

Title	Studies on Site-Selective C-H Activation of Aromatic Amides with Alkenes through Six-Membered Palladacycles
Author(s)	何, 其原
Citation	大阪大学, 2022, 博士論文
Version Type	VoR
URL	https://doi.org/10.18910/88012
rights	
Note	

Osaka University Knowledge Archive : OUKA

<https://ir.library.osaka-u.ac.jp/>

Osaka University

Doctoral Dissertation

**Studies on Site-Selective C-H Activation of
Aromatic Amides with Alkenes through
Six-Membered Palladacycles**

Qiyuan He

January 2022

Department of Applied Chemistry
Graduate School of Engineering,
Osaka University

Contents

contents.....	1-2
Preface and Acknowledgement	3-4
General Introduction	5-8
 Chapter 1: Palladium-Catalyzed Benzylic C-H Alkylation of Benzamides with Maleimides	
1.1 Introduction.....	9-10
1.2 Results and Discussion.....	10-15
1.3 Conclusion	15-16
1.4 Experimental Section.....	16-30
1.5 References	30-31
 Chapter 2: Palladium-Catalyzed [3+2] Annulation of Benzamides and Anilides via benzylic and meta C-H Bond Activation	
2.1 Introduction.....	32
2.2 Results and Discussion.....	32-38
2.3 Conclusion	38
2.4 Experimental Section.....	38-64
2.5 References	64-65
 Chapter 3: Palladium-Catalyzed Site-Selective [5+1] Annulation of Aromatic Amides with Terminal Alkenes: Effect of Maleic Anhydride for β-H elimination	
3.1 Introduction.....	66-68
3.2 Results and Discussion.....	68-74
3.3 Conclusion	73-74
3.4 Experimental Section.....	74-92
3.5 References	92-94

Chapter 4: Rhodium-Catalyzed ortho C-H Alkylation of Aromatic Amides with Maleimides

4.1 Introduction.....	95-96
4.2 Results and Discussion.....	96-98
4.3 Conclusion	98
4.4 Experimental Section.....	98-114
4.5 References	114-115
List of Publications	116

Preface and Acknowledgement

The research presented in this thesis was carried out under the direction of Professor Naoto Chatani of the Department of Applied Chemistry, Faculty of Engineering, Osaka University from October 2016 to March 2022. The thesis is mainly concerned with transition-metal catalyzed site-selective C-H activation via kinetically unfavored six-membered palladacycles.

This thesis could not be completed without the support from the teammate and co-workers. Therefore, I deeply appreciate to all of them for their kind help over these years.

First and foremost, I would like to appreciate Prof. Naoto Chatani, my supervisor, for his kind guidance and research advise. He provided me a chance to study in Japan although I mainly studied in the field of polymer chemistry when I was an undergraduate student. He gave me enormous freedom for my study and research.

Additionally, I appreciate Dr. Yoshiya Fukumoto, Associate Professor in our group, for his kind support and management. I also wish to thank Dr. Yusuke Ano, our group's Assistant Professor, who support my research in the part of DFT calculation. Besides, I wish to thank Ms. Junko Ohmagari for her kind help.

I also appreciate Prof. Nobuaki Kambe, Prof. Mamoru Tobisu to support me to apply CSC scholarship.

I specially appreciate Dr. Yasuaki, Iyori. He is a kind person who let me adapt to live in Japan. I also wish to thank Mr. Takuma Yamaguchi and Ms. Satoko Natsui. I finished my first research project under their friendly help.

I also wish to thank other partners in Chatani lab: Dr. Yadagiri Kommagalla, Dr. Aymen Skhiri, Dr. Supriya Rej, Dr. Amrita Das, Dr. Sanjit Kumar Mahato, Dr. Shrikant Khake Manmathappa, Dr. Kaname Shibata, Dr. Takayuki Furukawa, Dr. Masaya Hirano, Dr. Toshifumi Morioka, Dr. Yoshihiro Masuya, Dr. Takuya Igarashi, Dr. Kosuke Yasui, Dr. Chen-an Wang, Dr. Shun Sakurai, Ms. Natsuki Okazaki, Ms. Mao Yamaguchi, Mr. Soudai Yamada, Mr. Atsushi Obata, Mr. Akihiro Nishizawa, Mr. Yuki Amano, Ms. Akane Sasagawa, Mr. Akira, Haito, Mr. Masaya, Higashino, Mr. Nao Matsubara, Mr. Shunsuke Ando, Ms. Rina Ueno, Mr. Kenjiro Takahashi, Mr. Yasuhiro Tamaki, Mr. Ken Yamazaki (co-worker in Chapter 3, DFT calculation), Mr. Hisayasu Ishibashi, Mr. Kazuki Azumagawa, Ms. Nozomi Ohara, Mr. Natsuki Kawai, Mr. Itsuki Nohira, Mr. Shizuki Monda, Mr. Hiroki Enomoto, Ms. Haruka Kawakami, Mr. Daichi Takahashi, Mr. Hikaru Noguchi, Mr. Akihisa Matsuura, Ms. Aoi Morishige, Mr. Tianhao Zhang (amazing classmate since Dalian University of Technology), Mr. Ryosuke, Nagamure,

Mr. Kumpei Nishimura, Mr. Tatsuya Hirano, Mr. Haruki, Hirosawa, Mr. Yuuki Nakamoto, Mr. Kazumune Yo, Mr. Syunsuke Watanabe, Ms. Sakura Takahashi, Ms. Nami Tanaka, Mr. Syoutarou Yano, Mr. Kippeï Yamamura.

I wish to thank my parents, Mr. Jin He and Ms. Rong Zhou; my beautiful wife, Ms. Yun Wen, who support me mentally in these five and half years. I specially appreciate my grandfather Mr. Fujian He; he encourages me to take up advanced studies.

As an elder said: you cannot really predict your future. Lots of unpredicted results might be appeared in any time. Our decision is also very important. To innocent or carefully analyze would lead to different results. This elder also said: You all, don't always think of making a headline. A great achievement might be initiated by a small thing. This thesis was also developed from a very weak peak on NMR spectrogram. However, I feel ashamed that I only did some tiny work. There still have a lot of challenges in the research field of C-H activation. I hope that my work might be useful for the future work. (Anyway, I still want to repeat this elder's talk: Then I read two lines from a poem, 'Were it to benefit my country I would lay down my life; What then is risk to me?' of course, I want to donate one second of my life for this elder! Exciting!)

Suita, Osaka, Japan.

January 2022

Qiyuan He

General Introduction

Transition-metal catalyzed C-H activation is one of the most attractive research fields in organic chemistry because it has been recognized as one of the more straightforward and ideal strategies for preparing complexes and molecules from structurally simple compounds. Since Murai and co-workers reported the first effective chelation-assisted C-H alkylation of aromatic ketones with terminal alkenes leading to the alkylation products in 1993 (Figure 1a),¹ various transformations have been achieved through directed C-H activation.² However, most of these reactions only use single heteroatom such as oxygen, nitrogen and phosphorus as directing group. In 2005, Daugulis reported a palladium-catalyzed C-H arylation of amides with aryl iodides utilizing an 8-aminoquinonyl group as a directing group (Figure 1b).³ Bidentate directing groups such as N-N, N-S and N-O type directing groups are started to be used in the research of direct C-H activation (Figure 2).⁴

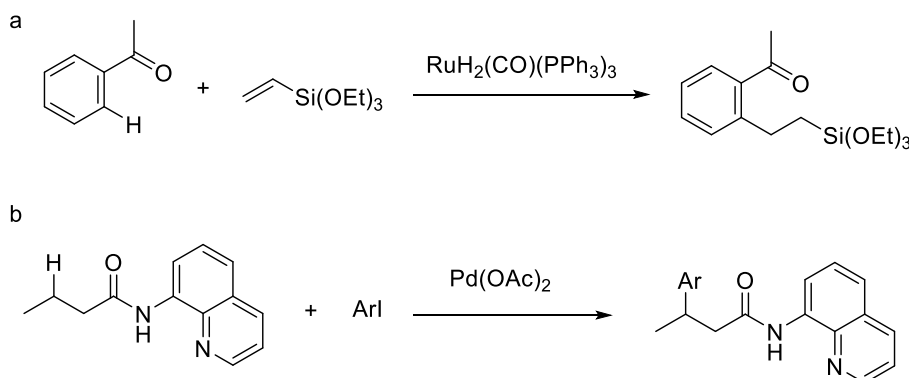


Figure 1. The Pioneering Examples of Directing C-H Activation.

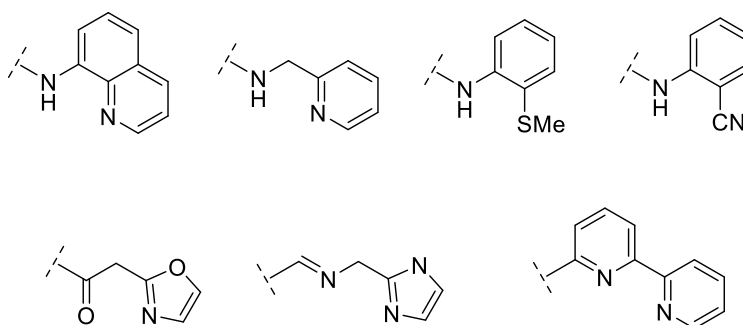


Figure 2. Bidentate Directing Groups.

In the research field of transition-metal catalyzed direct C-H activation, most of the reports involves the *ortho* or β C-H activation. Because these transformations are

normally undergone five-membered metallacycles, which are generally more kinetically and thermodynamically stable than six-membered metallacycles is less favored.⁵

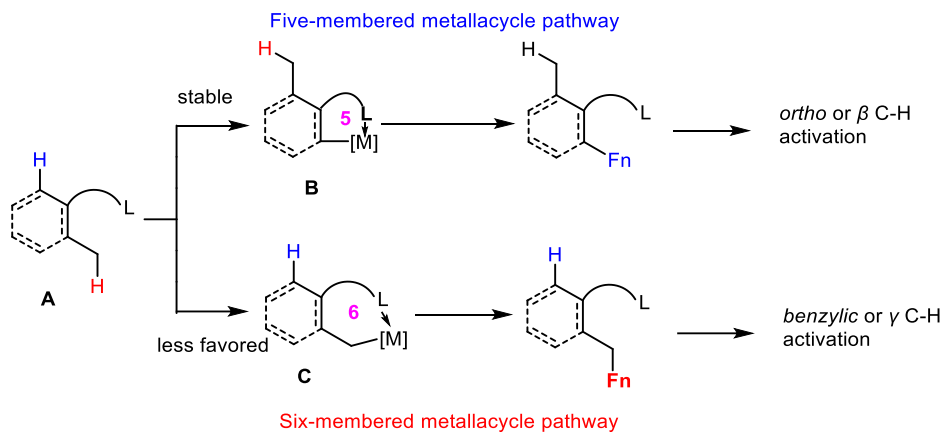


Figure 3. Five-membered & six-membered metallacycle in C-H activation.

Although most of the reactions proceed through kinetically favored five-membered metallacycle, there are several reactions that involve six-membered metallacycles. Yu reported a palladium-catalyzed C-H arylation of benzaldehydes (Figure 4a).^{6a} In this reaction, amino acids are utilized as a transient-directing group for constructing six-membered palladacycles. The similar transformation reactions were reported by other groups.⁶ Furthermore, Yu reported a palladium-catalyzed C-H fluorination of benzaldehyde (Figure 4b), which also involves benzylic C(sp³)-H bond rather the *ortho* C(sp²)-H bond.⁷ Both of the two reactions are underwent via a six-membered palladacycle.

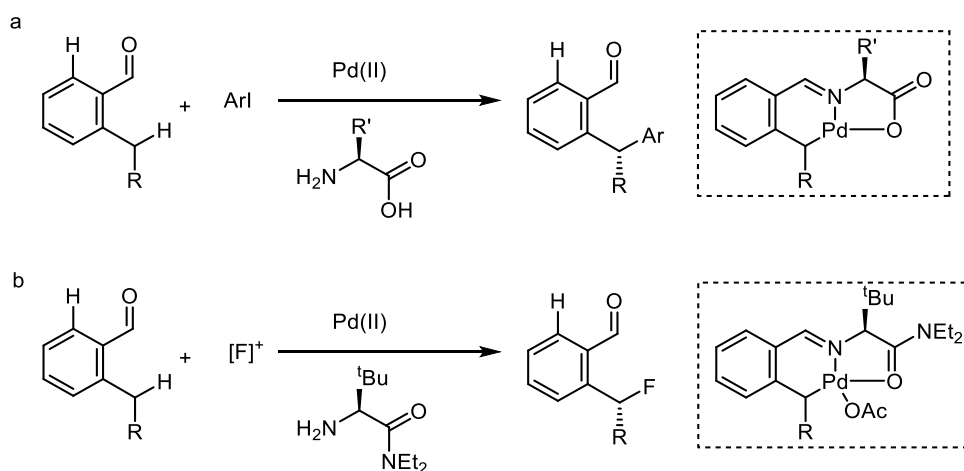


Figure 4. C-H arylation and fluorination via six-membered metallacycle.

Yu reported a palladium-catalyzed δ selective C-H arylation of amine using modified transient-directing groups.⁸ The δ C-H arylation product was produced by a six-membered palladacycle (Figure 5). This is an unusual example of C-H activation, in which a six-membered metallacycle pathway dominates over a pathway via a five-membered metallacycle. Besides, they also achieved a similar C-H arylation of ketones via six-membered palladacycles.⁹

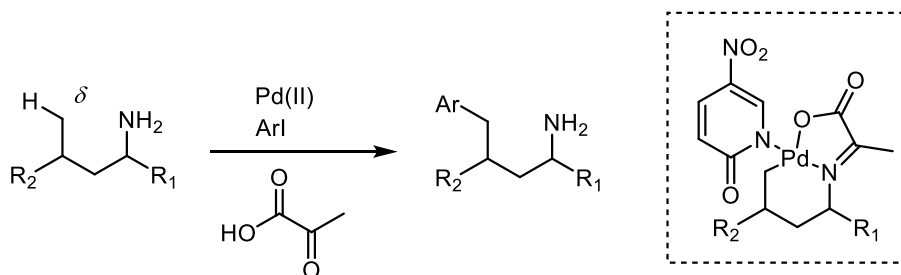


Figure 5. δ Selective C-H Arylation of Amines via Six-Membered Metallacycle.

Although there are some other examples about transition-metal catalyzed site-selective C-H activation via six-membered metallacycle, most of these reactions require special substrates, in which the generation of five-membered metallacycles are restricted.¹⁰

To the best of our knowledge, there are only few examples of site-selective benzylic C-H activation via six-membered palladacycle in the presence to *ortho* C(sp²)-H activation.

This thesis focuses on the research of site-selective C-H activation of aromatic compounds with alkenes.

Chapter 1 includes a palladium-catalyzed benzylic C-H alkylation of 8-aminoquinoyl group chelated aromatic amides with maleimides, which involves a six-membered palladacycle. Although the five-membered palladacycle, which could be initiated by an *ortho* C(sp²)-H activation is kinetically and thermodynamically stable.

Chapter 2 includes a palladium-catalyzed [3+2] annulation of *N*, *S*-chelated aromatic benzamides and anilides with maleimides. This reaction involves the activation of a benzylic C-H bond and a *meta* C-H bond.

Chapter 3 includes a palladium-catalyzed [5+1] annulation of *N*, *S*-chelated aromatic amides with terminal alkenes, which involves benzylic C-H activation. The site-selectivity was achieved by the use of maleic anhydride as the ligand.

Chapter 4 is a rhodium(I)-catalyzed *ortho* C-H alkylation of aromatic amides with maleimides. The use of ruthenium(II) as a catalyst also allows for a the similar transformation.

References

- (1) Murai, S.; Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N. *Nature* **1993**, *366*, 529-531.
- (2) For recent reviews on C-H functionalization see: (a) Chen, Z.; Wang, B.; Zhang, J.; Yu, W.; Liu, Z.; Zhang, Y. *Org. Chem. Front.* **2015**, *2*, 1107-1295. (b) Crisenza, G. E. M.; Bower, J. F. *Chem. Lett.* **2016**, *45*, 2-9. (c) Dong, Z.; Ren, Z.; Thompson, S. J.; Xu, Y.; Dong, G. **2017**, *117*, 9333-9403. (d) Ano, Y.; Chatani, N. *Org. React.* **2019**, *100*, 622-670. (e) Evano, G.; Theunissen, C. *Angew. Chem. Int. Ed.* **2019**, *58*, 7202-7236. (f) Woźniak, L.; Tan, J.-F.; Nguyen, Q.-H.; du Vigné, A. M.; Smal, V.; Cao, Y.-X.; Cramer, N. *Chem. Rev.* **2020**, *120*, 10516-10543. (g) Ali, W.; Prakash, G.; Maiti, D. *Chem. Sci.* **2021**, *12*, 2735-2759. (h) Aldhous, T. P. Chung, R. W. M.; Dalling, A. G.; Bower, J. F. *Synthesis* **2021**, *53*, 2961-2975.
- (3) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 13154-13155.
- (4) Rej, S.; Ano, Y.; Chatani, N. *Chem. Rev.* **2020**, *120*, 1788-1887.
- (5) For selected recent reviews and papers, see: Xu, J.-W.; Zhang, Z.-Z.; Rao, W.-H.; Shi, B.-F. *J. Am. Chem. Soc.* **2016**, *138*, 10750-10753. (b) Liu, Z.; Ni, H.-Q.; Zeng, T.; Engle, K. M. *J. Am. Chem. Soc.* **2018**, *140*, 3223-3227. (c) Chen, Y.-Q.; Wang, Z.; Wu, Y.; Wisniewski, S. R.; Qiao, J. X.; Ewing, W. R.; Eastgate, M. D.; Yu, J.-Q. *J. Am. Chem. Soc.* **2018**, *140*, 17884-17894.
- (6) (a) Zhang, F.-L.; Hong, K.; Li, T.-J.; Park, H.; Yu, J.-Q. *Science* **2016**, *351*, 252-256. (b) Ma, F.; Lei, M.; Hu, L. *Org. Lett.* **2016**, *18*, 2708-2711. (c) Park, H.; Yoo, K.; Jung, B.; Kim, M. *Tetrahedron* **2018**, *74*, 2048-2055. (d) Tang, M.; Yu, Q.; Wang, Z.; Zhang, C.; Sun, B.; Yi, Y.; Zang, F.-L. *Org. Lett.* **2018**, *20*, 7620-7623. (e) Wang, Z.; Dong, W.; Sun, B.; Yu, Q.; Zhang, F.-L. *Tetrahedron* **2019**, *75*, 4031-4041. (f) Wen, F.; Li, Z. *Adv. Synth. Catal.* **2020**, *362*, 133-138. (g) Wei, F.; Li, Z. *Synth. Commun.* **2020**, *50*, 3462-3474. (h) Ding, M.; Hua, W.; Liu, M.; Zhang, F. *Org. Lett.* **2020**, *22*, 7419-7423.
- (i) Lei, L.; Wu, P.; Liu, Z.; Lou, J. *Tetrahedron Lett.* **2021**, *67*, 152865.
- (7) Park, H.; Verma, P.; Hong, K.; Yu, J.-Q. *Nat. Chem.* **2018**, *10*, 755-762.
- (8) Chen, Y.-Q.; Wang, Z.; Wu, Y.; Wisniewski, S. R.; Qiao, J. X.; Ewing, W. R.; Eastgate, M. D.; Yu, J.-Q. *J. Am. Chem. Soc.* **2018**, *140*, 17884-17894.
- (9) Zhu, R.-Y.; Li, Z.-Q.; Park, H. S.; Senanayake, C. H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2018**, *140*, 3564-3568.
- (10) For selected reports, see: (1) Deb, A.; Singh, S.; Seth, K.; Pimparkar, S.; Bhaskararao, B.; Guin, S.; Sunoj, R. B.; Maiti, D. *ACS. Catal.* **2017**, *7*, 8171-8175. (b) Schreib, B. S.; Carreira, E. M. *J. Am. Chem. Soc.* **2019**, *141*, 8758-8763.

Chapter 1

Palladium-Catalyzed Benzylic C-H Alkylation of Benzamides with Maleimides

1.1 Introduction

C-H functionalization has found widespread applications in the fields of material science and the pharmaceutical industry.¹ The use of a directing group in chelation-assisted C-H functionalization reactions has been found to be the most reliable method for achieving high efficiency and high site-selectivity in such reactions. Most examples of chelation-assisted C-H functionalization reactions reported thus far show *ortho*-selectivity. In the reaction of a substrate with a methyl group at the *ortho*-position, as in A, the *ortho*-C-H bond is exclusively functionalized and a C-H bond in an *ortho*-methyl group remains unreactive in most C-H functionalization reactions that have been reported thus far. Maleimide is known as one of the reactive alkenes which has been widely used as a coupling partner in C-H activation.¹ In 2015, Miura reported a Cu-mediated reaction of aromatic amides with maleimides leading to the preparation of spiro products in the 8-aminoquinonyl chelation system (Figure 1a).² A similar transformation was also reported by Jeganmohan who used cobalt catalytic system.³ In contrast, our group reported a Rh(I)-catalyzed C-H alkylation of aromatic amides using the same chelation system (Figure 1b).⁴ These reactions involved the selective cleavage of the *ortho* C-H bond through a five-membered metallacycle.

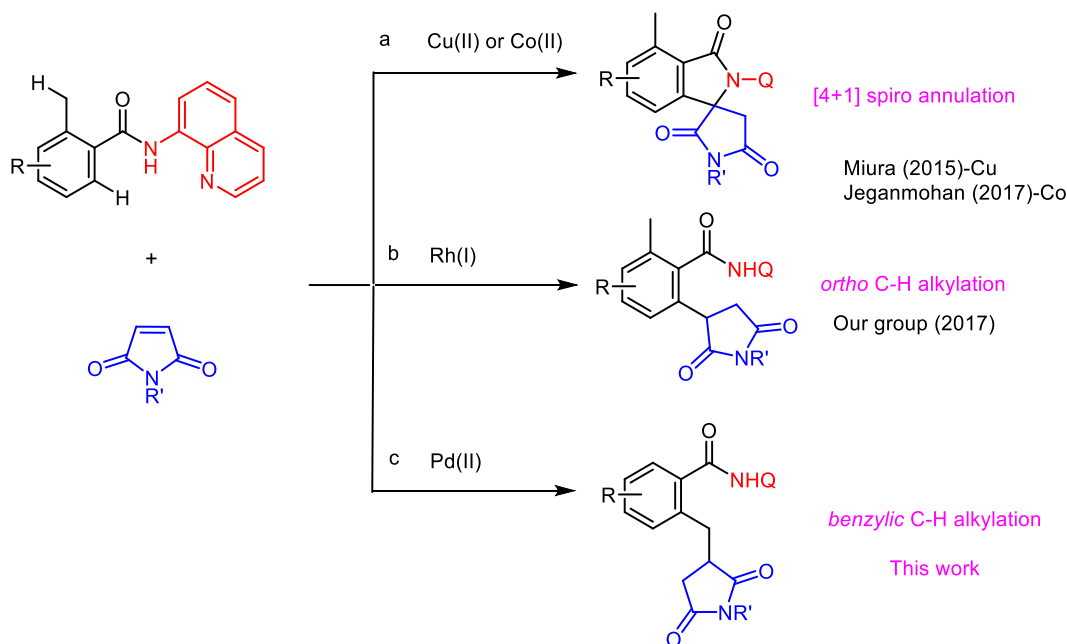


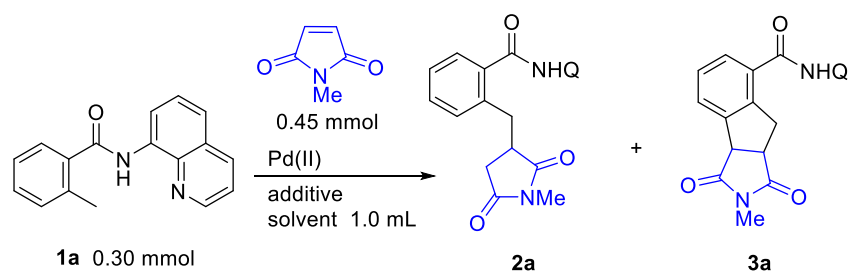
Figure 1. Transition-Metal Catalyzed/Mediate C-H Activation of 8-aminoquinonyl Chelated Aromatic Amide with Maleimide.

This chapter introduces a palladium-catalyzed benzylic selective C-H alkylation of aromatic amide with maleimide, which undergo a six-membered palladacycle although the five-membered metallacycle is more kinetically stable (Figure 1c).

1.2 Results and Discussion

The reaction of amide **1a** (0.3 mmol) with *N*-methylmaleimide (0.30 mmol) in the presence of Pd(OAc)₂ (0.045 mmol) as a catalyst, Ag(OAc)₂ (0.3 mmol), and LiCl (0.3 mmol) in toluene (1 mL) at 120 °C for 48 h gave a mixture of the alkylation product **2a** and the cyclized product **3a** in a total NMR yield of 14% in a 3:2 ratio (entry 1).

Table 1. Optimization of Reaction Conditions



The reaction scheme shows the reaction of amide **1a** (0.30 mmol) with *N*-methylmaleimide (0.45 mmol) in the presence of Pd(II), additive, and solvent (1.0 mL) to produce products **2a** and **3a**.

entry	catalyst (mol %)	additive (equiv)	temp (°C)	solvent	yield (2a : 3a) ⁱ
1 ^{a,b}	Pd(OAc) ₂ (10)	AgOAc (1.0), LiCl (1.0)	120	toluene	14% (3:2)
2 ^{a,b}	-	AgOAc (1.0), LiCl (1.0)	120	toluene	n.d
3 ^{b,c}	Pd(OAc) ₂ (10)	Cs ₂ CO ₃ (1.0)	160	toluene	n.d
4 ^{b,d}	Pd(OAc) ₂ (10)	AgOAc (1.0)	120	DCE	24% (3:2)
5 ^{b,e}	Pd(OAc) ₂ (15)	AgOAc (1.0)	120	AcOH	54% (3:2)
6 ^{b,e}	Pd(OAc) ₂ (15)	Cu(OAc) ₂ ·H ₂ O (1.0)	120	AcOH	55% (3:2)
7 ^{b,e}	Pd(OAc) ₂ (15)	Cu(OAc) ₂ ·H ₂ O (1.0)	120	HFIP	37% (3:2)
8 ^{d,f}	Pd(OAc) ₂ (15)	Cu(OAc) ₂ ·H ₂ O (2.0)	140	^t BuOH	64% (3:2)
9 ^{d,g}	Pd(OAc) ₂ (15)	Cu(OAc) ₂ ·H ₂ O (1.0)	160	DMF	n.d
10 ^{d,g}	Pd(OAc) ₂ (15)	Cu(OAc) ₂ ·H ₂ O (1.0)	160	PivOH	61% (7:1)
11 ^{d,g}	Pd(OAc) ₂ (15)	AgOAc (1.0)	160	PivOH	64% (7:1)
12 ^{d,g}	Pd(OAc) ₂ (15)	Ag ₂ O (1.0)	160	PivOH	trace
13 ^{d,g}	Pd(OAc) ₂ (15)	PhI(OAc) ₂ (1.0)	160	PivOH	n.d
14^h	Pd(OPiv)₂ (15)	AgOAc (1.2)	160	PivOH	91% (7:1)

^aFor 48 h. ^b*N*-Methylmaleimide (0.45 mmol) was used. ^cFor 18 h. ^dFor 36 h. ^eFor 42 h. ^f*N*-Methylmaleimide (0.90 mmol) was used. ^g*N*-Methylmaleimide (0.6 mmol) was used. ^h*N*-Methylmaleimide (1.50 mmol) was used for 24 h. ⁱIsolated yield.

The formation of **3a** involves a double activation of C-H bonds at the benzylic position and at the meta-position. Curiously, no *ortho*-alkylation product was detected.¹⁷ It was found that the use of Pd(OAc)₂ and AgOAc is essential for the reaction to proceed (entries 1-4). The use of Cu(OAc)₂ in place of AgOAc in acetic acid gave comparable product yields (entries 5 and 6). Although the use of DMF as a solvent gave no reaction, the other solvents tested had no effect on the efficiency and selectivity of the reaction (entries 6-8). However, the use of PivOH as a solvent at 160 °C resulted in a dramatic improvement in the selectivity to 7:1 in favor of **2a** (entries 10 and 11). Ag₂O and PhI(OAc)₂ did not give the expected product (entries 12-13). Finally, the optimized reaction conditions were determined to be as follows: amide (**1**, 0.3 mmol), maleimide (1.5 mmol), Pd(OPiv)₂ (0.045 mmol) in PivOH (1 mL) at 160 °C for 24 h. (entry 14).

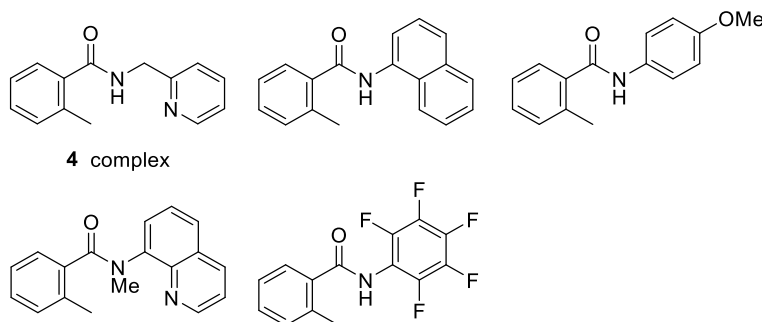


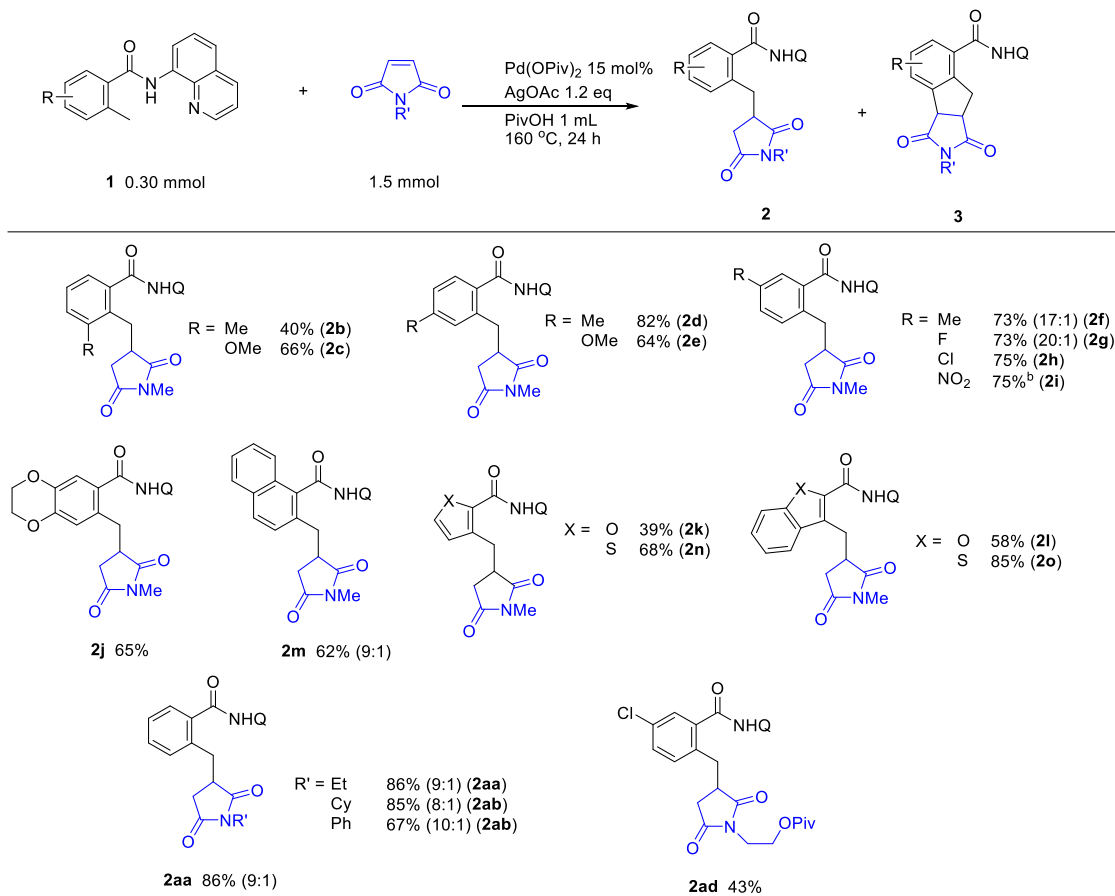
Figure 2. Ineffective Directing Groups.

After establishing the optimized reaction conditions, the effect of directing groups was examined (Figure 2). The use of a 2-pyridinylamine directing group, as in **4**, gave a complex mixture. No reaction occurred when other directing groups were used in the reaction. These results show that the presence of both an amide NH and a quinoline nitrogen is required for the success of this reaction.

The scope of the reaction with respect to the aromatic amide was also investigated (Scheme 1). The reaction of **1b** and **1c** gave the expected products **2b** and **2c**, respectively, even though the reaction site is sterically hindered. The reaction of the para-substituted aromatic amides **1d** and **1e** selectively gave **2d** and **2e**, respectively, with no double activation products **3d** and **3e** being formed, because of steric hindrance at the 3-position. The reaction showed a high functional group tolerance. It is also noteworthy that, even NO₂ was tolerated in the reaction, as in **2i** and that naphthalene and a variety of heterocycles such as furan, benzofuran, thiophene, and benzothiophene, as in **2k-2o** also participated in the reaction. Various maleimides bearing ethyl, cyclohexyl and phenyl groups showed a high reactivity. When *N*-ethylhydroxyl

maleimide was used as a coupling partner, the free hydroxyl group reacted with the acid solvent to give the pivalate ester **2ad**. In all cases, the C-H bond at the *ortho*-position remained inert.

Scheme 1. Pd(II)-Catalyzed Reaction of Aromatic Amides with Maleimides^a

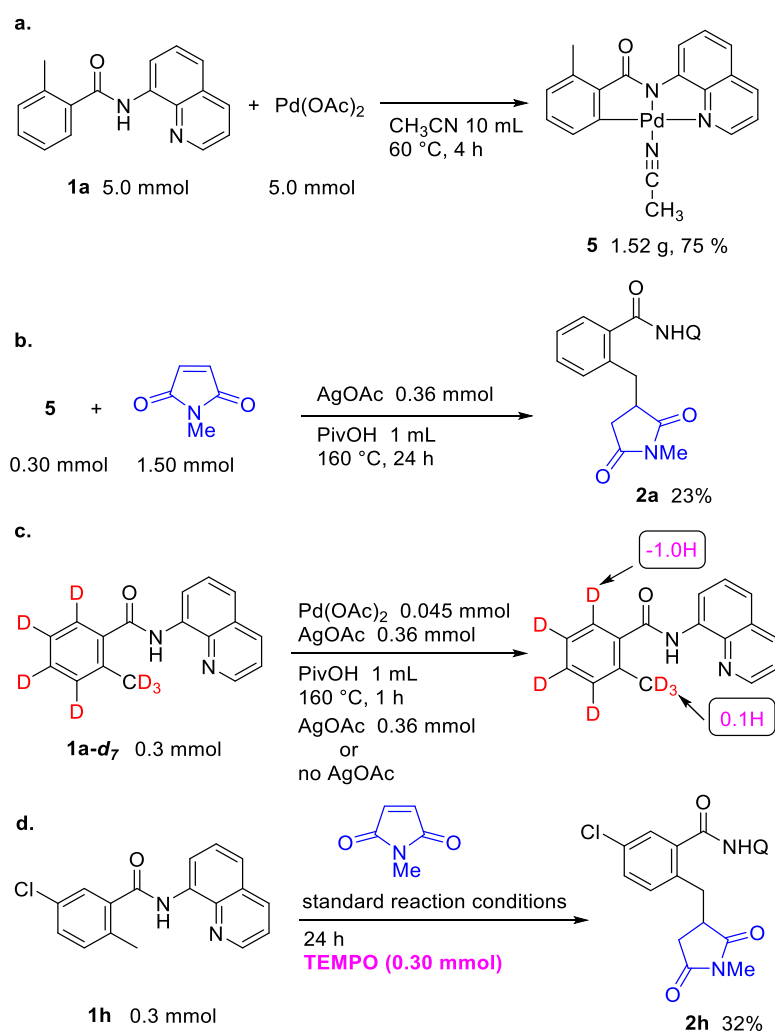


^aReaction conditions: amine (**1**, 0.3 mmol), maleimide (1.5 mmol), Pd(OPiv)₂ (0.045 mmol), AgOAc (0.36 mmol) in PivOH (1.0 mL) at 160 °C for 24 h. A number in parenthesis refers a ratio of **2** and **3**. ^bThe reaction was carried out at 140 °C.

To gain insights into the reaction mechanism, a stoichiometric reaction of **1a** with Pd(OAc)₂ was carried out (Scheme 2a). As expected, a five-membered palladacycle **5**¹⁹ was successfully isolated. The reaction of **5** with maleimide in the absence of Pd(OAc)₂ gave **2a** as the product, which was alkylated at the *ortho*-methyl C-H bond, as a single product (Scheme 2b). When the deuterated benzamide **1a-d₇** was reacted under the standard reaction conditions, but in the absence of maleimide, a D atom at the *ortho*-position was completely exchanged for a H atom, even within a short reaction time, i.e. 1 h, although no alkylation occurred at this position. In contrast, the D-content

of the methyl group at the *ortho*-position remained relatively constant (0.1H). Exactly the same result was obtained, even in the absence of AgOAc. These results suggest that 1) the cleavage of a C-H bond at the *ortho*-positions is reversible and the cleavage of an *ortho* C-H bond via the formation of a five-membered palladacycle is much faster than the cleavage of the *ortho* methyl C-H bond which proceeds via a six-membered palladacycle,⁵ 2) the subsequent reaction of the six-membered palladacycle with maleimide is much faster than the protonation (H/D exchange), 3) the subsequent reaction of the five-membered palladacycle with maleimide does not appear to occur. When the reaction of **1h** that was carried out under standard reaction conditions, but for 1h in the presence of 1 equivalent of 2,2,6,6-Tetramethylpiperidine 1-Oxyl (TEMPO), **2h** was produced in 32% isolated yield, suggesting that a radical species is not involved in this reaction (Scheme 2d).

Scheme 2. Mechanistic Experiments



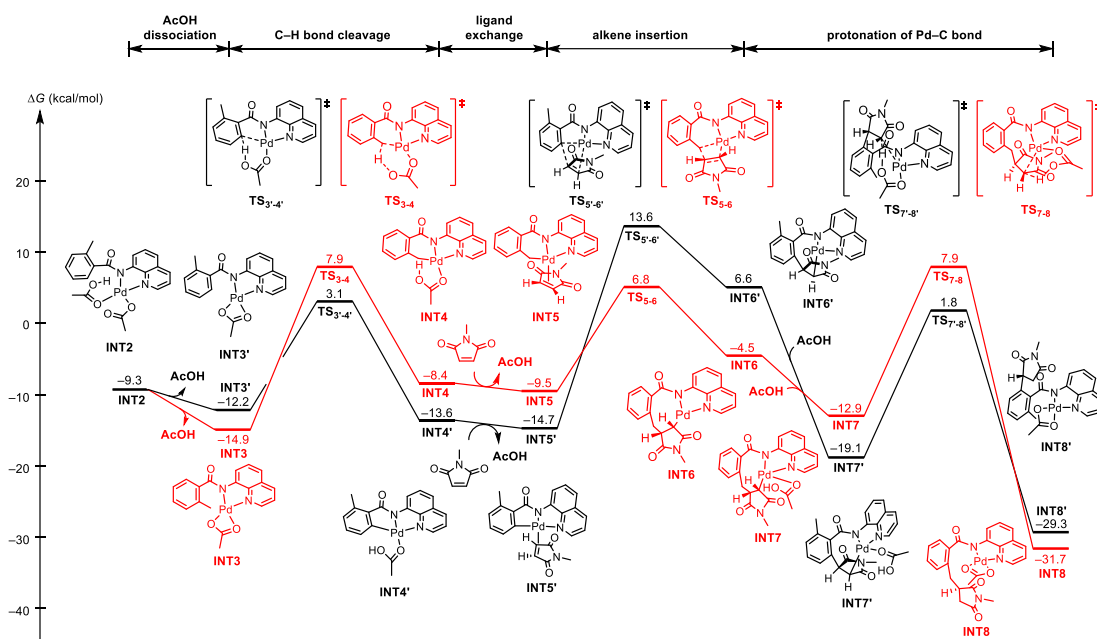


Figure 3. Comparison of Gibbs energy profiles for the pathways involving the cleavage of a C(sp³)-H bond (red line) and a C(sp²)-H bond (black line), alkene insertion and protonation of Pd-C bond, leading to **INT8** and **INT8'**, respectively. Values are relative to the separated catalyst and reagents.

Preliminary density functional theory (DFT) studies were conducted in an attempt to explain the selective alkylation at the benzylic position (Figure 3). The release of the coordinating AcOH from **INT2** gives **INT3** or **INT3'** with a loss of energy of 2.9 or 5.6 kcal/mol, respectively. The generation of a five-membered palladacycle **INT4'** from **INT3'** through **TS_{3'-4'}** requires only 15.3 kcal/mol, which is lower than the energy barrier for generating the six-membered palladacycle **INT4** from **INT3** (22.8 kcal/mol). In addition, the resulting five-membered palladacycle **INT4'** is more stable than **INT4**. The results of the DFT calculations are consistent with the deuterium labeling results. Thus, H/D exchange at the ortho C-H bond is very fast and the ortho C-D bond is completely converted into a C-H bond, even within 1 h. In sharp contrast, the insertion of the maleimide group into the Pd-C(sp²) bond of the five-membered palladacycle **INT5'** through **TS_{5'-6'}** requires 28.3 kcal/mol, but the insertion of the maleimide into the Pd-C(sp³) bond of the six-membered palladacycle **INT5**, leading to the generation of the eight-membered palladacycle **INT6** through **TS₅₋₆** requires only 16.3 kcal/mol. These results indicate that, while both five-membered and six-membered palladacycles can be generated, the formation of the five-membered palladacycle is the kinetically

favorable step, but the insertion of the maleimide into the six-membered palladacycle is energetically favored. The subsequent protonation of the Pd–C bond results in the formation of the more stable intermediates **INT8** and **INT8'**, with relatively lower energy barriers for **TS7-8** and **TS7'-8'**.

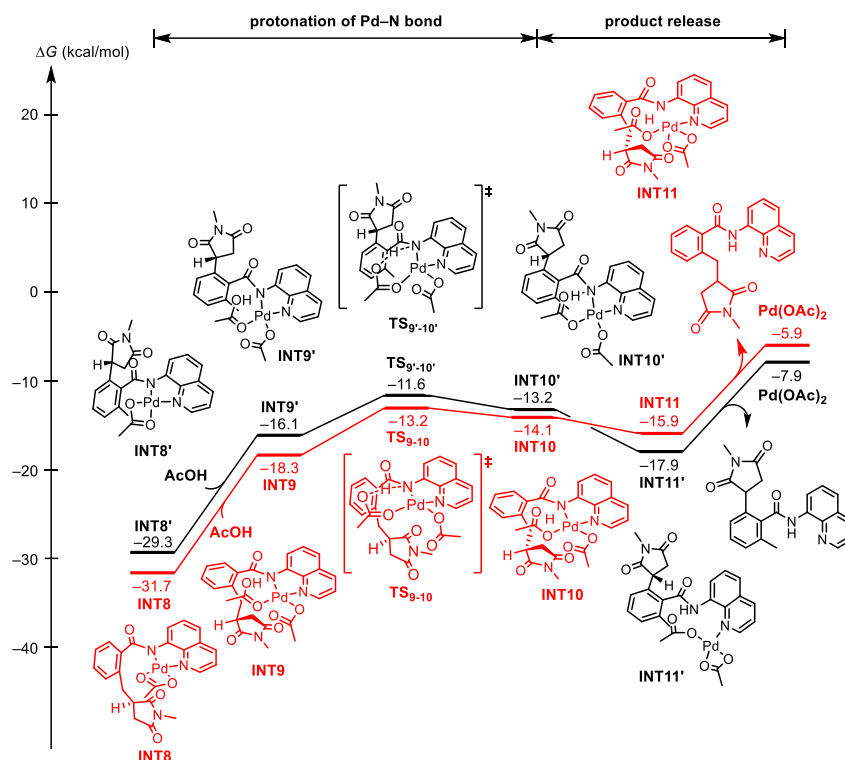


Figure 4. Comparison of Gibbs energy profiles for the pathways involving the protonation of Pd–N bond of **INT8** (red line, via **INT9**) and **INT8'** (black line, via **INT9'**), followed by the regeneration of Pd(OAc)₂. Values are relative to the separated catalyst and reagents.

Although the ligation of AcOH to **INT8** is thermodynamically uphill (13.4 kcal/mol), the energy barrier for the concerted protonation of the Pd–N bond via **TS9-10** is relatively low (4.5 kcal/mol), leading to the formation of **INT10**. After the release of the alkylation product, Pd(OAc)₂ is regenerated. The energy profile for the protonation of the Pd–N bond in **INT8'** is much the same.

1.3 Conclusion

In summary, this chapter introduced the first example of Pd-catalyzed C–H alkylations with alkenes where the reaction occurs exclusively at the *ortho*-methyl C–H bond, with no reaction occurring at the *ortho*-C–H bond. Mechanistic studies including

detailed DFT studies are developed a better understanding the reaction mechanism. The roll of silver might be a co-catalyst which could work with palladium to form Pd-Ag complex as the catalyst to promote the reaction.⁶

1.4 Experimental Section

I. General Information

¹H NMR and ¹³C NMR spectra were recorded on a JEOL ECS-400 spectrometer in CDCl₃ with tetramethylsilane as the internal standard. Data are reported as follows: chemical shift in ppm (δ), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, brs = broad singlet, and m = multiplet), coupling constant (Hz), and integration. In some cases, some peaks in the ¹³C NMR spectra cannot be analyzed because of overlapping peaks. Infrared spectra (IR) were obtained using a JASCO FT/IR-4200 spectrometer; absorptions are reported in reciprocal centimeters with the following relative intensities: s (strong), m (medium), or w (weak). Mass spectra and high resolution mass spectra (HRMS) were obtained using a JEOL JMS-700 spectrometer. Melting points were determined using a Yamato melting point apparatus. Column chromatography was performed with SiO₂ (Silicycle SiliaFlash F60 (230-400 mesh)). Some compounds were purified by LC-908 HPLC (GPC).

II. Materials.

8-Aminoquinoline (CAS 578-66-5), *N*-Methylmaleimide (CAS 930-88-1), *N*-Ethylmaleimide (CAS 128-53-0), *N*-Cyclohexylmaleimide (CAS: 1631-25-0), *N*-Phenylmaleimide (CAS: 941-69-5), *N*-(2-Hydroxyethyl)maleimide (CAS: 1585-90-6), Pivalic acid (CAS: 75-98-9) were purchased from Tokyo Chemical Industry Co., Ltd. Silver acetate (CAS: 563-63-3) was purchased from FUJIFILM Wako Pure Chemical Co. Palladium pivalate (CAS: 106224-36-6) was purchased from Sigma-Aldrich Co.

III. Synthesis of Starting Materials.

All amides bearing an 8-aminoquinoline moiety were prepared by reacting the corresponding acid or the corresponding acid chlorides with 8-aminoquinoline.⁷

General Procedure for the Preparation of Stating Amides.

(1) Synthesis of amides from acid chlorides.

The acid chloride (15 mmol) was dissolved in CH₂Cl₂ (20 mL). After cooling the reaction mixture to 0 °C, a solution of 8-aminoquinoline (15 mmol) and triethylamine (36 mmol) in 10 mL of CH₂Cl₂ was added dropwise. The resulting mixture was allowed

to warm to rt and was then stirred overnight. The crude mixture was then washed with saturated aqueous NaHCO₃ (20 mL), and CH₂Cl₂ (3x20 mL). The combined organic layers were washed with 1 M HCl aq. (20 mL). The organic phase was dried over anhydrous Na₂SO₄ and the solution taken to dryness. The resulting crude amide was purified by flash chromatography on silica gel (eluent: hexanes/EtOAc = 5/1).

(2) Synthesis of amides from carboxylic acid.

To a stirred solution of carboxylic acid (15 mmol) and DMF (5 drops) in CH₂Cl₂ (10 mL), (COCl)₂ (1.5 mL, 18 mmol) was added dropwise. The solution was magnetically stirred at room temperature for 2 h. The solvent was then eliminated under reduced pressure, and the resulting residue was dissolved in CH₂Cl₂ (15 mL). After cooling the reaction mixture to 0 °C, a solution of 8-Aminoquinoline (15 mmol) and triethylamine (36 mmol) in 10 mL of the same solvent were added dropwise. The resulting mixture was allowed to warm to rt and stirred overnight. The crude product was washed with saturated aqueous NaHCO₃ (20 mL), and CH₂Cl₂ (3x20 mL). The organic phase was washed with 1 M HCl aq. (20 mL). The organic phase was dried over anhydrous Na₂SO₄ and the solvent removed by evaporation of the solvent. The resulting crude amide was purified by flash chromatography on silica gel (eluent: hexanes/EtOAc = 5/1).

IV. Synthesis of target materials

(I) General procedure for the Palladium-catalyzed alkylation of aromatic amides with *N*-methylmaleimide.

To an oven-dried 5 mL screw-capped vial, 2-methyl-*N*-(quinolin-8-yl)benzamide (78.7mg, 0.3 mmol), *N*-methylmaleimide (165.2mg, 1.5 mmol), Pd(OPiv)₂ (13.89mg, 0.045mmol), AgOAc (60.1mg, 0.36 mmol) and PivOH (1 mL) were added. The mixture was stirred for 24 hours at 160°C and then cooled to room temperature. The resulting mixture was diluted with 1 mL EtOAc. The solvent was purified by column chromatography on silica gel (eluent: hexane/EtOAc= 1.5:1) to afford product (106.2 mg, 91 %) and further separated annulation byproduct through GPC to afford the alkylation product as a pale yellow powder and annulation product as a pale yellow colloid.

(2) Synthesis of five-member palladacycle.

To an oven-dried 100 mL flask, 2-methyl-*N*-(quinolin-8-yl)benzamide (1.3g, 5.0 mmol), Pd(OAc)₂ (1.12, 5.0 mmol), MeCN (10 mL) were added. The mixture was stirred for 4 hours at 60°C and then cooled to room temperature. The resulting mixture was filtered

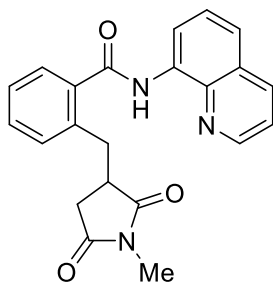
and removed insoluble substance, then solvent concentrated in vacuo. The residue was washed by 5 mL cold MeCN and dried. Finally observed palladacycle as deep yellow solid. The crystal was obtained from saturated palladacycle-MeCN solvent.

(3) Synthesis of alkylation product from five-member palladacycle.

To an oven-dried 5 mL screw-capped vial, palladacycle (122.3mg, 0.3 mmol), *N*-methylmaleimide (165.2mg, 1.5 mmol), AgOAc (60.1mg, 0.36 mmol) and PivOH (1 mL) were added. The mixture was stirred for 24 hours at 160°C and then cooled to room temperature. The resulting mixture was diluted with 1 mL EtOAc. The solvent was purified by column chromatography on silica gel (eluent: hexane/EtOAc= 1.5:1) to afford product (25.8 mg, 23 %) as a pale yellow colloid.

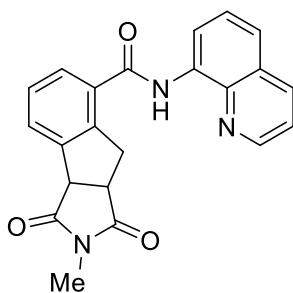
V. Spectroscopic Data.

2-((1-methyl-2,5-dioxopyrrolidin-3-yl)methyl)-*N*-(quinolin-8-yl)benzamide (2a)



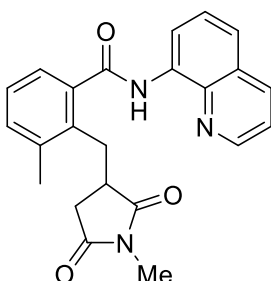
92.9mg, 83% yield. R_f 0.23 (hexane/ EtOAc = 1.5:1). Pale Yellow powder. m.p. 64.8-65.1 °C. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) 2.72-2.76 (m, 1H), 2.96 (s, 3H), 3.15 (dd, $J = 13.8, 9.3$ Hz, 1H), 3.33-3.37 (m, 1H), 3.59 (dd, $J = 13.8, 5.5$ Hz, 1H), 7.35 (d, $J = 7.7$ Hz, 1H), 7.42 (dd, $J = 7.7, 6.4$ Hz, 1H), 7.46-7.50 (m, 2H), 7.56-7.62 (m, 2H), 7.74 (dd, $J = 7.7, 1.3$ Hz, 1H), 8.19 (dd, $J = 8.3, 1.3$ Hz, 1H), 8.78 (q, $J = 1.9$ Hz, 1H), 8.88 (dd, $J = 7.1, 1.9$ Hz, 1H), 10.25 (s, 1H). $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) 24.9, 33.7, 33.7, 41.7, 116.9, 121.9, 122.2, 127.5, 127.5, 127.7, 128.1, 130.9, 131.0, 134.5, 136.7, 136.9, 137.3, 138.5, 148.4, 167.7, 176.9, 179.7. MS: m/z 374, 307, 230, 155, 154, 144, 136, 107, 89. HRMS (FAB+) m/z ($[\text{M}+\text{H}]^+$) Calcd for $\text{C}_{22}\text{H}_{20}\text{N}_3\text{O}_3$: 374.1504; Found: 374.1507.

2-methyl-1,3-dioxo-*N*-(quinolin-8-yl)-1,2,3,3a,8,8a-hexahydroindeno[1,2-*c*]pyrrole-7-carboxamide (3a)



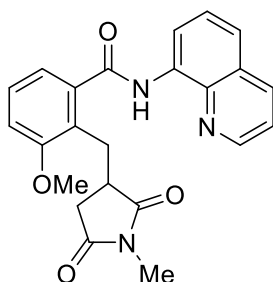
13.3mg, 8% yield. R_f 0.23 (hexane/ EtOAc = 1.5:1). Pale Yellow powder. m.p. 156.5-157.0 °C. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) 2.96 (s, 1H), 3.73 (q, $J = 7.1$ Hz, 1H), 3.90 (d, $J = 6.6$ Hz, 3H), 4.41 (d, $J = 8.0$ Hz, 1H), 7.46-7.51 (m, 2H), 7.56-7.63 (m, 2H), 7.79 (d, $J = 7.8$ Hz, 1H), 7.88 (d, $J = 7.8$ Hz, 1H), 8.21 (dd, $J = 8.2, 1.4$ Hz, 1 H), 8.83 (dd, $J = 4.1, 1.6$ Hz, 1H), 8.89 (dd, $J = 7.2, 1.7$ Hz, 1H), 10.52 (s, 1H). $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) 25.3, 35.3, 43.9, 51.6, 117.5, 121.8, 122.3, 127.7, 127.8, 128.3, 128.4, 132.9, 134.2, 137.4, 139.3, 141.7, 148.1, 165.9, 177.4, 179.7. MS: m/z 372, 326, 307, 289, 228, 154, 138, 136, 115, 107, 89, 77. HRMS (FAB+) m/z ($[\text{M}+\text{H}]^+$) Calcd for $\text{C}_{22}\text{H}_{18}\text{N}_3\text{O}_3$: 372.1348; Found: 372.1344.

3-methyl-2-((1-methyl-2,5-dioxopyrrolidin-3-yl)methyl)-*N*-(quinolin-8-yl)benzamide (2b)



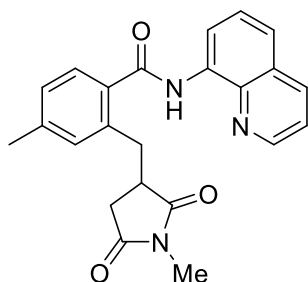
46.2mg, 40% yield. R_f 0.31 (hexane/ EtOAc = 1.5:1). Pale yellow colloid. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) 2.46 (s, 3H), 2.65 (t, $J = 9.2$ Hz, 1H), 2.89 (dd, $J = 18.6, 4.4$ Hz, 1H), 2.95 (s, 3H), 3.21-3.28 (m, 2H), 3.51 (d, $J = 8.7$ Hz, 1H), 7.30-7.37 (m, 2H), 7.46 (q, $J = 4.1$ Hz, 1H), 7.53-7.59 (m, 3H), 8.18 (dd, $J = 8.3, 1.8$ Hz, 1H), 8.76 (q, $J = 2.0$ Hz, 1H), 8.86 (dd, $J = 6.6, 2.1$ Hz, 1H), 10.17 (s, 1H). $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) 20.2, 24.9, 30.8, 34.2, 40.3, 116.8, 121.9, 122.2, 125.4, 127.3, 127.5, 128.1, 133.1, 134.6, 135.5, 136.5, 137.7, 138.2, 138.6, 148.5, 168.6, 177.1, 179.7. MS: m/z 388, 307, 244, 154, 136. HRMS (FAB+) m/z ($[\text{M}+\text{H}]^+$) Calcd for $\text{C}_{23}\text{H}_{22}\text{N}_3\text{O}_3$: 388.1661; Found: 388.1656.

3-methoxy-2-((1-methyl-2,5-dioxopyrrolidin-3-yl)methyl)-N-(quinolin-8-yl)benzamide (2c)



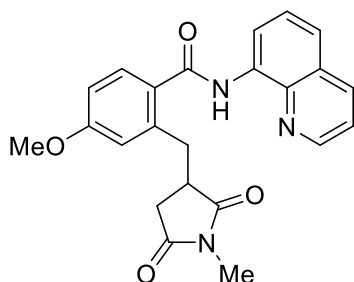
79.5mg, 66% yield. R_f 0.20 (hexane/ EtOAc = 1.5:1). Pale yellow colloid. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) 2.61 (q, $J = 9.0$ Hz, 1H), 2.91 (dd, $J = 18.3, 5.0$ Hz, 1H), 2.96 (s, 3H), 3.13-3.16 (m, 1H), 3.45-3.52 (m, 2H), 3.88(s, 3H), 7.04 (d, $J = 8.3$ Hz, 1H), 7.29-7.31 (m, 1H), 7.39 (t, $J = 7.8$ Hz, 1H), 7.46 (q, $J = 4.1$ Hz, 1H), 7.55-7.61 (m, 2H), 8.18 (dd, $J = 8.5, 1.6$ Hz, 1H), 8.77 (q, $J = 2.0$ Hz, 1H), 8.87 (dd, $J = 7.1, 2.1$ Hz, 1H), 10.18 (s, 1H). $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) 24.8, 28.3, 33.9, 40.0, 55.8, 112.4, 116.9, 119.5, 121.8, 122.2, 125.7, 127.5, 128.1, 128.5, 134.6, 136.6, 138.6, 138.7, 148.4, 158.4, 167.7, 177.6, 180.1. MS: m/z 404, 307, 289, 260, 154, 136, 120, 107, 89. HRMS (FAB+) m/z ($[\text{M}+\text{H}]^+$) Calcd for $\text{C}_{23}\text{H}_{22}\text{N}_3\text{O}_4$: 404.1610; Found: 404.1617.

4-methyl-2-((1-methyl-2,5-dioxopyrrolidin-3-yl)methyl)-N-(quinolin-8-yl)benzamide (2d)



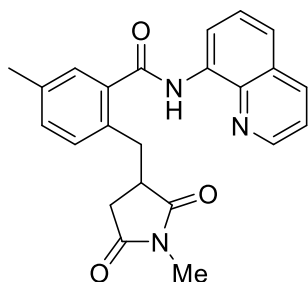
95.0mg, 82% yield. R_f 0.26 (hexane/ EtOAc = 1.5:1). Yellow colloid. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) 2.41 (s, 3H), 2.66-2.83 (m, 2H), 2.97 (s, 3H), 3.12 (dd, $J = 13.5, 9.4$ Hz, 1H), 3.35 (s, 1H), 3.57 (dd, $J = 13.5, 5.3$ Hz, 1H), 7.21-7.26 (m, 1H), 7.46 (q, $J = 4.1$ Hz, 1H), 7.56-7.59 (m, 2H), 7.65 (d, $J = 7.8$ Hz, 1H), 8.18 (dd, $J = 8.3, 1.4$ Hz, 1H), 8.78 (t, $J = 2.1$ Hz, 1H), 8.87 (d, $J = 6.9$ Hz, 1H), 10.25 (s, 1H). $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) 21.5, 24.9, 33.6, 33.7, 41.8, 116.7, 121.9, 122.1, 127.5, 127.8, 128.2, 131.8, 134.0, 134.7, 136.6, 137.5, 138.7, 141.3, 148.5, 167.8, 177.1, 179.8. MS: m/z 388, 307, 289, 244, 154, 144, 136, 107. HRMS (FAB+) m/z ($[\text{M}+\text{H}]^+$) Calcd for $\text{C}_{23}\text{H}_{22}\text{N}_3\text{O}_3$: 388.1661; Found: 388.1666.

4-methoxy-2-((1-methyl-2,5-dioxopyrrolidin-3-yl)methyl)-*N*-(quinolin-8-yl)benzamide (2e)



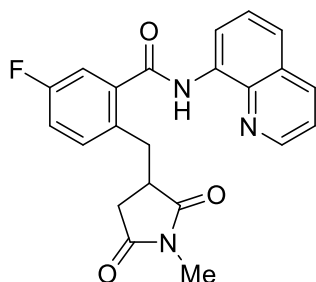
76.7mg, 64% yield. R_f 0.21 (hexane/ EtOAc = 1.5:1). Yellow colloid. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) 2.71-2.78 (m, 2H), 2.97 (s, 3H), 3.19 (dd, $J = 13.5, 8.9$ Hz, 1H), 3.34 (q, $J = 4.6$ Hz, 1H), 3.59 (dd, $J = 13.5, 5.3$ Hz, 1H), 3.86 (d, $J = 0.7$ Hz, 3H), 6.86 (d, $J = 2.3$ Hz, 1H), 6.91 (d, $J = 8.7$ Hz, 1H), 7.44-7.47 (m, 1H), 7.56 (dd, $J = 10.8, 8.5$ Hz, 2H), 7.73 (d, $J = 8.7$ Hz, 1H), 8.18 (d, $J = 8.3$ Hz, 1H), 8.79 (t, $J = 2.1$ Hz, 1H), 8.85 (d, $J = 6.9$ Hz, 1H), 10.24 (s, 1H). $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) 24.9, 33.7, 41.8, 55.6, 112.4, 116.6, 116.7, 121.8, 121.9, 127.5, 128.1, 129.1, 129.5, 134.8, 136.5, 138.7, 140.0, 148.4, 161.4, 167.4, 177.0, 179.8. MS: m/z 404, 307, 289, 260, 154, 137, 107, 89. HRMS (FAB+) m/z ($[\text{M}+\text{H}]^+$) Calcd for $\text{C}_{23}\text{H}_{22}\text{N}_3\text{O}_4$: 404.1610; Found: 404.1608.

5-methyl-2-((1-methyl-2,5-dioxopyrrolidin-3-yl)methyl)-*N*-(quinolin-8-yl)benzamide (2f)



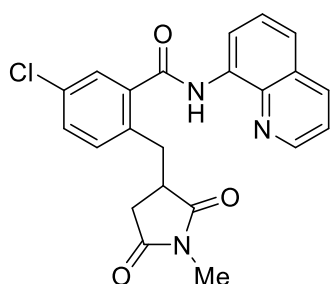
84.3mg, 73% yield. R_f 0.26 (hexane/ EtOAc = 1.5:1). Brown colloid. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) 2.43 (s, 3H), 2.66-2.82 (m, 2H), 2.95 (s, 3H), 3.10 (dd, $J = 13.8, 8.7$ Hz, 1H), 3.28-3.34 (m, 1H), 3.53 (dd, $J = 13.8, 5.5$ Hz, 1H), 7.21-7.29 (m, 2H), 7.47 (q, $J = 4.3$ Hz, 1H), 7.52 (s, 1H), 7.55-7.62 (m, 2H), 8.20 (dd, $J = 8.5, 1.6$ Hz, 1H), 8.80 (q, $J = 2.0$ Hz, 1H), 8.88 (dd, $J = 6.9, 1.8$ Hz, 1H), 10.21 (s, 1H). $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) 21.2, 24.9, 33.3, 33.7, 41.8, 116.9, 121.9, 122.2, 127.5, 128.2, 130.8, 131.6, 134.1, 134.7, 136.6, 136.9, 137.3, 138.7, 148.5, 168.0, 177.0, 179.8. MS: m/z 388, 307, 289, 244, 154, 144, 137, 120, 107, 89. HRMS (FAB+) m/z ($[\text{M}+\text{H}]^+$) Calcd for $\text{C}_{23}\text{H}_{22}\text{N}_3\text{O}_3$: 388.1661; Found: 388.1655.

5-fluoro-2-((1-methyl-2,5-dioxopyrrolidin-3-yl)methyl)-*N*-(quinolin-8-yl)benzamide (2g)



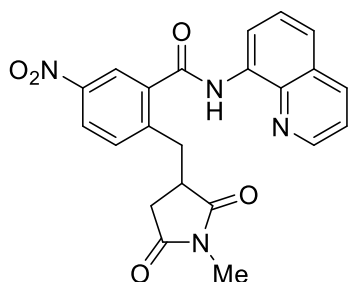
85.6mg, 73% yield. R_f 0.20 (hexane/ EtOAc = 1.5:1). Yellow colloid. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) 2.73 (d, $J = 7.3$ Hz, 2H), 2.96 (s, 3H), 3.13 (dd, $J = 13.8, 9.2$ Hz, 1H), 3.29-3.33 (m, 1H), 3.51 (dd, $J = 13.8, 5.5$ Hz, 1H), 7.19 (td, $J = 8.5, 2.8$ Hz), 7.34 (dd, $J = 8.5, 5.3$ Hz, 1H), 7.44 (dd, $J = 8.5, 2.5$ Hz, 1H), 7.47-7.51 (m, 1H), 7.59-7.60 (m, 2H), 8.21 (d, $J = 8.3$ Hz, 1H), 8.80-8.81 (m, 1H), 8.85 (dd, $J = 5.3, 3.4$ Hz, 1H), 10.24 (s, 1H). $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) 24.9, 33.1, 33.8, 41.7, 116.3 (dd, $J = 317, 21$ Hz), 117.0, 122.0, 122.6, 127.5, 128.2, 132.8 (d, $J = 8$ Hz), 133.1 (d, $J = 3$ Hz), 134.3, 136.7, 138.4 (d, $J = 6$ Hz), 138.6, 160.3, 162.7, 166.3, 176.7, 179.5. MS: m/z 392, 307, 289, 248, 154, 136, 107, 89. HRMS (FAB+) m/z ($[\text{M}+\text{H}]^+$) Calcd for $\text{C}_{23}\text{H}_{19}\text{FN}_3\text{O}_3$: 392.1410; Found: 392.1406.

5-chloro-2-((1-methyl-2,5-dioxopyrrolidin-3-yl)methyl)-*N*-(quinolin-8-yl)benzamide (2h)



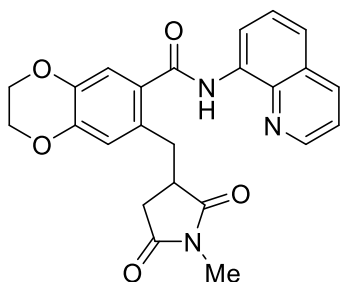
91.0mg, 75% yield. R_f 0.25 (hexane/ EtOAc = 1.5:1). Deep yellow colloid. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) 2.73 (d, $J = 6.9$ Hz, 2H), 2.96 (s, 3H), 3.12 (dd, $J = 13.8, 8.7$ Hz, 1H), 3.30 (d, $J = 6.4$ Hz, 1H), 3.50 (dd, $J = 13.8, 5.5$ Hz, 1H), 7.30 (d, $J = 8.3$ Hz, 1H), 7.44-7.51 (m, 2H), 7.60 (d, $J = 4.6$ Hz, 2H), 7.70 (d, $J = 1.8$ Hz, 1H), 8.21 (d, $J = 8.3$ Hz, 1H), 8.81-8.85 (m, 2H), 10.22 (s, 1H). $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) 25.0, 33.2, 33.7, 41.6, 117.0, 122.6, 127.4, 127.6, 128.1, 130.9, 132.4, 133.2, 134.2, 135.7, 136.7, 138.4, 138.6, 148.6, 166.3, 176.7, 179.4. MS: m/z 408, 307, 264, 154, 137, 107, 89. HRMS (FAB+) m/z ($[\text{M}+\text{H}]^+$) Calcd for $\text{C}_{23}\text{H}_{19}\text{ClN}_3\text{O}_3$: 408.1115; Found: 408.1113.

2-((1-methyl-2,5-dioxopyrrolidin-3-yl)methyl)-5-nitro-*N*-(quinolin-8-yl)benzamide (2i)



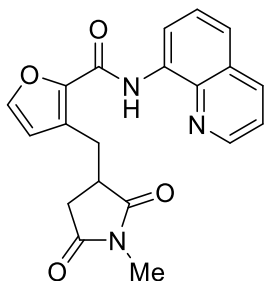
94.2mg, 75% yield. R_f 0.20 (hexane/ EtOAc = 1:1). Yellow powder. m.p. 190.5-190.9 °C. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) 2.74-2.80 (m, 2H), 2.97 (s, 3H), 3.28-3.37 (m, 2H), 3.57 (t, $J = 6.6$ Hz, 1H), 7.51 (q, $J = 4.3$ Hz, 1H), 7.58-7.63 (m, 3H), 8.22 (dd, $J = 8.3, 1.4$ Hz, 1H), 8.33 (dd, $J = 8.5, 2.5$ Hz, 1H), 8.59 (d, $J = 2.3$ Hz, 1H), 8.59 (d, $J = 2.3$ Hz, 1H), 8.80-8.85 (m, 2H), 10.35 (s, 1H). $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) 25.1, 34.0, 34.1, 41.3, 117.2, 122.1, 122.7, 123.0, 125.4, 127.4, 128.1, 132.3, 133.9, 136.7, 138.0, 138.5, 145.0, 146.9, 148.8, 165.3, 176.2, 178.9. MS: m/z 419, 307, 289, 154, 137, 120, 107, 89. HRMS (FAB+) m/z ($[\text{M}+\text{H}]^+$) Calcd for $\text{C}_{22}\text{H}_{19}\text{N}_4\text{O}_5$: 419.1355; Found: 419.1358.

7-((1-methyl-2,5-dioxopyrrolidin-3-yl)methyl)-*N*-(quinolin-8-yl)-2,3-dihydrobenzo[*b*][1,4]dioxine-6-carboxamide (2j)



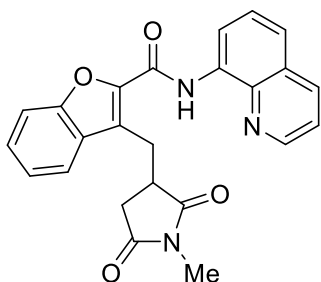
84.4mg, 65% yield. R_f 0.18 (hexane/ EtOAc = 1:1). Yellow powder. m.p. 78.9-79.2 °C. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) 2.68-2.80 (m, 2H), 2.97 (s, 3H), 3.05-3.11 (m, 1H), 3.27-3.32 (m, 1H), 3.49 (dd, $J = 13.8, 5.4$ Hz, 1H), 4.32 (s, 4H), 6.82 (s, 1H), 7.27 (s, 1H), 7.47 (q, $J = 4.2$ Hz, 1H), 7.54-7.60 (m, 2H), 8.18 (dd, $J = 8.2, 1.4$ Hz, 1H), 8.78-8.84 (m, 2H), 10.21 (s, 1H). $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) 24.9, 32.9, 33.6, 41.8, 64.5, 64.7, 116.7, 116.9, 119.6, 121.8, 122.0, 127.5, 128.1, 129.6, 131.3, 134.7, 136.6, 138.6, 142.2, 145.6, 148.4, 166.9, 177.1, 179.8.

3-((1-methyl-2,5-dioxopyrrolidin-3-yl)methyl)-*N*-(quinolin-8-yl)furan-2-carboxamide (2k)



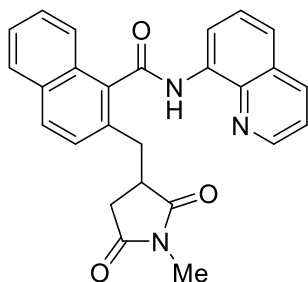
41.9mg, 39% yield. R_f 0.18 (hexane/ EtOAc = 1.5:1). Pale yellow powder. m.p. 66.2-66.5 °C. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) 2.77 (q, $J = 3.4$ Hz, 2H), 2.98 (s, 3H), 3.24-3.27 (m, 1H), 3.36 (q, $J = 7.1$ Hz, 1H), 3.60 (dd, $J = 13.5, 5.1$ Hz, 1H), 6.44 (d, $J = 1.9$ Hz, 1H), 7.49 (q, $J = 4.1$ Hz, 1H), 7.54-7.57 (m, 3H), 8.19 (dd, $J = 8.3, 1.3$ Hz, 1H), 8.81 (q, $J = 3.0$ Hz, 1H), 8.88-8.90 (m, 1H), 10.80 (s, 1H). $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) 25.0, 26.1, 33.3, 40.5, 114.6, 116.8, 121.9, 122.1, 127.5, 128.2, 128.4, 134.2, 136.5, 138.8, 143.7, 143.8, 148.6, 157.4, 176.9, 179.6. MS: m/z 364, 307, 171, 154, 136, 107, 89. HRMS (FAB+) m/z ($[\text{M}+\text{H}]^+$) Calcd for $\text{C}_{20}\text{H}_{18}\text{N}_3\text{O}_4$: 364.1297; Found: 364.1306.

3-((1-methyl-2,5-dioxopyrrolidin-3-yl)methyl)-*N*-(quinolin-8-yl)benzofuran-2-carboxamide (2l)



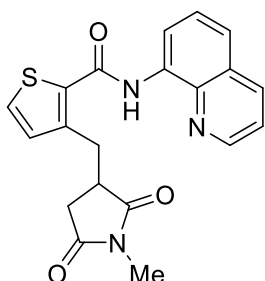
67.0mg, 58% yield. R_f 0.29 (hexane/ EtOAc = 1.5:1). yellow powder. m.p. 154.3-154.8 °C. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) 2.70 (q, $J = 9.1$ Hz, 1H), 2.91 (dd, $J = 18.5, 4.8$ Hz, 1H), 2.95 (s, 3H), 3.36-3.40 (m, 1H), 3.64-3.70 (m, 1H), 3.76-3.81 (m, 1H), 7.35 (t, $J = 7.5$ Hz, 1H), 7.48-7.52 (m, 2H), 7.57 (d, $J = 4.6$, 2H), 7.70 (q, $J = 7.9$ Hz, 2H), 8.19-8.21 (m, 1H), 8.85-8.87 (m, 1H), 8.94 (dd, $J = 4.1, 1.4$ Hz, 1H), 11.06 (s, 1H). $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) 24.98, 25.0, 33.5, 40.3, 112.5, 117.1, 121.1, 121.9, 122.5, 123.5, 123.8, 127.4, 127.9, 128.2, 128.4, 134.0, 136.5, 138.8, 144.2, 148.7, 153.8, 158.0, 176.8, 179.6.

2-((1-methyl-2,5-dioxopyrrolidin-3-yl)methyl)-*N*-(quinolin-8-yl)-1-naphthamide (2m)



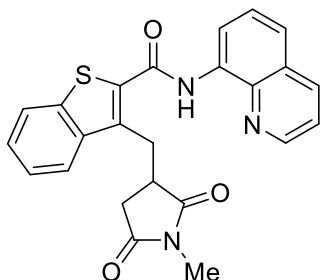
79.2mg, 62% yield. R_f 0.14 (hexane/ EtOAc = 1.5:1). Pale yellow powder. m.p. 96.3-96.7 °C. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) 2.62-2.87 (m, 2H), 2.94 (s, 3H), 3.09 (t, $J = 9.8$ Hz, 1H), 3.22-3.44 (m, 1H), 3.60 (dd, $J = 14.0, 4.8$ Hz, 1H), 7.43 (q, $J = 4.1$ Hz, 2H), 7.48-7.54 (m, 2H), 7.60-7.68 (m, 2H), 7.87-7.94 (m, 2H), 7.97-8.00 (m, 1H), 8.19 (dd, $J = 8.2, 1.8$ Hz, 1H), 8.66 (q, $J = 2.0$ Hz, 1H), 9.07 (dd, $J = 7.6, 1.6$ Hz, 1H), 10.13 (s, 1H). $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) 25.0, 33.7, 34.4, 41.6, 117.3, 121.9, 122.6, 125.2, 126.5, 127.5, 127.7, 128.2, 128.3, 130.1, 130.3, 132.5, 134.3, 135.4, 136.6, 138.6, 148.6, 167.9, 176.6, 179.5. MS: m/z 424, 307, 289, 167, 154, 137, 107, 89, 77. HRMS (FAB+) m/z ($[\text{M}+\text{H}]^+$) Calcd for $\text{C}_{26}\text{H}_{22}\text{N}_3\text{O}_3$: 424.1661; Found: 424.1658.

3-((1-methyl-2,5-dioxopyrrolidin-3-yl)methyl)-N-(quinolin-8-yl)thiophene-2-carboxamide (2n)



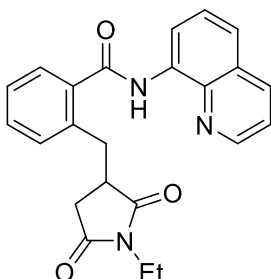
77.1mg, 68% yield. R_f 0.13 (hexane/ EtOAc = 2:1). Brown colloid. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) 2.76-2.78 (m, 2H), 2.98 (d, $J = 3.7$ Hz, 3H), 3.29-3.33 (m, 1H), 3.46 (dd, $J = 13.8, 8.3$ Hz, 1H), 3.70 (dd, $J = 13.8, 5.5$ Hz, 1H), 7.02 (d, $J = 5.0$ Hz, 1H), 7.42 (d, $J = 5.0$ Hz, 1H), 7.46 (q, $J = 4.1$ Hz, 1H), 7.52-7.57 (m, 2H), 8.16 (dd, $J = 8.3, 1.8$ Hz, 1H), 8.76 (dd, $J = 6.6, 2.1$ Hz, 1H), 8.82 (q, $J = 2.0$ Hz, 1H), 10.43 (s, 1H). $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) 24.9, 29.7, 33.5, 41.0, 116.6, 121.8, 122.0, 127.4, 127.7, 128.0, 131.1, 132.6, 134.4, 136.5, 138.6, 143.3, 148.5, 160.8, 176.8, 190.5. MS: m/z 380, 307, 236, 154, 137, 107, 89. HRMS (FAB+) m/z ($[\text{M}+\text{H}]^+$) Calcd for $\text{C}_{20}\text{H}_{18}\text{N}_3\text{O}_3\text{S}$: 380.1069; Found: 380.1064.

3-((1-methyl-2,5-dioxopyrrolidin-3-yl)methyl)-*N*-(quinolin-8-yl)benzo[*b*]thiophene-2-carboxamide (2o)



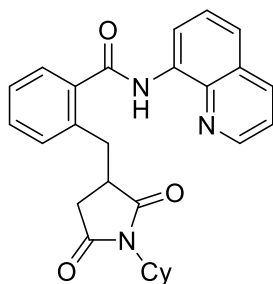
108.8mg, 85% yield. R_f 0.25 (hexane/ EtOAc = 1.5:1). Pale yellow powder. m.p. 84.6-85.3 °C. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) 2.64 (q, $J = 9.1$ Hz, 1H), 3.01 (s, 3H), 3.05-3.13 (m, 1H), 3.36-3.40 (m, 1H), 3.83 (d, $J = 7.8$ Hz, 2H), 7.48-7.52 (m, 3H), 7.54-7.58 (m, 2H), 7.91-7.97 (m, 2H), 8.19 (d, $J = 8.2$ Hz, 1H), 8.81 (q, $J = 3.0$ Hz, 1H), 8.87 (t, $J = 2.1$ Hz, 1H), 10.60 (s, 1H). $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) 25.0, 28.1, 33.7, 40.7, 116.9, 121.9, 122.4, 123.1, 123.3, 125.4, 127.3, 127.4, 128.1, 132.1, 134.3, 136.6, 138.5, 138.6, 138.9, 139.4, 148.6, 161.2, 177.0, 179.5.

3-((1-methyl-2,5-dioxopyrrolidin-3-yl)methyl)-*N*-(quinolin-8-yl)benzo[*b*]thiophene-2-carboxamide (2aa)



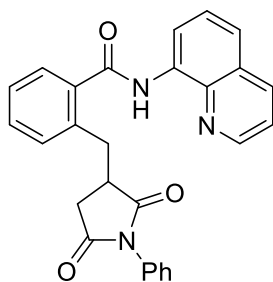
99.6mg, 86% yield. R_f 0.33 (hexane/ EtOAc = 1.5:1). Pale yellow colloid. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) 1.14 (t, $J = 7.1$ Hz, 3H), 2.71-2.74 (m, 2H), 3.16 (dd, $J = 13.8, 8.7$ Hz, 1H), 3.32-3.36 (m, 1H), 3.51-3.61 (m, 3H), 7.35 (d, $J = 7.3$ Hz, 1H), 7.40-7.49 (m, 3H), 7.59 (q, $J = 7.8$ Hz, 2H), 7.74 (d, $J = 7.3$ Hz, 1H), 8.20 (d, $J = 8.3$ Hz, 1H), 8.79 (d, $J = 4.1$ Hz, 1H), 8.89 (dd, $J = 6.6, 1.1$ Hz, 1H), 10.26 (s, 1H). $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) 13.2, 33.6, 33.7, 33.8, 41.6, 116.8, 121.9, 122.3, 127.5, 127.7, 128.1, 130.9, 131.0, 134.6, 136.6, 136.9, 137.3, 138.7, 148.5, 167.7, 176.7, 179.5. MS: m/z 388, 307, 289, 154, 136, 107, 89. HRMS (FAB+) m/z ($[\text{M}+\text{H}]^+$) Calcd for $\text{C}_{23}\text{H}_{22}\text{N}_3\text{O}_3$: 388.1661; Found: 388.1662.

2-((1-cyclohexyl-2,5-dioxopyrrolidin-3-yl)methyl)-*N*-(quinolin-8-yl)benzamide (2ab)



112.2mg, 85% yield. R_f 0.37 (hexane/ EtOAc = 1.5:1). Yellow colloid. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) 1.15-1.31 (m, 3H), 1.53 (d, $J = 11.0$ Hz, 2H), 1.62 (d, $J = 11.9$ Hz, 1H), 1.77 (t, $J = 10.1$ Hz, 2H), 2.11 (qd, $J = 12.7, 3.3$ Hz, 2H), 2.67 (d, $J = 6.9$ Hz, 2H), 3.15 (dd, $J = 13.8, 8.3$ Hz, 1H), 3.25 (td, $J = 7.1, 5.5$ Hz, 1H), 3.56 (dd, $J = 13.8, 5.5$ Hz, 1H), 3.92 (qd, $J = 8.3, 4.0$ Hz, 1H), 7.35 (dd, $J = 7.6, 1.1$ Hz, 1H), 7.39-7.49 (m, 3H), 7.56-7.62 (m, 2H), 7.73 (dd, $J = 7.6, 1.1$ Hz, 1H), 8.20 (dd, $J = 8.5, 1.6$ Hz, 1H), 8.79 (q, $J = 2.0$ Hz, 1H), 8.89 (dd, $J = 6.9, 1.8$ Hz, 1H), 10.25 (s, 1H). $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) 25.1, 26.0, 28.8, 28.9, 33.6, 33.7, 41.1, 51.7, 117.0, 121.9, 122.3, 127.4, 127.5, 127.6, 128.2, 130.8, 131.1, 134.6, 136.7, 137.0, 137.3, 138.6, 148.4, 167.8, 176.9, 179.8. MS: m/z 442, 307, 298, 216, 154, 136, 107, 89. HRMS (FAB+) m/z ($[\text{M}+\text{H}]^+$) Calcd for $\text{C}_{27}\text{H}_{28}\text{N}_3\text{O}_3$: 442.2130; Found: 442.2139.

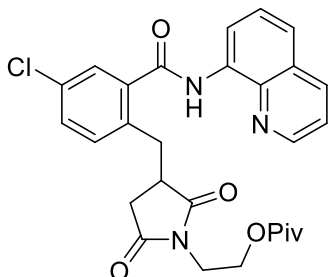
2-((2,5-dioxo-1-phenylpyrrolidin-3-yl)methyl)-*N*-(quinolin-8-yl)benzamide (2ac)



87.0mg, 67% yield. R_f 0.25 (hexane/ EtOAc = 1.5:1). Yellow powder. m.p. 183.7-184.1 °C. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) 2.86-3.01 (m, 2H), 3.31 (dd, $J = 13.5, 8.5$ Hz, 1H), 3.52-3.56 (m, 1H), 3.67 (dd, $J = 13.8, 5.5$ Hz, 1H), 7.25-7.27 (m, 1H), 7.34-7.52 (m, 8H), 7.56-7.63 (m, 2H), 7.76-7.78 (m, 1H), 8.19 (dd, $J = 8.3, 1.4$ Hz, 1H), 8.78 (q, $J = 2.0$ Hz, 1H), 8.90 (dd, $J = 7.1, 1.6$ Hz, 1H), 10.30 (s, 1H). $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) 33.7, 33.9, 41.8, 116.9, 121.9, 122.3, 126.6, 127.5, 127.6, 127.7, 128.1, 128.6, 129.2, 131.0, 131.2, 132.1, 134.6, 136.7, 136.9, 137.2, 138.6, 148.5, 167.7, 175.8,

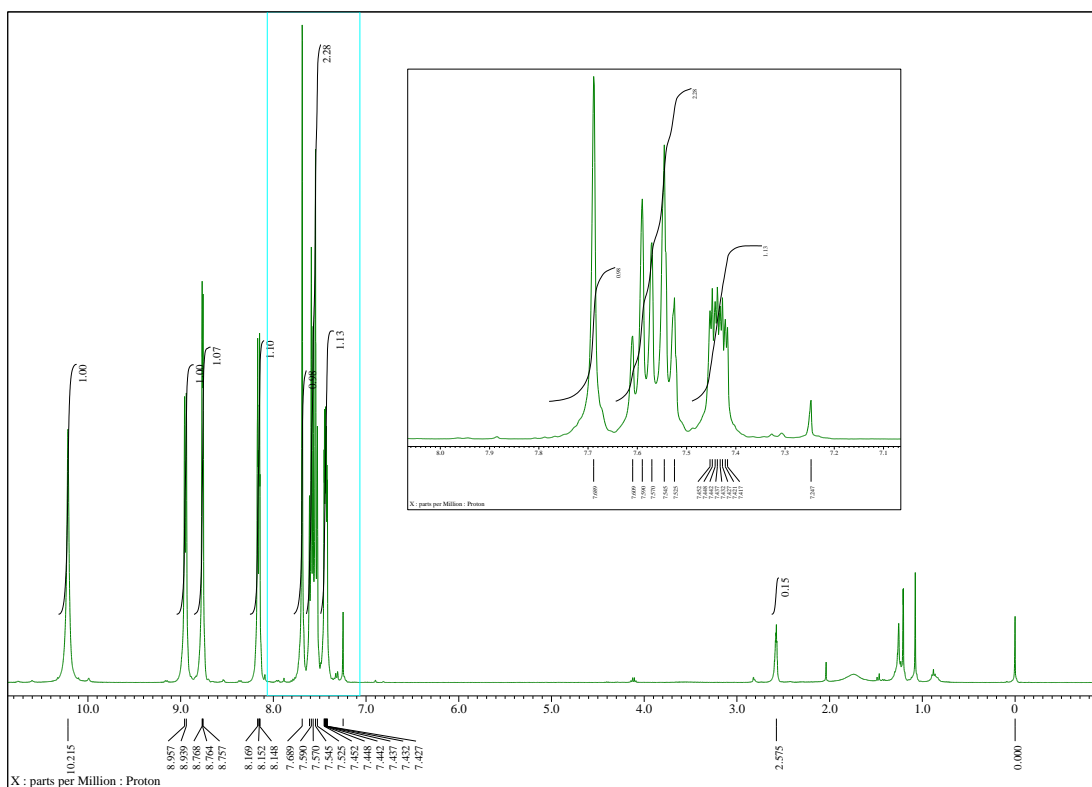
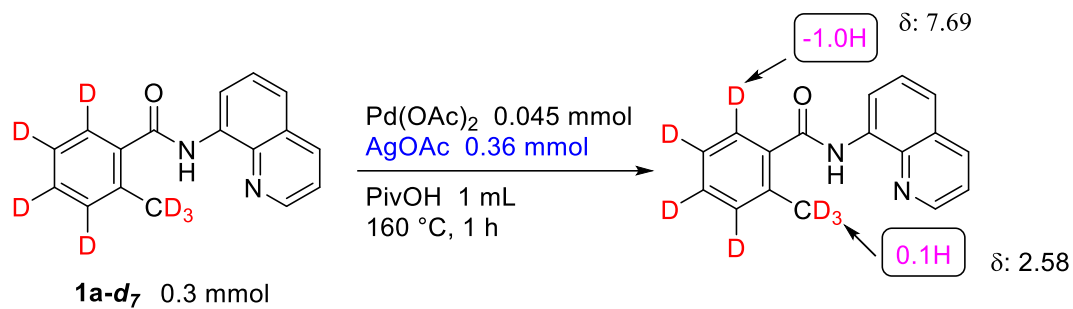
178.6. MS: m/z 436, 292, 171, 144, 136, 120, 115, 107, 89. HRMS (FAB+) m/z ($[M+H]^+$) Calcd for $C_{27}H_{22}N_3O_3$: 436.1661; Found: 436.1657.

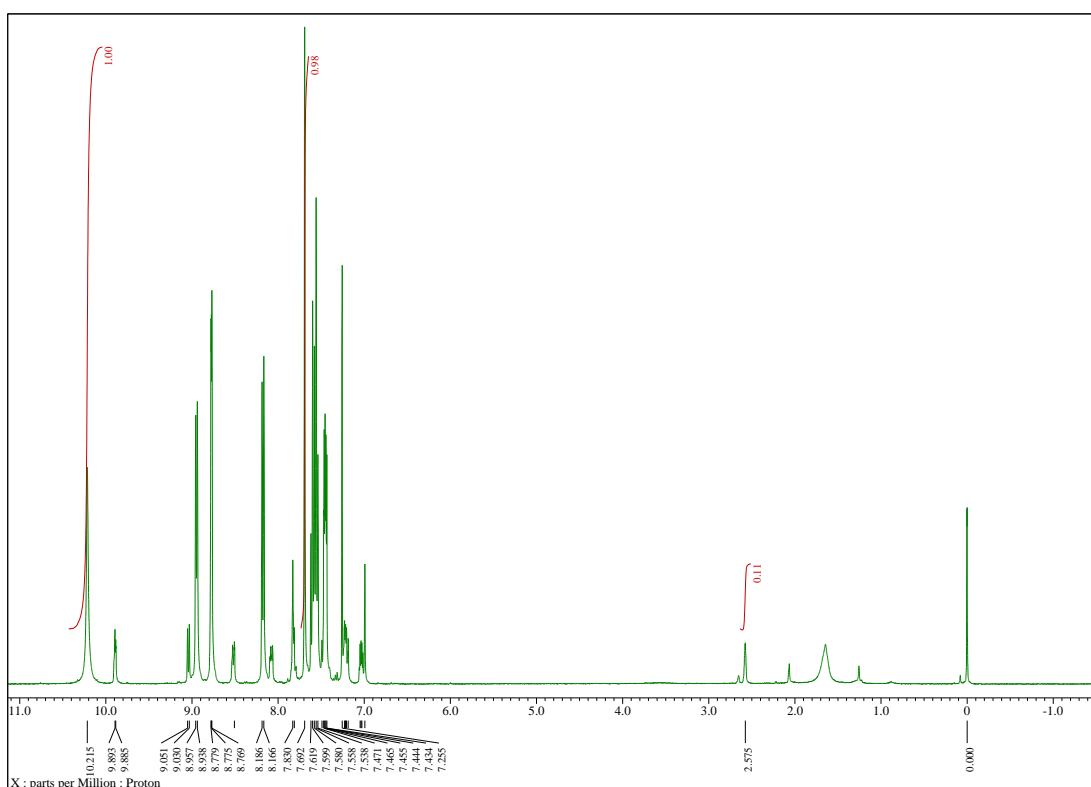
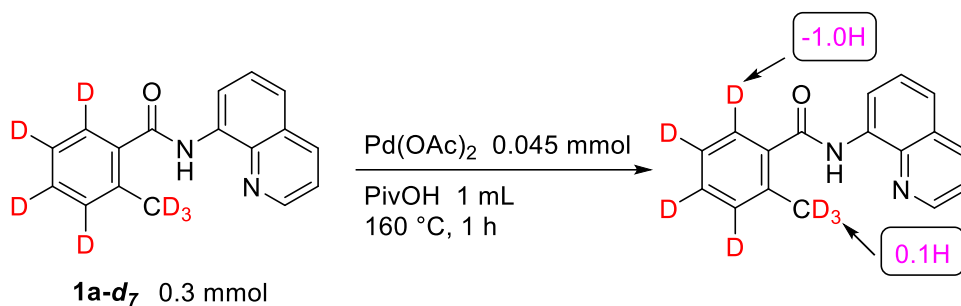
2-(3-(4-chloro-2-(quinolin-8-ylcarbamoyl)benzyl)-2,5-dioxopyrrolidin-1-yl)ethyl pivalate (2ad)



66.5mg, 43% yield. R_f 0.33 (hexane/ EtOAc = 1.5:1). Yellow colloid. 1H -NMR ($CDCl_3$, 400 MHz) 1.12 (s, 9H), 2.73 (d, $J = 7.8$ Hz, 2H), 3.11 (dd, $J = 14.0, 8.9$ Hz, 1H), 3.30-3.33 (m, 1H), 3.50 (dd, $J = 13.5, 5.3$ Hz, 1H), 3.76 (t, $J = 4.1$ Hz, 2H), 4.22 (d, $J = 5.5$ Hz, 2H), 7.32 (d, $J = 8.3$ Hz, 1H), 7.44-7.50 (m, 2H), 7.59 (t, $J = 2.3$ Hz, 2H), 7.70 (d, $J = 2.3$ Hz, 1H), 8.20 (dd, $J = 8.3, 1.8$ Hz, 1H), 8.80-8.85 (m, 2H), 10.22 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) 27.2, 33.3, 33.7, 38.1, 38.8, 41.4, 60.9, 117.0, 122.0, 122.6, 127.4, 127.6, 128.1, 130.9, 132.4, 133.3, 134.3, 135.7, 136.7, 138.4, 138.6, 148.6, 166.2, 176.2, 178.4, 179.0. MS: m/z 522, 328, 154, 144, 136, 129, 107, 89, 57. HRMS (FAB+) m/z ($[M+H]^+$) Calcd for $C_{28}H_{29}ClN_3O_3$: 522.1795; Found: 522.1792.

VI. Deuterium Labeling Experiments.





1.5 References

- (1) (a) Dong, Z.; Ren, Z.; Thompson, S.; Xu, Y.; Dong, G. *Chem. Rev.* **2017**, *117*, 9333-9403. (b) Xue, X.-S.; Ji, P.; Zhou, B.; Cheng, J.-P. *Chem. Rev.* **2017**, *117*, 8622-8648. (c) Yi, H.; Zhang, G.; Wang, H.; Huang, Z.; Wang, J.; Singh, A.; Lei, A. *Chem. Rev.* **2017**, *117*, 9016-9085. (d) Chu, J. K.; Rovis, T. *Angew. Chem., Int. Ed.* **2018**, *57*, 62-101.
- (2) For a review, see: Manoharan, R.; Jeganmohan, M. *Asian J. Org. Chem.* 2019, *8*, 1949-1969.
- (3) (a) Miura, W.; Hirano, K.; Miura, M. *Org. Lett.* **2015**, *17*, 4034-4037. (b) Manoharan, R.; Jeganmohan, M. *Org. Lett.* **2017**, *19*, 5884-5887.
- (4) He, Q.; Yamaguchi, T.; Chatani, N. *Org. Lett.* **2017**, *19*, 4544-4547.

- (5) (a) Xu, J.-W.; Zhang, Z.-Z.; Rao, W.-H.; Shi, B.-F. *J. Am. Chem. Soc.* **2016**, *138*, 10750-10753. (b) Liu, M.; Yang, P.; Karunananda, M.; Wang, Y.; Liu, P.; Engle, K. *J. Am. Chem. Soc.* **2018**, *140*, 5805-5813.
- (6) (a) Gu, Y.; Leng, X.; Shen, Q. *Nat. Commun.* **2014**, *5*, 5405. (b) B, Bhaskararao., S, Singh.; M, Anand.; P, Verma.; P, Athira C.; S, Malakar.; H, Schaefer.; R. Sunoj. *Chem. Sci.* **2020**, *11*, 208-216.
- (7) Shibata, K.; Chatani, N. *Org. Lett.* **2014**, *16*, 5148-5151.

Chapter 2

Palladium-Catalyzed [3+2] Annulation of Benzamides and Anilides via *benzylic* and *meta* C-H Bond Activation

2.1 Introduction

Catalytic annulation reactions *via* C-H bond activation are now recognized as one of the more attractive methods for the synthesis of cyclic compounds because the reaction is straightforward and highly atom efficient.¹ The catalytic [4+2] annulation of aromatic amides or carboxylic acids with alkynes or alkenes, which involves the activation of the *ortho* C-H bond and the cleavage of N-H or O-H bonds have been extensively studied in the last decades (Figure 1a).² Compared with C-H annulation *via* mono C-H bond activation, the preparation of cyclic compounds through double C-H activation is more attractive and challenging because the reaction can be used to construct complex frameworks which might be difficult to prepare by other existing methods. The [2+2+2] annulation with alkynes, leading to the production of naphthalene derivatives, is one of the most extensively studied C-H annulation reaction (Figure 1b).³ On the other hand, there are only a few examples of the construction of four or five-membered annulation compounds *via* [2+2]⁴ or [3+2]⁵ annulation involving double C-H bond activation. In 2019, Li reported on the rhodium-catalyzed [3+2] annulation of aromatic amides with 7-azabenzonorbornadienes, in which a nitrogen atom bearing an electron-withdrawing group functions as one coupling atom to form five-membered rings.^{5a} Yan and Cao reported on the visible-light-induced intermolecular [3+2] cycloaddition of indolizines and alkynes.^{5b} Yu recently reported on a Pd-catalyzed [3+2] annulation of aliphatic amides with maleimides, which involves dual C(sp³)-H bond activation.⁶ In this chapter, a palladium-catalyzed site-selective [3+2] annulation of secondary aromatic amides with maleimides in which both the *benzylic* C-H bond and *meta* C-H bond would be introduced (Figure 1c). This reaction was achieved only by the use of a *N,S*-bidentate chelation system, which was first used by Daugulis in 2010.⁷ In the present reaction, none of the products arising from *ortho*-C-H/N-H annulation, alkylation products at the *ortho* C-H bond, and alkylation products at a benzylic C-H bond were observed. Furthermore, this [3+2] annulation reaction can be applied to anilide type substrates. The presence of both an N-H bond and a SMe group in the substrates is essential for the reaction to proceed.

2.2 Results and Discussion

After optimizing the reaction conditions using 2-methyl-*N*-(2-(methylthio)phenyl)benzamide (**1a**) (see Table SI-S4 for more details),

the following reaction conditions were determined as standard reaction conditions: **1a** (0.3 mmol), maleimide (2.2 equiv), Pd(OPiv)₂ (15 mol%), CuO (2 equiv), PivOH (4 equiv) and NaOTf (1 equiv) in 1,1,2,2-tetrachloroethane (TCE, 1 mL) at 160 °C for 18 h.

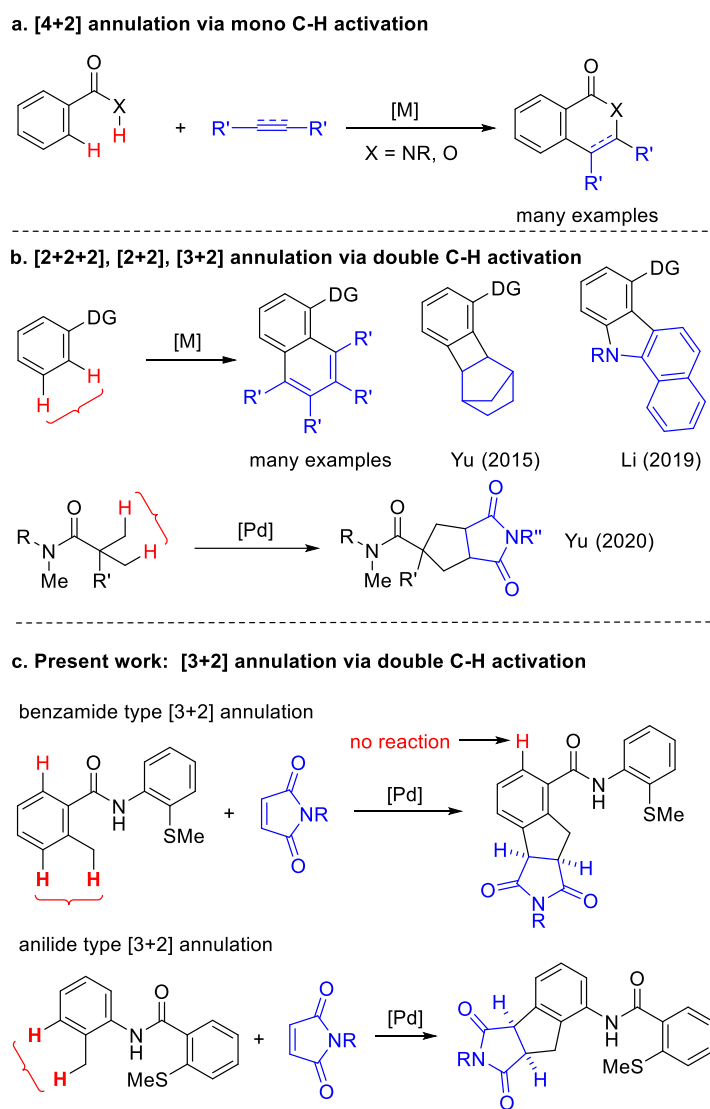
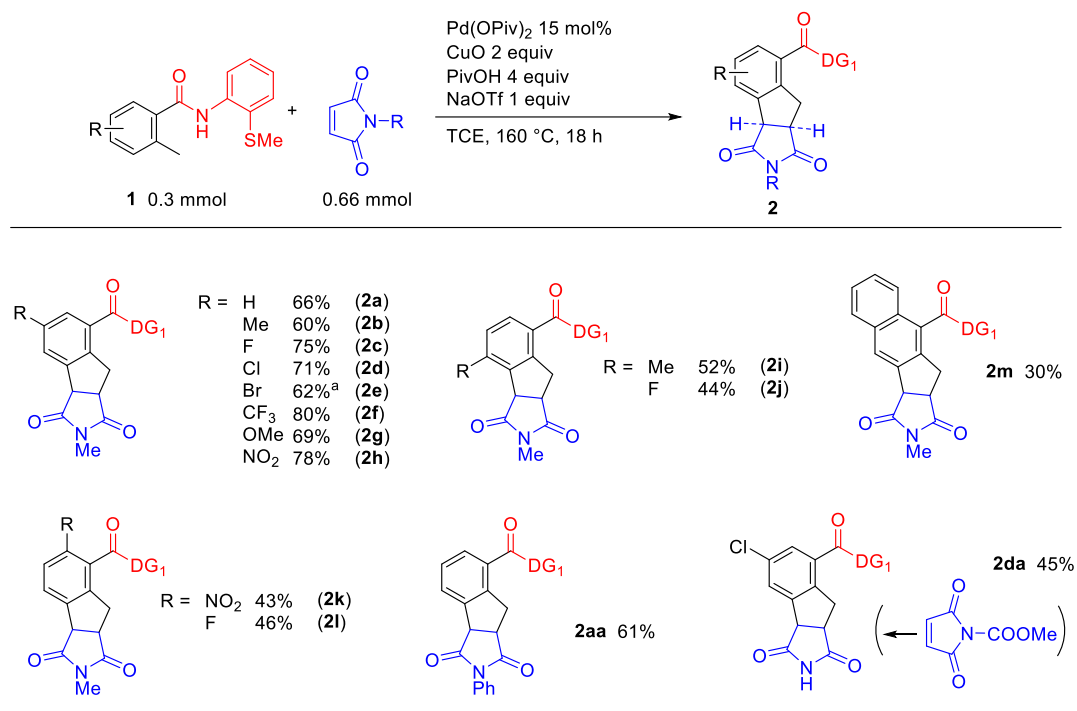


Figure 1. Transition-metal catalyzed C-H annulation via dual C-H activation.

The scope of the reaction for aromatic amides bearing various substituents is shown in Scheme 1. The reaction of **1a** under the standard reaction conditions gave **2a** as a single diastereomer in 66% isolated yield. The reaction shows a high functional group tolerance. Halogen atoms, such as fluoro, chloro, and even bromo were tolerated in this catalytic reaction to give **2c-2e**, **2j**, and **2l**. Nitro-substituted amides **1h** and **1k** also

participated in the reaction to give good yields of the corresponding annulation products **2h** and **2k**. 4-Substituted aromatic amides also gave the corresponding annulation products **2i** and **2j**, even though the *meta* C-H bonds are sterically hindered. The reaction was also applicable to the 2-methyl-1-naphthamide **1m** to give the corresponding product **2m**. Curiously, in the reaction of **1d** with *N*-methoxycarbonylmaleimide as a coupling partner, the free *N*-H product **2da** was selectively formed. The reaction with the free *N*-H maleimide gave **2da** in low yield probably because the free *N*-H maleimide is only sparingly soluble in TCE. Using *N*-Methoxycarbonylmaleimide can be used as an alternative of free *N*-H maleimide.

Scheme 1. Pd(II)-catalyzed [3+2] of benzamide type substrates.

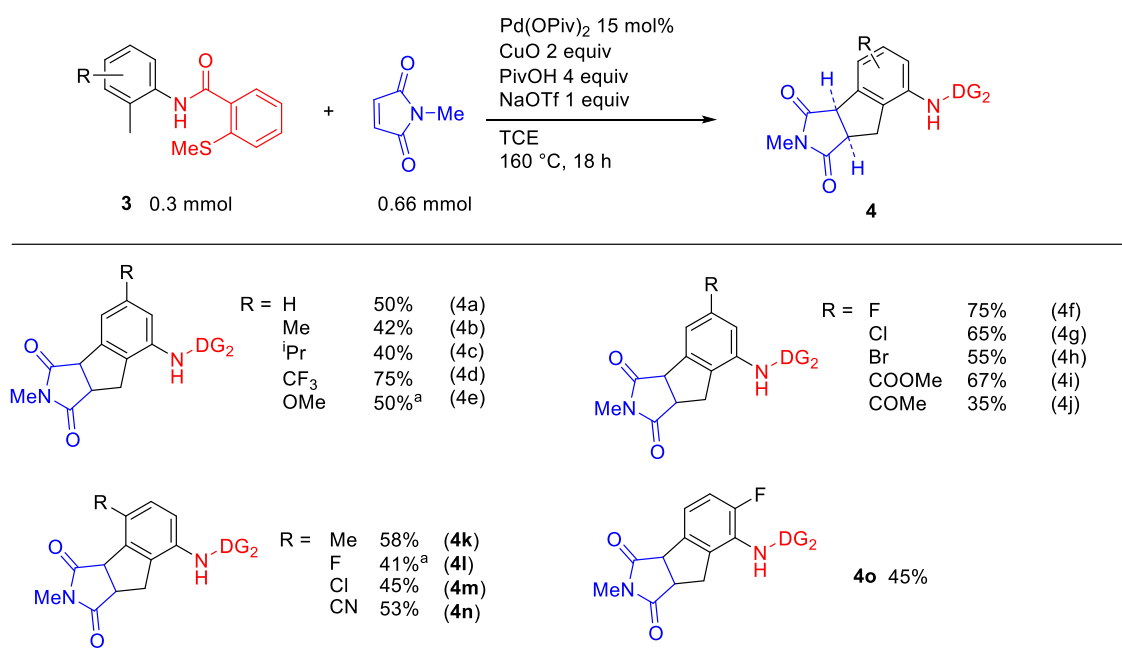


Encouraged by these results, we hypothesized that similar transformations would occur when anilide type substrates **3** are used, in which a 2-thiomethylbenzoyl group is attached to the aniline nitrogen. Gratifyingly, similar [3+2] annulation products were obtained under reaction conditions similar to those used in the reaction of benzamides **1** (Scheme 2). [3+2] Annulation of anilide type substrates also showed a high functional group compatibility.

To gain insights into the mechanism for this [3+2] annulation reaction, some mechanistic experiments were conducted. We first examined the effect of directing

groups (Scheme 3a). No expected annulation products were obtained when the NH group in the substrate was changed to an O atom or when a SMe group was changed to an OMe group. The same results were observed in the case of anilide type substrates. These results indicate that both the presence of NH and SMe groups are crucial for this transformation to proceed. Deuterium-labeling experiments were carried out in the absence of maleimide (Scheme 3b).

Scheme 2. Pd(II)-catalyzed [3+2] of anilide type amide.

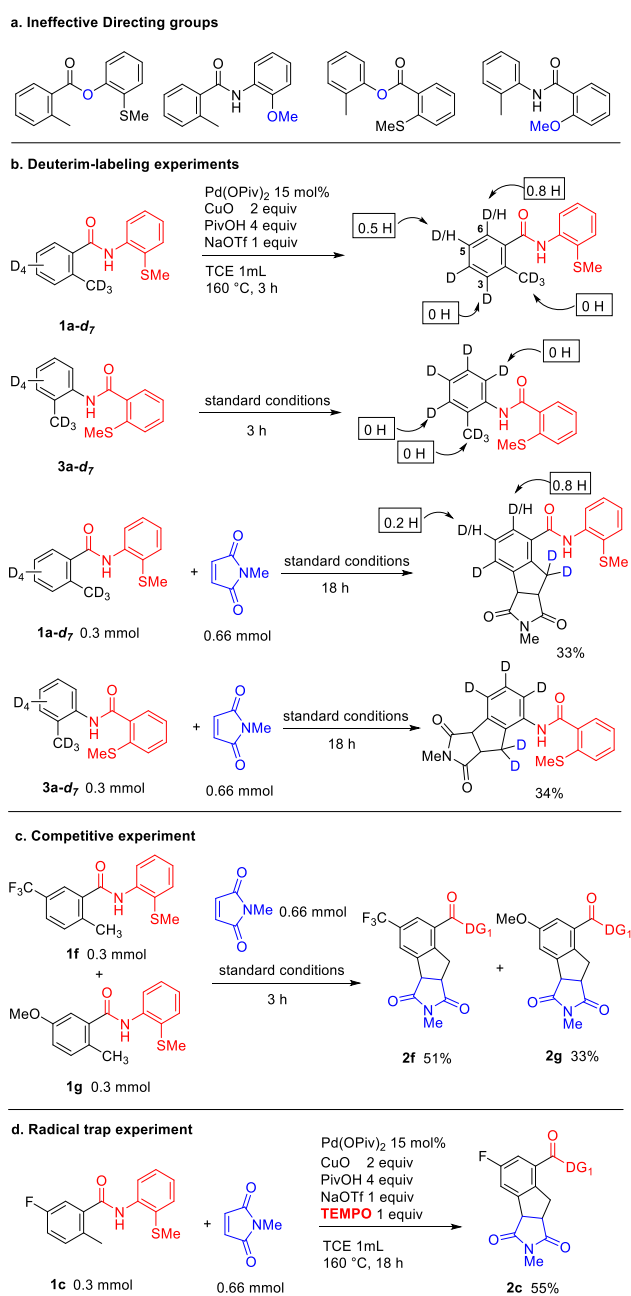


^a Without NaOTf.

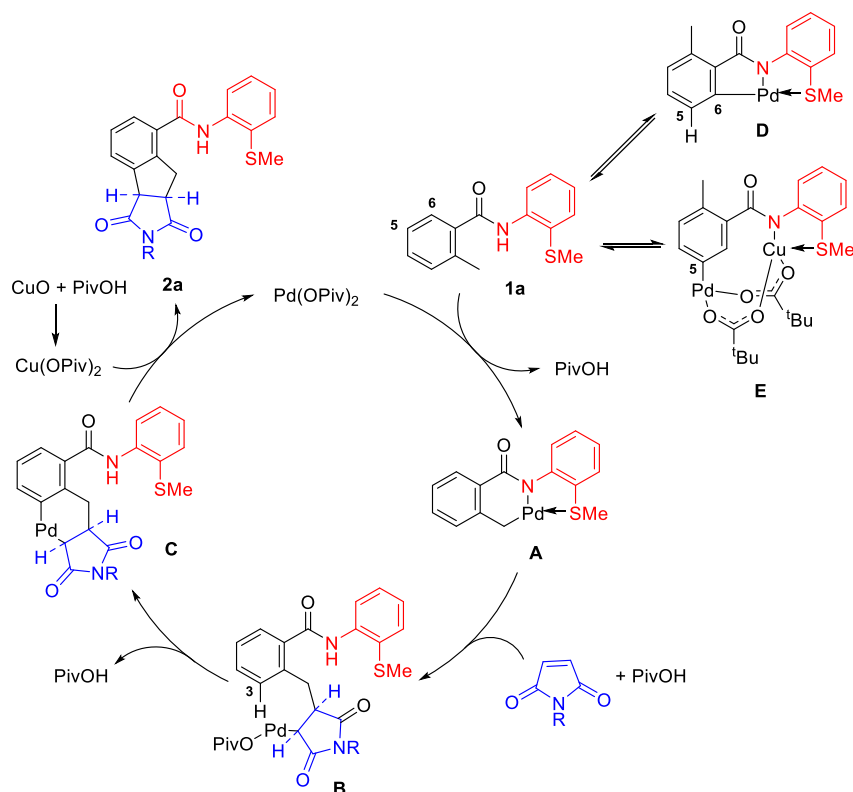
In the reaction of **1a-d₇**, unexpectedly, no H/D exchange was detected at the *benzylic* position and at the 3-position, but a significant amount of H/D exchange took place at the *ortho* position (6-position) (0.8 H) and the 5-position (0.5 H). These results indicate that the activation of the 5- and 6-positions is very fast and reversible, however these processes are a non-productive route. In contrast, the activation of the *benzylic* C-H bond and the C-H bond at the 3-position is irreversible. In sharp contrast to **1a-d₇**, no H/D exchange was detected in the anilide substrate **3a-d₇**. Essentially the same results were observed even in the presence of maleimide. It is particularly noteworthy that the annulation product was obtained in only 33% yield when the deuterated substrate **1a-d₇** was used, while **1a** gave **2a** were produced in 66% yield, indicating that the C-H bond cleavage is the rate determining step. A competition experiment was carried out to

evaluate the electronic effect of a substituent on the aromatic amides. The reaction of an equal molar ratio of **1f** and **1g** under the standard conditions gave **2f** and **2g** in 51% and 33% yields, respectively. This result indicates that the presence of an electron-withdrawing group causes a slight increase in substrate reactivity. Finally, a radical trap experiment was performed (Scheme 3d). When the reaction was carried out in the presence of 1 equiv of TEMPO, **2c** was produced in 55% yield, indicating that the reaction does not proceed through a radical mechanism.

Scheme 3. Mechanistic Studies.



Scheme 4. Plausible mechanism.



A proposed mechanism for the [3+2] annulation reaction of aromatic amides, based on the results of mechanistic experiments is shown in Scheme 4. A six-membered palladacycle **A** is generated through the coordination of **1a** to the palladium(II) complex followed by the activation of a *benzylic* C-H bond, the latter step being irreversible. The *syn*-insertion of the maleimide into a Pd-C bond in **A** and protonation of the Pd-N bonds by pivalic acid gives intermediate **B**. Activation of the *meta* C-H bond (3-position) gives another six-membered palladacycle **C**. Finally, the annulation product **2a** is formed through reductive-elimination with the palladium catalyst being regenerated by oxidation by copper pivalate. H/D exchange at both the 5- and 6-position was observed in the recovered starting amide (Scheme 3b). H/D exchange at the 6-position commonly occurs in many C-H functionalization reactions that involve aromatic systems. To explain the unexpected result of the deuterium-labeling experiment in which H/D exchange occurred at the 5-position, we propose the intermediacy of two intermediates **D** and **F**. The formation of **D** is known to be kinetically favored because of the formation of a five-membered palladacycle through *ortho* C-H bond activation. However, the insertion of the maleimide into the Pd-C bond in a five-membered palladacycle in **D** is energetically unfavorable.¹⁰ An alternative route for H/D exchange

at the 5-position proceeds through the Pd-Cu complex **E**, in which a copper atom is coordinated with the sulfur atom and a pivalate ion functions as a bridging ligand between palladium and copper.⁸ Because these steps are reversible, H/D exchange took place at both the 5- and 6-positions.

2.3 Conclusion

In summary, this chapter concludes the site-selective Pd(II)-catalyzed [3+2] annulation of aromatic amides with maleimides via double C-H bond activation. This [3+2] annulation can occur on both of benzamide type and anilide type substrates, in which the presence of both N-H and SMe moieties is required for the reaction to proceed. The activation of the benzylic C-H bond and the *meta* C-H bond is irreversible.

2.4 Experimental Section

I. General Information.

¹H NMR and ¹³C NMR spectra were recorded on a JEOL ECS-400 spectrometer in CDCl₃ with tetramethylsilane as the internal standard. Data are reported as follows: chemical shifts in ppm (δ), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, brs = broad singlet, and m = multiplet), coupling constant (Hz), and integration. In some cases, it was not possible to analyze some of the peaks in the ¹³C NMR spectra because of overlapping peaks. Infrared spectra (IR) were recorded on a JASCO FT/IR-4000 spectrometer using the ATR method. Absorption data are reported in reciprocal centimeters from 800 to 3500 cm⁻¹ with the following relative intensities: s (strong), m (medium), or w (weak). Mass spectra and high-resolution mass spectra (HRMS) were obtained using a JMS-T100LP spectrometer. Melting points were determined using a Stanford Research Systems MPA100 apparatus equipped with a digital thermometer. Medium-pressure liquid chromatography (MPLC) was performed with Biotage Isolera[®] equipped with Biotage[®] Sfär Silica HC D-High Capacity Duo 20 μm chromatography cartridges.

II. Materials.

Palladium catalyst:

Pd(OPiv)₂ (Sigma-Aldrich Co.)

Additives:

CuO (FUJIFILM Wako Pure Chemical Co.); PivOH (Tokyo Chemical Industry Co., Ltd.); NaOTf (Tokyo Chemical Industry Co., Ltd.).

Maleimides:

N-Methylmaleimide (Tokyo Chemical Industry Co., Ltd.); *N*-Phenylmaleimide (Tokyo Chemical Industry Co., Ltd.); *N*-Methoxycarbonylmaleimide (Tokyo Chemical Industry Co., Ltd.).

Benzoic acids:

o-Toluic acid, 5-Fluoro-2-methylbenzoic acid; 2,4-Dimethylbenzoic acid; 2,5-Dimethylbenzoic acid; 4-Fluoro-2-methylbenzoic acid; 5-Chloro-2-methylbenzoic Acid; 5-Bromo-2-methylbenzoic acid; 2-(Methylthio)benzoic Acid (Tokyo Chemical Industry Co., Ltd.).

2-Methyl-5-nitrobenzoic acid, 2-Methyl-6-nitrobenzoic acid, 2-Methylnaphthalene-1-carboxylic acid (Sigma-Aldrich Co.)

5-Methoxy-2-methylbenzoic acid; 2-Methyl-5-(trifluoromethyl) benzoic acid (BLD Pharmatech Ltd.)

Anilines:

o-Toluidine; 2,5-Dimethylaniline; 2,4-Dimethylaniline; 2-Methyl-5-isopropylaniline; 2-Methyl-5-(trifluoromethyl)aniline; 5-Methoxy-2-methylaniline; 4-Methoxy-2-methylaniline; 6-Fluoro-2-methylaniline; 5-Fluoro-2-methylaniline; 4-Fluoro-2-methylaniline; 5-Chloro-2-methylaniline; 4-Chloro-2-methylaniline; 5-Bromo-2-methylaniline; Methyl 3-Amino-4-methylbenzoate; 4-Amino-3-methylbenzotrile; 2-(Methylthio)aniline (Tokyo Chemical Industry Co., Ltd.).

1-(3-Amino-4-methylphenyl)ethenone; (Sigma-Aldrich Co.)

III. Synthesis of Starting Materials.

To a stirred solution of the carboxylic acid (5 mmol) and DMF (3 drops) in CHCl₃ (5 mL), (COCl)₂ (0.5 mL, 6 mmol) was added dropwise. The solution was magnetically stirred at room temperature for 4 h. After removing the solvent under reduced pressure, the resulting residue was dissolved in CHCl₃ (15 mL). After cooling the reaction mixture to 0 °C, a solution of aniline (6 mmol) and triethylamine (10 mmol) in 10 mL of CHCl₃ was added dropwise. The resulting mixture was allowed to warm to room temperature and stirred overnight. The crude product was washed with 1 M HCl aq. (20 mL). The organic phase was dried over anhydrous Na₂SO₄ and the solvent was removed by evaporation. The resulting crude amide was purified by MPLC (eluent: hexanes/EtOAc = 4/1).

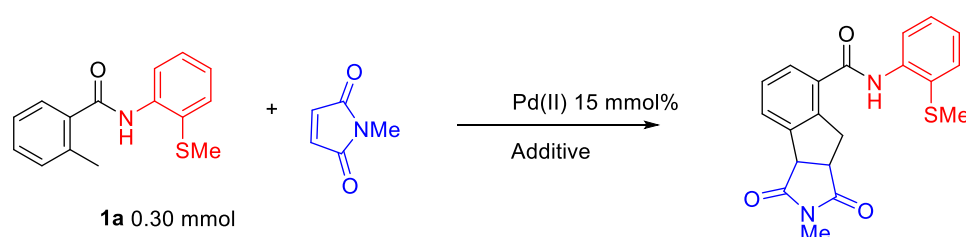
IV. General Synthesis of [3+2] Annulation Products

To an oven-dried 5 mL screw-capped vial, 2-methyl-*N*-(2-(methylthio)phenyl)benzamide (77.2 mg, 0.3 mmol),

N-methylmaleimide (72.7 mg, 0.66 mmol), Pd(OPiv)₂ (13.9 mg, 0.045mmol), CuO (49.7 mg, 0.6 mmol), PivOH (122.6 mg, 1.2 mmol), NaOTf (51.6 mg, 0.3 mmol) and Cl₂CHCHCl₂ (1 mL) were added. The mixture was stirred at 160 °C for 24 hours and then cooled to room temperature. The resulting mixture was diluted with 1 mL of EtOAc. The product was purified by column chromatography on silica gel (eluent: hexane/EtOAc= 1.5:1) to afford the product (73 mg, 66 %) as a pale-yellow powder.

V. Optimization of Reaction Conditions

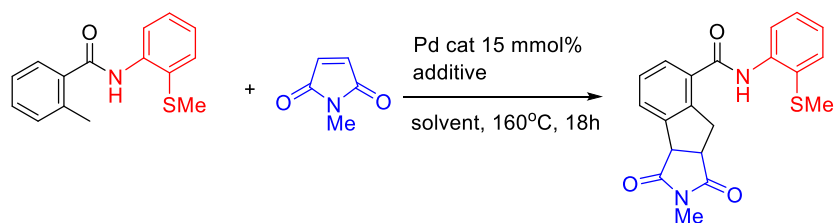
Table S1



entry	Pd catalyst	additive (equiv)	solvent	yield
1 ^a	Pd(OAc) ₂	none	DMF	n.d.
2 ^a	Pd(OAc) ₂	AgOAc (2.5)	DMF	trace
3 ^b	Pd(OPiv) ₂	MnO ₂ (1.2)	PivOH	50%
4 ^b	Pd(OPiv) ₂	MnO ₂ (2.0)	3-Pentanone	trace
5 ^b	Pd(OPiv) ₂	MnO ₂ (2.0) LiOAc (1.0)	PivOH	mixture
6 ^a	Pd(OPiv) ₂	AgOAc (1.2)	PivOH	28 %
7 ^a	Pd(OPiv) ₂	Cu(OAc) ₂ ·H ₂ O (1.2)	PivOH	42 %

^a 160 °C; ^b 180 °C; ^c isolated yield;

Table S2



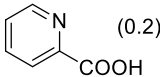
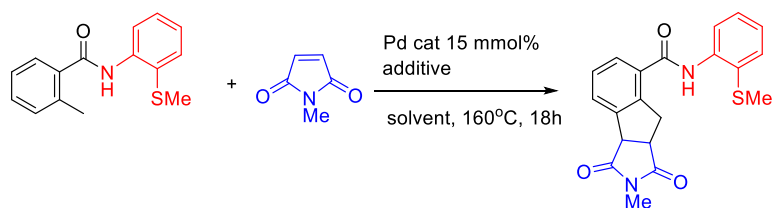
entry	cat	additive(equiv)	sol	yield
1	PdI ₂	MnO ₂ (1.2)	PivOH	n.d
2	PdI ₂	MnO ₂ (1.2)	C ₂ H ₂ Cl ₄	n.d
3	Pd(NO ₃) ₂ •2H ₂ O	MnO ₂ (1.2)	PivOH	55%
4	Pd(NO ₃) ₂ •2H ₂ O	AgNO ₃ (2.0)	PivOH	trace
5	Pd(NO ₃) ₂ •2H ₂ O	MnO ₂ (1.2) C ₆ F ₅ COOH (4.0)	C ₂ H ₂ Cl ₄	trace
6	Pd(NO ₃) ₂ •2H ₂ O	MnO ₂ (1.2) CCl ₃ COOH (4.0)	C ₂ H ₂ Cl ₄	n.d
7	Pd(NO ₃) ₂ •2H ₂ O	MnO ₂ (1.2)	C ₁₂ H ₂₆	trace
8	Pd(NO ₃) ₂ •2H ₂ O	BQ (2.0)	C ₂ H ₂ Cl ₄	n.d
9	Pd(NO ₃) ₂ •2H ₂ O	BQ (2.0) Cs ₂ CO ₃ (1.0)	C ₂ H ₂ Cl ₄	n.d
10	Pd(NO ₃) ₂ •2H ₂ O	MnO ₂ (1.2) 1-AdCOOH (4.0) Li ₂ CO ₃ (1.0)	C ₂ H ₂ Cl ₄	trace
11	Pd(NO ₃) ₂ •2H ₂ O	MnO ₂ (1.2) HOOCCH ₂ COOH (2.0)	C ₂ H ₂ Cl ₄	n.d
12	Pd(NO ₃) ₂ •2H ₂ O	MnO ₂ (1.2)  (0.2)	C ₂ H ₂ Cl ₄	n.d
13	Pd(NO ₃) ₂ •2H ₂ O	MnO ₂ (1.2) 3-Cl-PivOH (4.0)	C ₂ H ₂ Cl ₄	n.d
14	Pd(NO ₃) ₂ •2H ₂ O	Cu(OAc) ₂ (1.2) PhSO ₂ Na (1.0)	C ₂ H ₂ Cl ₄	trace
15	Pd(NO ₃) ₂ •2H ₂ O	Cu(OAc) ₂ (1.2) NaO ^t Bu (1.0)	C ₂ H ₂ Cl ₄	n.d
16	Pd(NO ₃) ₂ •2H ₂ O	Cu(OAc) ₂ (1.2) NaOTf (1.0)	C ₂ H ₂ Cl ₄	40%
17	Pd(NO ₃) ₂ •2H ₂ O	Cu(OAc) ₂ (1.2) NaBH ₄ (1.0)	C ₂ H ₂ Cl ₄	n.d

Table S3



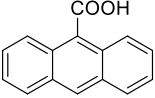
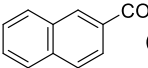
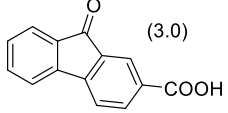
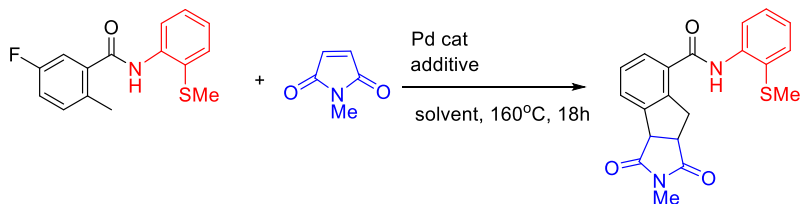
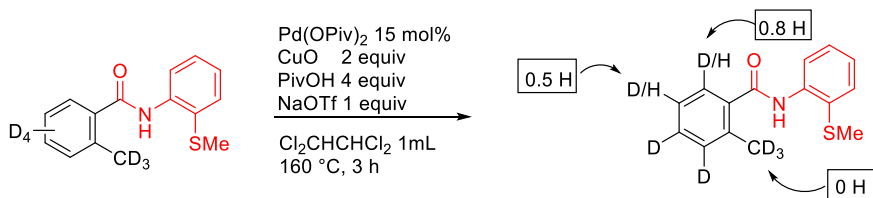
entry	cat	additive(equiv)	sol	yield
1	Pd(NO ₃) ₂ •2H ₂ O	MnO ₂ (1.2) <i>N</i> -acetylglycine (0.3)	C ₂ H ₂ Cl ₄	trace
2	Pd(NO ₃) ₂ •2H ₂ O	MnO ₂ (1.2) <i>N,N</i> -dimethylglycine (0.3)	C ₂ H ₂ Cl ₄	trace
3	Pd(NO ₃) ₂ •2H ₂ O	CuO (1.2) <i>N</i> -acetylglycine (3.0)	C ₂ H ₂ Cl ₄	n.d
4	Pd(NO ₃) ₂ •2H ₂ O	CuO (1.2) PivOH (4.0)	CyCOOMe	n.d
5	Pd(NO ₃) ₂ •2H ₂ O	CuO (1.2)  (3.0)	C ₂ H ₂ Cl ₄	27%
6	Pd(NO ₃) ₂ •2H ₂ O	CuO (1.2) pyridine (0.5)	C ₂ H ₂ Cl ₄	n.d
7	Pd(NO ₃) ₂ •2H ₂ O	CuO (1.2)  (3.0)	C ₂ H ₂ Cl ₄	trace
8	Pd(NO ₃) ₂ •2H ₂ O	CuO (1.2)  (3.0)	C ₂ H ₂ Cl ₄	n.d
9	Pd(NO ₃) ₂ •2H ₂ O	MnO ₂ (1.2) NaOTf (1.0)	C ₂ H ₂ Cl ₄	n.d
10	Pd(cod)Cl ₂	MnO ₂ (1.2) KOTf (1.0)	C ₂ H ₂ Cl ₄	n.d
11	Pd(OPiv) ₂	AgOTf (2.0)	C ₂ H ₂ Cl ₄	n.d
12	Pd(OPiv) ₂	AgOTf (2.0)	C ₂ H ₂ Cl ₄	n.d
13	Pd(OPiv) ₂	CuO (2.0) PivOH (4.0) NaOTf (1.0)	C ₂ H ₂ Cl ₄	66%

Table S4

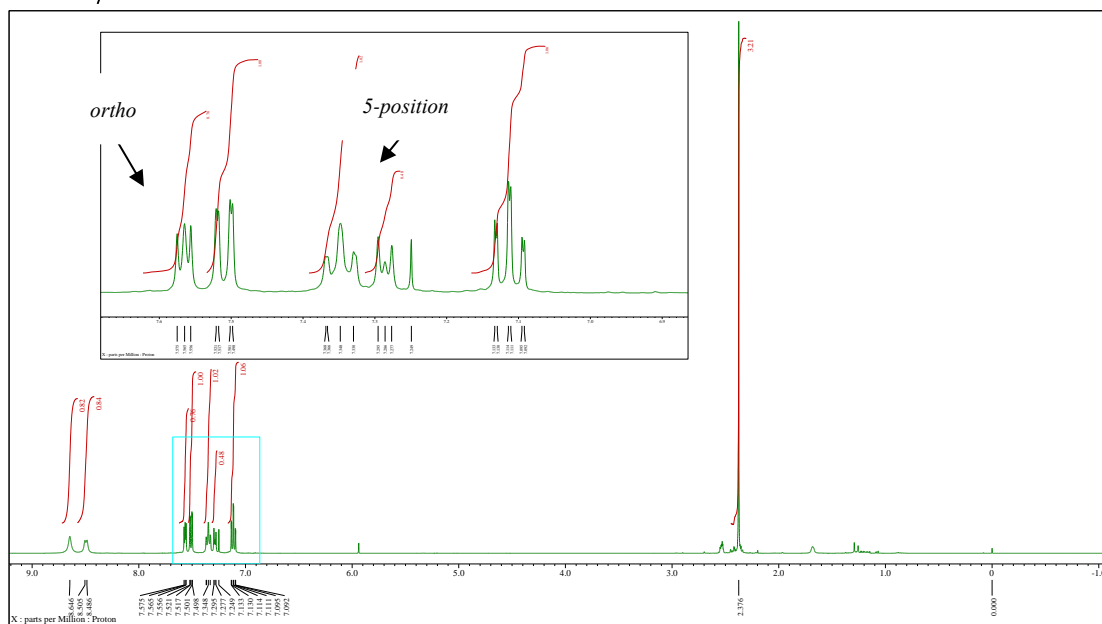


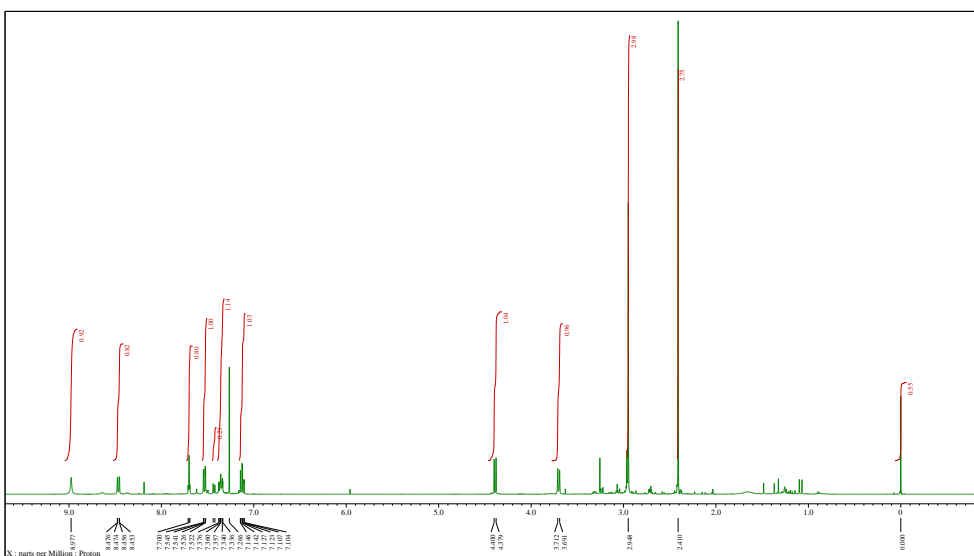
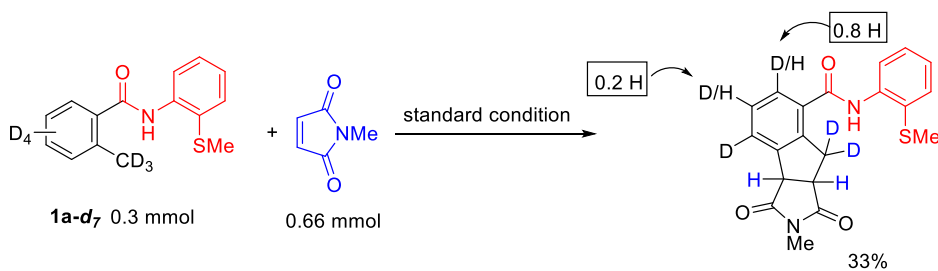
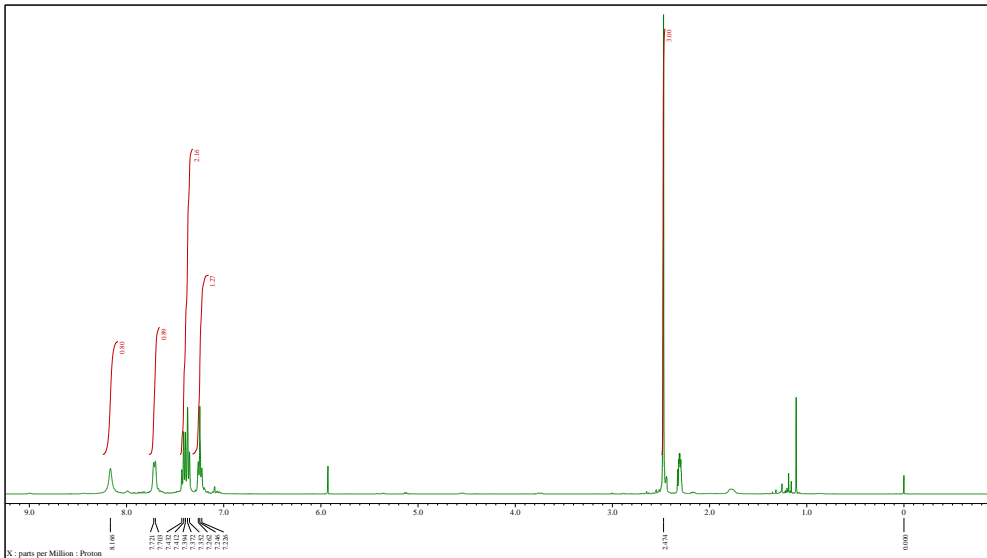
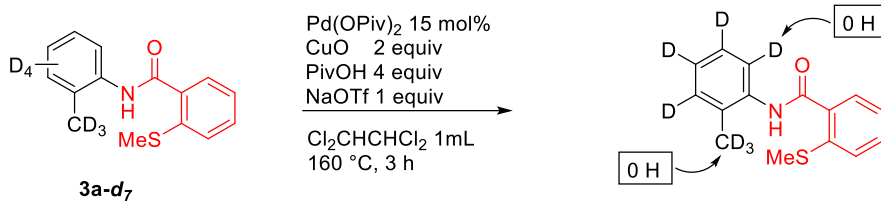
entry	cat	additive(equiv)	sol	yield
1	Pd(OPiv) ₂ (10 mol%)	CuO (2.0) PivOH (4.0) NaOTf (1.0)	C ₂ H ₂ Cl ₄	56%
2	Pd(OPiv) ₂ (15 mol%)	CuO (2.0) PivOH (4.0) NaOTf (1.0)	C ₂ H ₂ Cl ₄	75%

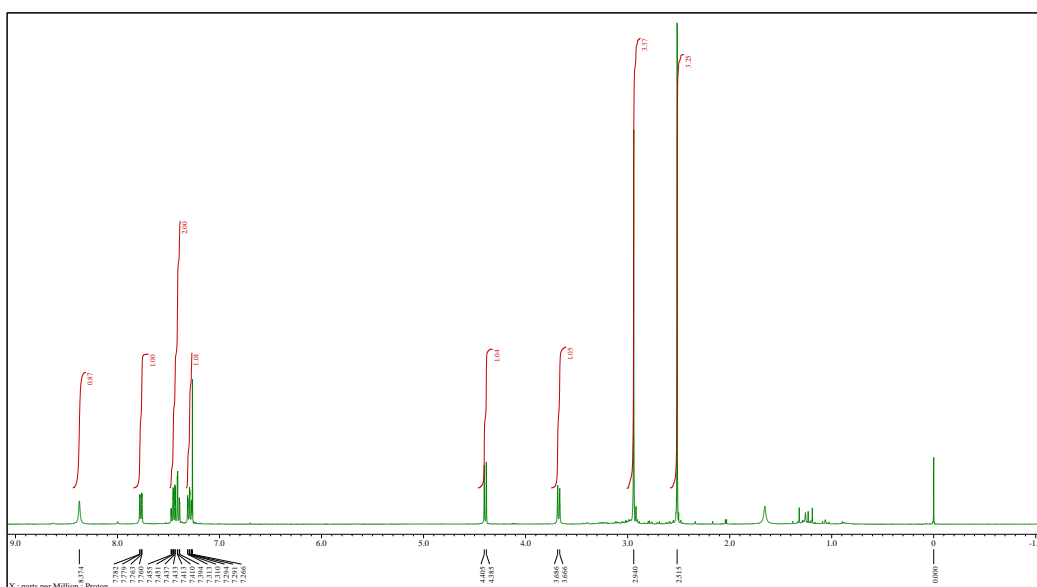
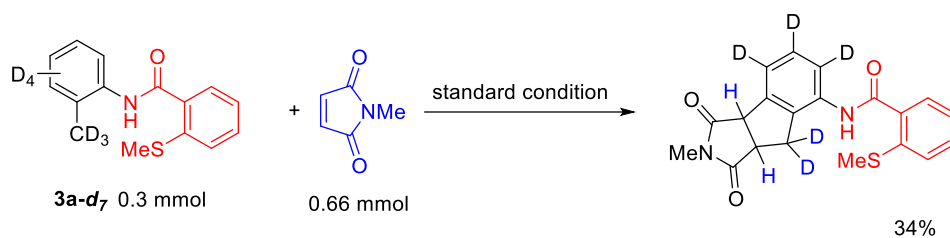
VI. Deuterium Labeling Experiments



1a-d₇



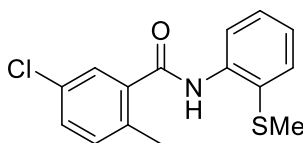




VII. Spectroscopic Data

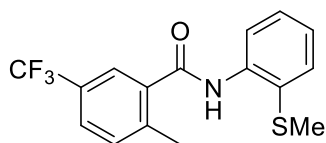
Unknown starting materials

5-chloro-2-methyl-*N*-(2-(methylthio)phenyl)benzamide (**1d**)



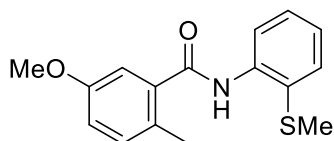
1.30g, 77% yield (5 mmol scale). $R_f = 0.54$ (Hex: EtOAc = 3:1). White solid. m.p. 120.2-120.7°C. ¹H-NMR (CDCl₃, 400 MHz) δ 8.57 (s, 1H), 8.44 (d, J = 7.8 Hz, 1H), 7.54-7.51 (m, 2H), 7.38-7.34 (m, 2H), 7.23 (d, J = 8.2 Hz, 1H), 7.14 (td, J = 7.7, 1.4 Hz, 1H), 2.51 (s, 3H), 2.40 (s, 3H). ¹³C NMR (CDCl₃, 100 MHz) δ 166.6, 138.1, 137.8, 135.1, 132.9, 131.9, 130.5, 129.0, 127.0, 126.1, 125.1, 121.0, 19.7, 19.1. HRMS (DART+) m/z ([M+H]⁺) Calcd for C₁₅H₁₅NO₂Cl: 292.0563; Found: 292.0575.

2-methyl-*N*-(2-(methylthio)phenyl)-5-(trifluoromethyl)benzamide (1f)



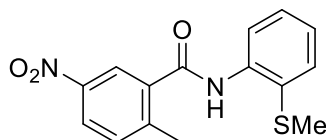
1.21g, 74% yield (5 mmol scale). $R_f = 0.51$ (Hex: EtOAc = 3:1). White powder. m.p. 122.9-123.2°C. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 8.62 (s, 1H), 8.44 (d, $J = 8.0$ Hz, 1H), 7.81 (s, 1H), 7.63 (dd, $J = 8.0, 1.1$ Hz, 1H), 7.52 (dd, $J = 7.8, 1.1$ Hz, 1H), 7.42 (d, $J = 8.0$ Hz, 1H), 7.36 (t, $J = 7.5$ Hz, 1H), 7.15 (td, $J = 7.7, 1.4$ Hz, 1H), 2.61 (s, 3H), 2.40 (s, 3H). $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) δ 166.6, 140.9, 138.0, 137.0, 132.9, 132.0, 129.0, 128.7 (q, $d = 34$ Hz), 127.1 (d, $J = 4$ Hz), 126.2, 125.3, 124.0 (d, $J = 4$ Hz), 122.6, 121.0, 20.2, 19.1. HRMS (DART+) m/z ($[\text{M}+\text{H}]^+$) Calcd for $\text{C}_{16}\text{H}_{15}\text{NOSF}_3$: 326.0826; Found: 326.0834.

5-methoxy-2-methyl-*N*-(2-(methylthio)phenyl)benzamide (1g)



1.35g, 94% yield (5 mmol scale). $R_f = 0.26$ (Hex: EtOAc = 3:1). White solid. m.p. 69.5-70.2°C. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 8.64 (s, 1H), 8.50 (d, $J = 7.8$ Hz, 1H), 7.52 (dd, $J = 7.8, 1.4$ Hz, 1H), 7.38-7.34 (m, 1H), 7.20 (d, $J = 8.5$ Hz, 1H), 7.14-7.10 (m, 2H), 6.93 (dd, $J = 8.5, 2.7$ Hz, 1H), 3.83 (s, 3H), 2.48 (s, 3H), 2.38 (s, 3H). $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) δ 167.9, 157.8, 138.5, 137.2, 133.1, 132.6, 129.1, 128.3, 125.8, 124.8, 120.8, 116.2, 112.5, 55.6, 19.3, 19.2. HRMS (DART+) m/z ($[\text{M}+\text{H}]^+$) Calcd for $\text{C}_{16}\text{H}_{18}\text{NO}_2\text{S}$: 288.1058; Found: 288.1075.

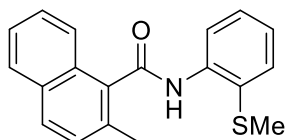
2-methyl-*N*-(2-(methylthio)phenyl)-5-nitrobenzamide (1h)



1.47g, 97% yield (5 mmol scale). $R_f = 0.37$ (Hex: EtOAc = 3:1). Pale yellow powder. m.p. 143.6-144.1°C. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 8.67 (s, 1H), 8.42 (d, $J = 9.6$ Hz, 2H), 8.24 (dd, $J = 8.2, 2.1$ Hz, 1H), 7.54 (d, $J = 7.8$ Hz, 1H), 7.48 (d, $J = 8.5$ Hz, 1H),

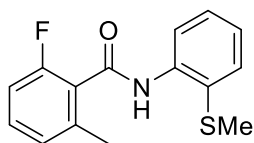
7.37 (t, $J = 7.7$ Hz, 1H), 7.20-7.16 (m, 1H), 2.66 (s, 3H), 2.43 (s, 3H). ^{13}C NMR (CDCl_3 , 100 MHz) δ 165.6, 146.2, 144.7, 137.7, 137.4, 132.8, 132.6, 129.0, 126.5, 125.5, 125.1, 122.2, 121.1, 20.5, 19.1. HRMS (DART+) m/z ($[\text{M}+\text{H}]^+$) Calcd for $\text{C}_{15}\text{H}_{15}\text{N}_2\text{O}_3\text{S}$: 303.0798; Found: 303.0797.

2-methyl-*N*-(2-(methylthio)phenyl)-1-naphthamide (1m)



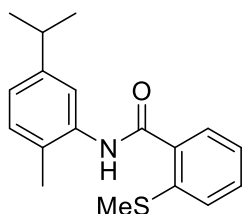
1.91g, 62% yield (10 mmol scale). $R_f = 0.47$ (Hex: EtOAc = 3:1). White solid. m.p. 96.4-96.8°C. ^1H -NMR (CDCl_3 , 400 MHz) δ 8.65 (dd, $J = 8.2, 1.1$ Hz, 1H), 8.55 (s, 1H), 7.97-7.95 (m, 1H), 7.86-7.83 (m, 2H), 7.53-7.37 (m, 5H), 7.16 (td, $J = 7.7, 1.4$ Hz, 1H), 2.61 (s, 3H), 2.31 (s, 3H). ^{13}C NMR (CDCl_3 , 100 MHz) δ 13C-NMR (101 MHz, CHLOROFORM-D) δ 168.3, 138.2, 133.9, 133.0, 132.4, 131.9, 130.2, 129.4, 129.0, 128.6, 128.2, 127.2, 126.1, 125.7, 125.1, 124.6, 121.2, 19.9, 19.1. HRMS (DART+) m/z ($[\text{M}+\text{H}]^+$) Calcd for $\text{C}_{19}\text{H}_{17}\text{NOS}$: 308.1109; Found: 308.1110.

2-fluoro-6-methyl-*N*-(2-(methylthio)phenyl)benzamide (1l)



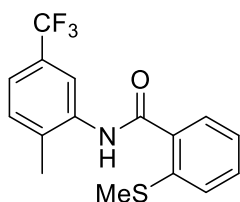
1.28g, 93% yield (5 mmol scale). $R_f = 0.34$ (Hex: EtOAc = 3:1). Colorless oil. ^1H -NMR (CDCl_3 , 400 MHz) δ 8.66 (s, 1H), 8.51 (dd, $J = 8.2, 1.1$ Hz, 1H), 7.52 (dd, $J = 7.8, 1.4$ Hz, 1H), 7.38-7.27 (m, 2H), 7.12 (td, $J = 7.5, 1.4$ Hz, 1H), 7.06 (d, $J = 7.5$ Hz, 1H), 6.99 (t, $J = 8.9$ Hz, 1H), 2.49 (s, 3H), 2.36 (s, 3H). ^{13}C NMR (CDCl_3 , 100 MHz) δ 163.4, 159.4 (d, $J = 245$ Hz), 139.1, 138.3, 133.4, 131.1 (d, $J = 9$ Hz), 129.1, 126.6 (d, $J = 19$ Hz), 125.8, 125.0, 124.8, 121.0, 113.4 (d, $J = 22$ Hz), 19.7, 19.1. HRMS (DART+) m/z ($[\text{M}+\text{H}]^+$) Calcd for $\text{C}_{15}\text{H}_{15}\text{NOSF}$: 276.0853; Found: 276.0864.

N-(5-isopropyl-2-methylphenyl)-2-(methylthio)benzamide (3c)



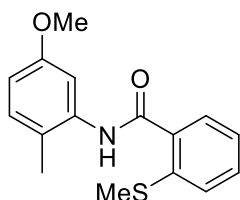
1.40g, 94% yield (5 mmol scale). R_f = 0.37 (Hex: EtOAc = 3:1). White solid. m.p. 82.9-83.1°C. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 8.13 (s, 1H), 7.95 (s, 1H), 7.76 (d, J = 6.6 Hz, 1H), 7.45-7.38 (m, 2H), 7.29-7.25 (m, 1H), 7.14 (d, J = 7.8 Hz, 1H), 6.99 (dd, J = 7.8, 1.4 Hz, 1H), 2.92 (t, J = 6.7 Hz, 1H), 2.50 (s, 3H), 2.31 (s, 3H), 1.26 (d, J = 6.6 Hz, 6H). $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) δ 166.0, 147.9, 136.7, 135.8, 135.6, 131.1, 130.6, 129.3, 128.1, 126.5, 125.8, 123.3, 121.2, 77.5, 77.2, 76.8, 34.0, 24.1, 17.9, 17.2. HRMS (DART+) m/z ($[\text{M}+\text{H}]^+$) Calcd for $\text{C}_{18}\text{H}_{22}\text{NOS}$: 300.1422; Found: 300.1449.

***N*-(2-methyl-5-(trifluoromethyl)phenyl)-2-(methylthio)benzamide (3d)**



1.08g, 66% yield (5 mmol scale). R_f = 0.31 (Hex: EtOAc = 3:1). White powder. m.p. 153.6-154.0°C. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 8.41 (d, J = 8.5 Hz, 2H), 7.77 (d, J = 7.3 Hz, 1H), 7.48-7.39 (m, 2H), 7.36-7.27 (m, 3H), 2.51 (s, 3H), 2.40 (s, 3H). $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) δ 166.1, 136.6, 136.5, 134.8, 132.8, 131.5, 131.0, 129.6, 129.4 (q, d = 33 Hz), 128.4, 126.1, 124.1 (d, J = 271 Hz), 121.7 (d, J = 4 Hz), 119.6, 18.4, 17.3. HRMS (DART+) m/z ($[\text{M}+\text{H}]^+$) Calcd for $\text{C}_{16}\text{H}_{15}\text{NOSF}_3$: 326.0821; Found: 326.0818.

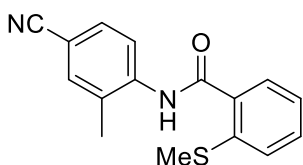
***N*-(5-methoxy-2-methylphenyl)-2-(methylthio)benzamide (3e)**



1.22g, 85% yield (5 mmol scale). R_f = 0.45 (Hex: EtOAc = 3:1). White solid. m.p. 119.8-120.2°C. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 8.16 (s, 1H), 7.84 (s, 1H), 7.74 (d, J = 7.5 Hz, 1H), 7.46-7.38 (m, 2H), 7.30-7.26 (m, 1H), 7.09 (d, J = 8.5 Hz, 1H), 6.66 (dd, J = 8.5, 2.7 Hz, 1H), 3.82 (s, 3H), 2.50 (s, 3H), 2.27 (s, 3H). $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz)

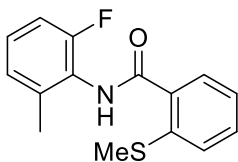
δ 158.5, 136.8, 136.7, 135.5, 131.2, 131.1, 129.3, 128.2, 125.9, 120.2, 111.3, 107.6, 55.6, 17.4, 17.2. HRMS (DART+) m/z ($[M+H]^+$) Calcd for $C_{16}H_{18}NO_2S$: 288.1053; Found: 288.1061.

***N*-(4-cyano-2-methylphenyl)-2-(methylthio)benzamide (3n)**



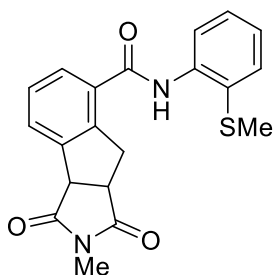
0.55g, 39% yield (5 mmol scale). R_f = 0.20 (Hex: EtOAc = 3:1). White solid. m.p. 114.6-114.8°C. 1H -NMR ($CDCl_3$, 400 MHz) δ 8.55 (s, 1H), 8.43 (d, J = 8.5 Hz, 1H), 7.79-7.77 (m, 1H), 7.55 (d, J = 8.5 Hz, 1H), 7.50-7.46 (m, 2H), 7.42 (d, J = 7.5 Hz, 1H), 7.33-7.29 (m, 1H), 2.51 (s, 3H), 2.38 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.0, 140.4, 136.6, 134.6, 134.1, 131.8, 131.3, 129.7, 128.5, 126.1, 121.7, 119.1, 114.3, 107.5, 18.1, 17.3. HRMS (DART+) m/z ($[M+H]^+$) Calcd for $C_{16}H_{15}N_2OS$: 283.0905; Found: 283.0927.

***N*-(2-fluoro-6-methylphenyl)-2-(methylthio)benzamide (3o)**



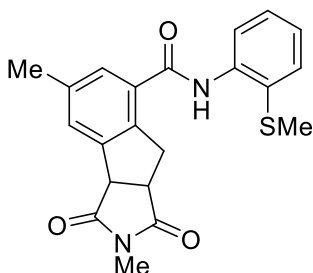
0.97g, 70% yield (5 mmol scale). R_f = 0.29 (Hex: EtOAc = 3:1). White solid. m.p. 126.6-126.9°C. 1H -NMR ($CDCl_3$, 400 MHz) δ 7.97 (s, 1H), 7.79 (d, J = 4.8 Hz, 1H), 7.46-7.38 (m, 2H), 7.28-7.25 (m, 1H), 7.17 (dd, J = 13.7, 7.8 Hz, 1H), 7.05 (d, J = 7.5 Hz, 1H), 6.99 (t, J = 8.9 Hz, 1H), 2.51 (s, 3H), 2.37 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.4, 159.0, 156.6, 138.1, 137.3, 134.5, 131.4, 129.5, 128.0, 127.9, 126.1 (d, J = 3 Hz), 125.7, 123.2 (d, J = 12 Hz), 113.3 (d, J = 20 Hz), 18.7, 17.2. HRMS (DART+) m/z ($[M+H]^+$) Calcd for $C_{16}H_{15}N_2OS$: 283.0905; Found: 283.0927.

2-methyl-*N*-(2-(methylthio)phenyl)-1,3-dioxo-1,2,3,3a,8,8a-hexahydroindeno[1,2-*c*]pyrrole-7-carboxamide (2a)



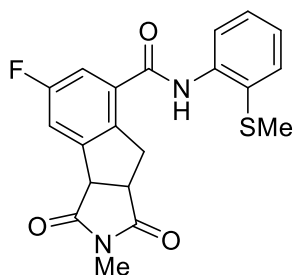
72.8mg, 66% yield. $R_f = 0.23$ (Hex: EtOAc = 1.5:1). Yellow powder. m.p. 72.7-73.1°C. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 8.98 (s, 1H), 8.47 (d, $J = 8.2$ Hz, 1H), 7.78 (d, $J = 7.7$ Hz, 1H), 7.70 (d, $J = 7.7$ Hz, 1H), 7.54 (dd, $J = 7.8, 1.5$ Hz, 1H), 7.43 (t, $J = 7.7$ Hz, 1H), 7.38-7.34 (m, 1H), 7.13 (td, $J = 7.6, 1.4$ Hz, 1H), 4.39 (d, $J = 8.0$ Hz, 1H), 3.83 (d, $J = 6.6$ Hz, 2H), 3.71 (dd, $J = 14.4, 6.9$ Hz, 1H), 2.95 (s, 3H), 2.41 (s, 3H). $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) 179.6, 177.3, 165.4, 142.1, 139.6, 138.4, 133.3, 132.6, 129.2, 128.4, 126.9, 125.7, 124.9, 120.6, 51.6, 43.9, 35.2, 25.3, 19.4. HRMS (DART+) m/z ($[\text{M}+\text{H}]^+$) Calcd for $\text{C}_{20}\text{H}_{19}\text{N}_2\text{O}_3\text{S}$: 367.1116; Found: 367.1121.

2,5-dimethyl-N-(2-(methylthio)phenyl)-1,3-dioxo-1,2,3,3a,8,8a-hexahydroindeno[1,2-c]pyrrole-7-carboxamide (2b)



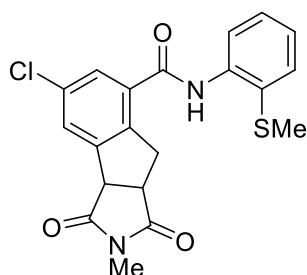
68.1mg, 60% yield. $R_f = 0.23$ (Hex: EtOAc = 1.5:1). Pale yellow powder. m.p. 155.2-155.7 °C. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 8.91 (s, 1H), 8.44 (d, $J = 8.2$ Hz, 1H), 7.58 (s, 1H), 7.54-7.50 (m, 2H), 7.35 (t, $J = 7.8$ Hz, 1H), 7.12 (t, $J = 7.5$ Hz, 1H), 4.34 (d, $J = 7.5$ Hz, 1H), 3.77-3.68 (m, 3H), 2.94 (s, 3H), 2.44 (s, 3H), 2.41 (s, 3H). $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) δ 179.7, 177.4, 165.6, 139.6, 138.8, 138.5, 138.4, 133.1, 132.4, 129.1, 128.9, 127.9, 125.8, 124.8, 120.7, 51.5, 44.1, 34.8, 25.2, 21.4, 19.3. HRMS (DART+) m/z ($[\text{M}+\text{H}]^+$) Calcd for $\text{C}_{21}\text{H}_{20}\text{N}_2\text{O}_3\text{S}$: 381.1273; Found: 381.1280.

5-fluoro-2-methyl-N-(2-(methylthio)phenyl)-1,3-dioxo-1,2,3,3a,8,8a-hexahydroindeno[1,2-c]pyrrole-7-carboxamide (2c)



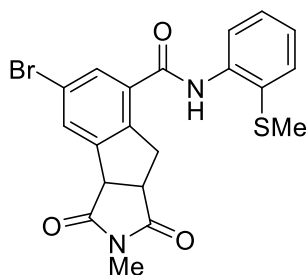
86.5mg, 75% yield. $R_f = 0.21$ (Hex: EtOAc = 1.5:1). Pale yellow oil. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 8.90 (s, 1H), 8.42 (d, $J = 7.9$ Hz, 1H), 7.53 (d, $J = 7.8$ Hz, 1H), 7.48 (d, $J = 7.9$ Hz, 1H), 7.41-7.33 (m, 2H), 7.14 (t, $J = 7.6$ Hz, 1H), 4.36 (d, $J = 7.0$ Hz, 1H), 3.75-3.74 (m, 3H), 2.96 (s, 3H), 2.42 (s, 3H). $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) δ 179.3, 176.6, 162.4 (d, $J = 247$ Hz), 161.1, 141.5, 141.5, 138.0, 137.2, 133.6, 133.6, 133.2, 129.2, 125.9, 125.2, 120.7, 115.5 (d, $J = 23$ Hz), 114.5 (d, $J = 24$ Hz), 51.5, 44.1, 34.5, 25.4, 19.4 HRMS (DART+) m/z ($[\text{M}+\text{H}]^+$) Calcd for $\text{C}_{20}\text{H}_{18}\text{FN}_2\text{O}_3\text{S}$: 385.1022; Found: 385.1042.

5-chloro-2-methyl-N-(2-(methylthio)phenyl)-1,3-dioxo-1,2,3,3a,8,8a-hexahydroindeno[1,2-c]pyrrole-7-carboxamide (2d)



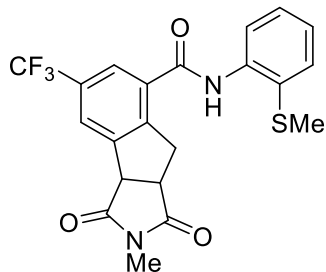
85.7mg, 71% yield. $R_f = 0.24$ (Hex: EtOAc = 1.5:1). Pale yellow powder. m.p. 181.0-181.4°C. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 8.86 (s, 1H), 8.38 (d, $J = 6.4$ Hz, 1H), 7.74 (s, 1H), 7.66 (s, 1H), 7.54-7.52 (m, 1H), 7.35 (t, $J = 7.8$ Hz, 1H), 7.16-7.12 (m, 1H), 4.35 (d, $J = 7.3$ Hz, 1H), 3.77-3.71 (m, 3H), 2.96 (s, 3H), 2.42 (s, 3H). $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) δ 179.2, 176.5, 164.2, 141.2, 140.2, 137.9, 134.2, 133.7, 133.0, 129.1, 128.4, 127.3, 126.2, 125.2, 120.8, 51.4, 43.9, 34.7, 25.3, 19.3. HRMS (DART+) m/z ($[\text{M}+\text{H}]^+$) Calcd for $\text{C}_{20}\text{H}_{18}\text{ClN}_2\text{O}_3\text{S}$: 401.0726; Found: 401.0747.

5-bromo-2-methyl-N-(2-(methylthio)phenyl)-1,3-dioxo-1,2,3,3a,8,8a-hexahydroindeno[1,2-c]pyrrole-7-carboxamide (2e)



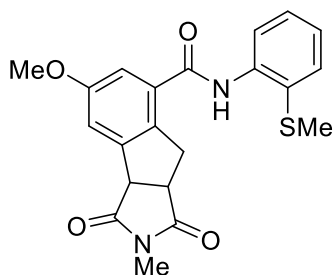
82.4mg, 72% yield. $R_f = 0.24$ (Hex: EtOAc = 1.5:1). Pale yellow powder. m.p. 183.3-183.5°C. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) δ 8.86 (d, $J = 5.3$ Hz, 1H), 8.37 (q, $J = 3.7$ Hz, 1H), 7.82 (dq, $J = 60.4, 0.8$ Hz, 1H), 7.74 (dd, $J = 58.4, 1.6$ Hz), 7.53 (dd, $J = 7.8, 1.6$ Hz, 1H), 7.37-7.33 (m, 1H), 7.15 (td, $J = 7.5, 1.4$ Hz, 1H), 4.37 (d, $J = 5.9$ Hz, 1H), 3.76-3.71 (m, 3H), 2.96 (s, 3H), 2.43 (s, 3H) $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) δ 179.1, 176.5, 164.2, 164.1, 141.4, 141.2, 140.7, 140.2, 137.8, 134.1, 134.0, 133.7, 132.9, 131.2, 130.1, 129.0, 128.3, 127.2, 126.2, 125.2, 121.7, 120.8, 51.3, 43.9, 34.7, 25.3, 19.2. HRMS (DART+) m/z ($[\text{M}+\text{H}]^+$) Calcd for $\text{C}_{20}\text{H}_{18}\text{BrN}_2\text{O}_3\text{S}$: 445.0221; Found: 445.0216.

2-methyl-*N*-(2-(methylthio)phenyl)-1,3-dioxo-5-(trifluoromethyl)-1,2,3,3a,8,8a-hexahydroindeno[1,2-*c*]pyrrole-7-carboxamide (2f)



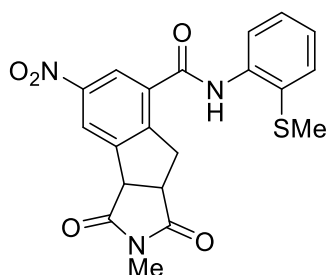
104.1mg, 80% yield. $R_f = 0.26$ (Hex: EtOAc = 1.5:1). Pale yellow powder. m.p. 173.3-173.6°C. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 8.93 (s, 1H), 8.40 (d, $J = 8.2$ Hz, 1H), 8.02 (s, 1H), 7.94 (s, 1H), 7.54 (dd, $J = 7.8, 1.4$ Hz, 1H), 7.36-7.34 (m, 1H), 7.16 (td, $J = 7.7, 1.4$ Hz, 1H), 4.44 (d, $J = 8.0$ Hz, 1H), 3.85 (d, $J = 5.3$ Hz, 2H), 3.77 (d, $J = 5.0$ Hz, 1H), 2.97 (s, 3H), 2.43 (s, 3H) $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) δ 179.0, 176.3, 164.2, 145.8, 140.6, 137.8, 133.4, 133.0, 131.2 (q, $J = 32$ Hz), 125.4, 125.1 (d, $J = 3$ Hz), 124.2 (d, $J = 4$ Hz), 123.6 (d, $J = 271$ Hz), 120.8, 51.4, 43.8, 35.2, 25.4, 19.2. HRMS (DART+) m/z ($[\text{M}+\text{H}]^+$) Calcd for $\text{C}_{21}\text{H}_{18}\text{F}_3\text{N}_2\text{O}_3\text{S}$: 435.0985; Found: 435.1027.

5-methoxy-2-methyl-*N*-(2-(methylthio)phenyl)-1,3-dioxo-1,2,3,3a,8,8a-hexahydroindeno[1,2-*c*]pyrrole-7-carboxamide (2g)



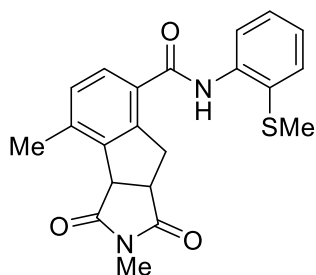
82.5 mg, 69% yield. $R_f = 0.21$ (Hex: EtOAc = 1.5:1). Pale yellow powder. m.p. 156.0-156.4°C. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 8.93 (s, 1H), 8.45 (dd, $J = 8.2, 1.1$ Hz, 1H), 7.53 (dd, $J = 7.8, 1.6$ Hz, 1H), 7.37-7.33 (m, 1H), 7.28 (q, $J = 1.1$ Hz, 1H), 7.25-7.25 (m, 1H), 7.12 (td, $J = 7.7, 1.4$ Hz, 1H), 4.34 (d, $J = 6.4$ Hz, 1H), 3.88 (s, 3H), 3.74-3.69 (m, 3H), 2.95 (s, 3H), 2.41 (s, 3H). ^{13}C NMR (CDCl_3 , 100 MHz) δ 179.7, 177.2, 165.3, 159.9, 140.8, 138.4, 133.2, 133.2, 133.1, 129.2, 125.7, 124.9, 120.6, 114.3, 112.7, 56.0, 51.7, 44.3, 34.4, 25.3, 19.4. HRMS (DART+) m/z ($[\text{M}+\text{H}]^+$) Calcd for $\text{C}_{21}\text{H}_{21}\text{N}_2\text{O}_4\text{S}$: 397.1222; Found: 397.1252.

2-methyl-N-(2-(methylthio)phenyl)-5-nitro-1,3-dioxo-1,2,3,3a,8,8a-hexahydroindeno[1,2-c]pyrrole-7-carboxamide (2h)



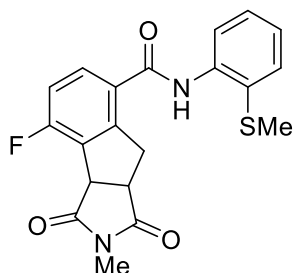
95.6 mg, 78% yield. $R_f = 0.14$ (Hex: EtOAc = 1.5:1). Yellow powder. m.p. 198.4-198.8°C. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 9.00 (s, 1H), 8.58 (d, $J = 9.3$ Hz, 2H), 8.36 (d, $J = 8.0$ Hz, 1H), 7.55 (d, $J = 7.8$ Hz, 1H), 7.39-7.35 (m, 1H), 7.18 (td, $J = 7.6, 1.4$ Hz, 1H), 4.48 (d, $J = 8.3$ Hz, 1H), 3.91-3.81 (m, 3H), 2.98 (s, 3H), 2.45 (s, 3H). ^{13}C NMR (CDCl_3 , 100 MHz) δ 178.7, 175.9, 163.3, 149.2, 148.1, 141.5, 137.5, 133.3, 132.9, 129.0, 125.6, 123.0, 122.2, 120.9, 51.2, 43.9, 35.4, 25.5, 19.2 179.7, 177.2, 165.3, 159.9, 140.8, 138.4, 133.2, 133.2, 133.1, 129.2, 125.7, 124.9, 120.6, 114.3, 112.7, 56.0, 51.7, 44.3, 34.4, 25.3, 19.4. HRMS (DART+) m/z ($[\text{M}+\text{H}]^+$) Calcd for $\text{C}_{20}\text{H}_{18}\text{N}_3\text{O}_5\text{S}$: 412.0967; Found: 412.1004.

2,4-dimethyl-N-(2-(methylthio)phenyl)-1,3-dioxo-1,2,3,3a,8,8a-hexahydroindeno[1,2-c]pyrrole-7-carboxamide (2i)



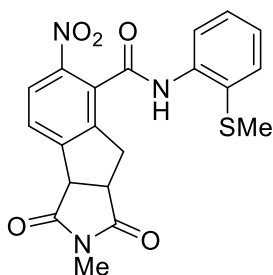
58.7 mg, 52 % yield. $R_f = 0.29$ (Hex: EtOAc = 1.5:1). Yellow powder. m.p. 81.2-81.6°C. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 8.95 (s, 1H), 8.46 (dd, $J = 8.2, 1.1$ Hz, 1H), 7.59 (d, $J = 7.8$ Hz, 1H), 7.53 (dd, $J = 7.8, 1.6$ Hz, 1H), 7.37-7.33 (m, 1H), 7.24 (d, $J = 7.8$ Hz, 1H), 7.11 (td, $J = 7.7, 1.4$ Hz, 1H), 4.51 (d, $J = 8.2$ Hz, 1H), 3.84-3.69 (m, 3H), 2.96 (s, 3H), 2.70 (s, 3H), 2.40 (s, 3H). $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) δ 179.4, 176.8, 165.6, 142.6, 140.8, 138.6, 138.1, 133.3, 130.0, 129.8, 129.2, 126.9, 125.6, 124.7, 120.5, 51.7, 43.7, 35.7, 25.2, 20.5, 19.4. HRMS (DART+) m/z ($[\text{M}+\text{H}]^+$) Calcd for $\text{C}_{21}\text{H}_{21}\text{N}_2\text{O}_3\text{S}$: 381.1273; Found: 381.1278.

4-fluoro-2-methyl-N-(2-(methylthio)phenyl)-1,3-dioxo-1,2,3,3a,8,8a-hexahydroindeno[1,2-c]pyrrole-7-carboxamide (2j)



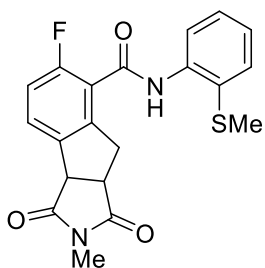
51.0 mg, 44 % yield. $R_f = 0.21$ (Hex: EtOAc = 1.5:1). Pale yellow powder. m.p. 78.6-79.1°C. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 8.90 (s, 1H), 8.42 (d, $J = 8.2$ Hz, 1H), 7.71 (q, $J = 4.3$ Hz, 1H), 7.53 (dd, $J = 7.8, 1.4$ Hz, 1H), 7.37-7.33 (m, 1H), 7.15-7.11 (m, 2H), 4.62 (d, $J = 8.0$ Hz, 1H), 3.86-3.84 (m, 2H), 3.77 (dd, $J = 8.2, 5.3$ Hz, 1H), 2.98 (s, 3H), 2.41 (s, 3H). $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) δ 178.8, 175.1, 164.5, 161.8 (d, $J = 257$ Hz), 146.4 (d, $J = 6$ Hz), 138.3, 133.2, 129.5 (d, $J = 8$ Hz), 129.2, 128.7, 126.0 (d, $J = 18$ Hz), 125.8, 125.0, 120.6, 115.5 (d, $J = 21$ Hz), 49.9 (d, $J = 3$ Hz), 44.2, 36.0, 25.4, 19.3. HRMS (DART+) m/z ($[\text{M}+\text{H}]^+$) Calcd for $\text{C}_{20}\text{H}_{18}\text{FN}_2\text{O}_3\text{S}$: 385.1022; Found: 385.1034.

2-methyl-N-(2-(methylthio)phenyl)-6-nitro-1,3-dioxo-1,2,3,3a,8,8a-hexahydroindeno[1,2-c]pyrrole-7-carboxamide (2k)



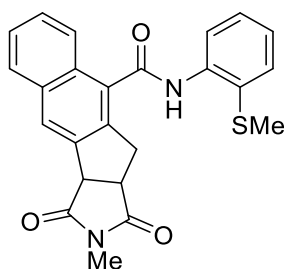
53.2 mg, 43 % yield. $R_f = 0.07$ (Hex: EtOAc = 1.5:1). Yellow powder. m.p. 118.4-119.0°C. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 8.39 (s, 1H), 8.31 (d, $J = 8.0$ Hz, 1H), 8.13 (d, $J = 8.5$ Hz, 1H), 7.81 (d, $J = 8.5$ Hz, 1H), 7.51 (dd, $J = 7.8, 1.4$ Hz, 1H), 7.40-7.36 (m, 1H), 7.19 (td, $J = 7.6, 1.3$ Hz, 1H), 4.46 (d, $J = 8.2$ Hz, 1H), 3.80-3.76 (m, 1H), 3.65-3.61 (m, 2H), 2.98 (s, 3H), 2.38 (s, 3H). $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) δ 178.4, 175.6, 163.3, 146.2, 144.7, 141.8, 137.2, 132.7, 130.1, 129.0, 127.0, 127.0, 125.9, 124.7, 122.0, 51.8, 43.7, 33.4, 25.6, 19.0. HRMS (DART+) m/z ($[\text{M}+\text{H}]^+$) Calcd for $\text{C}_{20}\text{H}_{18}\text{N}_3\text{O}_5\text{S}$: 412.0967; Found: 412.1004.

6-fluoro-2-methyl-N-(2-(methylthio)phenyl)-1,3-dioxo-1,2,3,3a,8,8a-hexahydroindeno[1,2-c]pyrrole-7-carboxamide (2l)



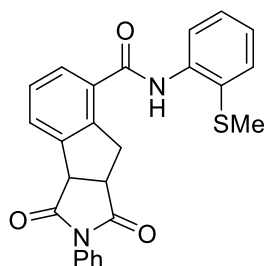
53.6 mg, 46 % yield. $R_f = 0.23$ (Hex: EtOAc = 1.5:1). Pale yellow powder. m.p. 158.6-158.9°C. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 9.24 (d, $J = 8.2$ Hz, 1H), 8.48 (d, $J = 8.2$ Hz, 1H), 7.69 (dd, $J = 8.3, 4.9$ Hz, 1H), 7.54 (dd, $J = 7.8, 1.4$ Hz, 1H), 7.38-7.34 (m, 1H), 7.17-7.11 (m, 2H), 4.32 (d, $J = 8.0$ Hz, 1H), 3.82-3.76 (m, 2H), 3.74-3.69 (m, 1H), 2.95 (s, 3H), 2.40 (s, 3H). $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) δ 179.4, 177.2, 161.5, 160.6 (d, $J = 247$ Hz), 145.5, 138.4, 135.0, 133.4, 129.1, 129.0 (d, $J = 11$ Hz), 126.0, 125.0, 121.0, 120.0 (d, $J = 15$ Hz), 116.2 (d, $J = 26$ Hz). HRMS (DART+) m/z ($[\text{M}+\text{H}]^+$) Calcd for $\text{C}_{20}\text{H}_{18}\text{N}_2\text{O}_3\text{FS}$: 385.1018; Found: 385.1050.

2-methyl-N-(2-(methylthio)phenyl)-1,3-dioxo-1,2,3,3a,10,10a-hexahydrobenzo[5,6]indeno[1,2-c]pyrrole-9-carboxamide (2m)



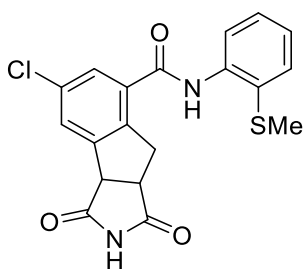
37.5 mg, 30 % yield. R_f = 0.19 (Hex: EtOAc = 1.5:1). Yellow powder. m.p. 99.1-99.7°C. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 8.63 (s, 1H), 8.59 (dd, J = 8.1, 1.3 Hz, 1H), 8.18 (s, 1H), 8.10-8.08 (m, 1H), 7.93-7.90 (m, 1H), 7.56-7.50 (m, 3H), 7.44-7.39 (m, 1H), 7.18 (td, J = 7.5, 1.4 Hz, 1H), 4.54 (d, J = 6.4 Hz, 1H), 3.78-3.73 (m, 3H), 2.97 (s, 3H), 2.35 (s, 3H). $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) δ 179.4, 177.0, 166.5, 138.0, 137.7, 135.9, 133.6, 133.0, 131.2, 130.4, 129.1, 128.8, 127.7, 126.6, 126.5, 126.2, 125.3, 124.7, 121.2, 51.2, 44.2, 33.7, 25.4, 19.3. HRMS (DART+) m/z ($[\text{M}]^+$) Calcd for $\text{C}_{24}\text{H}_{20}\text{N}_2\text{O}_3\text{S}$: 416.1195; Found: 416.1226.

***N*-(2-(methylthio)phenyl)-1,3-dioxo-2-phenyl-1,2,3,3a,8,8a-hexahydroindeno[1,2-c]pyrrole-7-carboxamide (2aa)**



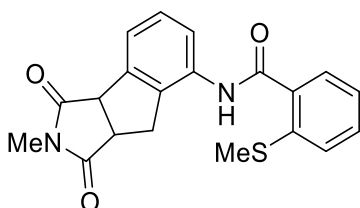
78.0 mg, 61 % yield. R_f = 0.26 (Hex: EtOAc = 1.5:1). Yellow powder. m.p. 82.7-82.9°C. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 9.02 (s, 1H), 8.48 (d, J = 8.2 Hz, 1H), 7.82 (d, J = 7.5 Hz, 1H), 7.74 (d, J = 7.8 Hz, 1H), 7.54 (dd, J = 7.8, 1.4 Hz, 1H), 7.48-7.41 (m, 3H), 7.38-7.34 (m, 2H), 7.25-7.22 (m, 2H), 7.13 (td, J = 7.5, 1.4 Hz, 1H), 4.53 (d, J = 7.8 Hz, 1H), 3.95-3.87 (m, 3H), 2.42 (s, 3H). $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) δ 178.6, 176.1, 165.4, 142.2, 139.6, 138.4, 133.2, 132.6, 131.9, 129.2, 128.7, 128.6, 128.5, 127.0, 126.5, 125.8, 124.9, 120.6, 51.6, 44.0, 35.6, 19.4. HRMS (DART+) m/z ($[\text{M}+\text{H}]^+$) Calcd for $\text{C}_{25}\text{H}_{21}\text{N}_2\text{O}_3\text{S}$: 429.1273; Found: 429.1267.

5-chloro-*N*-(2-(methylthio)phenyl)-1,3-dioxo-1,2,3,3a,8,8a-hexahydroindeno[1,2-c]pyrrole-7-carboxamide (2da)



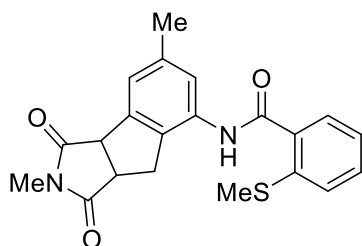
51.6 mg, 45 % yield. $R_f = 0.14$ (Hex: EtOAc = 1.5:1). Yellow powder. m.p. 104.4-104.8°C. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 8.87 (s, 1H), 8.46 (s, 1H), 8.38 (d, $J = 8.0$ Hz, 1H), 7.71 (t, $J = 1.3$ Hz, 1H), 7.66 (d, $J = 1.4$ Hz, 1H), 7.52 (dd, $J = 7.8, 1.6$ Hz, 1H), 7.37-7.32 (m, 1H), 7.14 (td, $J = 7.5, 1.4$ Hz, 1H), 4.37-4.35 (m, 1H), 3.76-3.73 (m, 3H), 2.42 (s, 3H). $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) δ 179.4, 176.6, 164.2, 140.9, 140.2, 137.8, 134.2, 133.7, 133.0, 129.1, 128.3, 127.3, 126.3, 125.3, 120.9, 52.5, 45.2, 34.7, 19.3. HRMS (DART+) m/z ($[\text{M}+\text{H}]^+$) Calcd for $\text{C}_{19}\text{H}_{16}\text{ClN}_2\text{O}_3\text{S}$: 387.0570; Found: 387.0600.

***N*-(2-methyl-1,3-dioxo-1,2,3,3a,8,8a-hexahydroindeno[1,2-c]pyrrol-7-yl)-2-(methylthio)benzamide (4a)**



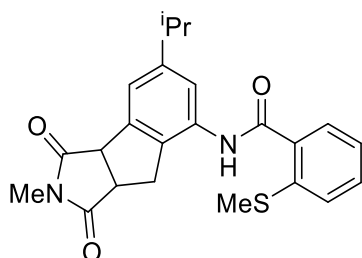
53.3 mg, 50 % yield. $R_f = 0.14$ (Hex: EtOAc = 1.5:1). Pale yellow powder. m.p. 153.9-154.4°C. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 8.37 (s, 1H), 8.00 (d, $J = 7.3$ Hz, 1H), 7.77 (d, $J = 7.5$ Hz, 1H), 7.47-7.44 (m, 1H), 7.42-7.39 (m, 2H), 7.32 (dd, $J = 15.6, 7.6$ Hz, 2H), 4.40 (d, $J = 7.9$ Hz, 1H), 3.69 (td, $J = 8.1, 4.0$ Hz, 1H), 3.48-3.38 (m, 2H), 2.94 (s, 3H), 2.51 (s, 3H). $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) δ 179.8, 177.1, 165.8, 138.5, 136.5, 134.7, 134.5, 132.6, 131.5, 129.7, 129.1, 128.4, 126.1, 122.0, 121.9, 52.2, 43.7, 32.9, 25.3, 17.4. HRMS (DART+) m/z ($[\text{M}+\text{H}]^+$) Calcd for $\text{C}_{20}\text{H}_{19}\text{N}_2\text{O}_3\text{S}$: 367.1116; Found: 367.1159.

***N*-(2,5-dimethyl-1,3-dioxo-1,2,3,3a,8,8a-hexahydroindeno[1,2-c]pyrrol-7-yl)-2-(methylthio)benzamide (4b)**



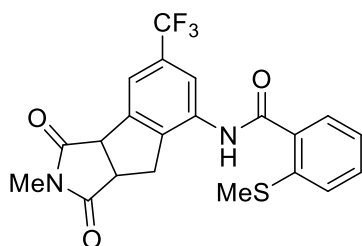
47.6 mg, 42 % yield. $R_f = 0.14$ (Hex: EtOAc = 1.5:1). Pale yellow powder. m.p. 234.0-234.4°C. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 8.29 (s, 1H), 7.87 (s, 1H), 7.76 (d, $J = 7.8$ Hz, 1H), 7.48-7.39 (m, 2H), 7.31-7.27 (m, 1H), 7.23 (s, 1H), 4.35 (d, $J = 7.8$ Hz, 1H), 3.67 (td, $J = 8.2, 4.4$ Hz, 1H), 3.39-3.36 (m, 2H), 2.94 (s, 3H), 2.51 (s, 3H), 2.38 (s, 3H). $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) δ 179.9, 177.3, 165.8, 139.4, 138.4, 136.5, 134.8, 134.1, 131.5, 129.6, 129.5, 128.4, 126.1, 122.7, 122.5, 52.1, 44.0, 32.5, 25.3, 21.6, 17.4. HRMS (DART+) m/z ($[\text{M}+\text{H}]^+$) Calcd for $\text{C}_{21}\text{H}_{21}\text{N}_2\text{O}_3\text{S}$: 381.1273; Found: 381.1278.

***N*-(5-isopropyl-2-methyl-1,3-dioxo-1,2,3,3a,8,8a-hexahydroindeno[1,2-*c*]pyrrol-7-yl)-2-(methylthio)benzamide (4c)**



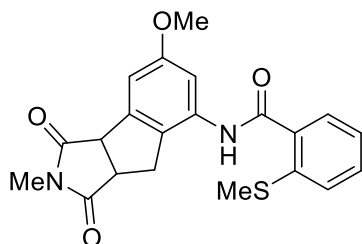
48.6 mg, 40 % yield. $R_f = 0.17$ (Hex: EtOAc = 1.5:1). Pale yellow powder. m.p. 177.1-177.5°C. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 8.33 (s, 1H), 7.90 (s, 1H), 7.78 (d, $J = 7.5$ Hz, 1H), 7.46-7.39 (m, 2H), 7.31-7.27 (m, 2H), 4.37 (d, $J = 7.8$ Hz, 1H), 3.68 (td, $J = 8.1, 4.5$ Hz, 1H), 3.40-3.38 (m, 2H), 2.95-2.95 (m, 4H), 2.52 (s, 3H), 1.27 (dd, $J = 6.9, 1.6$ Hz, 6H). $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) δ 179.9, 177.3, 165.8, 150.7, 138.5, 136.5, 134.8, 134.2, 131.5, 130.2, 129.7, 128.4, 126.1, 120.5, 119.9, 52.1, 44.0, 34.4, 32.6, 25.3, 24.3, 24.0, 17.4. HRMS (DART+) m/z ($[\text{M}+\text{H}]^+$) Calcd for $\text{C}_{23}\text{H}_{25}\text{N}_2\text{O}_3\text{S}$: 409.1586; Found: 409.1603.

***N*-(2-methyl-1,3-dioxo-5-(trifluoromethyl)-1,2,3,3a,8,8a-hexahydroindeno[1,2-*c*]pyrrol-7-yl)-2-(methylthio)benzamide (4d)**



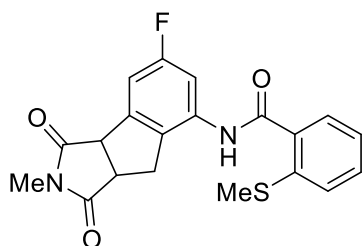
97.7 mg, 75 % yield. $R_f = 0.14$ (Hex: EtOAc = 1.5:1). Pale yellow powder. m.p. 195.9-196.3°C. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) 8.67 (s, 1H), 8.40 (s, 1H), 7.80 (d, $J = 7.8$ Hz, 1H), 7.65 (s, 1H), 7.50-7.41 (m, 2H), 7.33-7.29 (m, 1H), 4.43 (d, $J = 8.2$ Hz, 1H), 3.77-3.73 (m, 1H), 3.47 (d, $J = 8.7$ Hz, 2H), 2.96 (s, 3H), 2.53 (s, 3H). $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) δ 179.2, 176.3, 166.8, 139.3, 136.4, 135.9, 135.1, 134.0, 131.9, 131.7 (d, $J = 32$ Hz), 130.0, 128.7, 126.3, 123.8 (d, $J = 271$ Hz), 118.7 (d, $J = 37$ Hz). HRMS (DART+) m/z ($[\text{M}+\text{H}]^+$) Calcd for $\text{C}_{21}\text{H}_{18}\text{F}_3\text{N}_2\text{O}_3\text{S}$: 435.0990; Found: 435.1006.

***N*-(5-methoxy-2-methyl-1,3-dioxo-1,2,3,3a,8,8a-hexahydroindeno[1,2-c]pyrrol-7-yl)-2-(methylthio)benzamide (4e)**



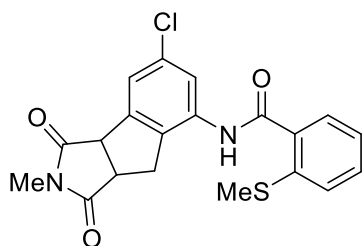
59.3 mg, 50 % yield. $R_f = 0.11$ (Hex: EtOAc = 1.5:1). Pale yellow powder. m.p. 201.2-201.3°C. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 8.37 (s, 1H), 7.77 (d, $J = 7.3$ Hz, 2H), 7.42 (dd, $J = 17.6, 7.5$ Hz, 2H), 7.31-7.27 (m, 1H), 6.94 (s, 1H), 4.34 (d, $J = 7.8$ Hz, 1H), 3.83 (s, 3H), 3.68 (d, $J = 4.8$ Hz, 1H), 3.33 (s, 2H), 2.95 (s, 3H), 2.51 (s, 3H). $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) δ 179.8, 177.1, 165.8, 160.7, 139.2, 136.4, 135.0, 134.7, 131.6, 129.8, 128.5, 126.1, 123.7, 108.1, 106.9, 55.9, 52.2, 44.1, 32.1, 25.3, 17.4. HRMS (DART+) m/z ($[\text{M}+\text{H}]^+$) Calcd for $\text{C}_{21}\text{H}_{21}\text{N}_2\text{O}_4\text{S}$: 397.1222; Found: 397.1263.

***N*-(5-fluoro-2-methyl-1,3-dioxo-1,2,3,3a,8,8a-hexahydroindeno[1,2-c]pyrrol-7-yl)-2-(methylthio)benzamide (4f)**



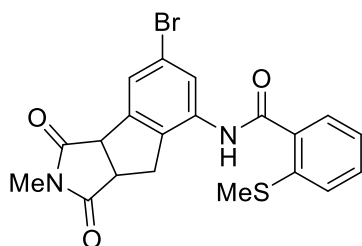
86.7 mg, 75 % yield. $R_f = 0.13$ (Hex: EtOAc = 1.5:1). Pale yellow powder. m.p. 183.8-184.1°C. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 8.56 (s, 1H), 7.98 (d, $J = 10.7$ Hz, 1H), 7.78 (d, $J = 7.5$ Hz, 1H), 7.48-7.40 (m, 2H), 7.30 (t, $J = 7.4$ Hz, 1H), 7.09 (d, $J = 7.8$ Hz, 1H), 4.35 (d, $J = 8.0$ Hz, 1H), 3.71 (td, $J = 7.9, 4.9$ Hz, 1H), 3.37-3.35 (m, 2H), 2.95 (s, 3H), 2.51 (s, 3H). $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) δ 179.4, 176.5, 165.7, 163.0 (d, $J = 244$ Hz), 139.4 (d, $J = 10$ Hz), 136.4, 135.4 (d, $J = 12$ Hz), 134.3, 131.8, 129.2, 128.7, 126.7, 126.3, 109.1 (d, $J = 29$ Hz), 108.5 (d, $J = 23$ Hz), 52.1, 43.9, 32.1, 25.3, 17.5. HRMS (DART+) m/z ($[\text{M}+\text{H}]^+$) Calcd for $\text{C}_{20}\text{H}_{18}\text{FN}_2\text{O}_3\text{S}$: 385.1022; Found: 385.1050.

***N*-(5-chloro-2-methyl-1,3-dioxo-1,2,3,3a,8,8a-hexahydroindeno[1,2-c]pyrrol-7-yl)-2-(methylthio)benzamide (4g)**



78.2 mg, 65 % yield. $R_f = 0.14$ (Hex: EtOAc = 1.5:1). White powder. m.p. 245.2-245.6°C. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 8.51 (s, 1H), 8.20 (s, 1H), 7.81 (dd, $J = 7.8, 1.1$ Hz, 1H), 7.49-7.42 (m, 2H), 7.39 (s, 1H), 7.32 (td, $J = 7.4, 1.1$ Hz, 1H), 4.37 (d, $J = 8.0$ Hz, 1H), 3.71 (dd, $J = 8.2, 3.7$ Hz, 1H), 3.39-3.37 (m, 2H), 2.97 (s, 3H), 2.53 (s, 3H). This compound cannot dissolve in acetone, chloroform (very low solubility), methanol and other solvents, we are failed to collect the $^{13}\text{C-NMR}$. HRMS (DART+) m/z ($[\text{M}+\text{H}]^+$) Calcd for $\text{C}_{20}\text{H}_{18}\text{ClN}_2\text{O}_3\text{S}$: 401.0726; Found: 401.0736.

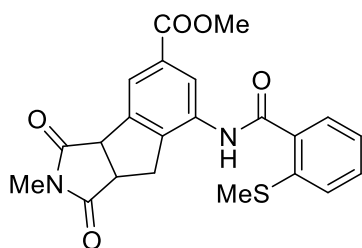
***N*-(5-bromo-2-methyl-1,3-dioxo-1,2,3,3a,8,8a-hexahydroindeno[1,2-c]pyrrol-7-yl)-2-(methylthio)benzamide (4h)**



73.9 mg, 55 % yield. $R_f = 0.14$ (Hex: EtOAc = 1.5:1). Pale yellow powder. m.p. 244.3-244.7°C. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 8.51 (s, 1H), 8.27 (s, 1H), 7.77 (d, $J = 7.5$ Hz, 1H), 7.52 (s, 1H), 7.47-7.36 (m, 2H), 7.31-7.27 (m, 1H), 4.35 (d, $J = 8.0$ Hz, 1H), 3.67 (q, $J = 4.0$ Hz, 1H), 3.35-3.33 (m, 2H), 2.93 (s, 3H), 2.50 (s, 3H). $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz). δ 179.3, 176.4, 165.7, 139.9, 136.3, 135.5, 134.4, 131.8, 131.0, 130.0, 128.9, 126.4, 124.7, 124.6, 122.3, 51.9, 43.8, 32.6, 25.4, 17.7. HRMS (DART+) m/z ($[\text{M}+\text{H}]^+$) Calcd for $\text{C}_{20}\text{H}_{18}\text{BrN}_2\text{O}_3\text{S}$: 445.0221; Found: 445.0256.

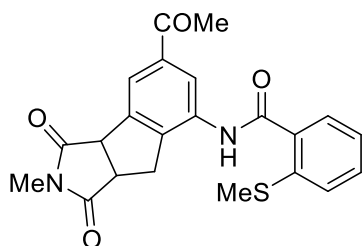
methyl

2-methyl-7-(2-(methylthio)benzamido)-1,3-dioxo-1,2,3,3a,8,8a-hexahydroindeno[1,2-c]pyrrole-5-carboxylate (4i)



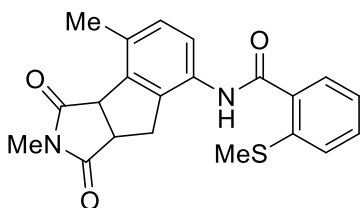
85.6 mg, 67 % yield. $R_f = 0.10$ (Hex: EtOAc = 1.5:1). Pale yellow powder. m.p. 106.4-106.7°C. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 8.55 (d, $J = 5.3$ Hz, 2H), 8.07 (s, 1H), 7.78 (dd, $J = 7.7, 1.5$ Hz, 1H), 7.48-7.39 (m, 2H), 7.29 (td, $J = 7.4, 1.4$ Hz, 1H), 4.42 (d, $J = 8.0$ Hz, 1H), 3.91 (s, 3H), 3.76-3.71 (m, 1H), 3.55-3.41 (m, 2H), 2.95 (s, 3H), 2.52 (s, 3H). $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz). δ 179.4, 176.6, 166.3, 165.8, 139.0, 138.5, 136.6, 134.4, 134.3, 131.7, 131.4, 129.8, 128.4, 126.1, 123.8, 123.2, 52.4, 51.9, 43.8, 33.3, 25.3, 17.4. HRMS (DART+) m/z ($[\text{M}+\text{H}]^+$) Calcd for $\text{C}_{22}\text{H}_{21}\text{N}_2\text{O}_5\text{S}$: 425.1171; Found: 425.1192.

N-(5-acetyl-2-methyl-1,3-dioxo-1,2,3,3a,8,8a-hexahydroindeno[1,2-c]pyrrol-7-yl)-2-(methylthio)benzamide (4j)



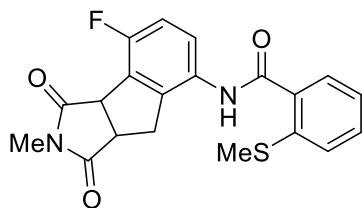
43.1 mg, 35 % yield. $R_f = 0.10$ (Hex: EtOAc = 1.5:1). Pale yellow powder. m.p. 232.7-232.8°C. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 8.56 (d, $J = 8.7$ Hz, 2H), 7.99 (s, 1H), 7.81 (dd, $J = 7.8, 1.4$ Hz, 1H), 7.50-7.41 (m, 2H), 7.31 (td, $J = 7.5, 1.1$ Hz, 1H), 4.44 (d, $J = 8.2$ Hz, 1H), 3.78-3.73 (m, 1H), 3.55-3.42 (m, 2H), 2.96 (s, 3H), 2.63 (s, 3H), 2.53 (s, 3H). $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz). δ 197.3, 179.3, 176.6, 165.9, 139.2, 138.5, 138.2, 136.5, 134.8, 134.3, 131.8, 129.9, 128.6, 126.2, 122.5, 121.7, 51.9, 43.8, 33.2, 27.1, 25.4, 17.5. HRMS (DART+) m/z ($[\text{M}+\text{H}]^+$) Calcd for $\text{C}_{22}\text{H}_{21}\text{N}_2\text{O}_4\text{S}$: 409.1222; Found: 409.1237.

***N*-(2,4-dimethyl-1,3-dioxo-1,2,3,3a,8,8a-hexahydroindeno[1,2-*c*]pyrrol-7-yl)-2-(methylthio)benzamide (4k)**



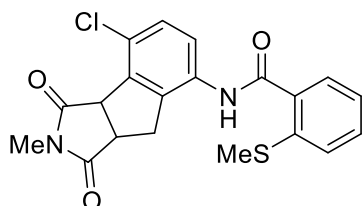
66.0 mg, 58 % yield. $R_f = 0.17$ (Hex: EtOAc = 1.5:1). Pale yellow powder. m.p. 207.9-208.4°C. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 8.23 (s, 1H), 7.86 (d, $J = 8.0$ Hz, 1H), 7.76 (d, $J = 7.5$ Hz, 1H), 7.46-7.38 (m, 2H), 7.29 (t, $J = 7.4$ Hz, 1H), 7.15 (d, $J = 8.0$ Hz, 1H), 4.51 (d, $J = 8.2$ Hz, 1H), 3.72-3.67 (m, 1H), 3.43-3.39 (m, 2H), 2.96 (s, 3H), 2.60 (s, 3H), 2.51 (s, 3H). $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz). δ 179.6, 176.6, 165.9, 136.7, 136.4, 135.0, 133.8, 133.3, 132.0, 131.4, 130.5, 129.7, 128.4, 126.1, 122.6, 52.4, 43.6, 33.3, 25.3, 19.7, 17.4. HRMS (DART+) m/z ($[\text{M}+\text{H}]^+$) Calcd for $\text{C}_{21}\text{H}_{21}\text{N}_2\text{O}_3\text{S}$: 381.1273; Found: 381.1285.

***N*-(4-fluoro-2-methyl-1,3-dioxo-1,2,3,3a,8,8a-hexahydroindeno[1,2-*c*]pyrrol-7-yl)-2-(methylthio)benzamide (4l)**



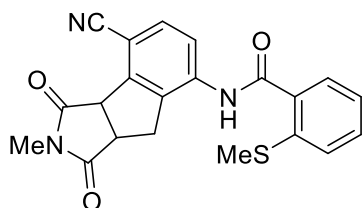
47.2 mg, 41 % yield. $R_f = 0.16$ (Hex: EtOAc = 1.5:1). Yellow powder. m.p. 220.0-220.4°C. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 8.32 (s, 1H), 7.90-7.89 (m, 1H), 7.77 (d, $J = 7.5$ Hz, 1H), 7.48-7.39 (m, 2H), 7.30 (t, $J = 7.2$ Hz, 1H), 7.04 (t, $J = 8.6$ Hz, 1H), 4.62 (d, $J = 8.2$ Hz, 1H), 3.74 (td, $J = 8.9, 4.2$ Hz, 1H), 3.47-3.44 (m, 2H), 2.98 (s, 3H), 2.52 (s, 3H). $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz). δ 179.0, 175.1, 165.9, 157.4 (d, $J = 250$ Hz), 136.7, 136.4, 134.6, 131.6, 130.3, 129.8, 128.6, 126.2, 124.9 (d, $J = 7$ Hz), 124.5 (d, $J = 19$ Hz), 115.8 (d, $J = 21$ Hz), 50.6 (d, $J = 3$ Hz), 44.0, 33.7, 25.4, 17.5. HRMS (DART+) m/z ($[\text{M}+\text{H}]^+$) Calcd for $\text{C}_{20}\text{H}_{18}\text{FN}_2\text{O}_3\text{S}$: 385.1022; Found: 385.1040.

***N*-(4-chloro-2-methyl-1,3-dioxo-1,2,3,3a,8,8a-hexahydroindeno[1,2-c]pyrrol-7-yl)-2-(methylthio)benzamide (4m)**



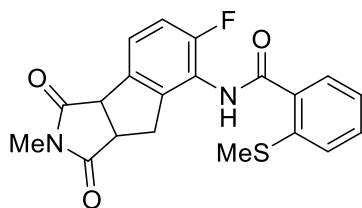
54.1 mg, 45 % yield. $R_f = 0.18$ (Hex: EtOAc = 1.5:1). White powder. m.p. 243.5-243.9°C. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 8.39 (s, 1H), 8.03 (d, $J = 8.5$ Hz, 1H), 7.79 (d, $J = 7.5$ Hz, 1H), 7.49-7.40 (m, 2H), 7.35-7.29 (m, 2H), 4.64 (d, $J = 8.2$ Hz, 1H), 3.76-3.72 (m, 1H), 3.52-3.39 (m, 2H), 2.99 (s, 3H), 2.52 (s, 3H). $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz). δ 178.8, 174.8, 165.8, 136.3, 135.9, 134.8, 134.6, 133.2, 131.7, 131.4, 129.9, 128.7, 128.2, 126.3, 123.6, 52.5, 43.4, 40.6, 33.9, 25.4, 17.6. HRMS (DART+) m/z ($[\text{M}+\text{H}]^+$) Calcd for $\text{C}_{20}\text{H}_{18}\text{ClN}_2\text{O}_3\text{S}$: 401.0726; Found: 401.0744.

***N*-(4-cyano-2-methyl-1,3-dioxo-1,2,3,3a,8,8a-hexahydroindeno[1,2-c]pyrrol-7-yl)-2-(methylthio)benzamide (4n)**



61.9 mg, 53 % yield. $R_f = 0.11$ (Hex: EtOAc = 1.5:1). Yellow powder. m.p. 241.1-241.3°C. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 8.84 (s, 1H), 8.40 (d, $J = 8.5$ Hz, 1H), 7.83 (d, $J = 7.5$ Hz, 1H), 7.65 (d, $J = 8.5$ Hz, 1H), 7.51-7.43 (m, 2H), 7.33 (t, $J = 7.4$ Hz, 1H), 4.67 (d, $J = 8.5$ Hz, 1H), 3.84-3.79 (m, 1H), 3.54-3.37 (m, 2H), 2.97 (s, 3H), 2.53 (s, 3H). $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) δ 178.5, 174.7, 165.8, 140.9, 138.9, 136.2, 134.5, 134.0, 132.3, 132.1, 130.3, 129.2, 126.5, 121.0, 117.5, 105.5, 52.5, 43.1, 33.3, 25.5, 17.8. HRMS (DART+) m/z ($[\text{M}+\text{H}]^+$) Calcd for $\text{C}_{21}\text{H}_{18}\text{N}_3\text{O}_3\text{S}$: 392.1069; Found: 392.1069.

***N*-(6-fluoro-2-methyl-1,3-dioxo-1,2,3,3a,8,8a-hexahydroindeno[1,2-*c*]pyrrol-7-yl)-2-(methylthio)benzamide (4o)**



51.9 mg, 45 % yield. $R_f = 0.11$ (Hex: EtOAc = 1.5:1). Orange powder. m.p. 94.2-94.7°C. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 8.21 (s, 1H), 7.76 (dd, $J = 7.5, 1.6$ Hz, 1H), 7.49-7.43 (m, 2H), 7.40 (d, $J = 6.9$ Hz, 1H), 7.30-7.26 (m, 1H), 7.09-7.04 (m, 1H), 4.35 (d, $J = 7.5$ Hz, 1H), 3.73-3.58 (m, 2H), 3.38 (d, $J = 17.2$ Hz, 1H), 2.95 (s, 3H), 2.53 (s, 3H). $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) δ 179.7, 177.3, 165.8, 155.8, 140.6, 137.5, 134.1, 133.9, 131.7, 129.5, 128.1, 125.8, 124.0 (d, $J = 9$ Hz), 121.6 (d, $J = 14$ Hz), 115.4 (d, $J = 21$ Hz), 51.5, 44.4, 34.4, 25.3, 17.2. HRMS (DART+) m/z ($[\text{M}+\text{H}]^+$) Calcd for $\text{C}_{20}\text{H}_{18}\text{FN}_2\text{O}_3\text{S}$: 385.1022; Found: 385.1037.

2.5 References

(1) For selected reviews dealing with the synthesis of cyclic compounds through C-H annulation, see: (a) Xiang, Y.; Wang, C.; Ding, Q.; Peng, Y. *Adv. Synth. Catal.* **2019**, *361*, 919–944. (b) Nishi, Y.; Miura, M. *ACS. Catal.* **2020**, *10*, 9747-9757. (c) Baudoin, O. *Angew. Chem., Int. Ed.* **2020**, *59*, 17798-17809. (d) Marchese, A.; Larin, E.; Mirabi, B.; Lautens, M. *Acc. Chem. Res.* **2020**, *53*, 1605–1619.

- (2) For recent reviews of [4+2] annulation reactions, see: (a) Kommagalla, Y.; Chatani, N. *Coord. Chem. Rev.* **2017**, *350*, 117-135. (b) Sambiagio, C.; Schönbauer, D.; Blicke, R.; Dao-Huy, T.; Pototschnig, G.; Schaaf, P.; Wiesinger, T.; Zia, M.; Wencel-Delord, J.; Besset, T.; Maes, B. W.; Schnürch, M. *Chem. Soc. Rev.* **2018**, *47*, 6603-6743. (c) Prakash, S.; Kuppusamy, R.; Cheng, C.-H. *ChemCatChem* **2018**, *10*, 683-705. (d) Gandeepan, P.; Mueller, T.; Zell, D.; Cera, G.; Warratz, S.; Ackermann, L. *Chem. Rev.* **2019**, *119*, 2192-2452.
- (3) For, recent reviews of [2+2+2] annulation reactions, see: (a) Feng, M.; Jiang, X. *Synthesis* **2017**, *49*, 4414-4433. (b) Rej, S.; Ano, Y.; Chatani, N. *Chem. Rev.* **2020**, *120*, 1788-1887.
- (4) Wang, X.-C.; Gong, W.; Fang, L.-Z.; Zhu, R.-Y.; Li, S.; Engle, K.; Yu, J.-Q. *Nature* **2015**, *519*, 334-338.
- (5) For selected recent reports on [3+2] C-H annulation reactions, see: (a) Mi, R.; Zheng, G.; Qi, Z.; Li, X. *Angew. Chem., Int. Ed.* **2019**, *58*, 17666–17670. (b) Zhang, Y.; Yu, Y.; Liang, B.-B.; Pei, Y.-Y.; Liu, X.; Yang, H.-G.; Cao, H. *J. Org. Chem.* **2020**, *85*, 10719-10727.
- (6) Park, H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2020**, *142*, 16552-16556.
- (7) Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2010**, *132*, 3965-3972.
- (8) (a) Fang, L.; Sanit-Denis, T.; Taylor, B. H.; Ahlquist, S.; Hong, K.; Liu, S.; Han, L.; Houk, K. N.; Yu, J.-Q. *J. Am. Chem. Soc.* **2017**, *139*, 31, 10702–10714. (b) Feng, W.; Wang, T.; Liu, D.; Wang, X.; Dang, Y. *ACS Catal.* **2019**, *9*, 6672–6680.

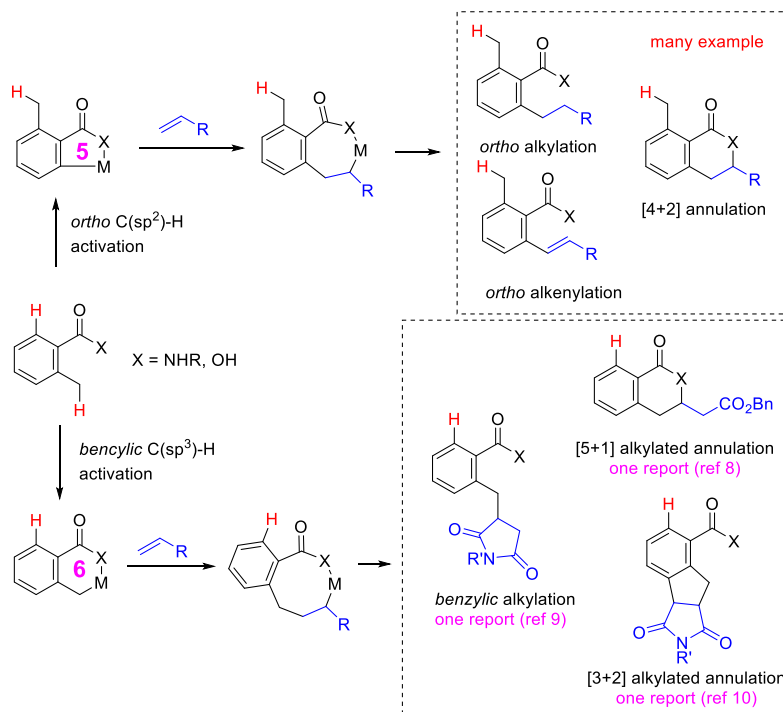
Chapter 3

Palladium-Catalyzed Site-Selective [5+1] Annulation of Aromatic Amides with Terminal Alkenes: Effect of Maleic Anhydride for β -H elimination

3.1 Introduction

The chelation-assisted functionalization of C-H bonds with alkenes is one of the more elegant strategies for efficient C-C bond formation because of high atom efficiency and the fact that the reaction is environmentally benign.¹ In fact, various C-H functionalization reactions with alkenes, involving alkylation, oxidative alkenylation, annulation, and others have been reported in which a diverse combination of catalysts, substrates, and alkene coupling partners have been used. Because a five-membered metallacycle is known to be both kinetically and thermodynamically more stable than a six-membered metallacycle,² the *ortho* C-H bond in 2-methyl-substituted aromatic compounds is exclusively activated and, as a result, functionalization occurs only at the *ortho* C-H bond (Scheme 1 upper).

Scheme 1. Transition-Metal Catalyzed C-H Activation via Five and Six-Membered Metallacycles.

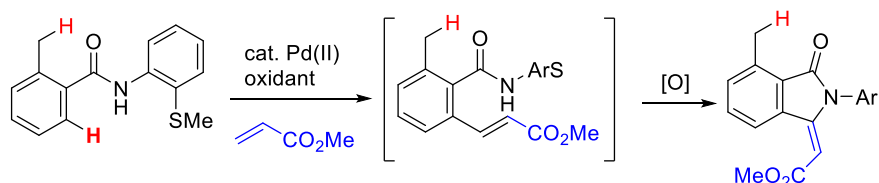


On the other hand, it is noteworthy that only a few examples of the functionalization of C-H bonds at the *ortho*-methyl group via a six-membered metallacycle have been

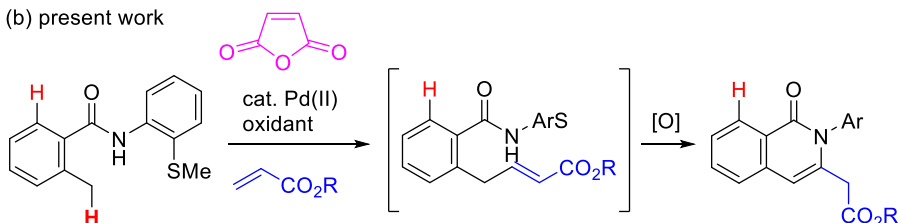
reported. Yu reported the Pd(II)-catalyzed reaction of aromatic aldehydes with aryl iodides using glycine as a transient directing group, in which the C-H bond at the *ortho*-methyl group was selectively arylated.³ Since then, several examples of arylation,⁴ fluorination,⁵ acetoxylation,⁶ and lactonization⁷ have been reported. On the other hand, to the best of our knowledge, only three examples of the selective functionalization of C-H bonds with alkenes at the *ortho*-methyl group have been reported thus far (Scheme 1 lower).⁸⁻¹⁰ Yu reported the Pd(II)-catalyzed reaction of 2-methylbenzoic acids with benzyl acrylate, in which alkenylation/cyclization occurred selectively at the *ortho*-methyl group to result in [5+1] annulation.⁸ Our group recently reported the Pd(II)-catalyzed C-H alkylation⁹ and [3+2] annulation¹⁰ of 2-methylbenzamides using *N,N*- or *N,S*-chelation systems. However, both of these reactions were limited to the use of maleimides as a coupling partner, which are known to be one of the more reactive alkene coupling partners in C-H functionalization reactions.¹¹

Scheme 2. Maleic Anhydride Dramatically Changes the Reaction Course in Pd-Catalyzed C-H Annulation of Aromatic Amides with Alkenes.

(a) Zhang (2019)



(b) present work

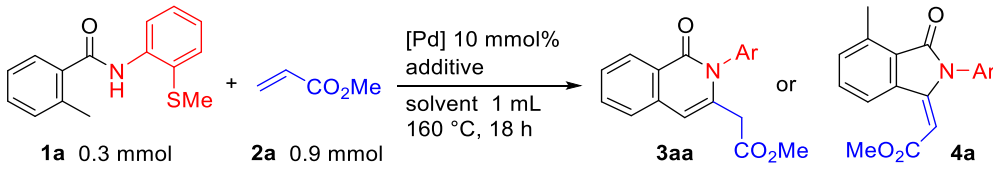


Zhang recently reported the Pd(II)-catalyzed reaction of 2-methylbenzamides with methyl acrylate (Scheme 2a).¹² The reaction took place selectively at the *ortho* C-H bond to give *ortho*-alkenylation products, which then underwent an aza-Walker type reaction to give [4+1] annulation products. In sharp contrast, we found that the use of maleic anhydride (MAH) as a ligand resulted in the selective activation of the benzylic C(sp³)-H bond and not the *ortho* C(sp²)-H bond (Scheme 2b). The role of MAH was deduced by DFT calculations (Figure 1). It was found that the coordination of MAH as a ligand stabilizes the transition state for β -hydride elimination and thus accelerates the

β -hydride elimination. While electron-deficient alkenes, such as MAH and dimethyl fumarate are known to serve as ligands and to accelerate the reductive elimination.¹³

3.2 Results and Discussion

Table 1. Optimization of Reaction Conditions



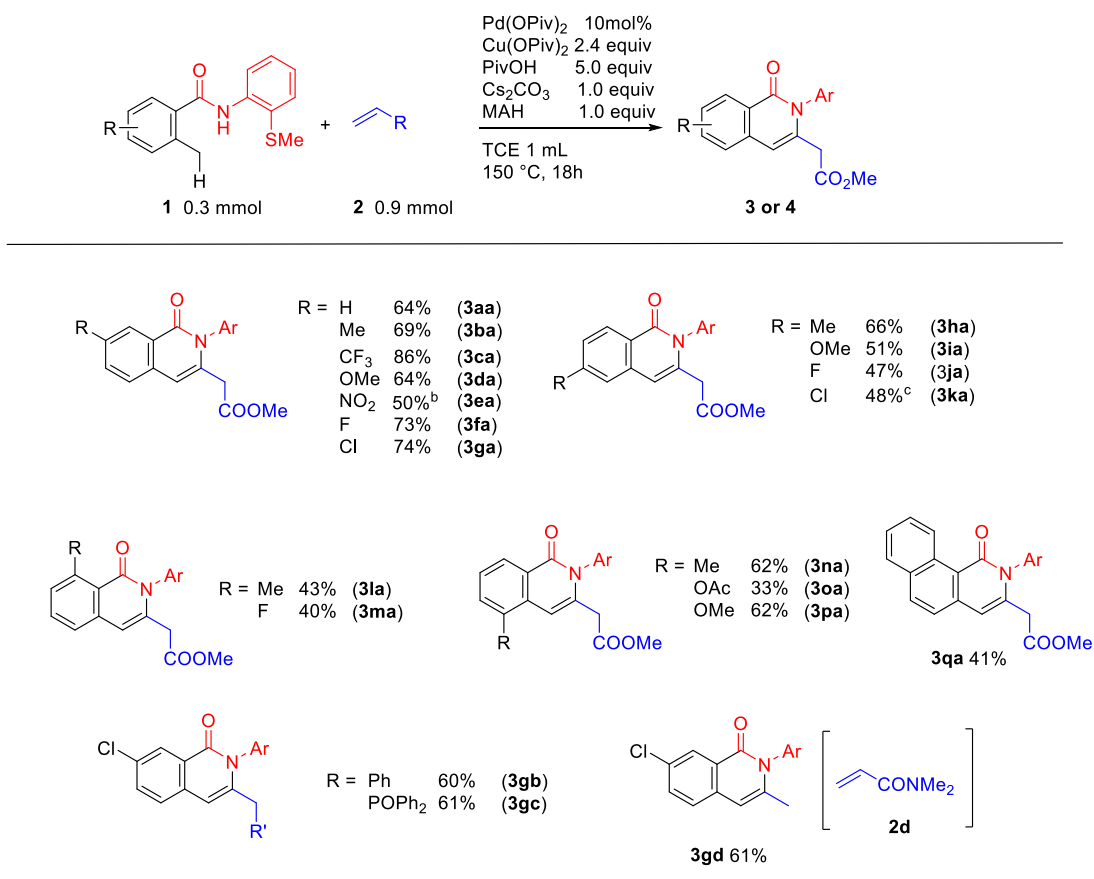
Entry	Catalyst	Additives (equiv)	Solvent	Yield ^a
1	Pd(OPiv) ₂	Cu(OAc) ₂ (2.0) PivOH (1.0)	TCE	4a 40% ^b
2	Pd(OPiv) ₂	Cu(OAc) ₂ (2.0) PivOH (1.0) MAH (1.0)	TCE	22%
3	Pd(OPiv) ₂	Cu(OAc) ₂ (2.0) PivOH (1.0) 1,2-dimethyl MAH (1.0)	TCE	n.d
4	Pd(OPiv) ₂	AgOAc (4.0) PivOH (1.0) MAH (1.0)	TCE	14%
5	Pd(OPiv) ₂	CuCl ₂ (2.0) PivOH (1.0) CsOPiv (4.0) MAH (1.0)	TCE	trace
6	Pd(OAc) ₂	Cu(OAc) ₂ (2.0) AcOH (1.0) MAH (1.0)	TCE	33%
7	Pd(OPiv) ₂	Cu(OAc) ₂ (2.0) PivOH (5.0) NaOTf (1.0) MAH (1.0)	TCE	24%
8	Pd(OPiv) ₂	Cu(OAc) ₂ (2.0) PivOH (5.0) NaOTs (1.0) MAH (1.0)	TCE	trace
9 ^c	Pd(OPiv) ₂	Cu(OPiv) ₂ (2.0) PivOH (5.0) Cs ₂ CO ₃ (1.0) MAH (1.0)	TCE	64%
10	Pd(OPiv) ₂	Cu(OAc) ₂ (2.0) PivOH (1.0) MAH (1.0)	^t AmylOH	6%
11	Pd(OPiv) ₂	Cu(OAc) ₂ (2.0) PivOH (1.0) MAH (1.0)	toluene	trace

^aIsolated yield. ^bNMR yield. ^cReaction temperature: 150 °C.

The reaction of **1a** with methyl acrylate (**2a**) in the presence of Pd(OPiv)₂ as a catalyst and Cu(OAc)₂ as an oxidant in PivOH in 1,1,2,2-tetrachloroethane (TCE) at 160 °C gave the Zhang-type product **4a** in 40% NMR yield as a sole product (Table 1, entry 1). Remarkably, when 1 equiv of MAH was used as an additive, **4a** was not formed and **3aa** was formed in 22% yield as the sole product (entry 2). Thus, the use of MAH as a ligand completely changed the reaction site from the *ortho* C-H bond to the *ortho*-methyl C-H bond. However, no product was detected when substituted MAH was used (entry 3). The use of AgOAc and CuCl₂ as an oxidant failed to further improve the product yield (entries 4 and 5). Additives, such as NaOTf or NaOTs had no effects on the reaction efficiency (entries 7 and 8). After an extensive screening of additives and solvents, the following conditions were determined to be the standard reaction

conditions (entry 9): amide **1a** (0.3 mmol), methyl acrylate (**2a**) (0.9 mmol), MAH (1.0 equiv), Pd(OPiv)₂ (10 mol%), Cu(OPiv)₂ (2.4 equiv), PivOH (5.0 equiv) and Cs₂CO₃ (1.0 equiv) in TCE (1 mL) at 150 °C for 18 h.

Scheme 3. Substrate scope.



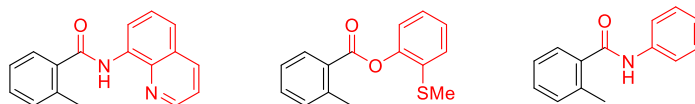
^aIsolated by silica chromatography. ^bWithout Cs₂CO₃. ^c180 °C.

Scheme 3 is the substrate scope of this reaction. Both an electron-withdrawing group and electron-donating group on the aromatic ring were tolerated in the reaction. The nitro-substituted amide **1e**, which has the potential to coordinate to a palladium complex also participated in the reaction to give the expected product, **3ea**. Halogen-substituted amides **1f** and **1g** were found to be highly reactive. When the 2,6-dimethyl substituted amide **1l** was used, only the desired product **3la** was obtained and the other benzylic C-H bond remained intact. Even the use of sterically hindered 3-substituted amides afforded the corresponding products **3na-3pa**. In all cases, no reaction at the *ortho* C-H bond was detected. Other alkenes, such as styrene (**2b**), vinylphosphine oxide (**2c**), and *N,N*-dimethylacrylamide (**2d**) (Scheme 4). While the reaction of **1g** with **2b** and **2c** gave

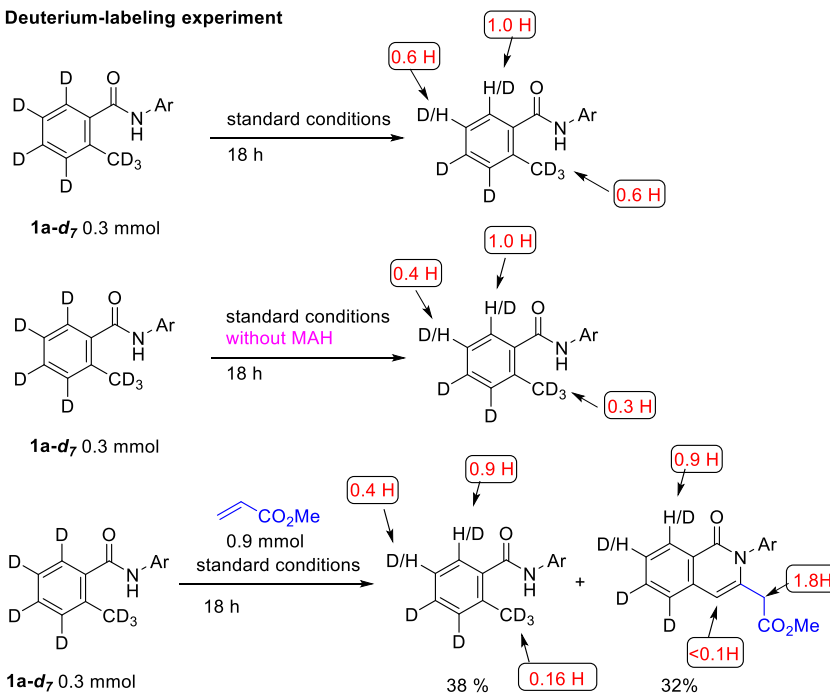
good yields of the corresponding products **3gb** and **3gc**, an unexpected result was obtained in the reaction with **2d**. Although the mechanism responsible for this is not clear, this result indicates that **2d** functions as an ethylene unit.

Scheme 4. Mechanistic studies.

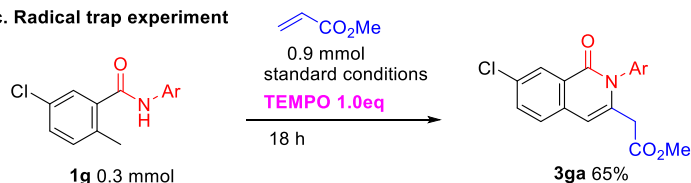
a. Ineffective directing groups



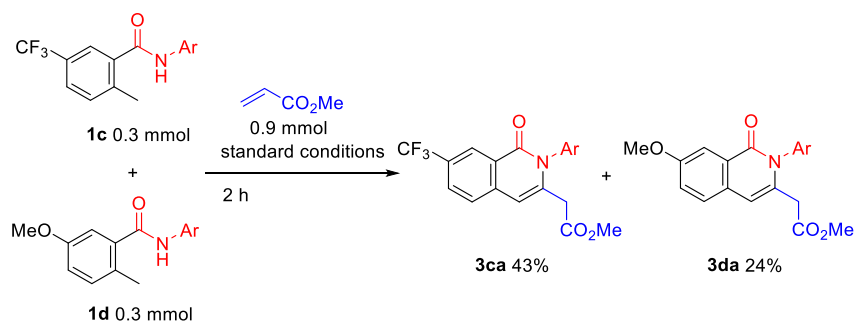
b. Deuterium-labeling experiment



c. Radical trap experiment



d. Competitive experiment



Some mechanistic experiments were conducted in attempts to understand the mechanism for this reaction, (Scheme 4). We first examined the effect of directing groups (Scheme 4a). The widely used 8-aminoquinolyl bidentate chelation system was not suitable for this reaction. On changing the amide to the corresponding ester, the expected product was not formed. An amide directing group without a methylthio group was also not effective. These results indicate that the 2-(methylthio)aniline directing group¹⁵ plays an important role in this transformation. Deuterium-labeling experiments were then carried out (Scheme 4b). Interestingly, regardless of whether the MAH ligand is present or not, a complete D/H exchange occurred at the *ortho*-position (1.0 H) of the amide and a significant amount of D/H exchange (0.6 H and 0.4 H) also occurred at the 5-position, and only a small amount of D/H exchange was detected at the benzylic position (total 0.6 H and 0.3 H) (Scheme 4b top and middle). These results indicate that the C-H activation step is reversible and that D/H exchange at the *ortho* C-H bond via a five-membered palladacycle is much faster than at the benzylic C-H bond via a six-membered palladacycle. In sharp contrast, only a trace amount of H atom was detected at the benzylic position in both the substrate and product when the reaction was carried out in the presence of methyl acrylate (Scheme 4b bottom), suggesting that the further reaction from a six-membered palladacycle is much faster than a reverse protonation. Additionally, the reaction was not inhibited when conducted in the presence of a radical trap compound (Scheme 4c). A competition experiment was carried out to evaluate the electronic effect of this reaction (Scheme 4d). The reaction of an equal molar amount of **1c** and **1d** under the standard conditions for 2 hours gave **3ca** and **3da** in 43% and 24% yields, respectively, indicating that the electron-withdrawing group facilitates the reaction.

To collect some mechanistic insights into the Pd(II)-catalyzed oxidative C-H alkenylation and cyclization sequence of 2-methylbenzamides **1** with **2a**, a density functional theory (DFT) analysis was performed (Figure 1). The catalytic cycle begins with the complexation of Pd(OAc)₂ and the amide substrate by eliminating one acetic acid molecule. The C-H activation step by a concerted-metalation deprotonation (CMD) mechanism preferably proceeds at the *ortho*-position through **TS1** ($\Delta G^\ddagger = 9.3 \text{ kcal mol}^{-1}$) rather than at the benzylic position through **TS2** ($\Delta G^\ddagger = 14.3 \text{ kcal mol}^{-1}$). This indicates that the formation of the five-membered palladacycle **Int1** is kinetically favored. In contrast to the lower energy barrier for the *ortho* C-H bond activation pathway, the migratory insertion of methyl acrylate is faster through **TS4** from the six-membered palladacycle **Int2**, which results in the formation of the eight-membered palladacycle **Int4**. The subsequent step is the β -hydride elimination, and transition

structures with or without MAH were compared. In the absence of MAH, the transition state **TS6** has a much higher energy than **TS5**, which prevents the formation of the six-membered product. On the other hand, the coordination of MAH as a ligand highly stabilizes the transition state structure for the six-membered product formation pathway, and β -hydride elimination then becomes more favorable through **TS8**. The origin of this reversed selectivity in the key β -hydride elimination step can be attributed to the nearly square planar structure of **TS8** that allows a less distorted geometry during the transition state (See more detail information in Figure S1-S3, Table S1-S3).

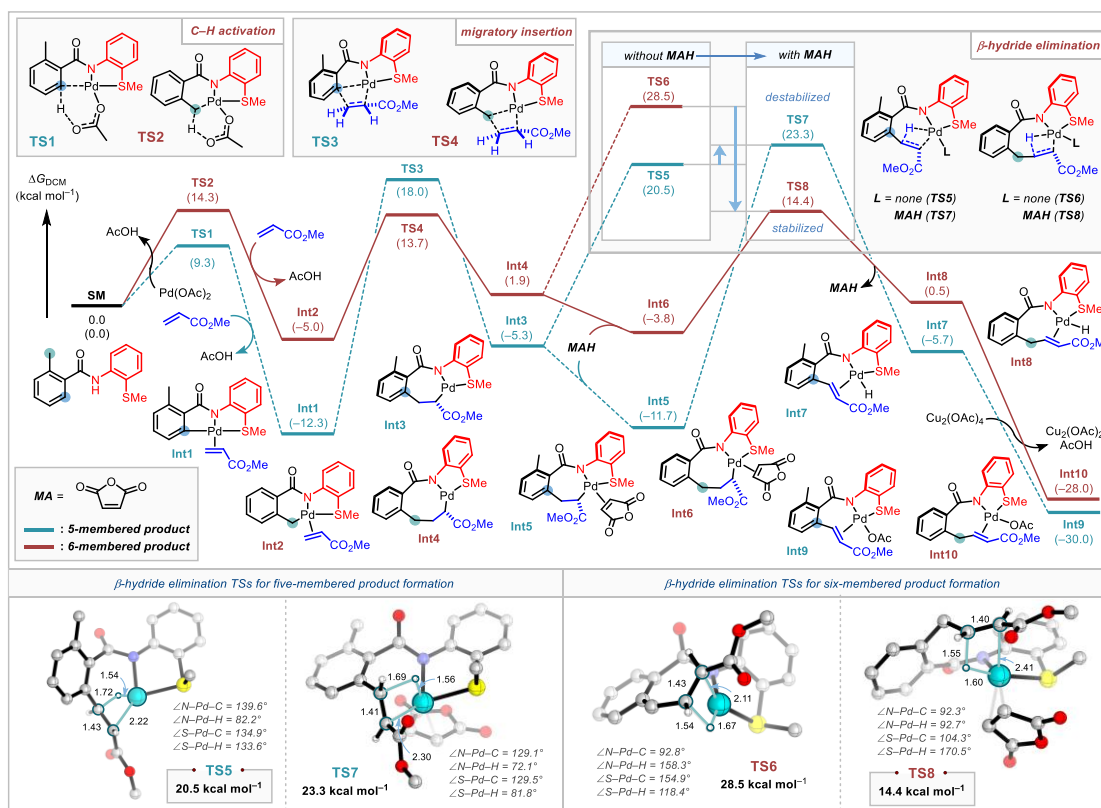


Figure 1. Computed potential energy surface (ΔG [kcal mol⁻¹]) for the Pd(II)-catalyzed oxidative C–H alkenylation and cyclization sequence of benzamides with methyl acrylate computed at SMD(DCM)/M06L/SDD(Pd,Cu)-6-311+G(d,p)//SMD(DCM)/B3LYP/Lan12dz(Pd,Cu)-6-31G(d) level of theory. Energies (kcal mol⁻¹), bond lengths (Å), and bond angles (°) of the TS geometries are provided in the insert.

As evidenced by the bond angles around the Pd center, **TS5** and **TS7**, the bond angles do not change appreciably, whereas the geometry in **TS8** is greatly changed from **TS6** with the formation of a more square planar-like structure with nearly 90° or 180° bond

angles. This clearly suggests that MAH promotes a large geometry change from **TS6** to **TS8** and lowers the energy of the β -hydride elimination transition state. Once MAH is dissociated after the β -hydride elimination step, the Pd-H bond in **Int8** is oxidized by copper(II) acetate with the generation of a stable Pd(II) complex **Int10**. The next step is an intramolecular migratory insertion through **TS9** ($\Delta G^\ddagger = 17.6 \text{ kcal mol}^{-1}$) to give a cyclized intermediate **Int11** with a newly-formed C-N bond at the benzylic position. A second β -hydride elimination step through **TS10** ($\Delta G^\ddagger = 18.2 \text{ kcal mol}^{-1}$) and reoxidation by copper(II) acetate furnishes a α,β -unsaturated product **Int12**, which is then isomerized to the more stable isoquinolinone product **P1**. These detailed DFT calculations on the catalytic cycle explain the reaction mechanism and the effect of MAH in selectively forming the six-membered product.

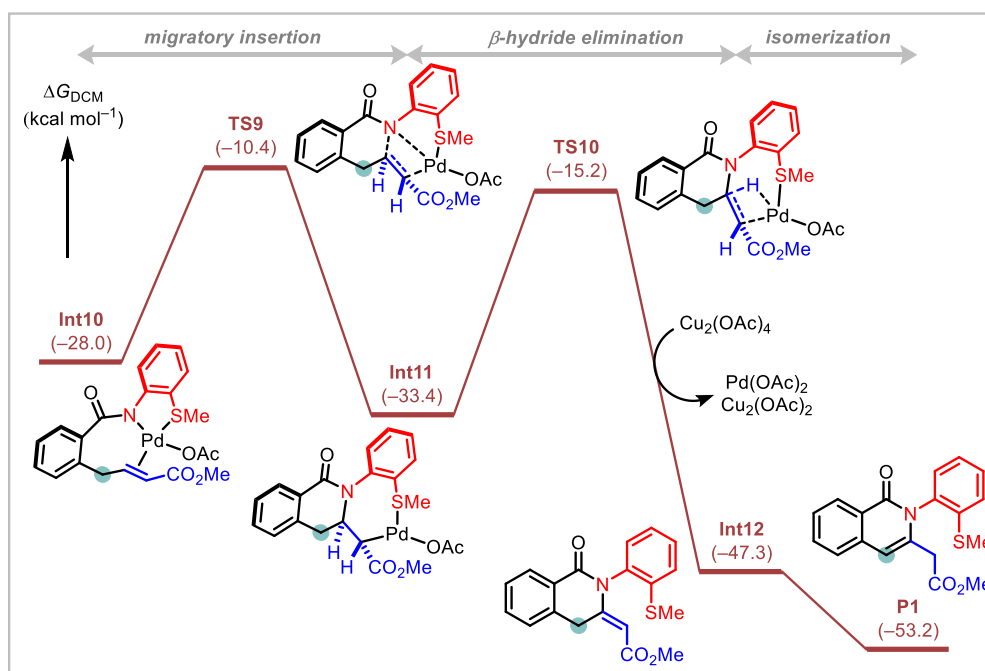


Figure 2. Computed potential energy surface (ΔG [kcal mol^{-1}]) for the Pd(II)-catalyzed oxidative C–H alkenylation and cyclization sequence of benzamides with methyl acrylate from **Int10** computed at SMD(DCM)/M06L/SDD(Pd,Cu)-6-311+G(d,p)//SMD(DCM)/B3LYP/Lan12dz(Pd,Cu)-6-31G(d) level of theory.

3.3 Conclusion

In summary, this chapter described the development of a novel type of C-H functionalization that proceeds via the palladium-catalyzed site-selective [5+1] annulation of 2-methylbenzamide derivatives with activated alkenes, utilizing a

2-(methylthio)aniline directing group. The use of MAH as a ligand completely changed the reaction site from the *ortho* C-H bond to the *ortho*-methyl C-H bond. The results of DFT calculations suggest that the coordination of MAH to a palladium center stabilizes the β -hydride elimination transition state by changing the geometry to a square planar-like structure and thus accelerates the β -hydride elimination. This method provides an alternative method for using alkenes rather the alkynes or allenes in the synthesis of alkenylated annulation products.¹⁴

3.4 Experimental Section

I. General Information.

¹H NMR and ¹³C NMR spectra were recorded on a JEOL ECS-400 spectrometer in CDCl₃ with tetramethylsilane as the internal standard. Data are reported as follows: chemical shifts in ppm (δ), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, brs = broad singlet, and m = multiplet), coupling constant (Hz), and integration. In some cases, it was not possible to analyze some of the peaks in the ¹³C NMR spectra because of overlapping peaks. Infrared spectra (IR) were recorded on a JASCO FT/IR-4000 spectrometer using the ATR method. Absorption data are reported in reciprocal centimeters from 800 to 3500 cm⁻¹ with the following relative intensities: s (strong), m (medium), or w (weak). Mass spectra and high-resolution mass spectra (HRMS) were obtained using a JMS-T100LP spectrometer. Melting points were determined using a Stanford Research Systems MPA100 apparatus equipped with a digital thermometer. Medium-pressure liquid chromatography (MPLC) was performed with Biotage Isolera[®] equipped with Biotage[®] Sfär Silica HC D-High Capacity Duo 20 μ m chromatography cartridges.

II. Materials.

Palladium catalyst:

Pd(OPiv)₂ (Sigma-Aldrich Co.)

Cu(OPiv)₂:

Cu(OPiv)₂ was synthesized using reported procedure.¹⁵

Additives:

Maleic anhydride (Tokyo Chemical Industry Co., Ltd.); PivOH (Tokyo Chemical Industry Co., Ltd.); Cs₂CO₃ (Tokyo Chemical Industry Co., Ltd.).

alkenes:

Methyl Acrylate (Tokyo Chemical Industry Co., Ltd.); Styrene (Tokyo Chemical Industry Co., Ltd.); Diphenylvinylphosphine Oxide (FUJIFILM Wako Pure Chemical Co.) *N,N*-Dimethylacrylamide (Tokyo Chemical Industry Co., Ltd.).

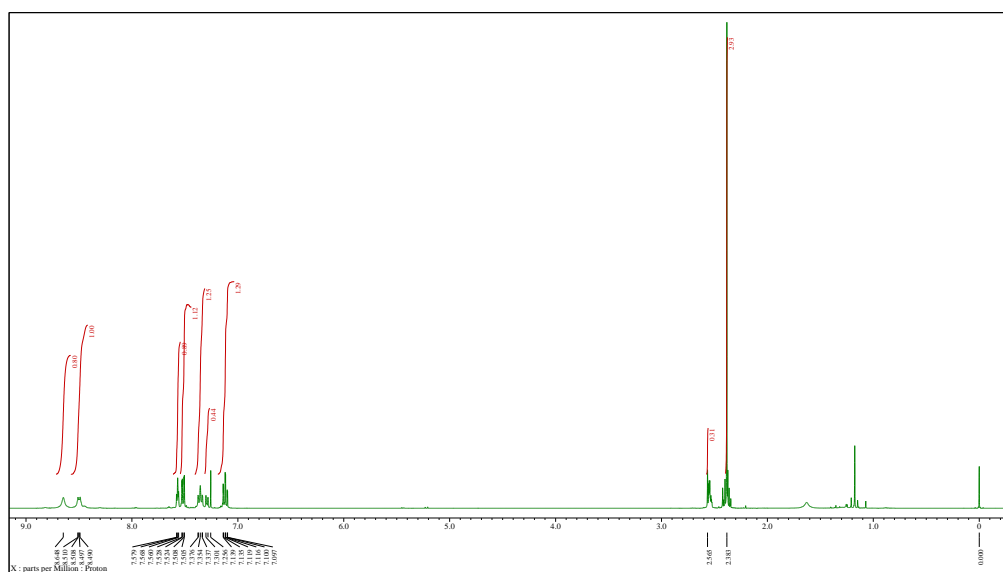
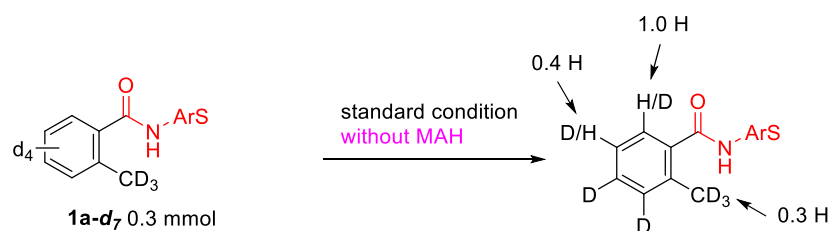
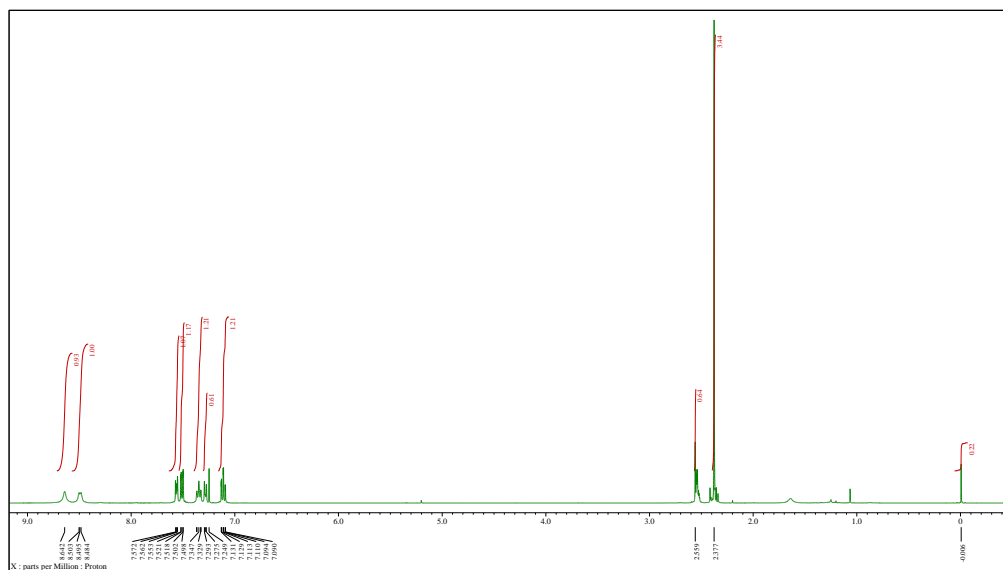
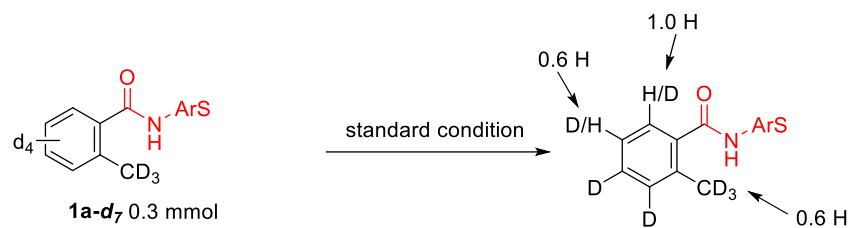
III. General synthesis of amides.

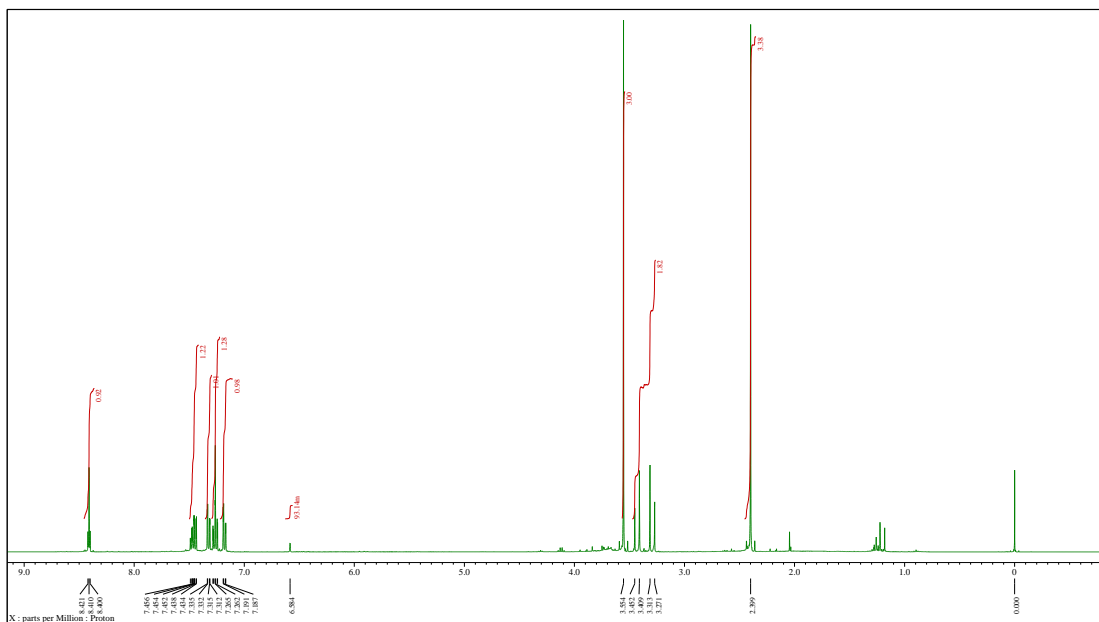
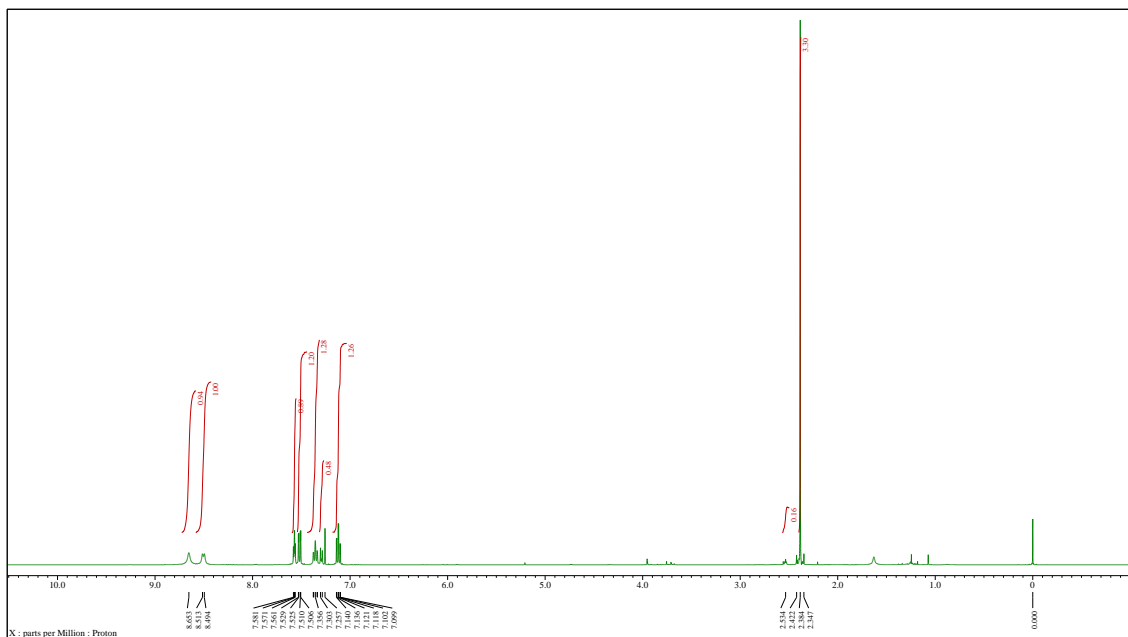
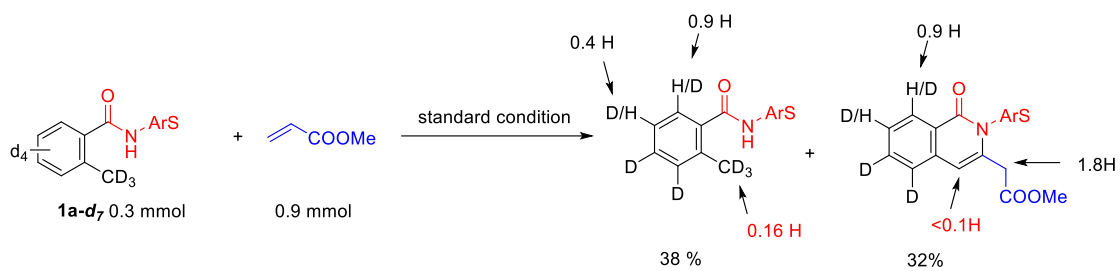
To a stirred solution of the carboxylic acid (5 mmol) and DMF (3 drops) in CHCl₃ (5 mL), (COCl)₂ (0.5 mL, 6 mmol) was added dropwise. The solution was magnetically stirred at room temperature for 4 h. After removing the solvent under reduced pressure, the resulting residue was dissolved in CHCl₃ (15 mL). After cooling the reaction mixture to 0 °C, a solution of aniline (6 mmol) and triethylamine (10 mmol) in 10 mL of CHCl₃ was added dropwise. The resulting mixture was allowed to warm to room temperature and stirred overnight. The crude product was washed with 1 M HCl aq. (20 mL). The organic phase was dried over anhydrous Na₂SO₄ and the solvent was removed by evaporation. The resulting crude amide was purified by MPLC (eluent: hexane/EtOAc = 4/1).

IV. General synthesis of [5+1] alkenylated annulation product

To an oven-dried 5 mL screw-capped vial, 2-methyl-*N*-(2-(methylthio)phenyl)benzamide (77.2 mg, 0.3 mmol), methyl acrylate (77.5 mg, 0.9 mmol), Pd(OPiv)₂ (9.3 mg, 0.03 mmol), Cu(OPiv)₂ (191.4 mg, 0.72 mmol), maleic anhydride (23.4 mg, 0.3 mmol), PivOH (152.1 mg, 1.5 mmol), Cs₂CO₃ (97.8 mg, 0.3 mmol) and Cl₂CHCHCl₂ (1 mL) were added. The mixture was stirred at 150 °C for 18 hours and then cooled to room temperature. The resulting mixture was diluted with 1 mL of EtOAc. The product was purified by column chromatography on silica gel (eluent: hexane/EtOAc= 1.5:1) to afford the product (73 mg, 66 %) as a white powder.

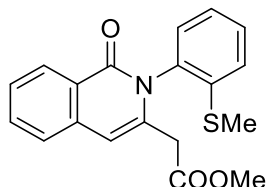
V. Deuterium Labeling Experiments.





VI. Spectroscopic Data.

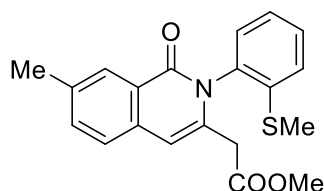
methyl 2-(2-(2-(methylthio)phenyl)-1-oxo-1,2-dihydroisoquinolin-3-yl)acetate (3aa)



65.2 mg, 64% yield. $R_f = 0.21$ (Hex: EtOAc = 1.5:1). White powder. m.p. 165.4-165.8 °C. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 8.41 (d, $J = 8.0$ Hz, 1H), 7.66-7.64 (m, 1H), 7.53 (d, $J = 7.8$ Hz, 1H), 7.49-7.43 (m, 2H), 7.33-7.31 (m, 1H), 7.28-7.24 (m, 1H), 7.18 (dd, $J = 7.8, 1.4$ Hz, 1H), 6.58 (s, 1H), 3.55 (s, 3H), 3.36 (dd, $J = 55.3, 16.9$ Hz, 2H), 2.39 (s, 3H). $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) δ 169.7, 162.7, 138.1, 136.8, 135.7, 135.2, 132.9, 130.1, 129.9, 128.4, 126.9, 126.0, 125.6, 125.5, 108.4, 52.3, 39.5, 14.4. HRMS (DART+) m/z ($[\text{M}+\text{H}]^+$) Calcd for $\text{C}_{19}\text{H}_{18}\text{NO}_3\text{S}$: 340.1007; Found: 340.1013.

methyl

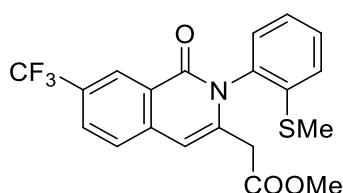
2-(7-methyl-2-(2-(methylthio)phenyl)-1-oxo-1,2-dihydroisoquinolin-3-yl)acetate (3ba)



73.3 mg, 69% yield. $R_f = 0.21$ (Hex: EtOAc = 1.5:1). Pale yellow powder. m.p. 151.2-151.5 °C. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 8.20 (s, 1H), 7.50-7.46 (m, 1H), 7.45-7.42 (m, 2H), 7.32 (dd, $J = 8.0, 1.4$ Hz, 1H), 7.28-7.24 (m, 1H), 7.17 (dd, $J = 7.8, 1.4$ Hz, 1H), 6.55 (s, 1H), 3.54 (s, 3H), 3.34 (dd, $J = 55.0, 16.8$ Hz, 2H), 2.47 (s, 3H), 2.39 (s, 3H). $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) δ 169.8, 162.7, 138.1, 137.0, 135.4, 134.6, 134.5, 134.3, 130.2, 129.8, 127.9, 125.9, 125.5, 125.5, 108.3, 77.5, 77.2, 76.8, 52.2, 39.4, 21.6, 14.5. HRMS (DART+) m/z ($[\text{M}+\text{H}]^+$) Calcd for $\text{C}_{20}\text{H}_{20}\text{NO}_3\text{S}$: 354.1164; Found: 354.1175.

methyl

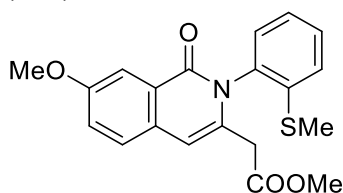
2-(2-(2-(methylthio)phenyl)-1-oxo-7-(trifluoromethyl)-1,2-dihydroisoquinolin-3-yl)acetate (3ca)



105.6 mg, 86% yield. $R_f = 0.29$ (Hex: EtOAc = 1.5:1). Pale yellow powder. m.p. 129.8-130.3 °C. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 8.69 (s, 1H), 7.86 (d, $J = 8.2$ Hz, 1H), 7.64 (d, $J = 8.5$ Hz, 1H), 7.50-7.48 (m, 1H), 7.36-7.34 (m, 1H), 7.30-7.26 (m, 1H), 7.18 (dd, $J = 7.8, 1.4$ Hz, 1H), 6.62 (s, 1H), 3.56 (s, 3H), 3.38 (dd, $J = 60.3, 17.0$ Hz, 2H), 2.41 (s, 3H). $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) δ 169.3, 162.1, 139.3, 138.5, 138.0, 134.7, 130.2, 130.0, 129.0 (d, $J = 4$ Hz), 128.8 (q, $J = 34$ Hz), 126.8, 126.2 (d, $J = 5$ Hz), 125.7, 125.7, 125.4, 107.7, 52.4, 39.5, 14.5. HRMS (DART+) m/z ($[\text{M}+\text{H}]^+$) Calcd for $\text{C}_{20}\text{H}_{17}\text{F}_3\text{NO}_3\text{S}$: 408.0881; Found: 408.0875.

methyl

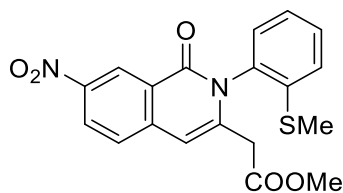
2-(7-methoxy-2-(2-(methylthio)phenyl)-1-oxo-1,2-dihydroisoquinolin-3-yl)acetate (3da)



71.2 mg, 64% yield. $R_f = 0.12$ (Hex: EtOAc = 1.5:1). Brown powder. m.p. 124.5-124.9 °C. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 7.83 (d, $J = 2.7$ Hz, 1H), 7.48-7.43 (m, 2H), 7.32 (dd, $J = 8.0, 1.1$ Hz, 1H), 7.30-7.24 (m, 2H), 7.17 (dd, $J = 7.8, 1.4$ Hz, 1H), 6.56 (s, 1H), 3.90 (s, 3H), 3.54 (s, 3H), 3.34 (dd, $J = 54.9, 16.9$ Hz, 2H), 2.40 (s, 4H). $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) δ 169.9, 162.5, 158.8, 138.1, 135.3, 133.2, 130.9, 130.1, 129.9, 127.7, 126.7, 125.4, 123.4, 108.3, 108.2, 55.7, 52.2, 39.3, 14.4. HRMS (DART+) m/z ($[\text{M}+\text{H}]^+$) Calcd for $\text{C}_{20}\text{H}_{20}\text{NO}_4\text{S}$: 307.1113; Found: 307.1119.

methyl

2-(2-(2-(methylthio)phenyl)-7-nitro-1-oxo-1,2-dihydroisoquinolin-3-yl)acetate (3ea)



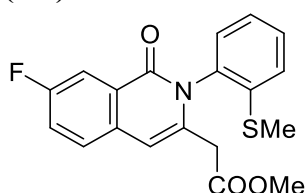
57.8 mg, 50% yield. $R_f = 0.17$ (Hex: EtOAc = 1.5:1). Yellow powder. m.p. 187.3-187.6 °C. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 9.25 (d, $J = 2.3$ Hz, 1H), 8.46 (dd, $J =$

8.7, 2.5 Hz, 1H), 7.66 (d, $J = 8.7$ Hz, 1H), 7.50 (td, $J = 7.7, 1.1$ Hz, 1H), 7.36 (dd, $J = 8.1, 1.0$ Hz, 1H), 7.30 (td, $J = 7.6, 1.2$ Hz, 1H), 7.18 (dd, $J = 7.9, 1.3$ Hz, 1H), 6.65 (s, 1H), 3.58 (s, 3H), 3.40 (dd, $J = 62.2, 16.9$ Hz, 2H), 2.43 (s, 3H). ^{13}C NMR (CDCl_3 , 100 MHz) δ 169.1, 161.7, 146.2, 141.5, 140.5, 137.9, 134.4, 130.5, 129.9, 127.4, 127.0, 126.0, 125.8, 125.7, 125.0, 107.4, 52.6, 39.7, 14.6. HRMS (DART+) m/z ($[\text{M}+\text{H}]^+$) Calcd for $\text{C}_{19}\text{H}_{17}\text{N}_2\text{O}_5\text{S}$: 385.0858; Found: 385.0872.

methyl

2-(7-fluoro-2-(2-(methylthio)phenyl)-1-oxo-1,2-dihydroisoquinolin-3-yl)acetate

(3fa)

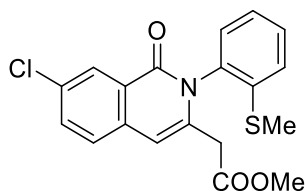


78.5 mg, 73% yield. $R_f = 0.22$ (Hex: EtOAc = 1.5:1). Pale yellow powder. m.p. 150.0-150.3 °C. ^1H -NMR (CDCl_3 , 400 MHz) δ 8.04 (dd, $J = 9.1, 2.7$ Hz, 1H), 7.53 (dd, $J = 8.7, 5.0$ Hz, 1H), 7.48-7.44 (m, 1H), 7.39 (td, $J = 8.5, 2.7$ Hz, 1H), 7.32 (dd, $J = 8.1, 1.3$ Hz, 1H), 7.28-7.24 (m, 1H), 7.17 (dd, $J = 7.8, 1.4$ Hz, 1H), 6.57 (s, 1H), 3.55 (s, 3H), 3.35 (dd, $J = 56.9, 16.9$ Hz, 2H), 2.40 (s, 3H). ^{13}C NMR (CDCl_3 , 100 MHz) δ 169.6, 161.9, 161.5 (d, $J = 246$ Hz), 138.0, 134.9 (d, $J = 11$ Hz), 133.4, 130.0, 128.3 (d, $J = 8$ Hz), 127.1, 1225.5, 121.6 (d, $J = 24$ Hz), 113.5 (d, $J = 22$ Hz), 107.8, 52.3, 39.3, 14.4. HRMS (DART+) m/z ($[\text{M}+\text{H}]^+$) Calcd for $\text{C}_{19}\text{H}_{17}\text{FNO}_3\text{S}$: 358.0913; Found: 358.0927.

methyl

2-(7-chloro-2-(2-(methylthio)phenyl)-1-oxo-1,2-dihydroisoquinolin-3-yl)acetate

(3ga)



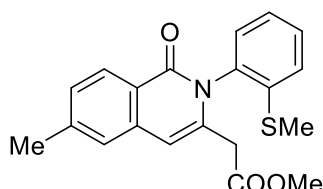
83.0 mg, 74% yield. $R_f = 0.29$ (Hex: EtOAc = 1.5:1). Pale yellow powder. m.p. 143.2-143.6 °C. ^1H -NMR (CDCl_3 , 400 MHz) δ 8.36 (d, $J = 2.3$ Hz, 1H), 7.60 (dd, $J = 8.5, 2.3$ Hz, 1H), 7.48-7.44 (m, 2H), 7.32 (dd, $J = 8.0, 1.4$ Hz, 1H), 7.29-7.24 (m, 1H), 7.17 (dd, $J = 7.8, 1.4$ Hz, 1H), 6.55 (s, 1H), 3.55 (s, 3H), 3.34 (dd, $J = 58.8, 16.9$ Hz, 2H), 2.40 (s, 3H). ^{13}C NMR (CDCl_3 , 100 MHz) δ 169.5, 161.7, 138.0, 136.2, 135.2, 134.9, 133.3, 132.8, 130.1, 130.0, 127.8, 127.6, 126.7, 125.6, 125.6, 107.7, 52.3, 39.4,

14.5. HRMS (DART+) m/z ($[M+H]^+$) Calcd for $C_{19}H_{17}ClNO_3S$: 374.0617; Found: 374.0631.

methyl

2-(6-methyl-2-(2-(methylthio)phenyl)-1-oxo-1,2-dihydroisoquinolin-3-yl)acetate

(3ha)

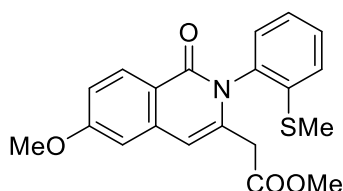


70.2 mg, 66% yield. $R_f = 0.22$ (Hex: EtOAc = 1.5:1). Pale yellow powder. m.p. 130.0-130.4 °C. 1H -NMR ($CDCl_3$, 400 MHz) δ 8.29 (d, $J = 8.0$ Hz, 1H), 7.45-7.42 (m, 1H), 7.32-7.28 (m, 3H), 7.26-7.24 (m, 1H), 7.17 (dd, $J = 7.8, 1.4$ Hz, 1H), 6.51 (s, 1H), 3.55 (s, 3H), 3.34 (dd, $J = 54.3, 16.8$ Hz, 2H), 2.48 (s, 3H), 2.39 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.8, 162.7, 143.5, 138.2, 137.0, 135.7, 135.3, 130.2, 129.8, 128.6, 128.4, 125.8, 125.5, 123.4, 108.3, 52.3, 39.5, 22.0, 14.5. HRMS (DART+) m/z ($[M+H]^+$) Calcd for $C_{20}H_{20}NO_3S$: 354.1164; Found: 354.1181.

methyl

2-(6-methoxy-2-(2-(methylthio)phenyl)-1-oxo-1,2-dihydroisoquinolin-3-yl)acetate

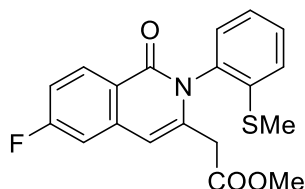
(3ia)



56.8 mg, 51% yield. $R_f = 0.15$ (Hex: EtOAc = 1.5:1). White powder. m.p. 174.4-174.8 °C. 1H -NMR ($CDCl_3$, 400 MHz) δ 8.32 (d, $J = 8.9$ Hz, 1H), 7.46-7.42 (m, 1H), 7.31 (dd, $J = 8.0, 1.1$ Hz, 1H), 7.25 (td, $J = 7.5, 1.4$ Hz, 1H), 7.17 (dd, $J = 7.8, 1.6$ Hz, 1H), 7.04 (dd, $J = 8.9, 2.5$ Hz, 1H), 6.89 (d, $J = 2.5$ Hz, 1H), 6.50 (s, 1H), 3.91 (s, 3H), 3.55 (s, 3H), 3.34 (dd, $J = 52.3, 16.8$ Hz, 2H), 2.39 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.7, 163.3, 162.4, 138.9, 138.2, 136.4, 135.2, 130.5, 130.2, 129.8, 125.4, 119.4, 116.3, 108.2, 107.0, 55.6, 52.3, 39.5, 14.4. HRMS (DART+) m/z ($[M+H]^+$) Calcd for $C_{20}H_{20}NO_4S$: 370.1113; Found: 370.1115.

methyl

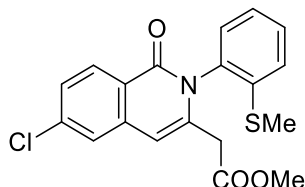
**2-(6-fluoro-2-(2-(methylthio)phenyl)-1-oxo-1,2-dihydroisoquinolin-3-yl)acetate
(3ja)**



50.1 mg, 47% yield. $R_f = 0.29$ (Hex: EtOAc = 1.5:1). White powder. m.p. 157.5-157.9 °C. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 8.43-8.40 (m, 1H), 7.48-7.44 (m, 1H), 7.32 (dd, $J = 8.0, 1.1$ Hz, 1H), 7.29-7.24 (m, 1H), 7.20-7.14 (m, 3H), 6.52 (s, 1H), 3.56 (s, 3H), 3.35 (dd, $J = 55.3, 16.9$ Hz, 2H), 2.41 (s, 3H). $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) δ 169.5, 165.7 (d, $J = 252$ Hz), 162.1, 139.1 (d, $J = 11$ Hz), 138.1, 137.3, 134.9, 131.7 (d, $J = 10$ Hz), 130.1 (d, $J = 5$ Hz), 125.5, 122.3, 115.5 (d, $J = 23$ Hz), 110.9 (d, $J = 22$ Hz), 107.7 (d, $J = 3$ Hz), 52.4, 39.5, 14.5. HRMS (DART+) m/z ($[\text{M}+\text{H}]^+$) Calcd for $\text{C}_{19}\text{H}_{16}\text{FNO}_3\text{S}$: 358.0913; Found: 358.0926.

methyl

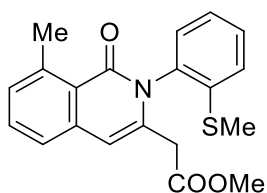
**2-(6-chloro-2-(2-(methylthio)phenyl)-1-oxo-1,2-dihydroisoquinolin-3-yl)acetate
(3ka)**



50.1 mg, 47% yield. $R_f = 0.29$ (Hex: EtOAc = 1.5:1). Pale yellow powder. m.p. 119.1-119.6 °C. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 8.33 (d, $J = 8.5$ Hz, 1H), 7.51 (d, $J = 2.1$ Hz, 1H), 7.46-7.44 (m, 1H), 7.41 (dd, $J = 8.6, 1.9$ Hz, 1H), 7.32 (dd, $J = 8.1, 1.3$ Hz, 1H), 7.25 (dd, $J = 7.5, 1.1$ Hz, 1H), 7.17 (dd, $J = 7.8, 1.4$ Hz, 1H), 6.49 (s, 1H), 3.56 (s, 3H), 3.35 (dd, $J = 56.9, 16.9$ Hz, 2H), 2.40 (s, 3H). $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) δ 169.5, 162.2, 139.4, 138.1, 137.4, 134.9, 130.3, 130.1, 127.4, 125.6, 125.3, 124.0, 107.4, 52.4, 39.5, 14.5. HRMS (DART+) m/z ($[\text{M}+\text{H}]^+$) Calcd for $\text{C}_{19}\text{H}_{16}\text{ClNO}_3\text{S}$: 374.0617; Found: 374.0613.

methyl

**2-(8-methyl-2-(2-(methylthio)phenyl)-1-oxo-1,2-dihydroisoquinolin-3-yl)acetate
(3la)**

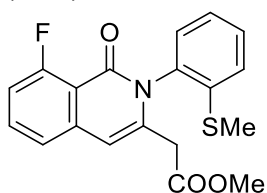


45.7 mg, 43% yield. $R_f = 0.29$ (Hex: EtOAc = 1.5:1). Yellow powder. m.p. 115.0-115.5 °C. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 7.49 (t, $J = 7.7$ Hz, 1H), 7.46-7.42 (m, 1H), 7.34 (d, $J = 7.8$ Hz, 1H), 7.30 (dd, $J = 8.0, 1.4$ Hz, 1H), 7.28-7.22 (m, 2H), 7.17 (dd, $J = 7.8, 1.4$ Hz, 1H), 6.50 (s, 1H), 3.55 (s, 3H), 3.32 (dd, $J = 54.8, 16.8$ Hz, 2H), 2.87 (s, 3H), 2.40 (s, 3H). $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) δ 169.8, 163.5, 142.6, 138.6, 138.2, 135.5, 135.4, 132.1, 130.3, 130.1, 129.7, 125.5, 125.4, 124.4, 124.0, 108.8, 52.3, 39.4, 23.9, 14.4. HRMS (DART+) m/z ($[\text{M}+\text{H}]^+$) Calcd for $\text{C}_{20}\text{H}_{20}\text{NO}_3\text{S}$: 354.1164; Found: 354.1160.

methyl

2-(8-fluoro-2-(2-(methylthio)phenyl)-1-oxo-1,2-dihydroisoquinolin-3-yl)acetate

(3ma)

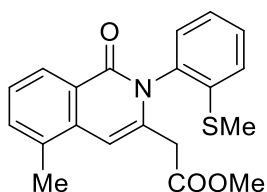


43.0 mg, 40% yield. $R_f = 0.20$ (Hex: EtOAc = 1.5:1). Pale yellow powder. m.p. 167.1-167.4 °C. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 7.58 (td, $J = 8.0, 4.8$ Hz, 1H), 7.45 (td, $J = 7.7, 1.3$ Hz, 1H), 7.33-7.23 (m, 3H), 7.16 (dd, $J = 7.8, 1.4$ Hz, 1H), 7.09 (ddd, $J = 11.4, 8.1, 1.0$ Hz, 1H), 6.53 (d, $J = 1.8$ Hz, 1H), 3.55 (s, 3H), 3.34 (dd, $J = 53.2, 17.0$ Hz, 2H), 2.41 (s, 3H). $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) δ 169.5, 162.9 (d, $J = 265$ Hz), 159.9, 139.6, 138.2, 137.1, 134.8, 133.8 (d, $J = 10$ Hz), 130.1 (d, $J = 33$ Hz), 125.6 (d, $J = 11$ Hz), 121.9 (d, $J = 4$ Hz), 114.8, 113.9 (d, $J = 21$ Hz), 107.7, 52.4, 39.4, 14.5. HRMS (DART+) m/z ($[\text{M}+\text{H}]^+$) Calcd for $\text{C}_{19}\text{H}_{16}\text{FNO}_3\text{S}$: 358.0913; Found: 358.0908.

methyl

2-(5-methyl-2-(2-(methylthio)phenyl)-1-oxo-1,2-dihydroisoquinolin-3-yl)acetate

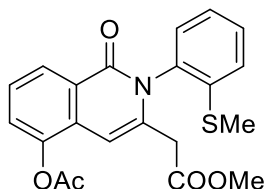
(3na)



65.4 mg, 62% yield. $R_f = 0.24$ (Hex: EtOAc = 1.5:1). White powder. m.p. 165.3-165.8 °C. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 8.28 (d, $J = 8.0$ Hz, 1H), 7.50 (dd, $J = 7.3, 0.5$ Hz, 1H), 7.47-7.43 (m, 1H), 7.38 (d, $J = 7.8$ Hz, 1H), 7.35-7.31 (m, 1H), 7.28-7.24 (m, 1H), 7.18 (dd, $J = 7.8, 1.4$ Hz, 1H), 6.69 (s, 1H), 3.55 (s, 3H), 3.40 (dd, $J = 58.9, 16.8$ Hz, 2H), 2.56 (s, 3H), 2.40 (s, 3H). $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) δ 169.8, 163.0, 138.1, 135.7, 135.3, 135.3, 133.8, 133.2, 130.2, 129.9, 126.6, 126.4, 125.8, 125.6, 125.5, 105.3, 52.3, 39.8, 19.1, 14.5. HRMS (DART+) m/z ($[\text{M}+\text{H}]^+$) Calcd for $\text{C}_{20}\text{H}_{20}\text{NO}_3\text{S}$: 354.1164; Found: 354.1158.

methyl

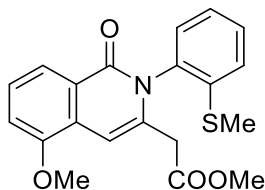
2-(5-acetoxy-2-(2-(methylthio)phenyl)-1-oxo-1,2-dihydroisoquinolin-3-yl)acetate (3oa)



39.7 mg, 33% yield. $R_f = 0.21$ (Hex: EtOAc = 1:1). Yellow powder. m.p. 133.7-134.1 °C. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 8.30 (ddd, $J = 5.4, 3.9, 0.7$ Hz, 1H), 7.48-7.44 (m, 3H), 7.32 (dd, $J = 8.0, 1.1$ Hz, 1H), 7.26 (td, $J = 7.7, 1.5$ Hz, 1H), 7.16 (dd, $J = 7.8, 1.4$ Hz, 1H), 6.59 (d, $J = 0.5$ Hz, 1H), 3.55 (s, 3H), 3.48-3.28 (m, 2H), 2.43 (s, 3H), 2.40 (s, 3H). $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) δ 169.5, 169.2, 162.1, 145.3, 138.1, 136.6, 135.0, 130.1, 130.0, 130.0, 127.1, 126.8, 126.2, 125.8, 125.6, 125.5, 101.8, 52.3, 39.8, 21.2, 14.5. HRMS (DART+) m/z ($[\text{M}+\text{H}]^+$) Calcd for $\text{C}_{21}\text{H}_{20}\text{NO}_5\text{S}$: 398.1062; Found: 398.1065.

methyl

2-(5-methoxy-2-(2-(methylthio)phenyl)-1-oxo-1,2-dihydroisoquinolin-3-yl)acetate (3pa)



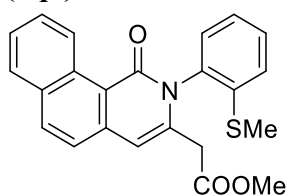
65.4 mg, 62% yield. $R_f = 0.24$ (Hex: EtOAc = 1.5:1). Pale yellow powder. m.p. 169.2-169.6 °C. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 7.99 (d, $J = 8.0$ Hz, 1H), 7.46-7.38 (m, 2H), 7.31 (d, $J = 7.8$ Hz, 1H), 7.27-7.23 (m, 1H), 7.17 (dd, $J = 7.9, 1.5$ Hz, 1H), 7.08 (d, $J = 8.0$ Hz, 1H), 6.96 (s, 1H), 3.95 (s, 3H), 3.54 (s, 3H), 3.38 (dd, $J = 67.7, 16.9$ Hz, 2H),

2.39 (s, 3H). ^{13}C NMR (CDCl_3 , 100 MHz) δ 169.8, 162.5, 154.4, 138.1, 135.3, 134.9, 130.1, 129.8, 127.8, 127.2, 126.7, 125.6, 125.5, 120.0, 112.1, 102.8, 55.9, 52.2, 39.7, 14.5. HRMS (DART+) m/z ($[\text{M}+\text{H}]^+$) Calcd for $\text{C}_{20}\text{H}_{20}\text{NO}_4\text{S}$: 370.1113; Found: 370.1116.

methyl

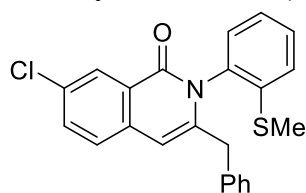
2-(2-(2-(methylthio)phenyl)-1-oxo-1,2-dihydrobenzo[h]isoquinolin-3-yl)acetate

(3qa)



48.3 mg, 41% yield. R_f = 0.38 (Hex: EtOAc = 1.5:1). Pale yellow powder. m.p. 66.3-66.7 °C. ^1H -NMR (CDCl_3 , 400 MHz) δ 10.10-10.08 (m, 1H), 8.05 (d, J = 8.5 Hz, 1H), 7.90 (dd, J = 7.9, 1.3 Hz, 1H), 7.69-7.64 (m, 1H), 7.60-7.54 (m, 2H), 7.51-7.47 (m, 1H), 7.36 (dd, J = 8.0, 1.1 Hz, 1H), 7.31 (td, J = 7.5, 1.3 Hz, 1H), 7.26-7.23 (m, 1H), 6.73 (s, 1H), 3.58 (s, 3H), 3.45 (dd, J = 59.1, 16.8 Hz, 2H), 2.40 (s, 3H). ^{13}C NMR (CDCl_3 , 100 MHz) δ 169.6, 163.2, 138.9, 138.0, 137.2, 135.8, 134.5, 132.5, 132.2, 130.1, 129.9, 128.6, 128.4, 127.5, 126.5, 125.6, 124.7, 119.0, 109.1, 52.4, 39.5, 14.5. HRMS (DART+) m/z ($[\text{M}+\text{H}]^+$) Calcd for $\text{C}_{23}\text{H}_{20}\text{NO}_3\text{S}$: 390.1164; Found: 390.1154.

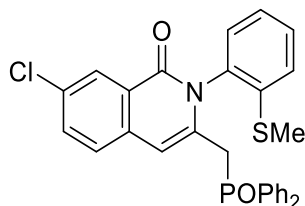
3-benzyl-7-chloro-2-(2-(methylthio)phenyl)isoquinolin-1(2H)-one (3gb)



63.5 mg, 60% yield. R_f = 0.23 (Hex: EtOAc = 1.5:1). Pale yellow powder. m.p. 157.0-157.3 °C. ^1H -NMR (CDCl_3 , 400 MHz) δ 8.35 (d, J = 2.3 Hz, 1H), 7.56 (dd, J = 8.5, 2.3 Hz, 1H), 7.45-7.41 (m, 1H), 7.38 (d, J = 8.5 Hz, 1H), 7.31 (dd, J = 8.0, 1.4 Hz, 1H), 7.26-7.23 (m, 3H), 7.17 (td, J = 7.7, 1.4 Hz, 1H), 7.00-6.94 (m, 3H), 6.19 (d, J = 0.5 Hz, 1H), 3.54 (dd, J = 54.8, 16.4 Hz, 2H), 2.38 (s, 3H). ^{13}C NMR (CDCl_3 , 100 MHz) δ 162.0, 143.0, 138.0, 136.4, 135.5, 135.5, 133.2, 132.3, 129.7, 129.4, 128.6, 127.8, 127.5, 127.0, 126.2, 125.8, 125.7, 106.3, 39.8, 14.7. HRMS (DART+) m/z ($[\text{M}+\text{H}]^+$) Calcd for $\text{C}_{23}\text{H}_{19}\text{ClNOS}$: 392.0876; Found: 392.0870.

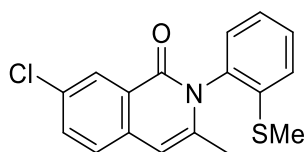
7-chloro-3-((diphenylphosphoryl)methyl)-2-(2-(methylthio)phenyl)isoquinolin-1(2H)-one

H)-one (3gc)



95.1 mg, 61% yield. $R_f = 0.14$ (Hex: EtOAc = 1:1.5). White powder. m.p. 96.1-96.5 °C. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 8.30 (d, $J = 2.1$ Hz, 1H), 7.66-7.61 (m, 2H), 7.59-7.55 (m, 2H), 7.52-7.35 (m, 9H), 7.30 (dd, $J = 7.9, 1.0$ Hz, 1H), 7.15 (td, $J = 7.7, 1.2$ Hz, 1H), 6.86 (d, $J = 2.7$ Hz, 1H), 6.66 (dd, $J = 7.8, 1.4$ Hz, 1H), 3.49 (t, $J = 15.8$ Hz, 1H), 3.14 (dd, $J = 16.0, 11.9$ Hz, 1H), 2.36 (s, 3H). $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) 161.8, 138.0, 135.1, 135.0, 133.9, 133.8, 133.4, 132.8, 132.7, 132.4, 132.4, 131.8, 131.6, 131.4, 131.3, 131.1, 131.0, 130.6, 130.4, 129.9, 129.0, 128.9, 128.9, 128.8, 127.8, 127.7, 126.5, 125.9, 125.6, 107.8 (d, $J = 7$ Hz), 34.0 (d, $J = 66$ Hz), 14.6. HRMS (DART+) m/z ($[\text{M}+\text{H}]^+$) Calcd for $\text{C}_{29}\text{H}_{24}\text{ClNO}_2\text{PS}$: 516.0954; Found: 516.0948.

7-chloro-3-methyl-2-(2-(methylthio)phenyl)isoquinolin-1(2H)-one (3gd)



57.8 mg, 61% yield. $R_f = 0.41$ (Hex: EtOAc = 1.5:1). White powder. m.p. 176.7-176.9 °C. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 8.35 (d, $J = 2.3$ Hz, 1H), 7.57 (dd, $J = 8.5, 2.3$ Hz, 1H), 7.45 (dd, $J = 7.5, 1.1$ Hz, 1H), 7.42 (d, $J = 8.5$ Hz, 1H), 7.36-7.29 (m, 2H), 7.19 (dd, $J = 7.8, 1.4$ Hz, 1H), 6.44 (s, 1H), 2.41 (s, 3H), 1.98 (s, 3H). $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) δ 161.9, 140.1, 137.9, 136.2, 135.8, 133.2, 131.9, 129.7, 129.0, 127.8, 127.0, 126.0, 105.2, 20.9, 14.7. HRMS (DART+) m/z ($[\text{M}+\text{H}]^+$) Calcd for $\text{C}_{17}\text{H}_{15}\text{ClNOS}$: 316.0563; Found: 316.0557.

VII. Computational Methods.¹⁶

Calculations were performed with the Gaussian 09 (G09) program.¹⁷ Geometry optimizations and frequency calculations for all reported structures were performed using B3LYP functional¹⁸ with the 6-31G(d) basis set for C, H, N, O, S and the Lanl2dz effective core potential (ECP) for Pd and Cu.¹⁹ Single point energy calculations were performed using M06L functional²⁰ with the 6-311+G(d,p) basis set for C, H, N, O, S and the SDD ECP for Pd and Cu.²¹ SMD solvent effects were incorporated for all

calculations with dichloromethane (DCM) as the solvent.²² Each reported minimum has zero imaginary frequency and each transition structure (TS) has only one imaginary frequency. Energy changes were shown by the use of Gibbs free energies (T = 298.15 K and P = 1 atm). Optimized structures were illustrated using CYLview20.²³

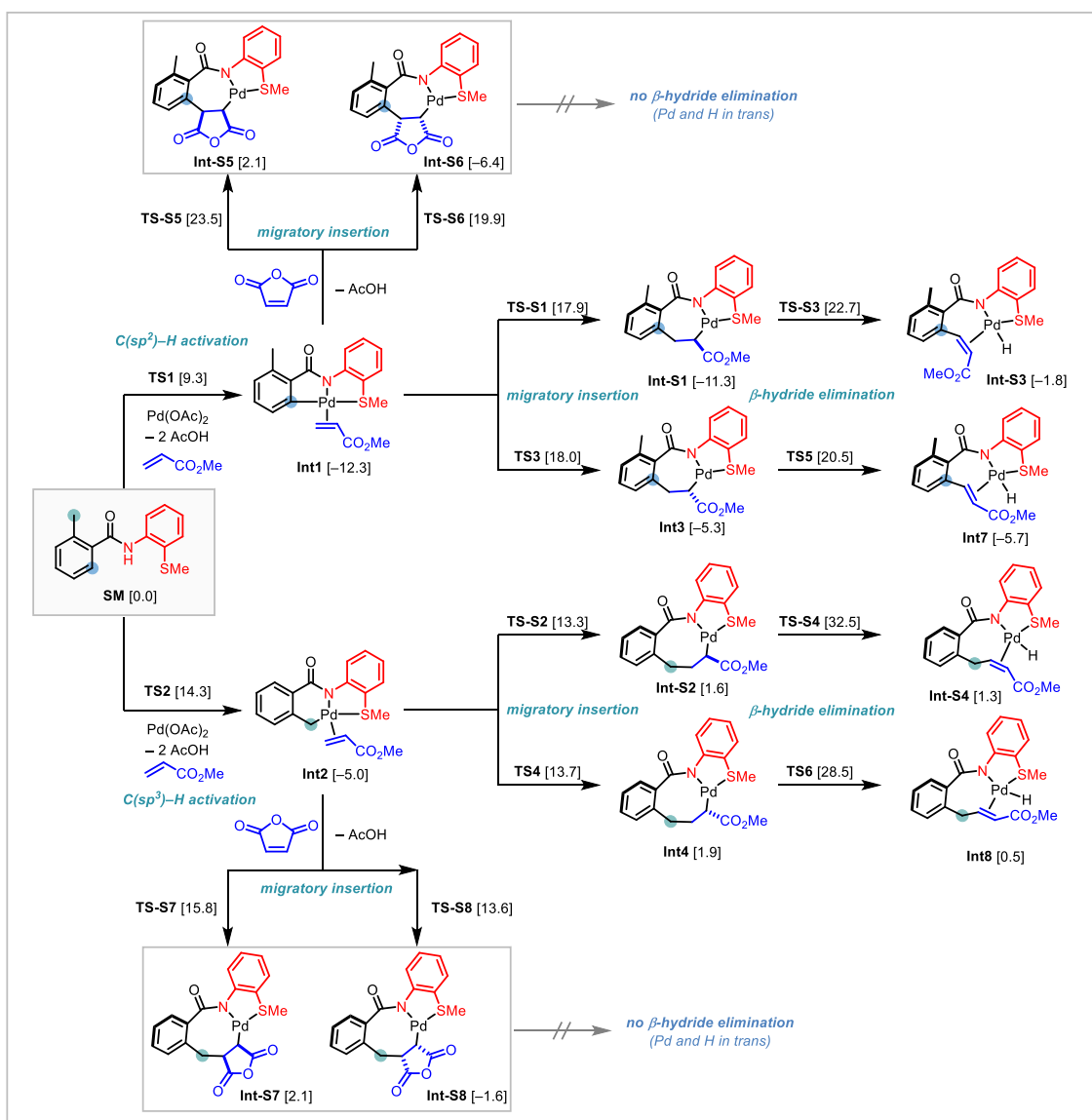


Figure S1. Other possible pathways and their associated energies (DG [kcal mol⁻¹]) for the Pd(II)-catalyzed oxidative C–H alkenylation and cyclization sequence of benzamides with methyl acrylate computed at SMD(DCM)/M06L/SDD(Pd,Cu)-6-311+G(d,p)//SMD(DCM)/B3LYP/Lan12dz(Pd,Cu)-6-31G(d) level of theory.

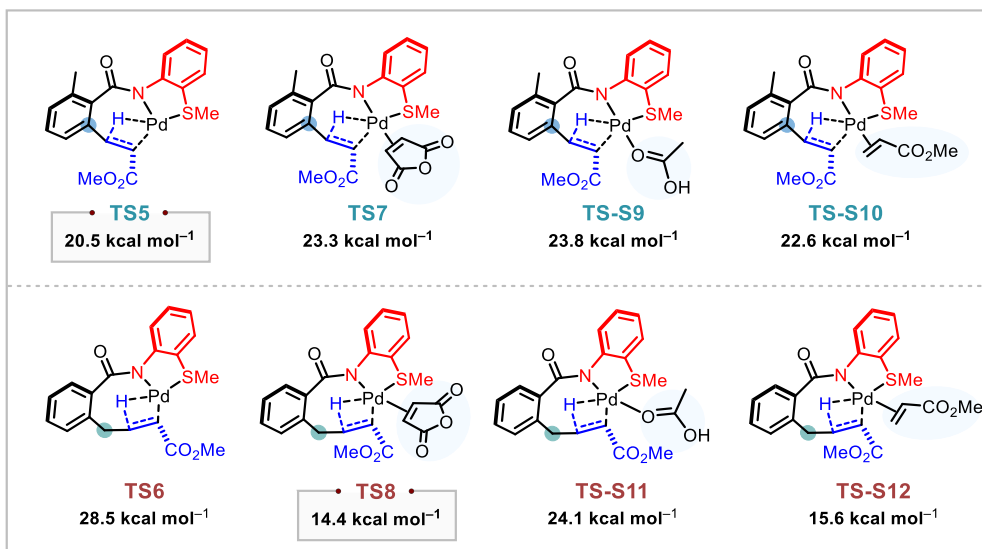


Figure S2. Comparison between β -hydride elimination transition state structures with different ligands (G [kcal mol⁻¹]) computed at SMD(DCM)/M06L/SDD(Pd,Cu)-6-311+G(d,p)//SMD(DCM)/B3LYP/Lan12dz(Pd,Cu)-6-31G(d) level of theory.

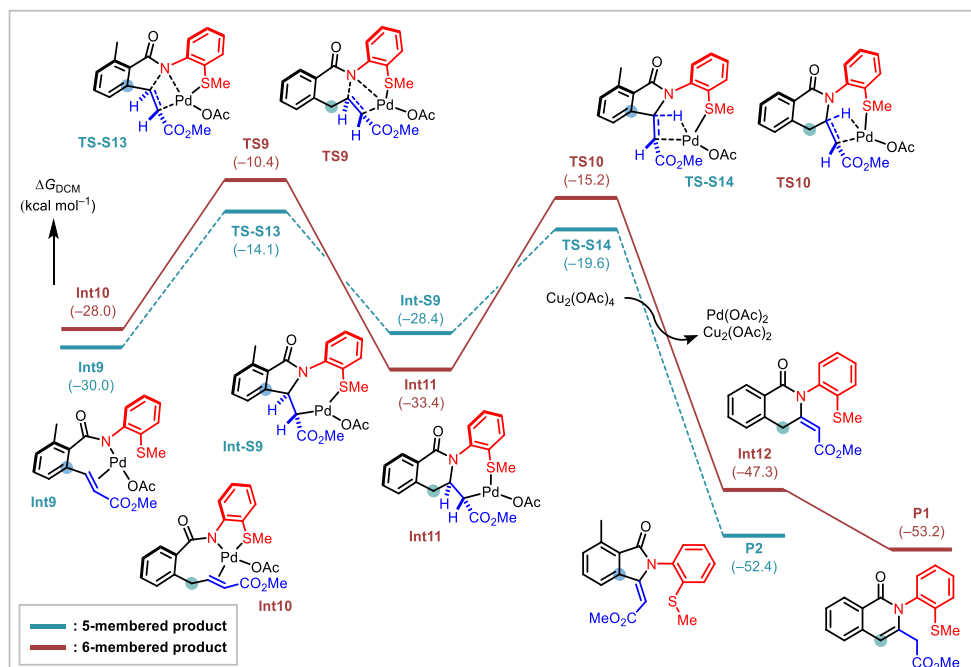
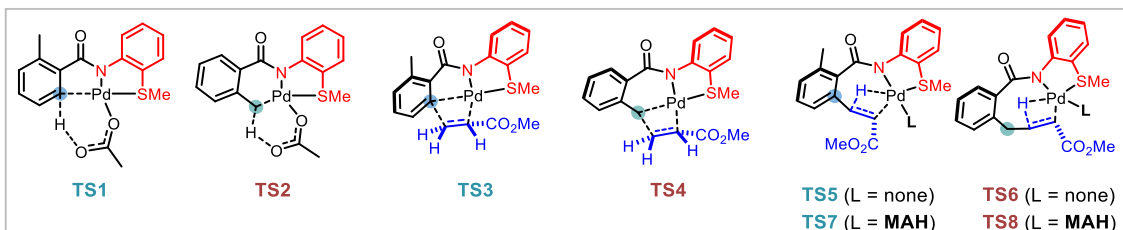


Figure S3. Computed potential energy surface (G [kcal mol⁻¹]) for the Pd(II)-catalyzed oxidative C–H alkenylation and cyclization sequence of benzamides with methyl acrylate from **Int9** and **Int10** computed at SMD(DCM)/M06L/SDD(Pd,Cu)-6-311+G(d,p)//SMD(DCM)/B3LYP/Lan12dz(Pd,Cu)-

6-31G(d) level of theory.

Table S1. Comparison of key transition states optimized with and without Grimme's dispersion correction. Energies (kcal mol^{-1}) of the TS geometries are provided in the insert.



	ΔG^\ddagger (kcal mol^{-1})							
	TS1	TS2	TS3	TS4	TS5	TS6	TS7	TS8
Method 1	9.3	14.3	18.0	13.7	20.5	28.5	23.3	14.4
Method 2	8.1	13.4	17.4	12.4	19.2	25.6	22.3	13.7

Method 1: SMD(DCM)/M06L/SDD-6-311+G(d,p)//SMD(DCM)/B3LYP/Lanl2dz-6-31G(d)
Method 2: SMD(DCM)/M06L/SDD-6-311+G(d,p)//SMD(DCM)/B3LYP-D3/Lanl2dz-6-31G(d)

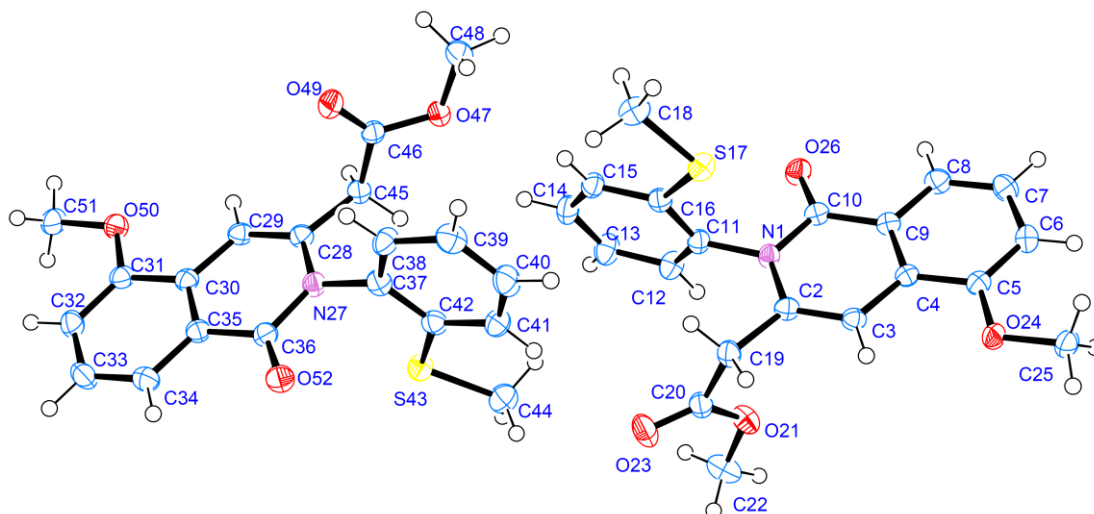
Table S2. Energies (electronic energies (E), enthalpies (H) and Gibbs free energies (G) in Hartrees) and imaginary frequencies (in $i\text{ cm}^{-1}$) of all stationary points computed at SMD(DCM)/B3LYP/Lan12dz(Pd,Cu)-6-31G(d) level of theory are provided. Electronic energies (E^{high} in Hartrees) at SMD(DCM)/M06L/SDD(Pd,Cu)-6-311+G(d,p)//SMD(DCM)/B3LYP/Lan12dz(Pd,Cu)-6-31G(d) level of theory are also provided.

structure	E	H	G	E^{high}	Imag. Freq.
SM	-1108.84324832	-1108.559530	-1108.624282	-1108.93897227	-
Pd(OAc) ₂	-583.75348560	-583.638601	-583.689843	-585.06214361	-
AcOH	-229.08953122	-229.022374	-229.055165	-229.13814452	-
TS1	-1463.47763026	-1463.152563	-1463.228301	-1464.84931352	1390.3
TS2	-1463.46515577	-1463.140229	-1463.216283	-1464.84081169	1434.7
Int1	-1540.89075247	-1540.523153	-1540.604872	-1542.27270139	-
Int2	-1540.87856186	-1540.511259	-1540.593416	-1542.26031346	-
methyl acrylate	-306.47411719	-306.370850	-306.408713	-306.52163940	-
TS3	-1540.84126343	-1540.475511	-1540.554761	-1542.22492488	294.7
TS4	-1540.85354976	-1540.486936	-1540.565741	-1542.23322518	304.4
Int3	-1540.88407494	-1540.516212	-1540.597543	-1542.26224236	-
Int4	-1540.87008468	-1540.501756	-1540.581764	-1542.25242555	-
TS5	-1540.83205485	-1540.469646	-1540.550725	-1542.21591948	711.4
TS6	-1540.81980808	-1540.456507	-1540.537173	-1542.20432888	940.5
maleic anhydride	-379.30106174	-379.239105	-379.274297	-379.37069370	-
Int5	-1920.20328242	-1919.770939	-1919.866105	-1921.66687404	-
Int6	-1920.18864784	-1919.755574	-1919.850283	-1921.65546493	-
TS7	-1920.13486996	-1919.708555	-1919.804663	-1921.60419405	580.3
TS8	-1920.15174632	-1919.724759	-1919.817889	-1921.62200914	642.8
Int7	-1540.87974066	-1540.515109	-1540.596207	-1542.25978414	-
Int8	-1540.86886768	-1540.503418	-1540.583810	-1542.25142639	-
Int9	-1768.78565970	-1768.371701	-1768.464644	-1770.21526796	-
Int10	-1768.78156871	-1768.367351	-1768.460419	-1770.21234964	-
Cu₂(OAc)₄	-1306.37410337	-1306.142435	-1306.222634	-1309.02863384	-
Cu₂(OAc)₂	-849.44702178	-849.328668	-849.383753	-851.95731696	-
TS9	-1768.76146255	-1768.348607	-1768.438085	-1770.18646144	207.4
Int11	-1768.79884146	-1768.383201	-1768.473322	-1770.22531465	-
TS10	-1768.76266109	-1768.352489	-1768.444940	-1770.18840926	605.1
Int12	-1412.92132825	-1412.577296	-1412.653546	-1413.07052208	-
P1	-1412.93099456	-1412.586541	-1412.662228	-1413.08094527	-
TS-S1	-1540.84338957	-1540.477537	-1540.557359	-1542.22464386	284.9
Int-S1	-1540.89499133	-1540.526946	-1540.606756	-1542.27340496	-
TS-S2	-1540.85379179	-1540.487108	-1540.565217	-1542.23449827	308.9
Int-S2	-1540.87011782	-1540.501739	-1540.583014	-1542.25167317	-
TS-S3	-1540.82787680	-1540.465357	-1540.545549	-1542.21327847	706.6
Int-S3	-1540.87201662	-1540.507247	-1540.588705	-1542.25341635	-
TS-S4	-1540.81094662	-1540.447808	-1540.528113	-1542.19830433	1019.9
Int-S4	-1540.86667284	-1540.501064	-1540.581689	-1542.25010330	-
TS-S5	-1613.65686207	-1613.333272	-1613.410941	-1615.06328724	295.8
Int-S5	-1613.70154930	-1613.375124	-1613.452700	-1615.10045431	-
TS-S6	-1613.66278049	-1613.338744	-1613.414750	-1615.07119702	285.4
Int-S6	-1613.70947787	-1613.383084	-1613.460826	-1615.11367990	-
TS-S7	-1613.67486495	-1613.349954	-1613.426427	-1615.07806852	277.4
Int-S7	-1613.69746177	-1613.370500	-1613.447986	-1615.10100116	-
TS-S8	-1613.67818709	-1613.353528	-1613.429786	-1615.08152848	294.6
Int-S8	-1613.70321475	-1613.376278	-1613.453045	-1615.10767411	-
TS-S9	-1769.93246900	-1769.500902	-1769.596683	-1771.36874654	691.7
TS-S10	-1847.310918	-1846.843227	-1846.943853	-1848.754503	630.1
TS-S11	-1769.93175	-1769.499136	-1769.593273	-1771.371067	323.0
TS-S12	-1847.325672	-1846.856884	-1846.952431	-1848.771831	623.3
TS-S13	-1768.765096	-1768.352704	-1768.443703	-1770.190371	206.5
Int-S9	-1768.794649	-1768.380116	-1768.470914	-1770.21546	-
TS-S14	-1768.764904	-1768.355739	-1768.452636	-1770.189979	615.5
P2	-1412.928821	-1412.585203	-1412.662477	-1413.077198	-

Table S3. Energies (electronic energies (E), enthalpies (H) and Gibbs free energies (G) in Hartrees) and imaginary frequencies (in $i\text{ cm}^{-1}$) of all stationary points computed at SMD(DCM)/B3LYP-D3/Lan12dz(Pd,Cu)-6-31G(d) level of theory are provided. Electronic energies (E^{high} in Hartrees) at SMD(DCM)/M06L/SDD(Pd,Cu)-6-311+G(d,p)//SMD(DCM)/B3LYP-D3/Lan12dz(Pd,Cu)-6-31G(d) level of theory are also provided.

structure	E	H	G	E^{high}	Imag. Freq.
SM	-1108.87434228	-1108.590148	-1108.652558	-1108.93969670	-
Pd(OAc) ₂	-583.76102560	-583.646176	-583.697494	-585.06214272	-
AcOH	-229.09253279	-229.025378	-229.058020	-229.13814599	-
methyl acrylate	-306.48058572	-306.377313	-306.415051	-306.52162843	-
maleic anhydride	-379.30509283	-379.243182	-379.278387	-379.37069370	-
TS1	-1463.52433580	-1463.199242	-1463.275089	-1464.84930063	1403.3 <i>i</i>
TS2	-1463.51225556	-1463.187171	-1463.262840	-1464.84098632	1380.9 <i>i</i>
TS3	-1540.89731392	-1540.531252	-1540.609550	-1542.22532220	300.7 <i>i</i>
TS4	-1540.90815030	-1540.541348	-1540.620293	-1542.23349902	304.3 <i>i</i>
TS5	-1540.88425116	-1540.521690	-1540.602702	-1542.21638116	700.1 <i>i</i>
TS6	-1540.87723796	-1540.513686	-1540.593764	-1542.20795095	1027.6 <i>i</i>
TS7	-1920.21378959	-1919.787351	-1919.881411	-1921.60624339	577.4 <i>i</i>
TS8	-1920.23263887	-1919.805378	-1919.896498	-1921.62360417	688.2 <i>i</i>

VIII. X-ray Crystallographic Data of **3pa**.



(Plots are drawn at 50% probability level.)

CCDC-2112430 contains the supplementary crystallographic data of **3pa**. The crystals of **3pa** were obtained by dissolving **3pa** in chloroform (with 5 drops hexane) followed by slow evaporation of chloroform. X-Ray crystallographic structure analysis of complex **3pa** was performed on a Rigaku XtaLAB Synergy-S diffractometer and HyPix-6000 detector (Cu-K α radiation). The data were collected at a temperature of $-150 \pm 1\text{ }^\circ\text{C}$ to a maximum 2θ value of 136.1° . A total of 26810 oscillation images were collected. The structure was solved by direct method (OLEX2) and expanded using

Fourier techniques. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined isotropically. ORTEP-3 programs were used to draw the molecules. The crystal data are mentioned below:

Crystal Data:

Empirical formula	C ₂₀ H ₁₉ NO ₄ S		
Formula weight	369.42		
Crystal system	monoclinic		
Space group	P2 ₁ /c (No. 14)		
Unit cell parameter	a = 14.4266(2) Å	α = 90.0°	
b = 7.40710(10) Å	β = 96.6820(10)°		
c = 33.2757(6) Å	γ = 90.0°		
Cell volume	V = 3531.66(9) Å ³		
Z	8		
Final R indexes [I>2σ (I)]	R1 = 0.0400, wR2 = 0.1065		
Final R indexes [all data]	R1 = 0.0434, wR2 = 0.1092		
Goodness of fit	1.052		

3.5 References

- (1) For recent reviews on C-H functionalization with alkenes, see: (a) Crisenza, G. E. M.; Bower, J. F. *Chem. Lett.* **2016**, *45*, 2-9. (b) Dong, Z.; Ren, Z.; Thompson, S. J.; Xu, Y.; Dong, G. *Chem. Rev.* **2017**, *117*, 9333-9403. (c) Chatani, N. *Bull. Chem. Soc. Jpn.* **2018**, *91*, 211-222. (d) Ano, Y.; Chatani, N. *Org. React.* **2019**, *100*, 622-670. (e) Evano, G.; Theunissen, C. *Angew. Chem. Int. Ed.* **2019**, *58*, 7202-7236. (f) Ali, W.; Prakash, G.; Maiti, D. *Chem. Sci.* **2021**, *12*, 2735-2759. (g) Aldhous, T. P. Chung, R. W. M.; Dalling, A. G.; Bower, J. F. *Synthesis* **2021**, *53*, 2961-2975.
- (2) For selected recent reviews and papers, see: Xu, J.-W.; Zhang, Z.-Z.; Rao, W.-H.; Shi, B.-F. *J. Am. Chem. Soc.* **2016**, *138*, 10750-10753. (b) Liu, Z.; Ni, H.-Q.; Zeng, T.; Engle, K. M. *J. Am. Chem. Soc.* **2018**, *140*, 3223-3227. (c) Chen, Y.-Q.; Wang, Z.; Wu, Y.; Wisniewski, S. R.; Qiao, J. X.; Ewing, W. R.; Eastgate, M. D.; Yu, J.-Q. *J. Am. Chem. Soc.* **2018**, *140*, 17884-17894. (d) Zhan, B.-B.; Li, Y.; Xu, J.-W.; Nie, X.-L.; Fan, J.; Jin, L.; Shi, B.-F. *Angew. Chem. Int. Ed.* **2018**, *57*, 5858-5862. (e) Mingo, M. M.; Rodríguez, N.; Arrayás, R. G.; Carretero, J. C. *Org. Chem. Front.* **2021**, *8*, 4914-4946.
- (3) Zhang, F.-L.; Hong, K.; Li, T.-J.; Park, H.; Yu, J.-Q. *Science* **2016**, *351*, 252-256.
- (4) (a) Ma, F.; Lei, M.; Hu, L. *Org. Lett.* **2016**, *18*, 2708-2711. (b) Park, H.; Yoo, K.; Jung, B.; Kim, M. *Tetrahedron* **2018**, *74*, 2048-2055. (c) Tang, M.; Yu, Q.; Wang, Z.; Zhang, C.; Sun, B.;

- Yi, Y.; Zang, F.-L. *Org. Lett.* **2018**, *20*, 7620-7623. (d) Wang, Z.; Dong, W.; Sun, B.; Yu, Q.; Zhang, F.-L. *Tetrahedron* **2019**, *75*, 4031-4041. (e) Wen, F.; Li, Z. *Adv. Synth. Catal.* **2020**, *362*, 133-138. (f) Wei, F.; Li, Z. *Synth. Commun.* **2020**, *50*, 3462-3474. (g) Ding, M.; Hua, W.; Liu, M.; Zhang, F. *Org. Lett.* **2020**, *22*, 7419-7423. (h) Lei, L.; Wu, P.; Liu, Z.; Lou, J. *Tetrahedron Lett.* **2021**, *67*, 152865.
- (5) Park, H.; Verma, P.; Hong, K.; Yu, J.-Q. *Nat. Chem.* **2018**, *10*, 755-762.
- (6) Chen, J.; Cai, C.; Tong, X.; Liu, D.; Sao, Y.-S. *RSC Adv.* **2020**, *10*, 12192-12196.
- (7) Qian, S.; Li, Z.-Q.; Li, M.; Wisniewski, S. R.; Qiao, J. X.; Richter, J. M.; Ewing, W. R.; Eastgate, M. D.; Chen, J. S.; Yu, J.-Q. *Org. Lett.* **2020**, *22*, 3960-3963.
- (8) Park, H. S.; Fan, Z.; Zhu, R.-Y.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2020**, *59*, 12853-12859.
- (9) He, Q.; Ano, Y.; Chatani, N. *Chem. Commun.* **2019**, *55*, 9983-9986.
- (10) He, Q.; Chatani, N. *Angew. Chem. Int. Ed.* **2021**, *60*, 5189-5192.
- (11) Manoharan, R.; Jegamohan, M. *Asian J. Org. Chem.* **2019**, *8*, 1949-1969.
- (12) Li, L.; Zhang, X.-G.; Zhang, X.-H. *Synthesis* **2019**, *51*, 3077-3084.
- (13) (a) Kurosawa, H.; Emoto, M.; Ohnishi, H.; Miki, K.; Kasai, N.; Tatsumi, K.; Nakamura, A. *J. Am. Chem. Soc.* **1987**, *109*, 6333-6340. (b) Derosa, J.; Kleinmans, R.; Tran, V. T.; Karunananda, M. K.; Wisniewski, S. R.; Eastgate, M. D.; Engle, K. M. *J. Am. Chem. Soc.* **2018**, *140*, 17878-17883.
- (14) For recent reviews and papers on the synthesis of alkenylated annulation product by using alkynes and allenes as coupling partners, see: (a) Ackermann, L. *Acc. Chem. Res.* **2014**, *47*, 281-295. (b) Li, T.; Zhang, C.; Tan, Y.; Pan, W.; Rao, Y. *Org. Chem. Front.* **2017**, *4*, 204-209. (c) Hua, R. *Catalysts* **2021**, *11*, 620.
- (15) Yin-Bandur, L.; Miguel, P. J. S.; Rodríguez-Santiago, L.; Sodupe, M.; Berghaus, M.; Lippert, B. *Chem. - Eur. J.* **2011**, *17*, 13653.
- (16) (a) Garcia-Cuadrado, D.; de Mendoza, P.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2007**, *129*, 6880-6886. (b) Gorelsky, S. I.; Lapointe, D.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 10848-10849. (c) Lapointe, D.; Fagnou, K. *Chem. Lett.* **2010**, *39*, 1118-1126. (d) Davies, D.; Macgregor, S. A.; McMullin, C. L. *Chem. Rev.* **2017**, *117*, 8649-8709.
- (17) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Keith, T.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.;

Millam, N. J.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö .; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. Gaussian 09, Revision D.01; Gaussian, Inc.: Wallingford, CT, 2013.

(18) (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648–5652. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785–789.

(19) (a) Hay, P. J.; Wadt, W. R. *J. Chem. Phys.* **1985**, *82*, 270–283. (b) Wadt, W. R.; Hay, P. J. *J. Chem. Phys.* **1985**, *82*, 284–298. (c) Hay, P. J.; Wadt, W. R. *J. Chem. Phys.* **1985**, *82*, 299–310.

(20) Zhao, Y.; Truhlar, D. G. *J. Chem. Phys.* **2006**, *125*, 194101.

(21) (a) Andrae, D.; Haussermann, U.; Dolg, M.; Stoll, H.; Preuss, H. *Theor. Chim. Acta* **1990**, *77*, 123–141. (b) Igelmann, G.; Stoll, H.; Preuss, H. *Mol. Phys.* **1988**, *65*, 1321–1328. (c) Vonszentpaly, L.; Fuentealba, P.; Preuss, H.; Stoll, H. *Chem. Phys. Lett.* **1982**, *93*, 555–559.

(22) Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. *J. Phys. Chem. B* **2009**, *113*, 6378–6396.

(23) CYLview20; Legault, C. Y., Université de Sherbrooke: Sherbrooke, 2020 (<http://www.cylview.org>).

Chapter 4

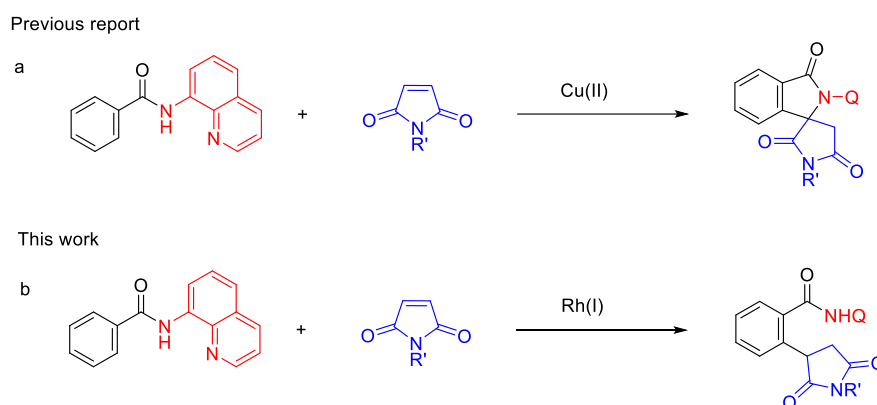
Rhodium-Catalyzed *ortho* C-H Alkylation of Aromatic Amides with Maleimides

4.1 Introduction

Catalytic C-H functionalization has proven to be a powerful tool for producing C-C and C-heteroatom bonds.¹ A wide variety of functionalization reactions of C-H bonds, including arylation, alkenylation, alkynylation, alkylation, carbonylation, silylation, borylation, hydroxylation, amination, and halogenation have been reported to date. Among them, C-H alkylation (hydroarylation) with alkenes is the most straightforward and atom- and step-economical route known for preparing alkyl-substituted aromatic compounds, because all of the atoms of the substrates and alkenes are incorporated into the desired products.²

Hirano and Miura recently reported that the Cu(II)-mediate reaction of aromatic amides that contain an 8-aminoquinoline directing group with maleimides resulted in oxidative cyclization to give spirocyclic products (Scheme 1a).³

Scheme 1. C-H Functionalization with Maleimides

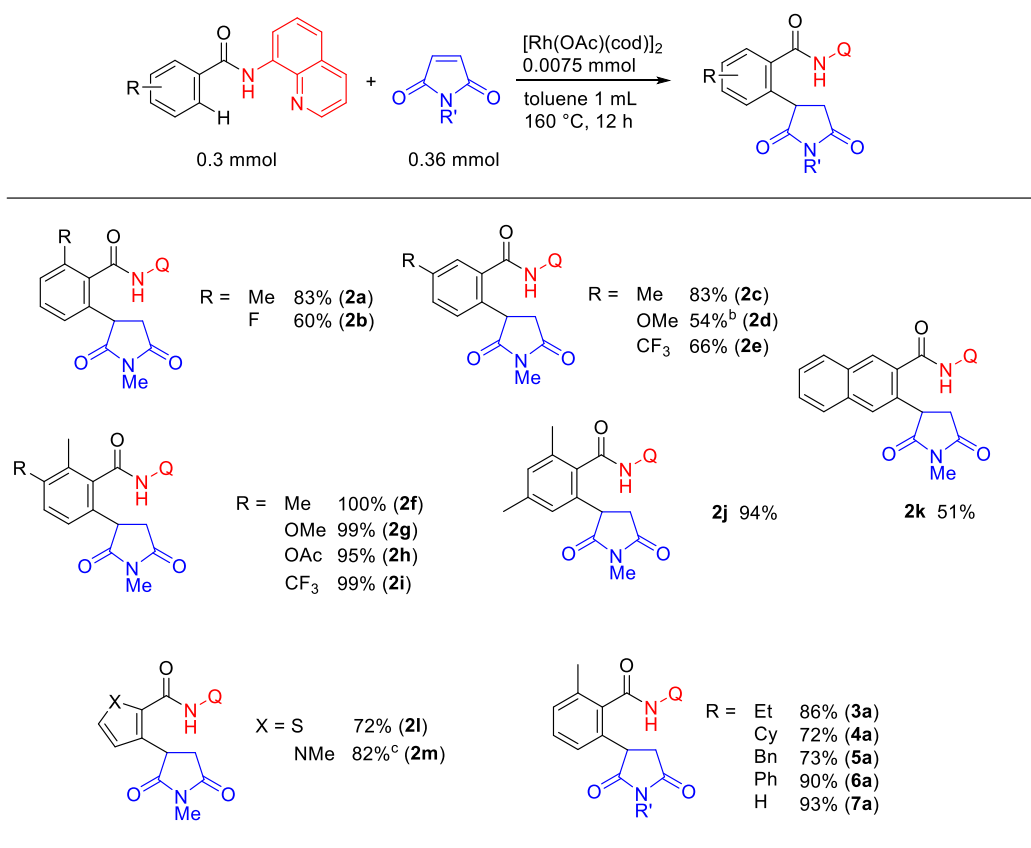


We previously reported on a series of Rh(I)-catalyzed reactions of aromatic amides that contain an 8-aminoquinoline directing group with various alkenes.⁴ In this chapter, maleimide was used as coupling partner in the similar case to achieve an *ortho* C-H alkylation of aromatic amides (Scheme 1b). The reaction of amide **1a** (0.3 mmol) with *N*-methylmaleimide (0.36 mmol) in the presence of [Rh(OAc)(cod)]₂ (0.0075 mmol) as the catalyst in toluene (1 mL) at 160 °C for 12 h produced the alkylation product **2a** in 97% NMR yield (Scheme 2). The addition of a carboxylic acid had only a marginal effect on the efficiency of the reaction (2-MeC₆H₄COOH: 97% NMR yield). Scheme 2 shows the substrate scope of this reaction. In the case of meta-substituted aromatic amides containing methyl, methoxy, and trifluoromethyl substituents, the less hindered

C-H bonds reacted selectively, irrespective of the electronic nature of the substituents, as in **2c**, **2d**, and **2e**. Heteroaromatic amides, such as thiophenes and pyrroles also participated in the reaction. Additionally, *N*-substituent maleimides were investigated. Methyl, ethyl, cyclohexyl, benzyl, and phenyl groups all gave the corresponding products in high yields. Even, when a simple maleimide was used, the corresponding alkylation product **7a** was produced in high yield.

4.2 Results and discussion

Scheme 2. Substrate Scope^a

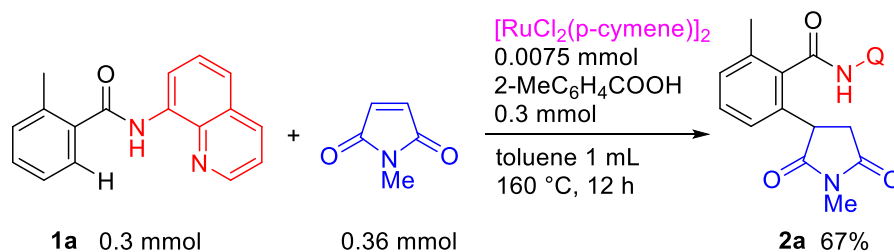


^aIsolated yield by column chromatography. ^bIsolated by GPC. ^c $[\text{Rh}(\text{OAc})(\text{cod})]_2$ (0.015 mmol) was used as the catalyst for 24 h.

After screening a series of catalysts, we found that a Ru(II) catalyst also showed a high catalytic activity. Prabhu previously reported on the Ru(II)-catalyzed reaction of aromatic amides with maleimides.⁵ In their case, no specific directing groups were needed, but 20 mol% of AgBF₄, 1.5 equivalents of Cu(OAc)₂ and an excess amount (10 equivalents) of acetic acid were required, although the role of Cu(OAc)₂ was not discussed. In our Ru(II) catalyst/8-aminoquinoline chelation system, the presence of one

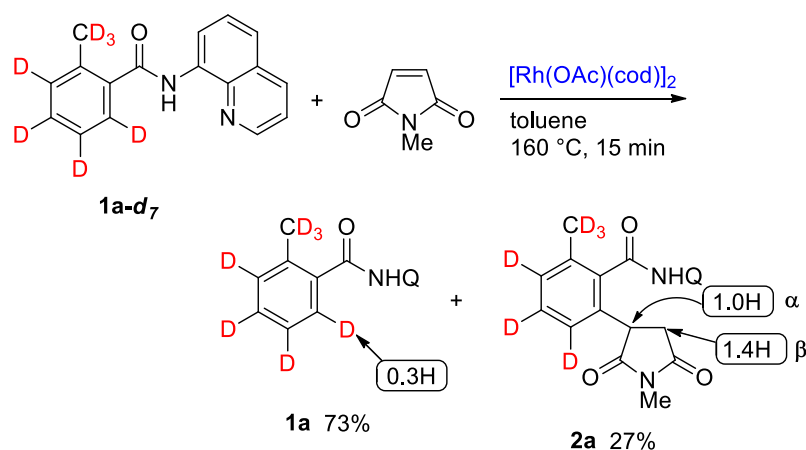
equivalent of carboxylic acid in the reaction solution was essential for the reaction to proceed, but both AgBF_4 and $\text{Cu}(\text{OAc})_2$ were not required (Scheme 3).⁶

Scheme 3. Ru(II)-Catalyzed C-H Alkylation of Aromatic Amides with Maleimides

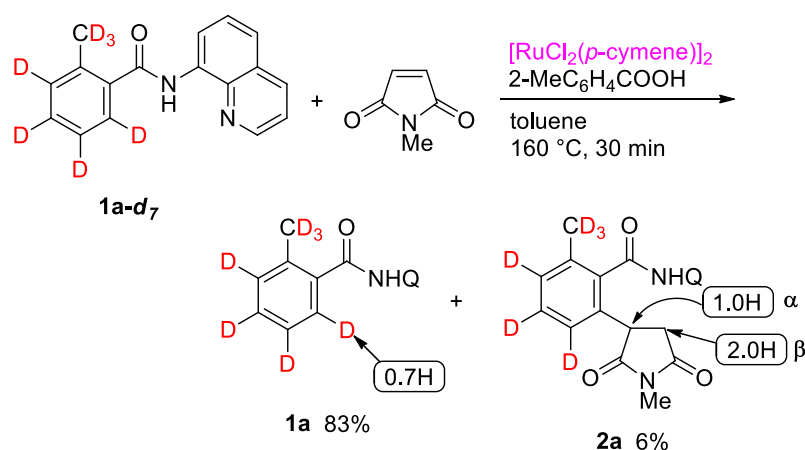


Scheme 4. Deuterium-Labeling Experiments: Rh(I) vs Ru(II)

a. Rh(I) system



b. Ru(II) system



To understand the difference in the reaction mechanism between the two catalytic systems, deuterium-labeling experiments using **1a-d₇** were carried out (Scheme 4). In

the Rh(I)-catalyzed reaction, H/D exchange took place at the ortho-position of **1a-d₇**, even within a short reaction time (15 min), indicating that C-H bond cleavage is reversible. In the product **2a**, no-deuterium atom was incorporated into the α -position of **2a**, which is different from the reaction with styrene, α,β -unsaturated lactones, and norbornene,⁹ However, 0.6D was observed at the β -position (Scheme 4a). In the case of the Ru(II) system, a significant amount of H/D exchange also took place at the ortho-position of the recovered **1a-d₇** (0.7H), because the Ru(II) system requires the addition of carboxylic acid as an additive (Scheme 4b). No-deuterium atom was incorporated into either the α and β position of the product **2a**, suggesting that a different mechanism is operating in the two systems. As proposed by Prabhu,^{5c} the mechanism responsible for the Ru(II)-catalyzed system involves the insertion of maleimide into the C-Ru bond in a ruthenacycle (carboruthenation) followed by protonation of the resulting a C-Ru bond by a carboxylic acid. This mechanism explains the deuterium-labeling results in which no deuterium atom was incorporated into the product **2a** (Scheme 4b). In contrast, the mechanism responsible for the Rh(I)-catalyzed reaction, more complicated paths appear to be involved.

4.3 Conclusion

This chapter described a rhodium-catalyzed alkylation of C(sp²)-H bonds in aromatic amides with maleimides by using an 8-aminoquinoline bidentate chelation system. In the case of the Cu(II) catalyst in an 8-aminoquinoline bidentate chelation system reported by Hirano and Miura,³ oxidative cyclization took place to give spirocyclic products. In addition, the use of a Ru(II) catalyst gave the same products as the Rh(I) system, but the mechanism was clearly different. The reaction is highly regioselective at the less hindered ortho C-H bonds in the case of meta-substituted aromatic amides.

4.4 Experimental section

I. General Information.

¹H NMR and ¹³C NMR spectra were recorded on a JEOL ECS-400 spectrometer in CDCl₃ with tetramethylsilane as the internal standard. Data are reported as follows: chemical shift in ppm (δ), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, brs = broad singlet, and m = multiplet), coupling constant (Hz), and integration. In some cases, some peaks in the ¹³C NMR spectra cannot be analyzed because of overlapping peaks. Infrared spectra (IR) were obtained using a JASCO FT/IR-4200 spectrometer; absorptions are reported in reciprocal centimeters with the following relative intensities: s (strong), m (medium), or w (weak). Mass spectra and high resolution mass spectra

(HRMS) were obtained using a JEOL JMS-700 spectrometer. Melting points were determined using a Yamato melting point apparatus. Column chromatography was performed with SiO₂ (Silicycle SiliaFlash F60 (230-400 mesh)). Some compounds were purified by LC-908 HPLC (GPC).

II. Materials.

Toluene (Kanto Chemical) was purified by passage through activated alumina using a GlassContour Solvent Dispensing System. 8-Aminoquinoline (CAS 578-66-5), Maleimide (CAS 541-59-3), *N*-Methylmaleimide (CAS 930-88-1), *N*-Ethylmaleimide (CAS 128-53-0), *N*-Cyclohexylmaleimide (CAS: 1631-25-0), *N*-Phenylmaleimide (CAS: 941-69-5), *N*-Benzylmaleimide (CAS: 1631-26-1), 2- Methylbenzoic acid (CAS: 118-90-1) were purchased from Tokyo Chemical Industry Co., Ltd. Ru(*p*-cymene)Cl₂ (CAS: 52462-29-0) was purchased from Sigma-Aldrich Co. [Rh(OAc)(cod)]₂ was prepared according to literature procedures.⁷

III. Synthesis of Starting Materials

General Procedure for the Preparation of Stating Amides.

(1) Synthesis of amides from acid chlorides.

The acid chloride (15 mmol) was dissolved in CH₂Cl₂ (20 mL). After cooling the reaction mixture to 0 °C, a solution of 8-aminoquinoline (15 mmol) and triethylamine (36 mmol) in 10 mL of CH₂Cl₂ was added dropwise. The resulting mixture was allowed to warm to rt and was then stirred overnight. The crude mixture was then washed with saturated aqueous NaHCO₃ (20 mL), and CH₂Cl₂ (3x20 mL). The combined organic layers were washed with 1 M HCl aq. (20 mL). The organic phase was dried over anhydrous Na₂SO₄ and the solution taken to dryness. The resulting crude amide was purified by flash chromatography on silica gel (eluent: hexanes/EtOAc = 5/1).

(2) Synthesis of amides from carboxylic acid.

To a stirred solution of carboxylic acid (15 mmol) and DMF (5 drops) in CH₂Cl₂ (10 mL), (COCl)₂ (1.5 mL, 18 mmol) was added dropwise. The solution was magnetically stirred at room temperature for 2 h. The solvent was then eliminated under reduced pressure, and the resulting residue was dissolved in CH₂Cl₂ (15 mL). After cooling the reaction mixture to 0 °C, a solution of 8-Aminoquinoline (15 mmol) and triethylamine (36 mmol) in 10 mL of the same solvent were added dropwise. The resulting mixture was allowed to warm to rt and stirred overnight. The crude product was washed with saturated aqueous NaHCO₃ (20 mL), and CH₂Cl₂ (3x20 mL). The organic phase was

washed with 1 M HCl aq. (20 mL). The organic phase was dried over anhydrous Na₂SO₄ and the solvent removed by evaporation of the solvent. The resulting crude amide was purified by flash chromatography on silica gel (eluent: hexanes/EtOAc = 5/1).

IV. Synthesis of Alkylation Products.

(1) General procedure for the Rh(I)-catalyzed alkylation of aromatic amides with *N*-methylmaleimide.

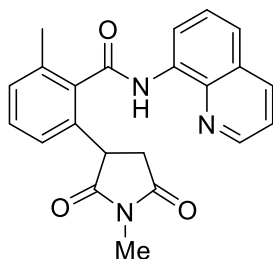
To an oven-dried 5 mL screw-capped vial, 2-methyl-*N*-(quinolin-8-yl)benzamide (78.7mg, 0.3mmol), *N*-methylmaleimide (39.6mg, 0.36mmol), [Rh(OAc)(cod)]₂ (4.1 mg, 0.0075mmol) and toluene (1 mL) were added. The mixture was stirred for 12 hours at 160°C and then cooled to room temperature. The resulting mixture was filtered through a celite pad and then concentrated in vacuo. The residue was purified by column chromatography on silica gel (eluent: hexane/EtOAc= 1.5:1) and further purified through GPC to afford the alkylation product (108.6mg, 97%) as a white powder.

(2) General procedure for the Ru(II)-catalyzed alkylation of aromatic amides with *N*-methylmaleimide.

To an oven-dried 5 mL screw-capped vial, 2-methyl-*N*-(quinolin-8-yl)benzamide (78.7mg, 0.3mmol), *N*-methylmaleimide (39.6mg, 0.36mmol), 2-Methylbenzoic acid (40.9mg, 0.3mmol), [RuCl₂(*p*-cymene)]₂ (4.6 mg, 0.0075mmol) and toluene (1 mL) were added. The mixture was stirred for 12 hours at 160°C and then cooled to room temperature. The resulting mixture was filtered through a celite pad and washed with saturated aqueous NaHCO₃ (20 mL), and EtOAc (3x20 mL); then concentrated in vacuo. The residue was purified by column chromatography on silica gel (eluent: hexane/EtOAc= 1.5:1) and further purified through GPC to afford the alkylation product (75.1mg, 67%) as a white powder.

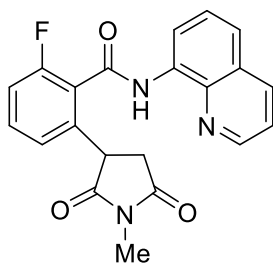
V. Spectroscopic Data.

2-methyl-6-(1-methyl-2,5-dioxopyrrolidin-3-yl)-*N*-(quinolin-8-yl)benzamide (2a)



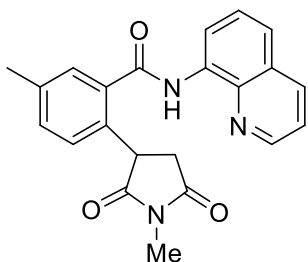
93.0mg, 83% yield (Rh(I)catalyzed); 75.1mg, 67%yield (Ru(II)catalyzed). R_f 0.23 (hexane/EtOAc = 1.5:1). White powder. m.p. 103.4-103.9°C. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) 2.48 (s, 3H), 2.88-2.94 (m, 4H), 3.24 (dd, $J = 18.3, 9.6$ Hz, 1H), 4.28 (dd, $J = 9.6, 5.5$ Hz, 1H), 7.02 (d, $J = 7.8$ Hz, 1H), 7.25 (d, $J = 6.4$ Hz, 1H), 7.36 (t, $J = 7.8$ Hz, 1H), 7.44-7.48 (m, 1H), 7.57-7.59 (m, 2H), 8.18 (dd, $J = 8.2, 1.4$ Hz, 1H), 8.80 (dd, $J = 4.1, 1.4$ Hz, 1H), 8.91 (dd, $J = 5.5, 3.7$ Hz, 1H), 10.19 (s, 1H); $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) 19.97, 25.24, 38.28, 44.41, 116.93, 121.94, 122.55, 125.00, 127.33, 128.11, 130.14, 130.29, 134.13, 134.87, 135.66, 136.41, 138.10, 138.62, 148.71, 167.82, 176.32 177.97 IR (neat) 3337 w 2951 w 1776 w 1699 s 1669 m, 1596 w, 1520 s, 1483 m, 1425 m, 1383 m, 1325 w, 1281 m, 1120 w, 758 m; MS m/z (relative intensity, %) 373 (23), 231 (12), 230 (82), 229 (100), 160 (20), 145 (52), 144 (81), 117 (12), 115 (11); HRMS Calcd for $\text{C}_{22}\text{H}_{19}\text{N}_3\text{O}_3$: 373.1426; Found: 373.1423.

2-fluoro-6-(1-methyl-2, 5-dioxopyrrolidin-3-yl)-*N*-(quinolin-8-yl)benzamide (2b)



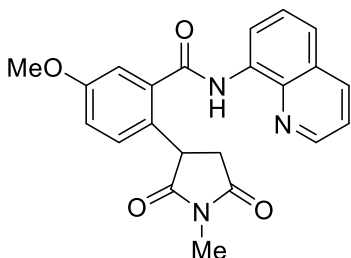
67.2mg, 60% yield. R_f 0.34 (hexane/EtOAc = 1:1). White powder. m.p. 75.8-76.1°C. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) 2.98 (m, 4H), 3.29 (dd, $J = 18.3, 9.6$ Hz, 1H), 4.43 (dd, $J = 9.6, 5.5$ Hz, 1H), 7.07 (d, $J = 7.8$ Hz, 1H), 7.22 (dd, $J = 9.6, 8.7$ Hz, 1H), 7.47 (m, 2H), 7.57 (m, 2H), 8.18 (dd, $J = 8.5, 1.6$ Hz, 1H), 8.82 (m, 2H), 10.51 (s, 1H); $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) 25.29, 38.22, 44.91, 116.03 (d, $J = 22.9$ Hz), 116.85, 121.96, 122.62, 124.62 (d, $J = 17.2$ Hz), 125.41, 127.35, 128.10, 132.18 (d, $J = 9.5$ Hz), 134.26, 136.42, 138.40, 138.86, 148.47, 158.65 (d, $J = 247.9$ Hz), 162.60, 176.19, 177.69; IR (neat) 3340 w, 3016 w, 2945 w, 1176 w, 1698 s, 1667 m, 1612 w, 1576 w, 1524 s, 1485 m, 1427 m, 1384 m, 1327 m, 1281 m, 1120 m, 827 w, 791 m, 752 s, 692 m; MS m/z (relative intensity, %) 377 (20), 234 (24), 233 (14), 149 (21), 145 (17), 144 (100); HRMS Calcd for $\text{C}_{21}\text{H}_{16}\text{FN}_3\text{O}_3$: 377.1176; Found: 377.1174.

5-methyl-2-(1-methyl-2, 5-dioxopyrrolidin-3-yl)-*N*-(quinolin-8-yl)benzamide (2c)



92.8mg, 83% yield. R_f 0.25 (hexane/EtOAc = 1.5:1). Yellow powder. m.p. 116.6-116.8°C. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) 2.46 (s, 3H), 2.94 (dd, $J = 18.1, 5.7$ Hz, 1H), 3.04 (s, 3H), 3.29 (dd, $J = 18.1, 9.4$ Hz, 1H), 4.48 (dd, $J = 9.6, 6.0$ Hz, 1H), 7.16 (d, $J = 8.2$ Hz, 1H), 7.33 (d, $J = 7.8$ Hz, 1H), 7.47 (dd, $J = 8.2, 4.1$ Hz, 1H), 7.56 (m, 2H), 7.62 (s, 1H), 8.18 (dd, $J = 8.2, 1.4$ Hz, 1H), 8.81 (m, 2H), 10.43 (s, 1H); ^{13}C NMR (CDCl_3 , 100 MHz) 21.27, 25.19, 38.49, 44.78, 116.58, 121.88, 122.21, 127.42, 128.10, 128.51, 130.23, 132.20, 133.78, 134.62, 135.83, 136.48, 138.45, 138.73, 148.52, 167.55, 176.75, 178.62. IR (neat) 3343 w, 3015 w, 2950 w, 1176 w, 1698 s, 1667 m, 1597 w, 1573 w, 1522 s, 1482 m, 1425 m, 1383 m, 1326 m, 1281 m, 1119 m, 1041 w, 953 m, 827 m, 792 m, 751 s, 693 m; MS m/z (relative intensity, %) 373 (14), 230 (50), 229 (100), 188 (20), 160 (25), 145 (29), 144 (65), 130 (10), 117 (10), 115 (10); HRMS Calcd for $\text{C}_{22}\text{H}_{19}\text{N}_3\text{O}_3$: 373.1426; Found: 373.1427.

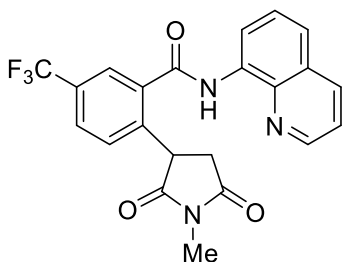
5-methoxy-2-(1-methyl-2,5-dioxopyrrolidin-3-yl)-N-(quinolin-8-yl)benzamide (2d)



63.0mg, 54% yield. R_f 0.18 (hexane/EtOAc = 2:1). Pale yellow powder. m.p. 81.2-81.6°C. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) 2.93 (dd, $J = 18.3, 6.0$ Hz, 1H), 3.04 (s, 3H), 3.28 (dd, $J = 18.3, 9.6$ Hz, 1H), 3.89 (s, 3H), 4.44 (dd, $J = 9.4, 5.7$ Hz, 1H), 7.05 (dd, $J = 8.5, 2.5$ Hz, 1H), 7.20 (d, $J = 8.2$ Hz, 1H), 7.34 (d, $J = 2.7$ Hz, 1H), 7.47 (dd, $J = 8.2, 4.1$ Hz, 1H), 7.57 (d, $J = 4.6$ Hz, 2H), 8.19 (dd, $J = 8.2, 1.4$ Hz, 1H), 8.79 (m, 2H), 10.44 (s, 1H); ^{13}C NMR (CDCl_3 , 100 MHz) 25.20, 38.53, 44.47, 55.78, 114.05, 116.33, 116.61, 121.93, 122.32, 127.40, 128.10, 128.52, 131.56, 134.52, 136.48, 137.02, 138.72, 148.56, 159.25, 167.14, 176.76, 178.75; IR (neat) 3341 w, 3012 w, 2947 w, 2360 m, 2340 w, 1776 w, 1697 s, 1670 m, 1606 w, 1576 w, 1525 s, 1482 m, 1425 m, 1383 m, 1326 m, 1281 m, 1223 m, 1119 m, 1041 w, 955 w, 826 m, 792 m, 751 s, 694 m;

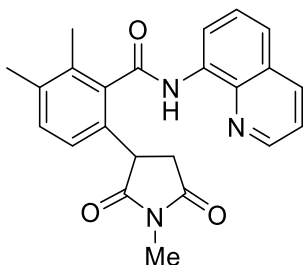
MS m/z (relative intensity, %) 389 (13), 246 (22), 245 (100), 204 (29), 176 (10), 144 (17); HRMS Calcd for $C_{22}H_{19}N_3O_4$: 389.1376; Found: 389.1378.

2-(1-methyl-2, 5-dioxopyrrolidin-3-yl)-N-(quinolin-8-yl)-5-(trifluoromethyl)benzamide (2e)



84.5mg, 66% yield. R_f 0.20 (hexane/EtOAc = 1.5:1). White powder. m.p. 84.9-85.4°C. 1H -NMR ($CDCl_3$, 400 MHz) 2.97 (dd, $J = 17.9, 6.0$ Hz, 1H), 3.03 (s, 3H), 3.33 (dd, $J = 18.3, 9.6$ Hz, 1H), 4.56 (dd, $J = 9.6, 6.0$ Hz, 1H), 7.44 (d, $J = 7.8$ Hz, 1H), 7.49 (q, $J = 4.3$ Hz, 1H), 7.58 (m, 2H), 7.79 (dd, $J = 8.2, 1.4$ Hz, 1H), 8.05 (d, $J = 0.9$ Hz, 1H), 8.20 (dd, $J = 8.2, 1.8$ Hz, 1H), 8.76 (dd, $J = 6.4, 2.3$ Hz, 1H), 8.83 (q, $J = 2.0$ Hz, 1H), 10.49 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) 25.30, 38.11, 45.02, 116.81, 122.06, 122.18, 122.76, 124.84(d, $J = 3.0$ Hz), 127.32, 128.11, 130.65, 130.98, 131.03, 134.19, 136.53, 136.95, 138.67, 140.60, 148.77, 166.01, 175.96, 177.55; IR (neat) 3333 w, 3016 w, 2945 m, 1778 m, 1700 s, 1672 m, 1525 s, 1484 m, 1429 m, 1384 m, 1333 m, 1282 m, 1172 m, 1124 s, 1085 w, 955 w, 916 w, 756 m; MS m/z (relative intensity, %) 427 (11), 199 (11), 171 (10), 145 (15), 144 (100); HRMS Calcd for $C_{22}H_{16}FN_3O_3$: 427.1144; Found: 427.1142.

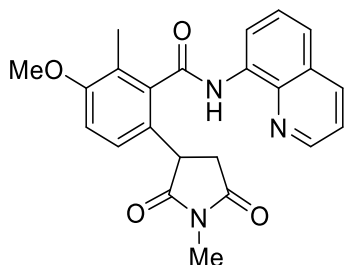
2, 3-dimethyl-6-(1-methyl-2, 5-dioxopyrrolidin-3-yl)-N-(quinolin-8-yl)benzamide (2f)



116.1mg, 100% yield. R_f 0.24 (hexane/EtOAc = 1.5:1). White powder. m.p. 104.2-104.7°C. 1H -NMR ($CDCl_3$, 400 MHz) 2.32 (s, 3H), 2.35 (s, 3H), 2.89 (m, 4H), 3.21 (dd, $J = 18.8, 9.6$ Hz, 1H), 4.22 (dd, $J = 9.6, 5.5$ Hz, 1H), 6.93 (d, $J = 7.8$ Hz, 1H), 7.24 (d, $J = 7.8$ Hz, 1H), 7.46 (dd, $J = 8.2, 4.1$ Hz, 1H), 7.59 (m, 2H), 8.18 (d, $J =$

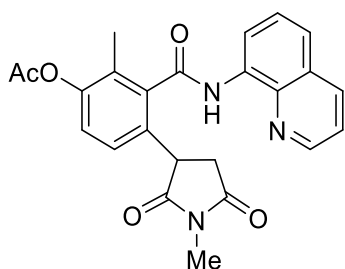
8.2 Hz, 1H), 8.79 (dd, $J = 4.1, 1.4$ Hz, 1H), 8.93 (m, 1H), 10.16 (s, 1H); ^{13}C NMR (CDCl_3 , 100 MHz) 17.03, 20.20, 25.20, 38.28, 44.25, 116.91, 121.93, 122.52, 124.67, 127.32, 128.10, 131.45, 132.19, 133.94, 134.17, 136.38, 137.52, 138.38, 138.60, 148.68, 168.44, 176.42, 178.10; IR (neat) 3338 w, 3014 w, 2948 w, 1777w, 1697 s, 1669 m, 1597 w, 1577 w, 1520 s, 1483 m, 1425 m, 1384 m, 1326 m, 1281 m, 1119 m, 827 w, 793 w, 753 m, 692 w; MS m/z (relative intensity, %) 387 (17), 245 (11), 244 (71), 243 (100), 174 (21), 159 (21), 144 (16); HRMS Calcd for $\text{C}_{23}\text{H}_{21}\text{N}_3\text{O}_3$: 387.1583; Found: 387.1588.

3-methoxy-2-methyl-6-(1-methyl-2, 5-dioxopyrrolidin-3-yl)-*N*-(quinolin-8-yl)benzamide (2g)



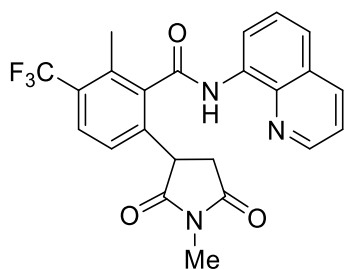
120.6mg, 99% yield. R_f 0.33 (hexane/EtOAc = 1:1). Pale yellow powder. m.p. 97.9-98.3°C. ^1H -NMR (CDCl_3 , 400 MHz) 2.31 (s, 3H), 2.89 (m, 4H), 3.21 (dd, $J = 18.5, 9.4$ Hz, 1H), 3.86 (s, 3H), 4.20 (dd, $J = 9.6, 5.5$ Hz, 1H), 6.91 (d, $J = 8.7$ Hz, 1H), 7.01 (d, $J = 8.2$ Hz, 1H), 7.45 (dd, $J = 8.2, 4.1$ Hz, 1H), 7.58 (m, 2H), 8.17 (d, $J = 8.2$ Hz, 1H), 8.78 (dd, $J = 4.1, 1.4$ Hz, 1H), 8.90(m, 1H), 10.16 (s, 1H); ^{13}C NMR (CDCl_3 , 100 MHz) 13.39, 25.15, 38.35, 44.00, 55.78, 111.41, 116.84, 121.92, 122.50, 124.41, 126.15, 126.28, 127.30, 128.08, 134.10, 136.36, 138.57, 139.14, 148.65, 157.49, 167.64, 176.46, 178.30. IR (neat) 3337 w, 3014 w, 2946 w, 1776 w, 1697 s, 1671 m, 1583 w, 1521 s, 1482 m, 1429 m, 1384 m, 1326 m, 1273 m, 1118 w, 1096 m, 826 w, 793 w, 752 m, 692 m; MS m/z (relative intensity, %) 403 (16), 260 (41), 259 (100), 218 (31), 190 (17); HRMS Calcd for $\text{C}_{23}\text{H}_{21}\text{N}_3\text{O}_4$: 403.1532; Found: 403.1527.

2-methyl-4-(1-methyl-2, 5-dioxopyrrolidin-3-yl)-3-(quinolin-8-ylcarbonyl)phenyl acetate (2h)



122.9mg, 95% yield. R_f 0.24 (hexane/EtOAc = 1:1). Pale pink powder. m.p. 105.2-105.4°C. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) 2.28 (s, 3H), 2.35 (s, 3H), 2.90 (m, 4H), 3.21 (dd, $J = 18.3, 9.6$ Hz, 1H), 4.26 (dd, $J = 9.6, 5.5$ Hz, 1H), 7.06 (d, $J = 8.7$ Hz, 1H), 7.15 (d, $J = 8.2$ Hz, 1H), 7.46 (qd, $J = 4.1, 1.8$ Hz, 1H), 7.58 (m, 2H), 8.18 (dt, $J = 8.2, 1.6$ Hz, 1H), 8.81 (m, 1H), 8.89 (t, $J = 4.4$ Hz), 10.19 (s, 1H); $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) 13.70, 20.91, 25.22, 38.11, 44.10, 116.97, 121.99, 122.71, 123.91, 126.20, 127.23, 128.06, 128.24, 132.49, 133.95, 136.35, 138.56, 139.72, 148.78, 149.11, 166.69, 169.08, 176.04, 177.55. IR (neat) 3332 w, 3018 w, 2939 w, 1761 w, 1698 s, 1670 m, 1595 w, 1521 s, 1483 m, 1427 m, 1383 m, 1326 m, 1281 m, 1200 m, 1119 m, 898 w, 827 w, 793 w, 749 s; MS m/z (relative intensity, %) 431 (16), 289 (12), 288 (70), 287 (78), 246 (23), 245 (100), 244 (10), 204 (63), 176 (24), 171 (10), 161 (21), 145 (18), 144 (55); HRMS Calcd for $\text{C}_{24}\text{H}_{21}\text{N}_3\text{O}_5$: 431.1481; Found: 431.1481.

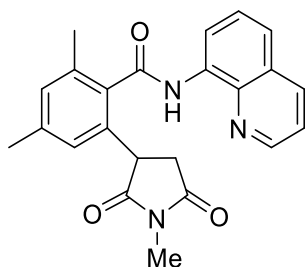
2-methyl-6-(1-methyl-2,5-dioxopyrrolidin-3-yl)-N-(quinolin-8-yl)-3-(trifluoromethyl) benzamide (2i)



119.5mg, 90% yield. R_f 0.26 (hexane/EtOAc = 1.5:1). White powder. m.p. 93.7-94.2°C. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) 2.58 (s, 3H), 2.90 (m, 4H), 3.25 (dd, $J = 18.8, 9.6$ Hz, 1H), 4.29 (dd, $J = 9.6, 5.5$ Hz, 1H), 7.15 (d, $J = 8.2$ Hz, 1H), 7.49 (dd, $J = 8.5, 4.4$ Hz, 1H), 7.61 (m, 2H), 7.73 (d, 8.2 Hz, 1H), 8.20 (dd, $J = 8.5, 1.6$ Hz, 1H), 8.82 (dd, $J = 4.4, 1.6$ Hz, 1H), 8.90 (dd, $J = 6.0, 2.7$ Hz, 1H), 10.23 (s, 1H); $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) 16.57, 25.38, 37.92, 44.38, 117.19, 122.12, 122.67, 123.03, 125.12, 125.40, 127.31, 127.58 (d, $J = 5.7$ Hz), 128.15, 129.49 (d, $J = 29.5$ Hz), 133.79, 134.89, 136.52, 138.55, 140.54, 148.89, 166.65, 175.72, 177.16; IR (neat) 3329 w, 3020 w, 2943 w, 1778 w, 1699 s, 1670 m, 1598 w, 1522 s, 1484 m, 1427 m, 1384 m, 1319 m, 1281 m, 1184 w,

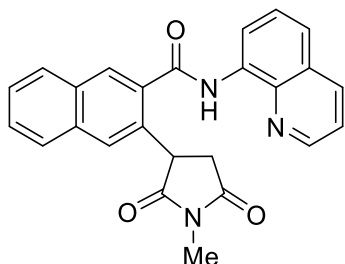
1121 m, 1110 m, 898 m, 793 m, 753, m, 695 m; MS m/z (relative intensity, %) 441 (16), 298 (27), 213 (27), 145 (16), 144 (100); HRMS Calcd for $C_{23}H_{18}F_3N_3O_3$: 441.1300; Found: 441.1299.

2, 4-dimethyl-6-(1-methyl-2, 5-dioxopyrrolidin-3-yl)-*N*-(quinolin-8-yl)benzamide (2j)



109.1mg, 94% yield. R_f 0.20 (hexane/EtOAc = 1.5:1). Yellow powder. m.p. 86.4-86.7°C. 1H -NMR ($CDCl_3$, 400 MHz) 2.34 (s, 3H), 2.44 (s, 3H), 2.87-2.94 (m, 4H), 3.23 (dd, $J = 18.3, 9.6$ Hz, 1H), 4.25 (dd, $J = 9.6, 5.5$ Hz, 1H), 6.81 (s, 1H), 7.06 (s, 1H), 7.44 (qd, $J = 4.1, 1.5$ Hz, 1H), 7.55-7.60 (m, 2H), 8.16 (dd, $J = 8.2, 1.8$ Hz, 1H), 8.78 (t, $J = 2.1$ Hz, 1H), 8.89 (q, $J = 3.1$ Hz, 1H), 10.16 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) 19.90, 21.35, 25.20, 38.31, 44.33, 116.77, 121.88, 122.38, 125.60, 127.29, 128.06, 131.02, 134.18, 134.87, 135.37, 135.49, 136.34, 138.56, 140.13, 148.62, 168.01, 176.40, 178.10; IR (neat); 3339 w, 3014 w, 1776 w, 1697 s, 1668 m, 1610 w, 1520 s, 1483 m, 1425 m, 1383 m, 1325 m, 1281 m, 1117 m, 827 w, 763 w, 751 s, 680 m ;MS m/z (relative intensity, %) 387 (10), 245 (12), 244 (82), 243 (100), 174 (23), 159 (43), 144 (26); HRMS Calcd for $C_{23}H_{21}N_3O_3$: 387.1583; Found: 387.1577.

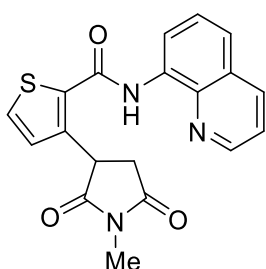
3-(1-methyl-2, 5-dioxopyrrolidin-3-yl)-*N*-(quinolin-8-yl)-2-naphthamide (2k)



62.0mg, 51% yield. R_f 0.24 (hexane/EtOAc = 1.5:1). Pale yellow powder. m.p. 216.0-216.5°C. 1H -NMR ($CDCl_3$, 400 MHz) 3.07 (m, 4H), 3.34 (dd, $J = 18.1, 9.4$ Hz, 1H), 4.67 (dd, $J = 9.4, 5.7$ Hz, 1H), 7.48 (dd, $J = 8.2, 4.1$ Hz, 1H), 7.59 (m, 4H), 7.76 (s, 1H), 7.85 (d, $J = 6.9$ Hz, 1H), 7.98 (d, $J = 7.3$ Hz, 1H), 8.19 (d, $J = 8.2$ Hz, 1H), 8.34 (s, 1H), 8.83 (m, 2H), 10.60 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) 25.25, 38.49,

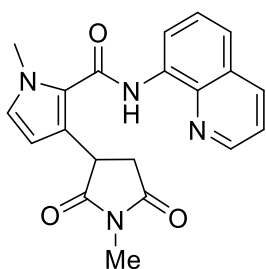
45.47, 116.61, 121.92, 122.29, 127.40, 127.47, 127.74, 128.16, 128.36, 128.47, 128.53, 130.70, 132.17, 133.22, 133.56, 134.29, 134.73, 136.53, 138.79, 148.56, 167.42, 176.72, 179.60. IR (neat) 3342 w, 3015 w, 2948 w, 1776 w, 1697 s, 1668 m, 1597 w, 1522 s, 1484 m, 1427 m, 1384 m, 1326 w, 1281 m, 1120 w, 827 w, 793 w, 752 m, 695 w; MS m/z (relative intensity, %) 409 (15), 266 (40), 265 (100), 224 (15), 196 (20), 181 (11), 153 (10), 152(11), 144 (17); HRMS Calcd for $C_{25}H_{19}N_3O_3$: 409.1426; Found: 409.1428.

2-(1-cyclohexyl-, 5-dioxypyrrolidin-3-yl)-6-methyl-N-(quinolin-8-yl)benzamide (2l)



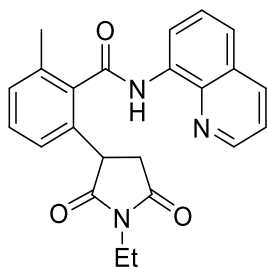
78.8mg, 72% yield. R_f 0.23 (hexane/EtOAc = 1:1). Brown powder. m.p. 187.4-187.8°C. 1H -NMR ($CDCl_3$, 400 MHz) 2.86 (dd, $J = 18.3, 6.0$ Hz, 1H), 3.12 (s, 3H), 3.31 (dd, $J = 18.3, 9.6$ Hz, 1H), 4.85 (dd, $J = 9.2, 6.0$ Hz, 1H), 7.02 (d, $J = 5.0$ Hz, 1H), 7.47 (m, 2H), 7.54 (m, 2H), 8.17 (dd, $J = 8.2, 1.8$ Hz, 1H), 8.72 (dd, $J = 5.5, 3.7$ Hz, 1H), 8.84 (dd, $J = 4.4, 1.6$ Hz, 1H), 10.49 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) 25.27, 37.41, 41.30, 116.75, 121.89, 122.12, 127.39, 127.93, 128.03, 130.12, 132.61, 134.32, 136.48, 138.57, 141.94, 148.53, 160.27, 176.52, 177.75; IR (neat) 3310 w, 3015 w, 2945 w, 1777 w, 1697 s, 1658 m, 1596 w, 1523 s, 1484 m, 1424 m, 1383 m, 1327 m, 1281 m, 1215w, 1118 m, 956 w, 792 m, 752 m, 752 s, 691 m, 665 m; MS m/z (relative intensity, %) 365 (31), 222 (21), 221 (24), 180 (15), 145 (17), 144 (100), 137 (21); HRMS Calcd for $C_{19}H_{15}N_3O_3S$: 365.0834; Found: 365.0836.

1-methyl-3-(1-methyl-2, 5-dioxypyrrolidin-3-yl)-N-(quinolin-8-yl)-1H-pyrrole-2-carboxamide (2m)



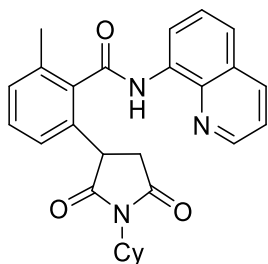
88.4mg, 82% yield. R_f 0.28 (hexane/EtOAc = 1:1). Brown powder. m.p. 67.0-67.2°C. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) 2.90 (dd, $J = 18.3, 5.0$ Hz, 1H), 3.06 (s, 3H), 3.37 (dd, $J = 18.3, 9.6$ Hz, 1H), 3.94 (s, 3H), 4.63 (dd, $J = 9.4, 5.3$ Hz, 1H), 5.99 (d, $J = 2.7$ Hz, 1H), 6.75 (d, $J = 2.7$ Hz, 1H), 7.46 (dd, $J = 8.2, 4.1$ Hz, 1H), 7.57 (m, 2H), 8.18 (dd, $J = 8.2, 1.4$ Hz, 1H), 8.77 (m, 2H), 10.35 (s, 1H); $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) 25.30, 36.84, 37.70, 39.16, 106.23, 117.57, 121.81, 122.15, 123.14, 126.43, 127.36, 127.46, 128.21, 134.74, 136.54, 139.09, 148.54, 160.04, 176.63, 178.62; IR (neat) 3347 w, 3014 w, 2950 w, 1776 w, 1697 s, 1658 m, 1521 s, 1482 m, 1425 m, 1383 m, 1326 m, 1281 m, 1119 m, 956 w, 887 w, 827 w, 792 w, 753 m, 689 w; MS m/z (relative intensity, %) 362 (20), 219 (27), 218 (100), 177 (54), 134 (17); HRMS Calcd for $\text{C}_{20}\text{H}_{18}\text{N}_4\text{O}_3$: 362.1379; Found: 362.1384.

2-(1-ethyl-2,5-dioxopyrrolidin-3-yl)-6-methyl-*N*-(quinolin-8-yl)benzamide (3a)



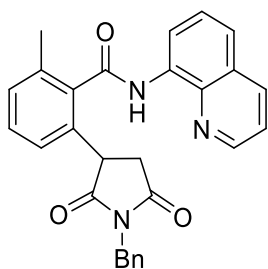
99.9mg, 86%yield. R_f 0.17 (hexane/EtOAc = 2:1). White powder. m.p. 82.1-82.5°C. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) 1.14 (t, $J = 7.1$ Hz, 3H), 2.48 (s, 3H), 2.87 (dd, $J = 18.5, 5.3$ Hz, 1H), 3.22 (dd, $J = 18.3, 9.6$ Hz, 1H), 3.54 (q, $J = 7.2$ Hz, 2H), 4.26 (dd, $J = 9.6, 5.5$ Hz, 1H), 7.00 (d, $J = 7.8$ Hz, 1H), 7.25 (d, $J = 8.7$ Hz, 1H), 7.36 (t, $J = 7.8$ Hz, 1H), 7.46 (qd, $J = 4.1, 1.4$ Hz, 1H), 7.59 (m, 2H), 8.18 (dt, $J = 8.2, 1.6$ Hz), 8.80 (m, 1H), 8.93 (m, 1H), 10.18 (s, 1H); $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) 13.12, 20.00, 34.12, 38.38, 44.20, 116.98, 121.92, 122.53, 124.68, 127.32, 128.12, 130.17, 130.22, 134.15, 135.16, 135.65, 136.39, 138.16, 138.66, 148.69, 167.82, 176.09, 177.65; IR (neat) 3334 w, 2951 w, 2876 w, 2360 w, 1772 w, 1701 s, 1673 m, 1522 s, 1483 m, 1400 m, 1326 m, 1224 m, 1126 m, 789 m, 773 m; MS m/z (relative intensity, %) 387 (11), 245 (11), 244 (77), 243 (100) 174 (11), 146 (12), 145 (49), 144 (53), 130 (10), 117 (11), 115 (11); HRMS Calcd for $\text{C}_{23}\text{H}_{21}\text{N}_3\text{O}_3$: 387.1583; Found: 387.1578.

2-(1-cyclohexyl-2,5-dioxopyrrolidin-3-yl)-6-methyl-*N*-(quinolin-8-yl)benzamide (4a)



95.1mg, 72% yield. R_f 0.29 (hexane/EtOAc = 2:1). White powder. m.p. 102.8-103.3°C. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) 1.15-1.29 (m, 3H), 1.15-1.63 (m, 3H), 1.71-1.86 (m, 2H), 2.10-2.16 (m, 2m), 2.47 (s, 3H), 2.80 (dd, $J = 18.5, 5.3$ Hz, 1H), 3.17 (dd, $J = 18.8, 9.6$ Hz, 1H), 3.98 (m, 1H), 4.21 (dd, $J = 9.6, 5.0$ Hz, 1H), 6.97 (d, $J = 7.8$ Hz, 1H), 7.24 (d, $J = 7.8$ Hz, 1H), 7.35 (t, $J = 7.8$, 1H), 7.46 (dd, $J = 8.2, 4.6$ Hz, 1H), 7.59 (m, 2H), 8.18 (dd, $J = 8.2, 1.8$ Hz, 1H), 8.80 (dd, $J = 4.1, 1.8$ Hz, 1H), 8.93 (dd, $J = 6.0, 3.2$ Hz, 1H), 10.19(s, 1H); $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) 19.97, 25.03, 25.85, 28.77, 28.83, 38.26, 43.73, 52.05, 117.02, 121.89, 122.50, 124.35, 127.29, 128.10, 130.11, 130.16, 134.16, 135.54, 135.58, 136.39, 138.17, 138.63, 148.65, 167.85, 176.38, 177.88; IR (neat) 3338 w, 3016 w, 2932 w, 2856 w, 1773 w, 1696 s, 1671 m, 1596 w, 1521 s, 1483 m, 1424 m, 1373 m, 1325 m, 1261 w, 1188 m, 1143 w, 897 w, 826 w, 752 s, 666 w; MS m/z (relative intensity, %) 441 (14), 298 (44), 297 (100), 217 (10), 216 (78), 215 (47), 146 (20), 145 (49), 144 (36), 117 (12), 115 (10); HRMS Calcd for $\text{C}_{27}\text{H}_{27}\text{N}_3\text{O}_3$: 441.2052; Found: 441.2057.

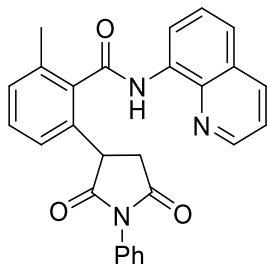
2-(1-benzyl-2,5-dioxopyrrolidin-3-yl)-6-methyl-N-(quinolin-8-yl)benzamide (5a)



98.5mg, 73% yield. R_f 0.33 (hexane/EtOAc = 2:1). White powder. m.p. 86.4-86.9°C. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) 2.47 (s, 3H), 2.86 (dd, $J = 18.5, 5.3$ Hz, 1H), 3.23 (dd, $J = 18.8, 9.6$ Hz, 1H), 4.28 (dd, $J = 9.6, 5.0$ Hz, 1H), 4.62 (dd, $J = 30.0, 14.0$ Hz, 2H), 6.90 (d, $J = 7.8$ Hz, 1H), 7.22-7.36 (m, 6H), 7.45 (dd, $J = 8.2, 4.1$ Hz, 1H), 7.58 (m, 2H), 8.17 (dd, $J = 8.2, 1.4$ Hz, 1H), 8.78 (dd, $J = 4.4, 1.6$ Hz, 1H), 8.90 (dd, $J = 5.5, 3.7$ Hz, 1H), 10.18 (s, 1H); $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) 20.01, 38.38, 42.75, 44.16, 117.02, 121.95, 122.58, 124.60, 127.36, 128.04, 128.12, 128.73, 128.89, 130.21, 130.24, 134.13, 135.09, 135.63, 135.84, 136.42, 138.18, 136.43, 138.18, 138.64, 148.69, 167.80, 175.85,

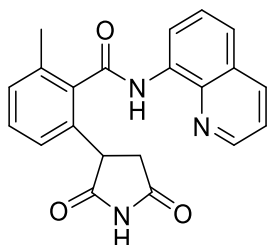
177.55; IR (neat) 3339 w, 3018 w, 2939 w, 1776 w, 1701 s, 1669 m, 1596 w, 1521 s, 1483 m, 1425 m, 1392 m, 1325 m, 1167 m, 827 s, 754 m, 701 m; MS *m/z* (relative intensity, %) 449 (17), 307 (10), 306 (55), 305 (95), 145 (20), 144 (34), 91 (100); HRMS Calcd for C₂₈H₂₃N₃O₃: 449.1739; Found: 449.1735.

2-(2, 5-dioxo-1-phenylpyrrolidin-3-yl)-6-methyl-N-(quinolin-8-yl)benzamide (6a)



118.1mg, 90% yield. *R_f* 0.21 (hexane/EtOAc = 2:1). Pale yellow powder. m.p. 91.0-91.4°C. ¹H-NMR (CDCl₃, 400 MHz) 2.51 (s, 3H), 3.10 (dd, *J* = 18.5, 5.7 Hz, 1H), 3.40 (dd, *J* = 18.5, 9.8 Hz, 1H), 4.45 (dd, *J* = 9.6, 5.5 Hz), 7.16 (d, *J* = 7.8 Hz, 1H), 7.25-7.44 (m, 8H), 7.58 (m, 2H), 8.16 (dd, *J* = 8.2, 1.4 Hz, 1H), 8.75 (t, *J* = 2.1 Hz, 1H), 8.93 (dd, *J* = 6.0, 3.2 Hz, 1H), 10.21 (s, 1H); ¹³C NMR (CDCl₃, 100 MHz) 20.16, 38.40, 44.72, 117.04, 121.94, 122.58, 125.46, 126.61, 127.33, 128.13, 128.67, 129.17, 130.29, 130.54, 132.05, 134.12, 135.07, 135.84, 136.41, 137.91, 138.66, 148.70, 167.87, 175.25, 176.79; IR (neat) 3338 w, 3015 w, 2941 w, 1779 w, 1711 s, 1666 m, 1596 w, 1521 s, 1483 m, 1424 m, 1382 s, 1326 m, 1269 w, 1179 m, 838 w, 751 s, 695 m, 664 m; MS *m/z* (relative intensity, %) 435 (25), 293 (12), 292 (71), 291 (100), 222 (10), 171 (10), 145 (81), 144 (54), 116 (10), 115 (15); HRMS Calcd for C₂₇H₂₁N₃O₃: 435.1583; Found: 435.1588.

2-(2, 5-dioxopyrrolidin-3-yl)-6-methyl-N-(quinolin-8-yl)benzamide (7a)

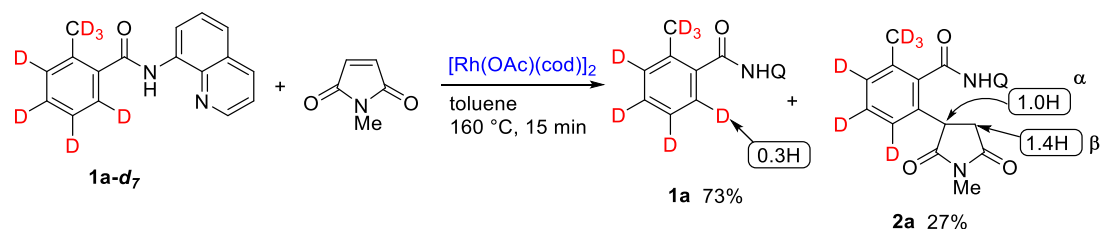


100.6mg, 93%yield. *R_f* 0.43 (hexane/EtOAc = 1:2). White powder. m.p.163.7-164.2°C. ¹H-NMR (CDCl₃, 400 MHz) 2.48 (s, 3H), 2.94 (dd, *J* = 18.8, 5.5 Hz, 1H), 3.25 (dd, *J* = 18.8, 9.6 Hz, 1H), 4.33 (dd, *J* = 9.6, 5.5 Hz, 1H), 7.09 (d, *J* = 7.8 Hz, 1H), 7.27 (d, *J* = 6.9 Hz, 1H), 7.38 (t, *J* = 7.8 Hz, 1H), 7.45 (dd, *J* = 8.2, 4.6 Hz, 1H), 7.59 (m, 2H), 8.18

(m, 2H), 8.79 (dd, $J = 4.1, 1.8$ Hz, 1H). 8.92 (dd, $J = 5.5, 3.2$ Hz, 1H), 10.18 (s, 1H); ^{13}C NMR (CDCl_3 , 100 MHz) 20.02, 39.39, 45.67, 117.12, 122.01, 122.65, 124.82, 127.43, 128.20, 130.27, 130.48, 134.19, 135.81, 136.47, 148.76, 167.84, 175.82, 177.81; IR (neat) 3333 w, 3074 w, 2987 w, 1775 w, 1705 s, 1669 m, 1596 w, 1521 s, 1483 m, 1425 m, 1384 m, 1326 m, 1244 m, 1177 w, 1126 w, 1045 w, 828 w, 792 w, 696 w; MS m/z (relative intensity, %) 359 (13), 216 (7), 145 (37), 144 (100); HRMS Calcd for $\text{C}_{21}\text{H}_{17}\text{N}_3\text{O}_3$: 359.1270; Found: 359.1271.

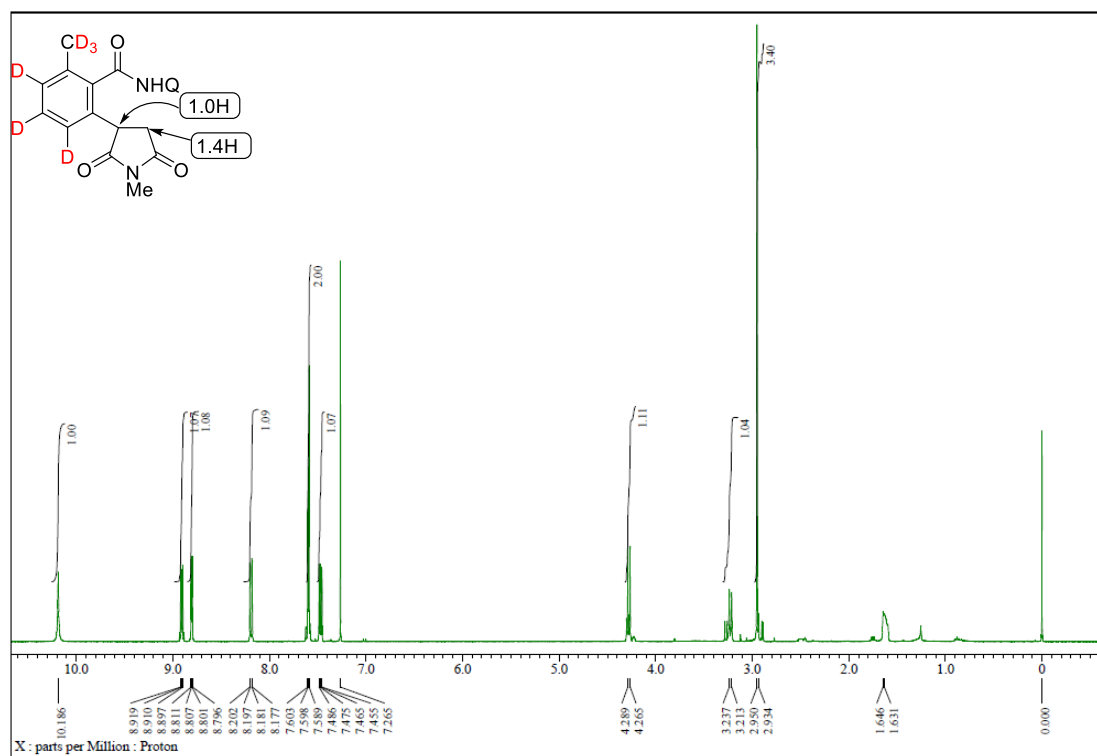
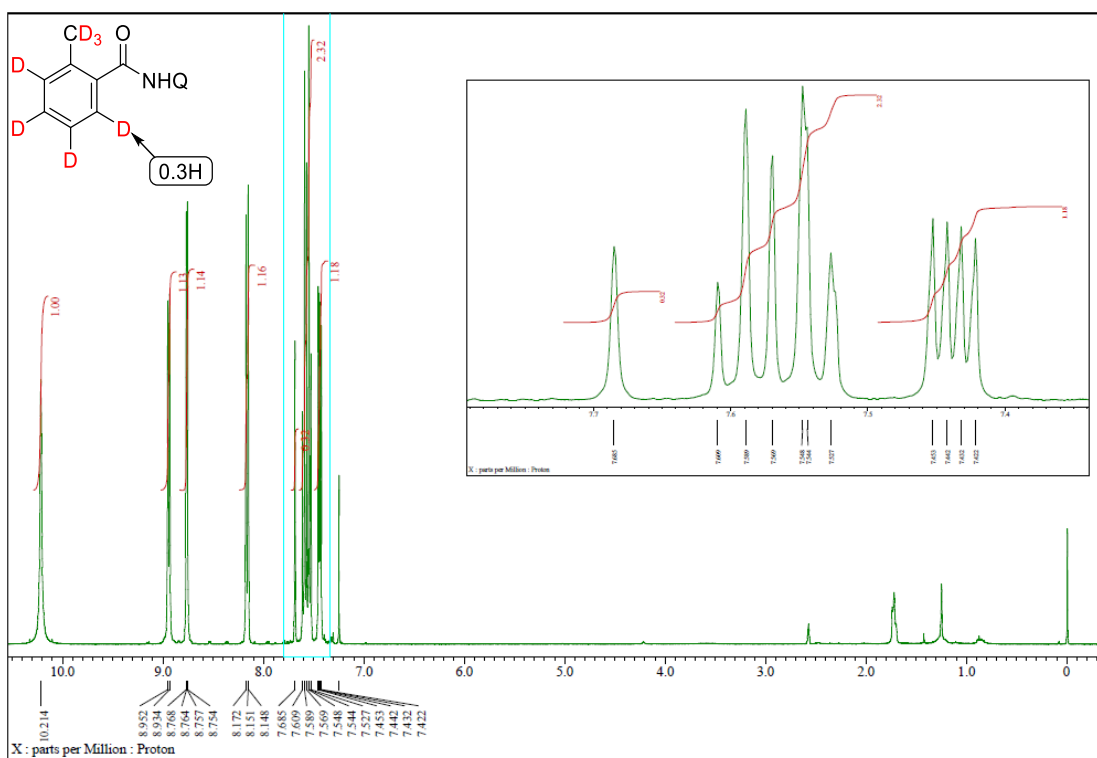
VI. Deuterium Labeling Experiments

(a) Rh (I) system

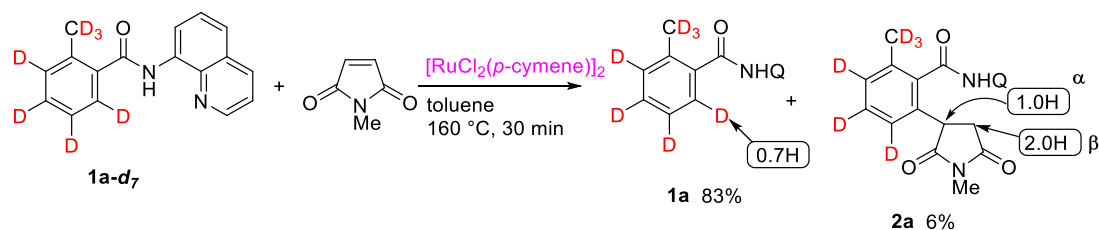


Representative procedure.

To an oven-dried 5 mL screw-capped vial, 2-methyl-*N*-(quinolin-8-yl)benzamide **1a-d₇** (80.8mg, 0.3mmol), *N*-methylmaleimide (39.6mg, 0.36mmol), $[\text{Rh}(\text{OAc})(\text{cod})]_2$ (4.1 mg, 0.0075mmol) and toluene (1 mL) were added. The mixture was stirred for 15 minutes at 160°C and then cooled to room temperature. The resulting mixture was filtered through a celite pad and then concentrated in vacuo. The residue was purified by column chromatography on silica gel (eluent: hexane/EtOAc= 1.5:1) to afford the desired product and starting material.

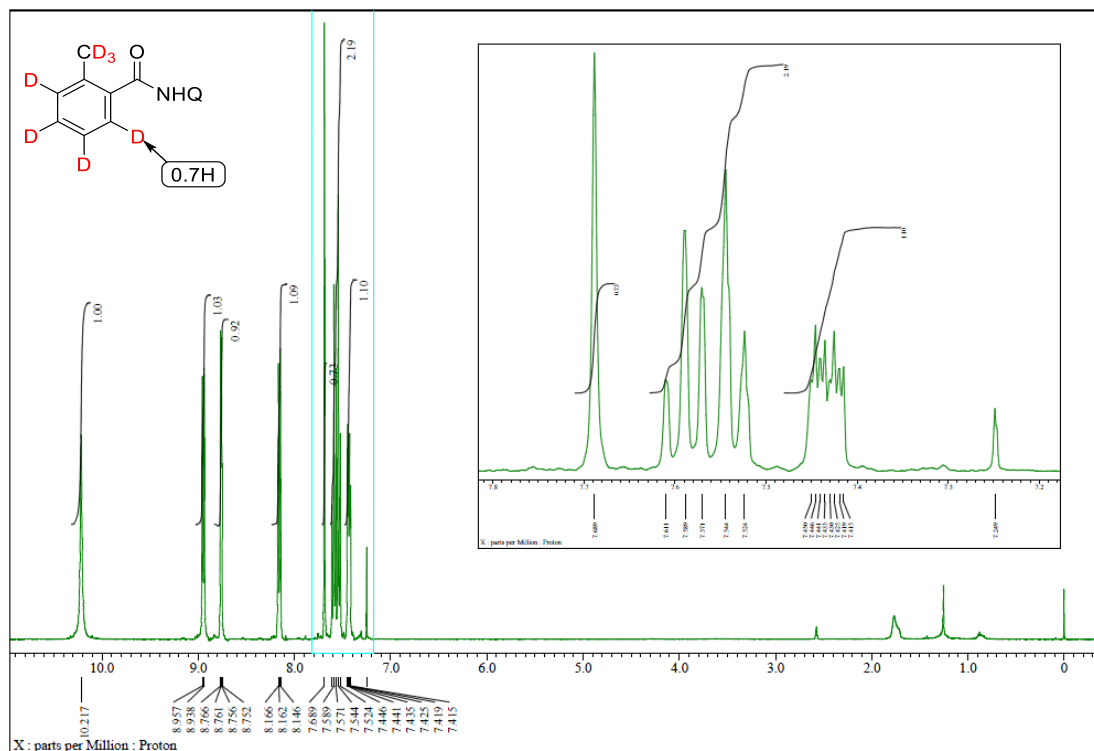


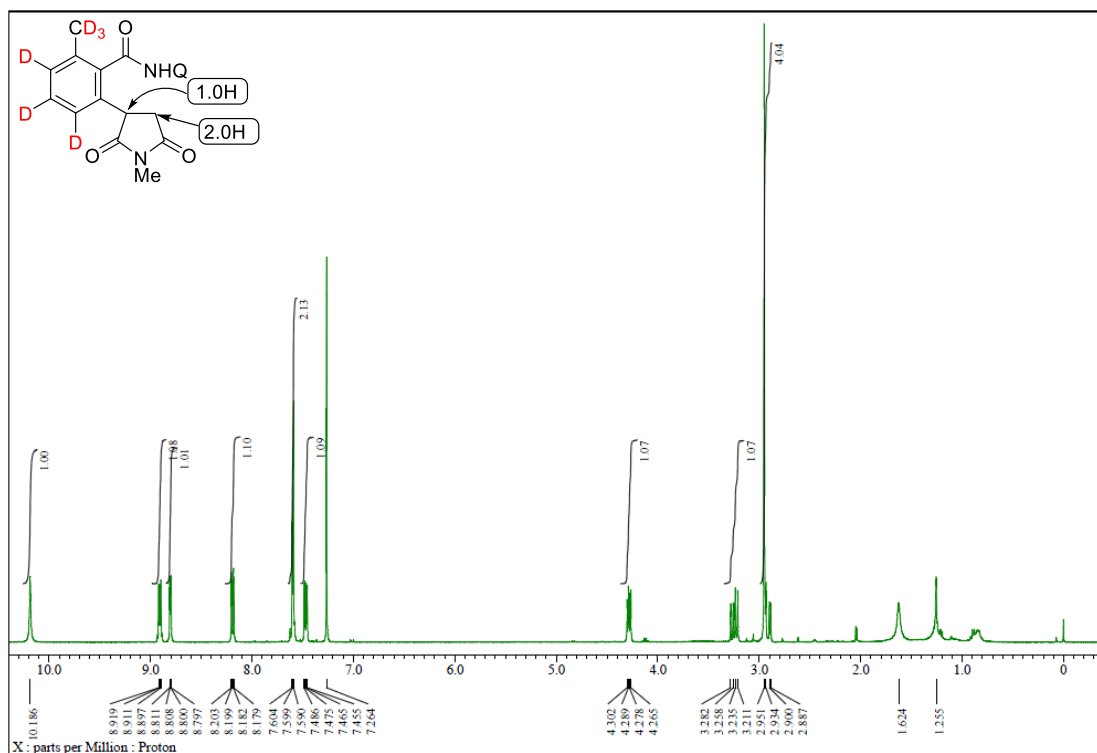
(a) Ru (II) system



Representative procedure.

To an oven-dried 5 mL screw-capped vial, 2-methyl-*N*-(quinolin-8-yl)benzamide (80.8mg, 0.3mmol), *N*-methylmaleimide (39.6mg, 0.36mmol), 2-Methylbenzoic acid (40.9mg, 0.3mmol), $[\text{RuCl}_2(p\text{-cymene})]_2$ (4.6 mg, 0.0075mmol) and toluene (1 mL) were added. The mixture was stirred for 30 minutes at 160°C and then cooled to room temperature. The resulting mixture was filtered through a celite pad and washed with saturated aqueous NaHCO_3 (20 mL), and EtOAc (3x20 mL); then concentrated in vacuo. The residue was purified by column chromatography on silica gel (eluent: hexane/EtOAc= 1.5:1) to afford the desired product and starting material.





4.5 References

- (1) Selected recent reviews on C-H functionalization, see: (a) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K *Angew. Chem. Int. Ed.* **2012**, *51*, 8960-9009. (b) Li, B.-J.; Shi, Z.-J. *Chem. Soc. Rev.* **2012**, *41*, 5588-5598. (c) Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H. *Chem. Rev.* **2012**, *112*, 5879-5918. (d) Colby, D. A.; Tsai, A. S.; Bergman, R. G.; Ellman, J. A. *Acc. Chem. Res.* **2012**, *45*, 814-825. (e) Kuhl, N.; Hopkinson, M. N.; Wencel-Delord, J.; Glorius, F. *Angew. Chem. Int. Ed.* **2012**, *51*, 10236-10254.
- (2) Dong, Z.; Ren, Z.; Thompson, S. J.; Xu, Y.; Dong, G. *Chem. Rev.* **2017**, *117*, 9333-9403.
- (3) Miura, W.; Hirano, K.; Miura, M. *Org. Lett.* **2015**, *17*, 4034-4037.
- (4) Chatani, N. *Bull. Chem. Soc. Jpn.* **2018**, *91*, 211-222.
- (5) Keshri, P.; Bettadapur, K. R.; Lanke, V.; Prabhu, K. R. *J. Org. Chem.* **2016**, *81*, 6056-6065.
- (6) Schinkel, M.; Marek, I.; Ackermann, L. *Angew. Chem. Int. Ed.* **2013**, *52*, 3977-3980.
- (7) Chatt, J.; Venanzi, L. M. *J. Chem. Soc.* **1957**, 4735.

Conclusion

The research in this thesis is mainly focused on the site-selective direct C-H activation of *ortho*-methyl substituted aromatic compounds via a six-membered metallacycle. Generally, transition-metal-catalyzed C-H activation proceeds through five-membered metallacycle, which is known as kinetically and thermodynamically stable. On the other hand, benzylic C(sp³)-H activation at the *ortho*-methyl group is difficult to be achieved because these transformations require to form a six-membered metallacycle, especially when the *ortho* C(sp²)-H bond exists in the same ring.

In chapter 1, a palladium-catalyzed benzylic C-H alkylation of aromatic amides bearing an 8-aminoquinonyl directing group with maleimides was introduced. In the 8-aminoquinonyl chelation case, most of the reactions are the *ortho* C-H activation. Although the cleavage of *ortho* C(sp²)-H bond is easier, the insertion of an alkene into a six-membered palladacycle requires low energy. To the best of our knowledge, this is the first example of benzylic C-H alkylation of aromatic amides with alkenes.

Chapter 2 describes a [3+2] annulation of aromatic amides with maleimides using a 2-(thiomethyl)-aniline directing group, which proceeds through the activation of both benzylic and *meta*-C-H bonds. This [3+2] annulation was also applicable to anilide derivatives. The cleavage of benzylic C-H bond and *meta* C-H bond is irreversible, and this step is suggested as a rate-determined step based on the deuterium-labeling experiment results.

Chapter 3 describes a palladium-catalyzed site-selective [5+1] annulation, which involves the activation of a benzylic C-H bond. In 2019, Zhang reported a [4+1] annulation of *N,S*-bidentate chelated aromatic amides, in which the reaction took place at the *ortho* C-H bond. In contrast, the use of maleic anhydride as a ligand significantly changed the course of the reaction to the benzylic C-H bond. DFT calculations revealed the effect of the maleic anhydride in the transformation process. The maleic anhydride coordinates to the palladium center, which changes the geometry which led to form a square-planer like structure in the step of β -H elimination.

Chapter 4 describes a rhodium(I)-catalyzed *ortho* C-H alkylation of aromatic amides with maleimides by using an 8-aminoquinoline bidentate chelation system. Meanwhile, the use of ruthenium(II) catalyst also could promote the same transformation, but the mechanisms are clearly different.

This thesis demonstrated that the C-H activation reaction can proceed through kinetically disfavored metallacycles by modifying the ligand or directing groups. These findings provide valuable insight to develop new C-H activation reactions.

List of Publication

1. The Pd-Catalyzed C-H Alkylation of ortho-Methyl-Substituted Aromatic Amides with Maleimide Occurs Preferentially at the ortho-Methyl C-H *Bond* over the *ortho*-C-H Bond

He, Q.; Ano, Y.; Chatani, N. *Chem. Commun.* **2019**, 55, 9983-9986.

2. Palladium-Catalyzed Site-Selective [3+2] Annulation via Benzylic and *meta* C-H Bond Activation

He, Q.; Chatani, N. *Angew. Chem. Int. Ed.* **2021**, 60, 5189 –5192.

3. Palladium-Catalyzed Site-Selective [5+1] Annulation of Aromatic Amides with Alkenes: Acceleration of β -Hydride Elimination by Maleic Anhydride from Palladacycle

He, Q.; Yamazaki, K.; Ano, Y.; Chatani, N. *ACS Catal.* in press.

4. Rh(I)-Catalyzed Alkylation of ortho C-H Bonds in Aromatic Amides with Maleimides

He, Q.; Yamaguchi, T.; Chatani, N. *Org. Lett.* **2017**, 19, 4544-4547.

Supplementary List of Publication

1. A Synthesis of 3, 4-Dihydroisoquinolin-1(2H)-one via the Rhodium-Catalyzed Alkylation of Aromatic Amides with *N*-Vinylphthalimide

He, Q.; Chatani, N. *J. Org. Chem.* **2018**, 83, 13587-13594.

2. Reaction Path Determination of Rhodium(I)-Catalyzed C–H Alkylation of *N*-8-Aminoquinolinylyl Aromatic Amides with Maleimides

Taborosi, A.; He, Q.; Ano, Y.; Chatani, N.; Mori, S. *J. Org. Chem.* in press.