par exemple.

\*\*\*\*

- [1] Yuan, Y.-C.; Kamaraj, R.; Bruneau, C.; Labasque, T.; Roisnel, T.; Gramage-Doria, R.\* "Unmasking Amides: Ruthenium-Catalyzed Protodecarbonylation of *N*-Substituted Phthalimide Derivatives." *Org. Lett.* 2017, *19*, 6404-6407. [Part of this contribution appears in Chapter 2]
- [2] Yuan, Y.-C.; Bruneau, C.; Gramage-Doria, R.\* "Merging Transition-Metal Catalysis with Phthalimides: A New Entry to Useful Building Blocks." *Synthesis* 2018, *50*, 4216-4228. [Part of this contribution appears in Chapter 1]
- [3] Yuan, Y.-C.; Bruneau, C.; Dorcet, V.; Roisnel, T.; Gramage-Doria, R.\* "Ru-Catalyzed Selective C-H Bond Hydroxylation of Cyclic Imides." *J. Org. Chem.*, 2019, 84, 1898-1907. [Part of this contribution appears in Chapter 3]
- [4] Yuan, Y.-C.; Bruneau, C.; Roisnel, T.; Gramage-Doria, R.\* "Ruthenium(II)-Catalysed Selective C(sp<sup>2</sup>)-H Bond Benzoxylation of Biologically Appealing *N*-Arylisoindolinones" *Org. Biomol. Chem.* 2019, *17*, 7517-7525. [Part of this contribution appears in Chapter 4]
- [5] Yuan, Y.-C.; Bruneau, C.; Roisnel, T.; Gramage-Doria, R.\* "Site-Selective Ru-Catalyzed C-H Bond Alkenylation with Biologically Relevant Isoindolinones: A Case of Catalyst Performance Controlled by Subtle Stereo-Electronic Effects of the Weak Directing Group" *Catal. Sci. Technol.* 2019, *9*, 4711-4717. [Part of this contribution appears in Chapter 5]
- [6] Yuan, Y.-C.; Bruneau, C.; Roisnel, T.; Gramage-Doria, R.\* "Site-Selective Ruthenium-Catalyzed C-H Bond Arylations with Boronic Acids: Exploiting Isoindolinones as a Weak Directing Group" *J. Org. Chem.* 2019, *84*, 12893-12903.
  [Part of this contribution appears in Chapter 6]

[7] Yuan, Y.-C.; Goujon, M.; Bruneau, C.; Roisnel, T.; Gramage-Doria, R.\* "C-H Bond Alkylation of Cyclic Amides with Maleimides via a Site-Selective-Determining Six-Membered Ruthenacycle" *manuscript submitted*. [Part of this contribution appears in Chapter 7]





Titre : Fonctionnalisation durable d'amides et d'imides cycliques avec des catalyseurs au ruthénium : développement, applicabilité et mécanismes.

Mots clés : catalyse homogène; ruthénium; chimie fine; économie d'atomes; économie d'étapes

Résumé : La synthèse durable et plus respectueuse dans l'environnement est très important dans le devenir de notre société. Dans ce contexte, la formation et la rupture des liaisons chimiques de manière contrôlée est au cœur de la chimie. Ainsi, réduire le nombre d'étapes pour l'élaboration des molécules, éviter l'utilisation des guantités sousstoichiometriges des réactifs dangereux et diminuer les quantités des déchets sont quelques-uns des principes relevés de la chimie verte. Dans cette thèse de doctorat, différents stratégies ont été développé de manière à accéder à des molécules à haute valeur partant de aiouté en molécules très peu fonctionnalisés. En utilisant des catalyseurs de ruthénium (qui sont plus abondant et moins couteux que ses homologues classiques Rh, Pd, Ir, etc.), il s'est avéré que des amides et des imides cycliques (qui sont des constituants très important pour la biolo-

-gie et les sciences des matériaux) se comportent comme des groupements directeurs pour la fonctionnalisation des liaisons très énergétiques C-H. En particuliers, des réactions très sélectives de formation carbone-oxygène et carbone-carbone, respectivement, ont été développés en utilisant des réactifs très disponibles tels que les acides carboxyliques, les alcènes et les acides boroniques. Plusieurs dérivatisations ont été effectués (i.e. indoprofen) pour illustrer le potentiel de ces méthodologies. Pendant ces études. la transformation inattendue groupement de phthalimides en amides secondaires en présence des catalyseurs au ruthénium a été relevée et analysée en détail. Les mécanismes réactionnels associés à toutes ces transformations ont été étudié en partie pour avoir une meilleure compréhension des catalyseurs au ruthénium.

Title: Sustainable Functionalization of Cyclic Amides and Imides with Ruthenium Catalysts: Development, Scope and Mechanisms.

Keywords: homogeneous catalysis; ruthenium; fine chemistry; atom-economy; step-economy

**Abstract:** The sustainable synthesis of fine chemicals is an important topic in view to drive our society to a more environmentally respectful way of living. In this context, forming and breaking chemical bonds at will with high levels of selectivity is at the central core of chemical synthesis. Consequently, reducing the number of chemical steps towards the target avoiding the utilization molecules. of overstoichiometric amounts of hazardous reagents and diminishing chemical wastes are only some of the challenges to be addressed by a future green chemistry. In this PhD thesis, different strategies are developed to prepare highly-added value chemicals starting from verv low-functionalized starting materials. Using ruthenium catalysts, which are more abundant and less expensive than other noble metals (i.e. Pd, Rh, Ir, etc.), it was found that cyclic amides and cyclic imides, which are important building blocks in biology and materials science, behave as excellent weak directing groups to functionalize traditionallybelieved inert aromatic C-H bonds.

Particular focus was devoted to the formation of new C-O and C-C chemical bonds using readily available and benchmark (air and moisture) stable carboxylic acids, alkenes and boronic acids, respectively, as coupling partners. These reactions led to excellent levels of selectivity (i.e. site, regio, stereo). Some derivatizations of the resulting compounds and the late-stage functionalization of a representative drug candidate were tackled to highlight the utility of these methodologies. In the course of these studies, an unexpected cleavage of phthalimides leading to secondary amides was identified in the presence of a ruthenium catalyst. Traditionally, phthalimides are cleaved in the presence of hydrazine to release primary amines, however, such unprecedented protodecarbonylation reaction fills the gap delivering secondary amides. The mechanisms associated to transformations all these were investigated experimentally to some extent with the aim to gain a better fundamental understanding.