2015

1, 2, 3-triazole as the Directing Group for Metal-Catalyzed C-H Activation

Xiaohan Ye

Follow this and additional works at: <https://researchrepository.wvu.edu/etd>

Recommended Citation

Ye, Xiaohan, "1, 2, 3-triazole as the Directing Group for Metal-Catalyzed C-H Activation" (2015). *Graduate Theses, Dissertations, and Problem Reports*. 7003.
<https://researchrepository.wvu.edu/etd/7003>

This Dissertation is protected by copyright and/or related rights. It has been brought to you by the The Research Repository @ WVU with permission from the rights-holder(s). You are free to use this Dissertation in any way that is permitted by the copyright and related rights legislation that applies to your use. For other uses you must obtain permission from the rights-holder(s) directly, unless additional rights are indicated by a Creative Commons license in the record and/ or on the work itself. This Dissertation has been accepted for inclusion in WVU Graduate Theses, Dissertations, and Problem Reports collection by an authorized administrator of The Research Repository @ WVU. For more information, please contact researchrepository@mail.wvu.edu.

1, 2, 3-triazole as the Directing Group for Metal-Catalyzed C-H Activation

Xiaohan Ye

**Dissertation submitted
to the Eberly College of Arts and Science
at West Virginia University**

in partial fulfillment of the requirements for the degree of

**Doctor of Philosophy in
Chemistry**

**Xiaodong Michael Shi, Ph.D., Chair
Björn Söderberg, Ph.D.
Brian Popp, Ph.D.
Jeffrey L. Petersen, Ph.D.
Rojanasakul Yon, Ph.D.**

C.Eugene Bennett Department of Chemistry

**Morgantown, West Virginia
2015**

**Key word: 1,2,3-triazole, Removable directing group, C-H activation,
Transition metal catalysis, Cyclization, Acetoxylation, Olefination, Sulfenylation
Copyright 2015 Xiaohan Ye**

Abstract

1, 2, 3-triazole as the Directing Group for Metal-Catalyzed C-H Activation

1,2,3-Triazoles as versatile directing group for selective sp^2 and sp^3 C-H activation: cyclization vs substitution

A selective cyclization and substitution was achieved with designated 1,2,3-triazole acid auxiliary groups as directing groups under Pd catalyzed C-H activation conditions. Both sp^2 and sp^3 C-H bonds were effectively activated, giving the desired products in good yields. This result revealed the first successful example of exclusive substitution using 1,2,3-triazole ligands, while other triazole-containing directing groups dominantly gave cyclization under identical conditions.

Palladium-Catalyzed Aerobic Oxidative C-H Olefination with Removable 1,2,3-Triazole Directing Group

Ortho-olefination of arenes was achieved with removable 1,2,3-triazole auxiliary through Pd-catalyzed C-H activation. Excellent yields were received even when molecular O_2 (1 atm) was used as the terminal oxidant. Other heterocyclic directing groups, such as pyridine and quinoline, gave poor reactivity under this aerobic oxidative condition, which highlighted the unique reactivity of triazole in promoting directed C-H activation.

Nickel-catalyzed directed sulfonylation of sp^2 and sp^3 C-H bonds

Directed sulfonylation of both sp^2 and sp^3 C-H bonds was achieved via nickel catalyzed C-S bond formation, giving the desired product in good to excellent yield (up to 90%). Other metal cations including Cu, Fe, Pd, Rh, Ru and Co, gave almost no reaction under identical conditions, which highlighted the unique reactivity of this Ni system.

DEDICATED TO

My grandmother

&

Family

Acknowledgements

I would like to express my deepest gratitude to my supervisor, Dr. Xiaodong Michael Shi. I feel so fortunate to have him as a mentor. His broad chemistry knowledge, enthusiasm and persistence have always inspired me. He has influenced and trained me to be diligent, hard working and meticulous, both in the lab and in everyday life. For these reasons, I will forever be grateful for his involvement in my life.

I am deeply thankful for the valuable advice and suggestion by Dr. Kung K. Wang, Dr. Dr. Björn Söderberg, Dr. Brian Popp, and Dr. Jessica Hoover in Organic Division. I would also like to thank Dr. Jeffrey Petersen for his great help of the X-ray crystallography studies and his guidance during my graduate studies. The kind and friendly help from Dr. Novruz Akhmedov during NMR analysis is always appreciated. Moreover, I am deeply grateful to Dr. Peter Gannett and Dr. Rojanasakul Yon for their roles on my Doctoral Research Committee.

I have always found great value in the Shi group due to our family-like relationships. I would like to thank my colleagues, Dr. Chen Zhong, Dr. Sujata Senqupta, Dr. Wuming Yan, Dr. Dawei Wang, Dr. Lekh Nath Gautam, Dr. Qiaoyi Wang, Dr. Yijin Su, Dr. Haihui Peng, Dr. Zhengrong He, Tao Liao, Rong Cai, Yanwei Zhang, Sraven Kumar, Siddhita Aparaj, Stephen Motika, Yumeng Xi, Boliang Dong, Seyedmorteza Hosseyni, Ying He, Mojtaba Hajiloo Shayegan, Edward J. McClain, Ellen Aguilera, Tonia Ahmed, Keith Weise, Sripadh Sharma. Besides those I have mentioned, I would also like to thank all my colleagues in the Chemistry Department for their kind help over the past six years.

I would like to express my appreciation to my family in China for their unconditional love and encouragement.

Financial support from the C. Eugene Bennett Department of Chemistry at West Virginia University (John H. Trotter Fellowship and travel support from Schuler family) and the National Science Foundation must also be acknowledged and has always been greatly appreciated.

TABLE OF CONTENT

Title Page	i
Abstract	ii
Dedication	iii
Acknowledgements	iv
Table of Contents	v
List of Scheme	viii
List of Table	x
List of Figure.....	xi

Part I

1,2,3-Triazoles as versatile directing group for selective sp^2 and sp^3 C–H activation: cyclization vs substitution

1.1 Introduction	1
1.1.1 Directing group for metal-catalyzed C-H activation	1
1.1.2 Bidentate auxiliary directed palladium catalyzed C-H bond functionalization ...	2
1.1.2.1 Application in amine derivatives	2
1.1.2.2 Application in acid derivatives	3
1.2 Research objective	5
1.2.1 Challenge for chemoselectivity.....	5
1.2.2 1,2,3-triazole metal complex.....	6
1.2.3 1,2,3-triazole as the potential directing group	7
1.2.3.1 Advantage	7
1.2.3.2 Potential problem	8
1.3 1,2,3-triazole directed C-H amidation: Cyclization	9
1.3.1 Evaluation of directing groups.....	9
1.3.2 Substrate scope.....	10

1.4 1,2,3-triazole directed C-H acetoxylation: substitution	12
1.4.1 Rational design of TA-Py directing group.....	12
1.4.2 Reaction condition optimization	15
1.4.3 Substrate scope.....	16
1.5 Conclusion	19

Part II

Palladium-Catalyzed Aerobic Oxidative C–H Olefination with Removable 1,2,3-Triazole Directing Group

2.1 Introduction.....	20
2.2 Optimization of 1,2,3-triazole directing group	22
2.3 Selected optimization of reaction conditions.....	24
2.4 Evaluation of other directing groups.....	25
2.5 Substrate scope.....	27
2.6 Kinetic isotope effect and derivatization	30
2.6.1 Kinetic isotope effect	30
2.6.2 Derivatization.....	31
2.7 Conclusion	32

Part III

Nickel-catalyzed directed sulfenylation of sp^2 and sp^3 C–H bonds

3.1 Introduction.....	33
3.2 Research objective	39
3.2.1 C-S bond formation.....	39
3.2.2 C-S bond formation through C-H activation	40
3.3 Evaluation of directing groups.....	42
3.4 Reaction condition optimization	44
3.5 Substrate scope.....	47

3.5.1 Substrate scope of nickel catalyzed sp^3 C-H sulfenylation	47
3.5.2 Substrate scope of nickel catalyzed sp^2 C-H sulfenylation	49
3.6 Mechanism investigation	51
3.6.1 Radical scavenger experiment	51
3.6.2 Mercury poison experiment	53
3.6.3 Competition experiment.....	53
3.6.4 Plausible mechanism.....	55
3.7 Conclusion	56

Part V

Experiment Section

Section A: General Methods and Materials	65
Section B: General Experiment Procedures	67
Section C: Compound Characterization	81

Part VI

^1H NMR, ^{13}C NMR

List of Schemes

Scheme 1. Directing group strategy for C-H activation	1
Scheme 2. Design auxiliary for amide derivatives	3
Scheme 3. Examples of bidentate auxiliary DGs for amide derivatives	4
Scheme 4. Design auxiliary for carboxylic acid derivatives.....	4
Scheme 5. Examples of bidentate auxiliary DGs for acid derivatives	6
Scheme 6. Challenge for picolinic acid directing group.....	6
Scheme 7. 1,2,3-triazoles based metal complexes.....	7
Scheme 8. Advantage: Easy deprotection with electron-deficient TA.....	7
Scheme 9. Challenge: C-H activation occurred dominantly on the acidic C-H bond	8
Scheme 10. Evaluation of directing groups	9
Scheme 11. Reaction scope for TAA directed sp^3 C-H activation.....	12
Scheme 12. Plausible Pd(IV) intermediate for cyclization.....	12
Scheme 13 Proposed Pd(IV) intermediate for substitution.	13
Scheme 14 Tridentate Py-TA directing group.....	13
Scheme 15. Designed TA-Py directed selective substitution	14
Scheme 16. Conformation for tridentate intermediate.....	14
Scheme 17. Ligand-promoted C-H olefination of pyridines.	20
Scheme 18. Selective C-H olefination using directing groups	21
Scheme 19. Tf amide directed Pd-catalyzed C-H Olefination	22
Scheme 20. TA-promoted selective C-H activation	23
Scheme 21. TA-promoted C-H olefination with AgOAc as oxidant.....	24
Scheme 22. Evaluation of other directing groups.....	27
Scheme 23. Kinetic Isotope effect	31
Scheme 24. Derivatization	31
Scheme 25. Proposed First-row transition metal catalyzed C-H activation	34
Scheme 26. Copper catalyzed/mediated bidentate DG assisted C-H activation.....	35
Scheme 27. Iron catalyzed bidentate DG assisted C-H activation.....	36
Scheme 28. Selected examples for nickel catalyzed C-H activation	38
Scheme 29. Five of top selling drugs in the USA in 2013 contain sulfur.....	39

Scheme 30. C-S formation through cross-coupling.....	40
Scheme 31 Selected examples for directed C-H sulfenylation.....	41
Scheme 32. Cu-catalyzed C-H sulfenylation: Challenge for sp^3 C-H	42
Scheme 33. Evaluation of directing groups	43
Scheme 34. Gram-scale synthesis.....	51
Scheme 35. Radical scavenger experiment.....	52
Scheme 36. Mercury poison experiment	53
Scheme 37. Competition experiment.....	54
Scheme 38. Proposed reaction mechanism.....	54

List of Tables

Table 1. Reaction scope for TAA directed sp^2 C-H activation.....	10
Table 2. Reaction scope for TAA directed sp^3 C-H activation	11
Table 3. Optimal condition for acetoxylation	15
Table 4. Reaction scope for TA-Py directed sp^2 C-H activation	17
Table 5. Reaction scope for TA-Py directed sp^3 C-H activation	18
Table 6. Selected Optimization of Reaction Conditions.....	26
Table 7. Substrate Scope for phenylethyl amine derivatives.....	29
Table 8. Substrate Scope for different alkenes	30
Table 9. Selected conditions on nickel catalyzed sp^3 C-H sulfenylation.....	46
Table 10. Reaction scope of sp^3 C-H sulfenylation with disulfides.....	47
Table 11. Reaction scope of sp^3 C-H sulfenylation with thiolphenols.....	48
Table 12. Reaction scope for sp^2 C-H sulfenylation with benzoic acid derivatives	50
Table 13. Reaction scope for sp^2 C-H sulfenylation with thiolphenols	52

List of Figures

Figure 1. ORTEP Drawing of the X-ray Crystal Structure 3a	122
Figure 2. ORTEP Drawing of the X-ray Crystal Structure 22a	175
Figure 3. ORTEP Drawing of the X-ray Crystal Structure 22e	175

Part I

1,2,3-Triazoles as versatile directing group for selective sp^2 and sp^3 C–H activation: cyclization *vs* substitution

1.1 Introduction

1.1.1 Directing group for metal-catalyzed C–H activation

During the last decade, transition metal catalyzed C–H functionalization has been utilized as an efficient and versatile approach in complex molecule synthesis.¹ Due to many different C–H bonds within nearly all molecular frameworks, the differentiation of C–H bonds with similar chemical environment becomes a general concern and inhibits the wide application of C–H activation strategy. Directing group (DG) approaches are particularly important since it can lead the metal to selectively activate specific C–H bonds.² As shown in **Scheme 1**, various functional groups have been successfully utilized as directing groups for the modification of ortho sp^2 C–H bond.

Scheme 1. Directing group strategy for C–H activation

Selected examples of DG:

On the other hand, relatively few effective directing groups have been reported for metal-catalyzed functionalization of inactivated sp^3 C-H bond (not on benzylic position or α to heteroatoms), mainly due to a higher bond dissociation energy for sp^3 C-H bonds, which demands a stronger directing group to facilitate cyclometalation. Thus, a novel directing group strategy is highly desirable.

1.1.2 Bidentate auxiliary directed palladium catalyzed C-H bonds functionalization

1.1.2.1 Application on amine derivatives

Amines are essential functional groups and widely exist in an abundance of natural products and many biologically active compounds. Selective functionalization of amine derivatives through C-H activation is therefore always attractive. Amines were not considered as a good directing group towards transition metals. It might be because the good binding affinity between nitrogen and late transition metal impedes the catalyst turnover. Also, most aliphatic amines are highly sensitive to oxidants, which are commonly involved in a C-H activation process for metal redox neutralization. An amide modification/protection becomes a general approach, which is widely applied for sp^2 C-H functionalization of amine derivatives. Attempts to utilize simple amides for sp^3 C-H bond were less successful. One successful example is demonstrated by Yu's group in which they adopt a Tf amide directing group.³ With assistance of amino acid ligands, sp^3 C-H arylation could be accomplished.⁴ However, the difficulty of Tf deprotection makes this approach less synthetically appealing. Recently, Daugulis initiated a bidentate auxiliary directing group approach to circumvent this challenging task (**Scheme 2**). With

a picolinic acid auxiliary, the first example of Pd-catalyzed sp^3 C-H arylation was accomplished in 2005.⁵ Notably, the reaction involves a 5,5-bidentate palladacycle intermediate, leading to functionalization on the inner γ - sp^3 C-H bond. Whether the anionic amide serves as an X-type or L-type ligand is still unclear. However, this bidentate chelating mode presumably enhanced the reactivity of Pd for C-H bond metallation as well as enhancing the stability to overcome unwanted byproduct pathways (predominantly β -H elimination).

Scheme 2. Design auxiliary for amide derivatives

First Example by Daugulis:

Later, Chen and other groups further extended the category with several newly designed bidentate acid auxiliaries, which allows the enrichment of synthetic scope and functional group tolerance. The results are summarized in **Scheme 3**.^{6,7}

1.1.2.2 Application on acid derivatives

Under a revised procedure, the aminoquinoline auxiliary was employed for the activation of carboxylic acid derivatives, promoting a β - sp^3 C-H functionalization

(**Scheme 4**). In general, the aminoquinoline amide presented a stronger directing effect towards palladium, as the arylation could be achieved on the methylene C-H bond under a milder condition (110 °C) with higher yield (92%) obtained.⁵

Scheme 3. Examples of bidentate auxiliary DGs for amide derivatives

Scheme 4. Design auxiliary for carboxylic acid derivatives

Similarly, several new bidentate amine auxiliaries were designed to supplement the category and target more challenging transformations (**Scheme 5**).⁸

Scheme 5. Examples of bidentate auxiliary DGs for acid derivatives

1.2 Research objective

1.2.1 Challenge for chemoselectivity

Significant progress have been achieved for effective functionalization of sp^2 and sp^3 C-H bonds with bidentate auxiliary directing group, however, one challenge is the chemoselectivity between cyclization and substitution when $\text{PhI}(\text{OAc})_2$ was employed as oxidant. As shown in **Scheme 6**, with the picolinic acid (**PA**) directing groups, the cyclization products were dominant, even in the formation of highly strained azetidine rings.⁹ Recently, Chen and coworkers reported the application of alcohols as the co-solvents to promote the substitution over the cyclization.¹⁰ Although this work provided one successful example of O-substitution upon C-H activation using this strategy, the requirement of an alcohol as a co-solvent limited the potential application for the

incorporation of other functional groups due to the crucial competition from the alcohol solvent. Thus, alternative versatile directing groups that render effective chemoselectivity control are highly desired.

Scheme 6. Challenge for picolinic acid directing group

Picolinic acid DG: dominant cyclization, poor substitution

1.2.2 1,2,3-triazole metal complex

The 1,2,3-triazoles are highly electron-deficient aromatic heterocycles and therefore have been overlooked as potential ligands in transition metal coordination due to the assumed “poor” electron donating ability. In the last several years, our group has been working towards the development of new metal catalysts with 1,2,3-triazole ligands. Several stable triazole complexes were successfully prepared and characterized, revealing good binding ability of 1,2,3-triazole toward transition metal cations, unlike the previous assumption (**Scheme 7**).¹¹ Thus, we wondered whether triazole derivatives could be used as suitable directing groups in the Pd-catalyzed C-H activation.

Scheme 7. 1,2,3-triazoles based metal complexes

(A) Triazonium-Au: Carbene like ligand

(B) Triazole-Au: new catalyst

(C) Triazole-Borane: hydrogen radical donor

(D) Triazole-Ir: new photo catalyst

1.2.3 1,2,3-triazole as the potential directing group

1.2.3.1 Advantage

To be synthetically useful, the designed directing/protecting group has to be easily deprotected after C-H functionalization. As demonstrated in **Scheme 8**, the 1,2,3-triazole 4-carboxylic acid (**TAA**) can undergo facile deprotection under relatively mild conditions.

Scheme 8. Advantage: Easy deprotection with electron-deficient TAA

1.2.3.2 Potential problem

One potential problem associated with our proposed strategy is the acidic C-H proton on 1,2,3-triazole ring. As shown in **Scheme 9**, Ackermann and coworkers have done comprehensive studies regarding the metal catalyzed C-H activation on conjugated triazole-phenyl compounds. Based on their results, under the Pd catalyzed conditions, C-H activation exclusively occurred on the triazole C5-H bond (instead of the arene C-H).¹² On the other hand, the arene C-H bond activation was achieved under Ru catalyzed conditions with 1,2,3-triazole directing group.¹³ When this project started, no Pd-catalyzed triazole-directed C-H activation has ever been reported in the literature.

Scheme 9. Challenge: C-H activation occurred dominantly on the acidic C-H bond

1.3 1,2,3-Triazole directed C-H amidation: Cyclization

1.3.1 Evaluation of directing groups

To test our hypothesis, triazole amide **2a** was prepared along with several other similar heteroaromatic amides. These substrates were screened under identical conditions, (Pd(OAc)₂ and PhI(OAc)₂ in DCE, 80 °C). As shown in **Scheme 10**, the TAA

directing group could effectively promote arene C-H activation, giving the cyclization product **3a** in 83% isolated yield, similar to quinaldic acid (**QA**) and picolinic acid (**PA**) directing groups. To the best of our knowledge, this is the first example of 1,2,3-triazole directed arene C-H activation with Palladium catalysts. Interestingly, other tested hetero aromatic compounds, such as imidazole, furan and pyrazole, could not promote this reaction at all, despite being more electron-rich than triazole.

Scheme 10. Evaluation of directing groups

1.3.2 Substrate scope

As shown in **Table 1**, the triazole amide protecting/directing group effectively promoted the C-H activation of both sp^2 and sp^3 C-H bonds, furnishing the corresponding cyclization products in good to excellent yields. This transformation tolerated a large group of substrates. With the presence of both sp^2 and sp^3 C-H at the γ -positions, the reaction occurred exclusively on the sp^2 carbon (**4b**). Both EDG (**4g**, **4j**) and EWG (**4d**, **4i**, **4l**) substituted benzene were suitable for this reaction. Remarkably, with halides present on the *ortho* positions (**4c-4e**), the directed C-H activation occurred preferentially

over oxidative addition, even for the aryl iodide (**4e**). Excellent regioselectivity was observed for the *meta*-substituted benzenes (**4h**, **4i**), giving the single cyclization products on the less sterically hindered *ortho*-carbon.

Table 1. Reaction scope for TAA directed sp^2 C-H activation^{a,c}

^a The reactions were carried out with Pd(OAc)_2 (5 mol%) and PhI(OAc)_2 (2 equiv) in 1,2-dichloroethane at 80°C under Ar, unless otherwise mentioned. ^b Run at 100 °C. ^c Isolated yield.

N1-*p*-methoxypenyl-1, 2, 3-triazole was then identified as the effective directing group to promoting the sp^3 C-H cyclization (the yield of **4m** was improved from 72% to 81% and the d.r. selectivity was almost the same). Similarly to PA-directed C-H

activation, the reaction selectively occurred on the primary carbon (CH₃) over the secondary carbon (CH₂, **4o**) for the sp³ C–H bonds (**Table 2**). Formation of azetidines was observed in all cases, even with the presence of a C–H at the δ-position (**4o**, for the synthesis of pyrrolidine). Good to excellent diastereoselectivity was observed.

Table 2. Reaction scope for TAA directed sp³ C–H activation ^{a,b,d}

^a The reactions were carried out with Pd(OAc)₂ (5 mol%), PhI(OAc)₂ (2.5 equiv), AcOH (2 equiv.) in 1,2-dichloroethane at 120 °C under Ar, unless otherwise mentioned. ^b TAA = N1-p-methoxyphenyl-1,2,3-triazole-4-carboxylic acid. ^c Determined by ¹H NMR analysis. ^d Isolated yield.

As shown in **Scheme 11**, TAA amide from tert-octylamine was also prepared and tested as a substrate that could undergo cyclization to form a pyrrolidine (activation on CH₃ at the δ-position) with 84% isolated yield. Notably, for sp² and sp³ substrates, cyclization products were the dominant products observed with the TAA directing/protecting group.

Scheme 11. Reaction scope for TAA directed sp^3 C-H activation

1.4 1,2,3-triazole directed C-H acetoxylation: Substitution

1.4.1 Rational design of TA-Py directing group

Encouraged by the TAA directed C-H activation, we then focused on the more challenging substitution reaction. **PA**, **QA** and **TAA** directing groups all gave dominant cyclization products due to a bidentate Pd-N coordination mode, which results in favored *in-plane* reductive elimination.

Scheme 12. Plausible Pd(IV) intermediate for cyclization

We wondered whether the incorporation of a tridentate directing group could force a change of the overall Pd transition state which may favor selective reductive elimination of N/C (cyclization) or O/C (substitution).^{14,15,16} As shown in **Scheme 13**, the formed Pd-C bond would be forced into an axial position, favoring C-O bond reductive elimination.

Scheme 13. Proposed Pd(IV) intermediate for substitution.

Therefore, tridentate Py-TA directing group **5a'** was prepared and charged with standard oxidation conditions. No indoline product was observed. This result was consistent with our hypothesis that tridentate directing group would successfully block the cyclization reaction path (*in-plane* reductive elimination vs. *out-of-plane* reductive elimination). However, under the standard reaction conditions, no substitution product was obtained (**Scheme 14**).

Scheme 14. Tridentate Py-TA directing group

Interestingly, when switching the protecting group from Py-TA to TA-Py, an effective arene C-H activation was achieved and the substitution product **6a** was successfully obtained in 56% isolated yield (67% conversion, **Scheme 15**).

Scheme 15. Designed TA-Py directed selective substitution

Notably, when the amide is replaced with an analogous ester or N is substituted with methyl, no acetoxylation reaction occurred, which indicated the importance of amide coordination, and further confirmed the proposed tridentate TA-Py intermediate (**Scheme 16**).

Scheme 16. Conformation for tridentate intermediate

Table 3. Optimal condition for acetoxylation^a

Oxidant	Additive (0.5 equiv)	Conversion ^b	Yield ^c	Mono:Di ^d
$\text{PhI}(\text{OAc})_2$ 2.0 equiv.	none	43%	35%	1:0.15
$\text{PhI}(\text{OAc})_2$ 2.5 equiv.	none	67%	56%	1:0.4
$\text{PhI}(\text{OAc})_2$ 3.0 equiv.	none	72%	60%	1:0.55
$\text{PhI}(\text{OAc})_2$ 2.0 equiv.	AgOAc	84%	70%	1:0.5
$\text{PhI}(\text{OAc})_2$ 2.5 equiv.	HOAc	40%	28%	1:0.1
$\text{PhI}(\text{OAc})_2$ 2.5 equiv.	KOAc	65%	51%	1:0.2
$\text{PhI}(\text{OAc})_2$ 2.5 equiv.	NaOAc	<5%		
$\text{PhI}(\text{OAc})_2$ 2.5 equiv.	AgOAc	100%	85%	1:0.8
$\text{PhI}(\text{OAc})_2$ 2.5 equiv.	AgOTf	<5%		
$\text{PhI}(\text{OAc})_2$ 2.5 equiv.	Ag_2CO_3	80%	63%	1:0.25
AgOAc 1.5 equiv.	none	<5%		

^aThe reactions were carried out with $\text{Pd}(\text{OAc})_2$ (10 mol%), additive (0.5 equiv.) and $\text{PhI}(\text{OAc})_2$ (2.5 equiv.) in 1,2-dichloroethane at 80 °C under Ar. ^bConversions were determined based on the consumption of **5a**; ^cNMR yields of product were determined with 1,3,5-trimethoxybenzene as internal standard. ^dThe ratio of the mono-substitution to di-substitution was determined by ¹H NMR analysis.

1.4.2 Reaction condition optimization

We then sought to increase the conversion by the screening of different additives, which are summarized in **Table 3**. With the presence of 0.5 equiv of AgOAc as the co-

oxidant, the reaction could reach 100% conversion, giving the substitution product **6a** (mixture of mono-OAc and di-OAc, m:d=1:0.8) in excellent yields (85% isolated yields). Notably, no cyclization product was observed under these conditions at all. To the best of our knowledge, the exclusive substitution (for the substrates that gave dominant cyclization reaction with PA, QA and TAA directing groups) revealed the first example of directing group controlled (over substrate controlled) selective C-H functionalization through designated protecting group tuning.

1.4.3 Substrate scope

Various TA-Py amides were prepared to evaluate the reaction scope. The results are summarized in **Table 4**. Similar to TAA, the TA-Py directing group could effectively promote the Pd catalyzed C-H activation for both sp^3 and sp^2 C-H bonds. A wide substrate scope was observed with this TA-Py protecting group. For sp^2 substrates, reactions occurred selectively on the *ortho*-C-H over the *ortho*-halides, including aryl iodide (**7c**, **7d**, **7f**). Both EDG (**7e**) and EWG (**7d**) modified arenes were suitable under the reaction conditions. Typically, mixtures of mono and di-acetoxylation products were observed when both *ortho* C-Hs were present. Good yields were obtained for di-substitution in the presence of excess oxidants (**7m-7o**). Excellent regioselectivity was received with the *meta*-substituted benzene, with substitution occurring at the less hindered carbons (**7g-7i**).

Table 4. Reaction scope for TA-Py directed sp² C-H activation^{a,e}

^aThe reactions were carried out with Pd(OAc)₂ (10 mol%), AgOAc (0.5 equiv.) and PhI(OAc)₂ (2.5 equiv.) in 1,2-dichloroethane at 80°C under Ar, unless otherwise mentioned. ^bRun at 100°C. ^cPhI(OAc)₂ (3 equiv.) was used at 100°C.

^dThe ratio of the mono-substitution to di-substitution was determined by ¹H NMR analysis. ^eIsolated yield.

The reaction also worked well with sp³ C-H substrates, giving the desired substitution products in good isolated yields (**Table 5**). Notably, all these substrates gave the

dominant cyclization products with PA, QA and TAA directing groups while the TA-Py directing group gave no cyclization products in all cases. Similar to TAA, the TA-Py selectively dictated C-H activation at the primary carbon (CH₃) over the secondary carbon (CH₂, **7r**). The reaction also gave very good diastereoselectivity as shown in **7p-7r**. The stereogenic centers in starting materials did not epimerize under the reaction conditions, which suggests potential applications of this strategy in complex molecule synthesis.

Table 5. Reaction scope for TA-Py directed sp³ C-H activation^{a,c}

^aThe reactions were carried out with Pd(OAc)₂ (10 mol%), AgOAc (1.5 equiv.) and PhI(OAc)₂ (3.0 equiv.) in 1,2-dichloroethane at 140°C under Ar, unless otherwise mentioned. ^bThe ratio of the mono-substitution to di-substitution was determined by ¹H NMR analysis. ^cIsolated yield.

1.5 Conclusion

In conclusion, we have developed a directing/protecting group controlled selective substitution or cyclization with designated 1,2,3-triazole in the Pd-catalyzed sp^2 and sp^3 C-H activation. This work provided the first example of Pd catalyzed C-H activation with the 1,2,3-triazole directing group. The success in the challenging substitution with the TA-Py directing group provided the opportunity for other C-H functionalization through the Pd catalyzed C-H activation by overcoming the inherent cyclization path. In addition, the sequence dependent directing group effect (TA-Py over Py-TA) further emphasized the unique reactivity of 1,2,3-triazoles as ligands in Pd catalyzed reactions, which will open the door for further developments.

This project is collaborated with Dr. Zhengrong He, Tonia Ahmed, Keith Weise, Dr. Novruz G. Akhmedov, and Dr. Jeffrey Petersen. Dr. Zhengrong He, Tonia Ahmed, Keith Weise helped with part of the substrate synthesis. Dr. Petersen helped with the X-ray crystallography study for product **3a**. Dr. Akhmedov carried out the NMR analysis.

This project is published on *Chem. Sci.*, **2013**, 4, 3712-3716

Part II

Palladium-Catalyzed Aerobic Oxidative C–H Olefination with Removable 1,2,3-Triazole Directing Group

2.1 Introduction

During the last decade, transition metal catalyzed C-H functionalization has been utilized as an efficient approach in complex molecule synthesis. One applicable transformation is the Pd-catalyzed C-H olefination of arene. This method, known as Fujiwara-Moritani oxidative Heck reaction, allows direct installation of alkene functional groups on aromatic rings.¹⁷ However, poor selectivity remains a challenge for this transformation, since selectivity generally relies on the reactivity of different C-H bonds for given substrates.^{18,19} Recently, Yu reported one suitable approach to selective olefination on the C-3 position of pyridine derivatives by employing a bidentate ligand (**Scheme 17**).²⁰ However, a large excess of arene (16 equiv.) was required, limiting the potential application.

Scheme 17. Ligand-promoted C-H olefination of pyridines.

On the other hand, directing group (DG) strategies were still a dominant approach for selective C-H activation.² Various directing groups have been investigated for C-H olefination, such as OR, COOH and pyridine (**Scheme 18**).^{21,22}

Scheme 18. Selective C-H olefination using directing groups

As mentioned in the previous part, amine is usually not an effective directing group. An interesting approach is then using a removable amide protecting group for chelation control. Among literature reported examples, picolinic acid (**PA**) and quinaldic acid (**QA**) moieties were the most successful precursors. Interestingly, neither compound has been used as directing groups for C-H olefination under oxidative Heck conditions. The only successful example of C-H olefination for protected amine derivatives was the -NHTf system reported by Yu and coworkers (**Scheme 19**).²³ However, there were some problems associated with this approach. First, excess silver salts (2.5 equiv) were required as oxidant to facilitate the reaction. Second, the reaction proceeded with a low reaction rate (72h under 130 °C). Additionally, Tf is not a good protecting group for amines due to some difficulty in the deprotection process. Thus, a new removable

directing group is highly desired to promote the reaction under “silver-free” oxidative condition.

Scheme 19. Tf amide directed Pd-catalyzed C-H Olefination

2.2 Optimization of 1,2,3-triazole directing group

As discussed in **Part I**, 1,2,3-triazoles (TA) were demonstrated as a new versatile removable directing group in promoting sp² and sp³ C-H activation. Impressively, the triazole DGs demonstrated excellent chemoselectivity, achieving selective C-N reductive elimination (cyclization) or C-O reductive elimination (substitution) through alternating the triazole DG coordination patterns (TAA vs TA-Py, **Figure 20**).²⁴ Unfortunately, under previous standard conditions (PhI(OAc)₂ as the oxidant, 100 °C), no C-H olefination was observed with either the TAA or TA-Py directing group. The presence of acrylate prevented the formation of the undesired cyclization or acetoxylation with complete recovery of starting material. Due to its strong oxidizing ability, PhI(OAc)₂ was commonly involved in Pd(II)-Pd(IV) reaction cycle. Considering the well accepted

Pd(0)-Pd(II) catalytic cycle for an oxidative Heck reaction, we then turned our attention to weaker oxidants.

Scheme 20. TA-promoted selective C-H activation

Interestingly, a brief screening of oxidants revealed AgOAc (2.5 equiv) effectively promoted this C-H olefination, giving the desired alkene **8a** in good yield (51% conversion and 49% yield). Moreover, cyclization product was not observed even with the bi-dentate TA(Bn) as the directing group under this new condition (AgOAc as oxidant). In fact, the desired C-H olefination product **8b** was obtained in 31% yield along with olefination on the triazole C-H bond (**Scheme 21-A**). Thus, Pd-catalyzed direct triazole C-H activation, which has been reported by Ackermann, Jiang, and others, is the main problem for achieving C-H olefination with good regioselectivity.²⁵ We then postulated that the 4,5-disubstituted triazoles TA(Ph), shown in **Scheme 21-B**, should be an effective DG to promote this C-H olefination by substituting the reactive triazole C-H bond. As expected, reaction of TA(Ph) modified **11** under the standard condition gave the desired C-H olefination product **12a** in excellent yield (94%). This result was crucial

since it confirmed the possibility of using triazole DG to promote C-H activation under Pd(0)-Pd(II) conditions.

Scheme 21. TA-promoted C-H olefination with AgOAc as oxidant

A) TA-promoted C-H olefination: undesired TA-C-H activation

B) Success C-H olefination with modified TA(Ph) directing group

2.3 Selected Optimization of Reaction Conditions

Next, we put our effort into exploring the feasibility of using molecular O₂ as the terminal oxidant to substitute silver salts with the knowledge of a low oxidation potential between Pd(0) and Pd(II).^{26,27} The screening of conditions is summarized in **Table 6**.

Firstly, the TA(Ph) amide **11** alone could give the desired C-H olefination with O₂ oxidant (entry 2), though in low yield (22%). Addition of HOAc (2.5 equiv) slightly improved the reaction performance (entry 3) with significant amount of **11** leftover. Finally, addition of Cu(OTf)₂ as co-catalysts (10 mol %) led to complete **11** conversion, giving the desired C-H olefination product **12a** in excellent isolated yield (95%).²⁸ To the best of our knowledge, this is the first successful example of removable directing group promoted C-H olefination using O₂ as the terminal oxidant.²⁹

2.4 Evaluation of other directing groups

Substrates containing other common directing groups were also prepared and evaluated under the same conditions. As shown in **Scheme 22**, poor yields were obtained in all tested cases, including PA and QA modified substrates. Notably, PA and QA could not promote effective C-H olefination due to the rapid Pd decomposition (formation of palladium black). These results highlighted the unique reactivity of 1,2,3-triazole directing groups in promoting C-H activation. Triazole ester and N-methyl triazole amide gave no reactions, which was consistent with the chelation model (for successful C-H activation) as reported in other similar systems. To evaluate the reaction scope, various TA(Ph) modified substrates were prepared and treated with the optimal conditions.

Table 6. Selected Optimization of Reaction Conditions^a

entry	Variations from the 'standard' conditions	Conversion of 11a (%)	Yield of 12a (%) ^b
1	w/o Pd(OAc) ₂	0	0
2	w/o HOAc and Cu(OTf) ₂	24	22
3	w/o Cu(OTf) ₂	30	28
4	w/o HOAc	50	48
5	CuCl ₂ instead of Cu(OTf) ₂	<5	<5
6	Cu(OAc) ₂ instead of Cu(OTf) ₂	65	61
7	HOAc as solvent	33	31
8	Toluene as solvent	78	75
9	PdCl ₂ instead of Pd(OAc) ₂	<10	<10
10	Air	75	60
11	no O ₂ (Ar protection)	trace	trace

^aReaction conditions: **11** (0.1 mmol), Butyl acrylate (0.4 mmol), catalyst, additives and solvent (0.2 M) in 20 mL Schlenk tube with O₂ balloon; ^bYield was determined by ¹H NMR using 1,3,5 trimethoxybenzene as the internal standard.

Scheme 22. Evaluation of other directing groups

1.5 Substrate scope

As shown in **Table 7**, this new TA-directing group tolerated a large number of substrates, furnishing the corresponding olefination in good to excellent yields. Both EDG (**13b**) and EWG (**13c**) modified arenes were suitable for this reaction. Notably, substrates with *ortho*-halides (**13c**, **13d**) could survive the reaction, giving the desired C-H activation (over oxidative addition) in good yields. Good regioselectivity was obtained for the *meta*-substituted benzenes, with substitution occurring primarily at the less hindered *ortho*-carbon position (**13e-13g**). Typically, the selectivity of mono and diolefination would be poor when both *ortho*-C-Hs were present (**13j** and **13k**). This problem was overcome through increasing the steric bulk at the benzylic position. As shown in **13l**, incorporation of a methyl group effectively improved the m:d selectivity to

>20:1. Meanwhile, using excess amount of alkene (12 equiv.) gave the di-olefination in good yields (**13m-13o**).

The scope of alkene was also evaluated. Besides acrylate, most of the other activated alkenes, such as, acrylonitrile (**14c**), acrylamide (**14d**), vinyl phosphate (**14e**) and vinyl sulfone (**14f**) are suitable for this transformation, giving the desired olefins in excellent yields. Impressively, non-active olefins, such as styrene derivatives, could also undergo this transformation with good to excellent yields (**14g-14i**). However, similar to other reported Heck-type reactions, α or β substituted alkenes failed to give the desired products due to steric hindrance on either alkene insertion or β -hydride elimination steps. Nevertheless, the broad substrate scope, simple reaction conditions and use of atmospheric oxygen as the oxidant highlighted the advantages of this new triazole-directing group in promoting selective C-H olefination.

Table 7. Substrate Scope for phenylethyl amine derivatives^a

^aGeneral reaction conditions: **11** (0.2 mmol), alkene (0.8 mmol), HOAc (5.0 mmol) and catalyst in 1,4-dioxane (1.0 mL), and Condition **A**: 7.5 mol % Pd(OAc)₂ and 10 mol % Cu(OTf)₂, O₂ balloon, 105 °C, 20 h; Condition **B**: 10 mol % Pd(OAc)₂ and 10 mol % Cu(OTf)₂, 1 atm O₂ charged in seal tube, 115 °C, 20 h; Condition **C**: 15 mol % Pd(OAc)₂ and 10 mol % Cu(OTf)₂, 2.4 mmol *n*-butyl acrylate, 1 atm O₂ charged in seal tube, 115 °C, 20 h. Isolated yield. ^b The ratio of mono- and di-substitution was determined by ¹HNMR.

Table 8. Substrate Scope for different alkenes

General reaction conditions: **11** (0.2 mmol), alkene (0.8 mmol), HOAc (5.0 mmol), 10 mol % $\text{Pd}(\text{OAc})_2$ and 10 mol % $\text{Cu}(\text{OTf})_2$, 1 atm O_2 charged in seal tube, 115 °C, 20 h. Isolated yield.

1.6 Kinetic isotope effect and derivatization

1.6.1 Kinetic isotope effect

Kinetic isotope studies were also performed to probe the reaction mechanism. A primary KIE was observed ($k_{\text{H}}/k_{\text{D}} = 2.1$) as shown in **Scheme 23**, suggesting C-H activation over a Lewis acid catalyzed Friedel-Craft type mechanism.

Scheme 23. Kinetic isotope effect

1.6.2 Derivatization

Removal of TA directing group was demonstrated in **Scheme 24-A** using the general protocol reported by Chen.^{29a} The Boc protected alkene-amine was obtained in excellent yield. Finally, treating the resulting acrylate-amide product (**3a**) with NaH gave the tetrahydroisoquinoline in excellent yield (**Scheme 24-B**), further highlighting the efficiency and potential application of this method in complex molecules synthesis.

Scheme 24. Derivatization

A) Removal TA directing group

B) Synthesis of tetrahydroisoquinoline

1.7 Conclusion

In conclusion, we have exposed 1,2,3-triazoles as effective directing groups in promoting aerobic C-H oxidative olefination. This study not only revealed a new efficient and economic approach (using 1 atm O₂ as the terminal oxidant) in achieving selective C-H olefination, but also further affirmed the versatile reactivity of 1,2,3-triazole in promoting metal catalyzed C-H activation. Other synthetic applications using this new TA-directed C-H activation strategy are currently under investigation.

This project is published on *Org. Lett.* **2014**, *16*, 4448-4451.

Part III

Nickel-catalyzed directed sulfenylation of sp^2 and sp^3 C–H bonds

3.1 Introduction

As discussed in the previous section, directing group assisted palladium C-H activation of sp^3 C-H bonds has been well studied and explored. However, the use of precious late transition metals such as palladium or rhodium presents issues due to the higher cost when compared to first row transition metals. For this reason, a directed C-H activation process involving abundant first row transition metals, such as iron, nickel, and copper, become more attractive. However, the differences in electronic character of first row transition metals, may present further challenges in the C-H activation and functionalization steps. With less electron density presented in first-row transition metals, direct insertion into carbon-hydrogen bonds may be less favored.³⁰ Additionally, the reduced stability of carbon-metal bonds for first row transition metals may lead to uncontrollable and unpredictable reactivity upon C-H activation. In previously reported examples using first row metals, the C-H activation processes are suggested to be more complicated than simple base induced metallation. Single electron mechanisms may also be operable, which potentially leads to C-H activation predicated more strongly on electronic character, rather than chelation control.

To circumvent the issues mentioned earlier, more complex bidentate and tridentate chelating directing groups may be applied. Given the higher oxidation potential of first

row-metals (such as Cu(III), Ni(IV)), the formation of higher valent species for reductive elimination and desired product formation can be difficult. Higher coordination modes brought about by auxiliary tethered DGs offers an opportunity to achieve C-H activation in first row-metals due to: 1) a closer and more intimate interaction of smaller metal-center with the desired CH bond. 2) more rigid and entropically favored metallacycle upon C-H activation and 3) a metallacycle intermediate more poised for subsequent oxidation (using either electrophilic reaction partner or external oxidant) following C-H activation (**Scheme 25**). With these benefits brought by bidentate and tridentate chelating directing groups, first-row transition metals may be more effectively utilized in future C-H activation approaches.

Scheme 25. Proposed First-row transition metal catalyzed C-H activation

Recent progress on copper catalyzed/mediated C-H activation with the assistance of a bidentate directing group was illustrated in **Scheme 26**. Copper has been widely explored as an alternative metal for converting the *ortho*-C-H bond on benzoic acid derivatives into C-heteroatoms, including F and SCF₃ functional group. However, copper is still not an efficient catalyst towards sp³ C-H bond activation. So far, the only

successful example was reported by Ge and coworkers for C-H amidation, giving β -lactam as major products.³¹

Meanwhile, iron was also investigated for both sp^2 and sp^3 C-H activation in cooperation with Grignard or organozinc reagent, which allows the reaction to proceed under milder condition for C-C bond formation (**Scheme 27**). One general disadvantage is the functional group tolerance of highly reactive Grignard or organozinc reagents, limiting the substrate scope. The detailed mechanism is still unclear, however, the requirement of a bidentate chelating directing group under these oxidative conditions highlighted the importance of greater saturation around the metal.

Scheme 26. Copper catalyzed/mediated bidentate DG assisted C-H activation

Scheme 27. Iron catalyzed bidentate DG assisted C-H activation

Nickel was always considered as a potential substitute for palladium (same group with d^{10} electron around). Nickel catalyzed directed C-H activation was rarely reported until bidentate directing groups were applied (**Scheme 28**). Recently, most palladium-mimicked transformations, such as arylation, alkylation, alkenylation, and alkynylation, have been accomplished by nickel towards unactivated C-H bonds (sp^2 and sp^3). When

comparing to previously reported palladium-catalyzed reactions, no silver salt is required as an external oxidant or halide scavenger. The associated limitation is that Thorpe–Ingold effect, which required two more substituents on α -carbon center, is pivotal to enhance reactivity. Besides, the reaction scopes could be extended with other coupling partners, which are not compatible in palladium systems. For example, when internal alkynes are employed, the oxidative cycloaddition will occur, furnishing annulated isoquinolone products.

The detailed mechanism for these transformations is still unclear at this point. This chelation directing group strategy unveiled one potential C-H activation protocol for first-row transition metals, thus, more practical transformation will be expected.

Scheme 28. Selected examples for nickel catalyzed C-H activation

3.2 Research objective

3.2.1 C-S bond formation

Organosulfur compounds present significant roles in chemical and biological research. Therefore, effective formation of a C-S bond is a synthetically important transformation (**Scheme 29**).

Scheme 29. Five of top selling drugs in the USA in 2013 contain sulfur

Previously, the cross coupling approach between aryl-halide and thiol/disulfide has been achieved for the sp^2 C-S bond construction under special conditions (solvents, catalyst and ligand) with limited reaction scope (**Scheme 30**).³² The biggest concern is the coordination ability of sulfur atoms toward various metal cations, thus leading to

potential poisoning of the catalyst. Thus, new approaches that can efficiently construct C-S bonds are always highly desirable.

Scheme 30. C-S formation through cross-coupling

3.2.2 C-S bond formation through C-H activation

Directed C-H sulfenylation offers high efficiency and good atom economy (by avoiding the usage of aryl halides), though challenges still arise.³³ These issues are manifested by the strong coordination between metal and sulfur, potentially inhibiting C-H activation and or catalyst turnover.

In 2006, Yu and co-workers developed the first directed C-H sulfenylation by coupling 2-phenylpyridine with disulfide or thiol precursors.³⁴ One limitation of this reaction is the use of a stoichiometric amount of copper (**Scheme 31-A**). Nevertheless, this reaction provides insight for reaching the catalytic C-H sulfenylation by first-row transition metals. More recently, directed C-H sulfenylation was further developed and accomplished with precious transition metals like Rh and Pd.³⁵ The directing group is limited to N-containing heterocyclic rings in these cases. Also, other metal salts and ligand additives are required, which makes this transformation less practical. (**Scheme 31-B**). Thus, an efficient and economical approach for catalytic C-H sulfenylation with abundant first-row transition metals is in high demand.

Scheme 31. Selected examples for directed C-H sulfenylation

A) Cu mediated C-H sulfenylation

B) Rh or Pd catalyzed C-H sulfenylation

Reaction conditions

Very recently, Daugulis and co-workers reported a successful example of sp^2 C-H sulfenylation using 8-aminoquinoline (Q) moiety as the chelate directing group with $\text{Cu}(\text{OAc})_2$ as catalyst precursor (up to 50% loading).³⁶ However, under their optimal conditions, sp^3 C-H sulfenylation did not occur (< 15% yield) when using 1 equiv. of $\text{Cu}(\text{OAc})_2$ (**Scheme 32**). Moreover, disulfides were required as the sulfur source/oxidant, decreasing atom economy with limited scope. Inspired by previous works, we wanted to forge this bidentate directing group strategy into a general protocol for C-H sulfenylation of both sp^3 and sp^2 C-H bonds under catalytic conditions. Additionally, thiols are enlisted as the sulfur source.³⁷

Scheme 32. Cu catalyzed C-H sulfenylation: Challenge for sp^3 C-H

3.3 Evaluation of directing groups

To explore the possibility of sp^3 C-H sulfenylation, we turned our attention to nickel complexes. Nickel catalysis is known for its versatile reactivity including an operable and rapid single electron transfer (SET).³⁸ During the past several years, nickel catalysis has received increasing attention due to the promising reactivity toward directed sp^3 C-H functionalization. This is evidenced through several examples reported in the literature for C-C and C-N formation. To explore the feasibility of directed C-H sulfenylation, we prepared various amide **18** (containing different directing groups) and charged them with nickel catalysts under different conditions. The results are summarized in **Scheme 33**.

As shown in **Scheme 33**, substrates with various literature-reported directing groups were prepared, including quinoline (**18a**), pyridine (**18b**), Yu-Wasa auxiliary (**18c**)³⁹ and 1,2,3-triazole (**18d**). In Daugulis' previous report, DMSO was revealed to be the optimal solvent for sp^2 C-H sulfenylation. One plausible reason was the inherent redox stabilization ability of DMSO towards thiol-disulfide interconversion.⁴⁰ However, with a nickel catalyst, no sp^3 C-H activation was observed using DMSO as solvent under various conditions. Interestingly, the only condition giving the desired sp^3 C-H

sulfenylation was the reaction of the quinoline directing group modified substrate **18a** in DMF with LiOtBu as the base (50% yield, 58% conversion). Notably, both the choice of solvent and base are crucial: using other solvents (DMSO, DCE or MeCN) with LiOtBu or using other bases (Cs₂CO₃, KOtBu or NaOtBu) in DMF gave significantly lower reactivity. Moreover, the quinoline substrate **18a** gave significantly better results than other directing groups.

Scheme 33. Evaluation of directing groups

Notably, complete conversion of starting materials was observed with 1,2,3-triazole modified substrate **18d**, though rather complex reaction mixtures were obtained. Investigation of other triazole-directing groups are currently undergoing in the group.

3.3 Reaction condition optimization

Based on these preliminary results, we conducted detailed condition screening. As shown in **Table 9**, under the optimal conditions with Ni(OTf)₂ as a catalyst precursor, LiO^tBu as base, DMF as solvent and with argon protection, the desired sp³ C–H sulfenylation product **19a** was obtained in 86% isolated yields. Interestingly, reaction parameters under optimal conditions seemed to be crucial. First, under the identical conditions, other tested metal complexes, including Cu(OAc)₂, CuI, Pd(OAc)₂, [Rh(COD)Cl]₂, RuCl₃, and Fe(OTf)₃, gave little reactivity with less than 10% C–H sulfenylation products obtained (entry 2). Similarly, both DMF and LiO^tBu were critical for the reaction performance (entries 3–5); Ni(OTf)₂ gave the best results when compared with other nickel salts (entries 6 and 7). The reaction could not reach total completion without argon protection (entry 8), suggesting the decomposition of nickel catalysts under an air atmosphere over time. Finally, the addition of previously reported assisting ligands (dppbz and MesCOOH, entries 9 and 10) did not show improvement. Considering the strict reliance on DMF as the optimal solvent and lithium base, it suggested the formation of Ni–DMF complexes under the reaction conditions, which served as the actual catalysts in promoting the reaction. Decreasing nickel catalyst loading or reducing the amount of disulfide caused lower yields due to incomplete reaction over time (entries 11 and 12). Interestingly, thiophenol also gave 15% yield under optimal conditions, suggesting the

importance of oxidants involved in the catalytic cycle. Inspired by this result, coupling with thiophenol was explored. As shown in entry 14, the reaction of thiophenol could not reach a full conversion (56%) under air and significant product decomposition was observed. To our delight, electron-deficient benzenethiol exhibits better performance with 83% yield (100% conversion). To the best of our knowledge, this is the first example that successfully achieved sp^3 C–H sulfenylation with disulfide or thiol in excellent yields.

Table 9. Selected conditions on Ni catalyzed sp³ C-H sulfenylation^a

entry	Variations from the “standard” conditions	yield (convn.) ^c
1	none	88% (100%)
2	Other catalysts (100%), including Cu(OAc) ₂ , CuI, Pd(OAc) ₂ , [Rh(COD)Cl] ₂ , RuCl ₃ , Fe(OTf) ₃ et al.	<5% (<10%)
3	Other solvents, including DMSO, CH ₃ CN, DMA	<20% (<30%)
4	NaO ^t Bu as base	<5% (<5%)
5	KO ^t Bu as base	9% (15%)
6	NiCl ₂ (DME) 20 % as cat.	84% (95%)
7	Ni(acac) ₂ 20 % as cat.	82% (91%)
8	Under air, no argon	75% (82%)
9	Air, Ni(OTf) ₂ + dppbz	70% (82%)
10	Air, Ni(OTf) ₂ + MesCOOH	78% (88%)
11	1.5 equiv PhSSPh	56% (67%)
12	10% Ni(OTf) ₂	52% (50%)
13	PhSH 2.5 equiv.	15% (20%)
14	PhSH under Air	50% (56%) ^b
15	<i>o</i>-FPhSH, under Air	83% (100%)^b

Reaction conditions: 1a (0.2 mmol), PhSSPh (2.5 equiv.), Ni(OTf)₂ (20 mol%), Base (5 equiv.) and additive (if applicable) in dry DMF (0.4 mL), Ar; ^b ArSH (4 equiv.), LiOtBu (7 equiv.) was used; ^c The yield was determined by ¹H NMR using 1,3,5-trimethoxybenzene as internal standard.

3.4 Substrate scope

3.4.1 Substrate scope of Ni catalyzed sp³ C-H sulfenylation

With this optimal condition in hand, we embarked on the evaluation of the reaction substrate scope.

Table 10. Reaction scope of Ni catalyzed sp³ C-H sulfenylation with disulfides

Reaction conditions: **1a** (0.3 mmol), PhSSPh (2.5 equiv.), $\text{Ni}(\text{OTf})_2$ (20 mol%), LiO^tBu (5 equiv.) in dry DMF (0.6 mL), Ar , $120\text{ }^\circ\text{C}$. Isolated yield.

As shown in **Table 10**, the quinoline directing group effectively promoted sp³ C–H bond activation and furnished the sulfenylation products in good yields. In general, the reaction targeted methyl C–H (CH_3) over methylene (CH_2), even in the presence of

benzylic CH₂ (**20d**). Similarly, 1-methyl-cyclobutane derivatives gave the desired sulfenylation product with **20i** without C-H sulfenylation on the ring. Notably, substrates with cyclopropane on the side chain could also tolerate this transformation (**20e**) without ring opening. Moderate selectivity was observed when two methyl groups were present (formation of a mixture of mono and disulfenylation, **20j**). The Thorpe–Ingold effect was also necessary for the transformation. The transformation is targeting exclusively on β-C-H, since γ-CH will not be activated even with more reactive sp² C-H bonds.

Table 11. Reaction scope of Ni-catalyzed sp³ C-H sulfenylation with thiolphenols

Reaction conditions: **amide** (0.3 mmol), Ni(OTf)₂ (20 mol%), ArSH (4 equiv.), LiO^tBu (7 equiv.) in dry DMF (0.6 mL), Air, 120 °C. Isolated yield.

Considering the obvious practical advantages, we then explored various thiols (instead of disulfides) as the sulfur source. Most EWG substituted thiolphenols gave good

yields (**21a**, **21b**, **21d–21f**). Lower yields were observed with electron rich thiophenols (**21g**) and ortho-CF₃ thiophenols (**21c**). Reactions with alkyl thiol or disulfide did not proceed under these conditions, even with 1 equiv of the nickel catalyst precursor being used. Nevertheless, even with some limitation, this method provides the first successful example to achieve sp³ C–H sulfenylation.

3.4.2 Substrate scope of Ni catalyzed sp² C–H sulfenylation

Although the exact reason for significantly better results using the combination of DMF and LiO^tBu is unclear, this new condition could presumably be extended to the sp² C–H sulfenylation. Furthermore, the application of thiophenol as the sulfur source greatly extended the reaction scope. After a brief screening, a general condition was revealed with air-stable NiCl₂(DME) as a catalyst precursor (10 mol%) at 100 °C under ambient pressure. Under this mild condition, good to excellent yield of sp² C–H sulfenylation was achieved.

The substrate scope is summarized in **Table 12**. First, both EWG and EDG substituted benzenes were suitable for this reaction. Good regioselectivity was observed for the *meta*-substituted benzenes (**22c** and **22d**) with sulfenylation occurring on the less hindered C–H bond. Interestingly, a reversed regioselectivity was obtained with *m*-Cl and *m*-F substituted benzene (**22e** and **22f**), leading to C–S bond formation at the adjacent C–H bond (confirmed by X-ray crystallography). The exact reason for this unusual regioselectivity is currently under investigation. The selectivity between mono- and di-sulfenylation was poor as other reported cases. In those cases, the di-sulfenylation products were achieved with good yields (**22m–22o**) with an increasing amount of

thiophenol/LiO^tBu. Notably, this strategy was also suitable for di-sulfenylation of meta-substituted benzene (**22k** and **22l**). Thiophene was also suitable for this reaction with C–S products formed in good yield (**22i**).

Table 12. Reaction scope for sp² C–H sulfenylation with benzoic acid derivatives^a

^aReaction conditions: **amide** (0.3 mmol), ArSH (2.2 equiv.), NiCl₂(DME) (10 mol%), LiO^tBu (5 equiv.) in dry DMF (0.6 mL), Air, 100 °C. Isolated Yield. ^b ArSH (4.0 equiv.), NiCl₂(DME) (15 mol%), LiO^tBu (7 equiv.) was used, 110 °C.

The scope of thiols was also evaluated in **Table 13**. Besides thiophenol, both electron-rich and electron-deficient benzenethiols were tolerated, giving promising yields. Notably, with halides present on the benzene ring, the C–S bond formation occurred over oxidative addition (**23h**, **23j**). Diphenylselenium (**23m**) was examined and gave the desired products in good yields. The challenging aliphatic thiols showed almost no reactivity under standard conditions. Remarkably, using aliphatic disulfide and 50% NiCl₂(DME), the reactions proceeded well and the desired products (**23n–23p**) were produced in good yields. These results clearly highlighted the significantly improved reactivity of this newly discovered catalytic system in C–H sulfenylation.

A gram-scale synthesis was carried out as shown in **Scheme 34**, which showcased the robust nature of this new method.

Scheme 34. Gram-scale synthesis

3.5 Mechanism investigation

3.5.1 Radical scavenger experiment

To understand the reaction mechanism, we first performed a radical trapping experiment (**Scheme 35**). TEMPO (3 equiv.) did not influence the reaction efficiency. This result suggested that a single electron transfer (SET) process was likely not involved.

Table 13. Reaction scope for sp^2 C-H sulfenylation with thiolphenols^{a,b}

^a Reaction conditions: **1a** (0.3 mmol), ArSH (2.2 equiv.), $NiCl_2(DME)$ (10 mol%), LiO^tBu (5 equiv.) in dry DMF (0.6 mL), Air, 100 °C. ^b Isolated yield. ^c 120 °C. ^d Disulfide 1.5 equiv. and 50 mol% $NiCl_2(DME)$ was used.

Scheme 35. Radical scavenger experiment

3.5.2 Mercury poison experiment

Mercury metal could inhibit the reactivity of heterogeneous catalyst by forming an alloy, while unaffected the homogeneous catalysis process. Thus, a mercury poison experiment was tested. As shown in Scheme 36, mercury poisoning was done at the starting pointing ($t = 0$) and/or at some reaction point ($t = 25$ min) and showed no quenching of reactions, indicating a homogenous nickel catalytic process.

Scheme 36. Mercury poison experiment

3.5.3 Competition experiment

The competition experiment between different arenes gave exclusively sulfenylation on electron-deficient aromatic rings (**Scheme 37**). This result strongly suggests that C–H bond cleavage might depend largely on acidity.

Scheme 37. Competition experiment

Scheme 38. Proposed reaction mechanism

3.5.4 Plausible Mechanism

Based on the evidence above, the proposed catalytic cycle was shown in **Scheme 38**. After the nickel coordination due to the presence of the directing group (quinoline amide), the C-H activation occurs with the assistance of strong base. Presumably, the disulfide performed as a true oxidant in promoting either Ni(I)/Ni(III) or Ni(II)/Ni(IV) catalytic cycle under disulfide/Ar conditions.⁴¹ Interestingly, the thiol/air system gave faster reaction kinetics than the disulfide reactions. Detailed mechanism is still unclear and the investigations are currently underway in our lab.

3.6 Conclusion

In summary, we have developed a general synthesis of substituted sulfide carboxylic acid derivatives by directed C–H sulfenylation. The efficient C–S bond formation was enabled through homogenous nickel catalysis with C–H bond activation on both sp^2 and sp^3 carbon atoms. Furthermore, this study revealed a new efficient and economical approach towards sulfur containing product formation (using thiol directly), highlighting the potential application of the former in biological and pharmaceutical sciences. Such investigations are currently underway in our laboratory.

This project is collaborated with Dr. Jeffrey Petersen. Dr. Petersen helped with the X-ray crystallography study for product **22a**, **22e**

This project is published on *Chem. Commun.*, **2015**, 51, 7863-7866

References

-
- 1 For Reviews, see: (a) Labinger. J. A.; Bercaw. J. E. *Nature* **2002**, *417*, 507; (b) Kakiuchi. F.; Chatani. N. *Adv. Synth. Catal.* **2003**, *345*, 1077–1101; (c) Davies. H. M. L.; Manning. J. R. *Nature* **2008**, *451*, 417; (d) Giri. R.; Shi. B.-F.; Engle. K. M.; Mangel. N.; Yu. J.-Q. *Chem. Soc. Rev.* **2009**, *38*, 3242–3272; (e) Ackermann. L.; Vicente. R.; Kapdi. A. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792–9826; (f) Bellina. F.; Rossi. R. *Chem. Rev.* **2010**, *110*, 1082–1146; (g) Messaoudi. S.; Brion. J.-D.; Alami. M. *Eur. J. Org. Chem.* **2010**, *21*, 6495–6516; (h) Cho. S. H.; Kim. J. Y.; Kwak. J.; Chang. S. *Chem. Soc. Rev.* **2011**, *40*, 5068–5083; (i) Baudoin. O. *Chem. Soc. Rev.* **2011**, *40*, 4902–4911; (j) Yeung. C. S.; Dong. V. M. *Chem. Rev.* **2011**, *111*, 1215–1292; (k) Li. B.-J.; Shi. Z.-J. *Chem. Soc. Rev.* **2012**, *41*, 5588–5598; (l) Kuhl. N.; Hopkinson. M. N.; Wencel-Delord. J.; Glorius. F. *Angew. Chem., Int. Ed.* **2012**, *51*, 10236–10254.
 - 2 For Reviews, see: (a) Daugulis. O.; Do. H.-Q.; Shabashov. D. *Acc. Chem. Res.* **2009**, *42*, 1074–1086; (b) Chen X.; Engle. K. M.; Wang. D.-H.; Yu. J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094–5115; (c) Lyons. T. W.; Sanford. M. S. *Chem. Rev.* **2010**, *110*, 1147–1169; (d) Colby. D. A.; Tsai. A. S.; Bergman. R. G.; Ellman. J. A. *Acc. Chem. Res.*, **2012**, *45*, 814–825; (e) Neufeldt. S. R.; Sanford. M. S. *Acc. Chem. Res.*, **2012**, *45*, 936–946; (f) Engle. K. M.; Mei. T.-S.; Wasa. M.; Yu. J.-Q. *Acc. Chem. Res.*, **2012**, *45*, 788–802; (g) Wang. C.; Huang. Y. *Synlett*, **2013**, *24*, 145–149; (h) Ackermann. L. *Acc. Chem. Res.*, **2014**, *47*, 281–295; (i) Shi. G.; Zhang. Y. *Adv. Synth. Catal.*, **2014**, *356*, 1419–1442; (j) Mo. F.; Tabor. J. R.; Dong. G. *Chem. Lett.*, **2014**, *43*, 264–271.
 - 3 For example of Tf amide as directing group: (a) Mei. T.-S.; Wang. X.; Yu. J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 10806; (b) Vickers. C. J.; Mei. T.-S.; Yu. J.-Q. *Org. Lett.* **2010**, *12*, 2511–2513.
 - 4 Chan. K. S. L.; Wasa. M.; Chu. L.; Laforteza. B. N.; Miura. M.; Yu. J.-Q. *Nature Chem.* **2014**, *6*, 146.
 - 5 Zaitsev. V. G.; Shabashov. D.; Daugulis. O. *J. Am. Chem. Soc.* **2005**, *127*, 13154.

- 6 For example of picolinic amide as directing group: a) Shabashov, D.; Daugulis, O.; *J. Am. Chem. Soc.* **2010**, *132*, 3965; b) Zhao, Y.; Chen, G. *Org. Lett.* **2011**, *13*, 4850; c) He, G.; Chen, G. *Angew. Chem. Int. Ed.* **2011**, *50*, 5192; d) He, G.; Lu, C.; Zhao, Y.; Nack, W. A.; Chen, G. *Org. Lett.* **2012**, *14*, 2944-2947; e) Zhang, S.-Y.; He, G.; Zhao, Y.; Wright, K.; Nack, W. A.; Chen, G. *J. Am. Chem. Soc.* **2012**, *134*, 7313; i) Zhao, Y.; He, G.; Nack, W. A.; Chen, G. *Org. Lett.* **2012**, *14*, 2948-2951
- 7 For examples of other bidentate auxiliary DGs for amide derivatives: a) Rodriguez, N.; Revilla, R. J. A.; FernandezIbanez, M. A.; Carretero, J. C. *Chem. Sci.* **2013**, *4*, 175; b) Fan, M.-Y.; Ma, D.-W. *Angew. Chem., Int. Ed.* **2013**, *52*, 12152; c) Wang, C.; Chen, C.; Zhang, J.; Han, J.; Wang, Q.; Guo, K.; Liu, P.; Guan, M.; Yao, Y.; Zhao, Y. *Angew. Chem. Int. Ed.* **2014**, *53*, 9884.
- 8 For example of amide as directing group for Pd-catalyzed C-H functionalization of acid derivatives: a) Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2010**, *132*, 3965; b) Tran, L. D.; Daugulis, O. *Angew. Chem., Int. Ed.* **2012**, *51*, 5188; c) Chen, F.-J.; Zhao, S.; Hu, F.; Chen, K.; Zhang, Q.; Zhang, S.-Q.; Shi, B.-F. *Chem. Sci.* **2013**, *4*, 4187
- 9 a) He, G.; Zhao, Y.; Zhang, S.; Lu, C.; Chen, G. *J. Am. Chem. Soc.* **2012**, *134*, 3; b) Nardes, E. T.; Daugulis, O. *J. Am. Chem. Soc.* **2012**, *134*, 7.
- 10 Zhang, S.-Y.; He, G.; Nack, W. A.; Zhao, Y.; Li, Q.; Chen, G. *J. Am. Chem. Soc.* **2013**, *135*, 2124.
- 11 a) Duan, H. F.; Sengupta, S.; Petersen, J. L.; Akhmedov, N. G.; Shi, X. D. *J. Am. Chem. Soc.* **2009**, *131*, 12100. b) Duan, H. F.; Sengupta, S.; Petersen, J. L.; Shi, X. D. *Organometallics* **2009**, *28*, 2352. c) Liao, W. Y.; Chen, Y. F.; Liu, Y. X.; Duan, H. F.; Petersen, J. L.; Shi, X. D. *Chem. Commun.* **2009**, 6436. d) Chen, Y. F.; Yan, W. M.; Akhmedov, N. G.; Shi, X. D. *Org. Lett.* **2010**, *12*, 344. e) Wang, D. W.; Ye, X. H.; Shi, X. D. *Org. Lett.* **2010**, *12*, 2088. f) Yan, W. M.; Ye, X. H.; Akhmedov, N. G.; Petersen, J. L.; Shi, X. D. *Org. Lett.* **2012**, *14*, 2358. g) Yan, W. M.; Ye, X. H.; Weise, K.; Petersen, J. L.; Shi, X. D. *Chem. Commun.* **2012**, 48, 3521. h) Xi, Y. M.; Wang, D. W.; Ye, X. H.; Akhmedov, N. G.; Petersen, J. L.; Shi, X. D. *Org. Lett.* **2014**, *16*, 306. i) Xi, Y. M.; Dong, B. L.; McClain, E. J.; Wang, Q. Y.; Gregg, T. L.;

-
- Akhmedov, N. G.; Petersen, J. L.; Shi, X. D. *Angew. Chem. Int. Ed.* **2014**, *53*, 4657. j) Wang, Q. Y.; Motika, S. E.; Akhmedov, N. G.; Petersen, J. L.; Shi, X. D. *Angew. Chem. Int. Ed.* **2014**, *53*, 5418. k) Cai, R.; Yan, W.; Bologna, M. G.; De Silva, K.; Finklea, H. O.; Petersen, J. L.; Shi, X. D. *Org. Chem. Front.* **2015**, *2*, 141.
- 12 Ackermann, L.; Vicente, R.; Born, R. *Adv. Synth. Catal.* **2008**, *350*, 741; b) Ackermann, L.; Jeyachandran, R.; Potukuchi, H. K.; Novak, P.; Buettner, L. *Org. Lett.* **2010**, *12*, 2056; c) Ackermann, L.; Potukuchi, H. K. *Org. Biomol. Chem.* **2010**, *8*, 4503.
- 13 Ackermann, L.; Vicente, R.; Althammer, A. *Org. Lett.* **2008**, *10*, 2299; b) Ackermann, L.; Born, R.; Vicente, R. *Chemsuschem.* **2009**, *2*, 546-549
- 14 For mechanistic studies on Pd-catalyzed acetoxylation: a) Stowers, K. J.; Sanford, M. S. *Org. Lett.* **2009**, *11*, 4584; b) Racowski, J. M.; Dick, A. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 10974; c) Gary, J. B.; Sanford, M. S. *Organometallics.* **2011**, *30*, 6143.
- 15 For selective examples of $\text{PhI}(\text{OAc})_2$ mediated, Pd(III) and Pd(IV) chemistry: a) Powers, D. C.; Geibel, M. A. L.; Klein, J. E. M. N.; Ritter, T. *J. Am. Chem. Soc.* **2009**, *131*, 17050; b) Powers, D. C.; Xiao, D. Y.; Geibel, M. A. L.; Ritter, T. *J. Am. Chem. Soc.* **2010**, *132*, 14530; c) Powers, D. C.; Ritter, T. *Acc. Chem. Res.* **2011**, *45*, 840; d) Powers, D. C.; Lee, E.; Ariafard, A.; Sanford, M. S.; Yates, B. F.; Canty, A. J.; Ritter, T. *J. Am. Chem. Soc.* **2012**, *134*, 12002.
- 16 For selective examples of Pd-catalyzed acetoxylation: a) Yoneyama, T.; Crabtree, R. H. *J. Mol. Catal. a-Chem.* **1996**, *108*, 35; b) Desai, L. V.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 9542; c) Dick, A. R.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 2300-2301; d) Desai, L. V.; Stowers, K. J.; Sanford, M. S. *J. Am. Chem. Soc.* **2008**, *130*, 13285; e) Gou, F.-R.; Wang, X.-C.; Huo, P.-F.; Bi, H.-P.; Guan, Z.-H.; Liang, Y.-M. *Org. Lett.* **2009**, *11*, 5726; f) Gu, S.; Chen, C.; Chen, W. *J. Org. Chem.* **2009**, *74*, 7203; g) Neufeldt, S. R.; Sanford, M. S. *Org. Lett.* **2010**, *12*, 532; h) Chernyak, N.; Dudnik, A. S.; Huang, C.; Gevorgyan, V. *J. Am. Chem. Soc.* **2010**, *132*, 8270; i) Rit, R. K.; Yadav, M. R.; Sahoo, A. K. *Org. Lett.* **2012**, *14*, 3724; j) Yadav, M. R.; Rit, R. K.; Sahoo, A. K., *Chem. Eur. J.* **2012**, *18*, 5541-5545.

-
- 17 Moritani, I.; Fujiwara, Y. *Tetrahedron Lett.* **1967**, 1119
- 18 Le Bras, J.; Muzart, J. *Chem. Rev.* **2011**, *111*, 1170.
- 19 For recent examples of transition metal catalyzed non-directed C-H olefination of arene, see: a). b) Kubota, A.; Emmert, M. H.; Sanford, M. S. *Org. Lett.* **2012**, *14*, 1760. c) Ying, C.-H.; Yan, S.-B.; Duan, W.-L. *Org. Lett.* **2014**, *16*, 500. d) Vora, H. U.; Silvestri, A. P.; Engelin, C. J.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2014**, *53*, 2683
- 20 Zhang, Y.-H.; Shi, B.-F.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 5072
- 21 For recent examples of Pd catalyzed directing C-H olefination, see: a) Wang, D.-H.; Engle, K. M.; Shi, B.-F.; Yu, J.-Q. *Science* **2010**, 327, 315. b) Lu, Y.; Wang, D.-H.; Engle, K. M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 5916. c) Garcia-Rubia, A.; Angeles Fernandez-Ibanez, M.; Gomez Arrayas, R.; Carlos Carretero, J. *Chem. Eur. J.* **2011**, *17*, 3567. d) Wang, C.; Ge, H. *Chem. Eur. J.* **2011**, *17*, 14371. e) Yu, M.; Xie, Y.; Xie, C.; Zhang, Y. *Org. Lett.* **2012**, *14*, 2164. f) Gandeepan, P.; Cheng, C.-H. *J. Am. Chem. Soc.* **2012**, *134*, 5738. g) Meng, X.; Kim, S. *Org. Lett.* **2013**, *15*, 1910. h) Wang, B.; Shen, C.; Yao, J.; Yin, H.; Zhang, Y. *Org. Lett.* **2013**, *16*, 46. i) Dai, H.-X.; Li, G.; Zhang, X.-G.; Stepan, A. F.; Yu, J.-Q. *J. Am. Chem. Soc.* **2013**, *135*, 7567. j) Tang, R.-Y.; Li, G.; Yu, J.-Q. *Nature* **2014**, *507*, 215.
- 22 For recent example of other metal catalyzed directing C-H olefination: see: a) Kwon, K.-H.; Lee, D. W.; Yi, C. S. *Organometallics* **2010**, *29*, 5748. b) Feng, C.; Loh, T.-P. *Chem. Commun.* **2011**, *47*, 10458. c) Garcia-Rubia, A.; Angeles Fernandez-Ibanez, M.; Gomez Arrayas, R.; Carlos Carretero, J. *Chem. Eur. J.* **2011**, *17*, 3567. d) Padala, K.; Jeganmohan, M. *Org. Lett.* **2011**, *13*, 6144. e) Patureau, F. W.; Besset, T.; Glorius, F. *Angew. Chem. Int. Ed.* **2011**, *50*, 1064.
- 23 a) J Li, J.-J.; Mei, T.-S.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2008**, *47*, 6452. b) Liu, Q.; Li, Q.; Ma, Y.; Jia, Y. *Org. Lett.* **2013**, *15*, 4528.
- 24 Ye, X. H.; He, Z. R.; Ahmed, T.; Weise, K.; Akhmedov, N. G.; Petersen, J. L.; Shi, X. D. *Chem. Sci.* **2013**, *4*, 3712.
- 25 For recent examples of C-H functionalization on C-4 of 1,2,3-triazole, see: a) Chuprakov, S.; Chernyak, N.; Dudnik, A. S.; Gevorgyan, V. *Org. Lett.* **2007**, *9*, 2333. b) Iwasaki, M.; Yorimitsu, H.; Oshima, K. *Chem. Asian. J.* **2007**, *2*, 1430. c)

-
- Ackermann, L.; Vicente, R.; Born, R. *Adv. Synth. Catal.* **2008**, *350*, 741. d) Jiang, H.; Feng, Z.; Wang, A.; Liu, X.; Chen, Z. *Eur. J. Org. Chem.* **2010**, *2010*, 1227. e) Liu, W.; Li, Y.; Xu, B.; Kuang, C. *Org. Lett.* **2013**, *15*, 2342.
- 26 a) Stahl, S. S. *Angew. Chem. Int. Ed.* **2004**, *43*, 3400. b) Campbell, A. N.; Stahl, S. S. *Acc. Chem. Res.* **2012**, *45*, 851. c) Shi, Z.; Zhang, C.; Tang, C.; Jiao, N. *Chem. Soc. Rev.* **2012**, *41*, 3381
- 27 For examples of Pd-catalyzed C-H olefination using O₂ as terminal oxidant, see: a) Beck, E. M.; Grimster, N. P.; Hatley, R.; Gaunt, M. J. *J. Am. Chem. Soc.* **2006**, *128*, 2528. b) Wang, J.-R.; Yang, C.-T.; Liu, L.; Guo, Q.-X. *Tetrahedron Lett.* **2007**, *48*, 5449. c) Cong, X.; You, J.; Gao, G.; Lan, J. *Chem. Commun.* **2013**, *49*, 662. d) Liu, B.; Jiang, H.-Z.; Shi, B.-F. *J. Org. Chem.* **2014**, *79*, 1521.
- 28 a) Werner, E. W.; Sigman, M. S. *J. Am. Chem. Soc.* **2010**, *132*, 13981. b) Mei, T.-S.; Werner, E. W.; Burckle, A. J.; Sigman, M. S. *J. Am. Chem. Soc.* **2013**, *135*, 6830.
- 29 For other two examples of PA auxiliary directing C-H functionalization using O₂ as terminal oxidant, see: a) Zhao, Y.; Chen, G. *Org. Lett.* **2011**, *13*, 4850. b) Zhang, L.-S.; Chen, G.; Wang, X.; Guo, Q.-Y.; Zhang, X.-S.; Pan, F.; Chen, K.; Shi, Z.-J. *Angew. Chem. Int. Ed.* **2014**, *53*, 3899.
- 30 The oxidative addition into C-H bond usually requires electron-rich, low-valent complexes of the late transition metals, see: Labinger, J. A.; Bercaw, J. E. *Nature* **2002**, *417*, 507.
- 31 Wu, X. S.; Zhao, Y.; Zhang, G.; Ge, H. *Angew. Chem. Int. Ed.* **2014**, *53*, 3706.
- 32 For reviews: (a) Hartwig, J. F. *Acc. Chem. Res.*, **2008**, *41*, 1534; (b) Beletskaya, I. P.; Ananikov, V. P. *Chem. Rev.*, 2011, **111**, 1596; (c) Liu, H.; Jiang, X. *Chem. Asian J.*, 2013, **8**, 2546.
- 33 For review: C. Shen.; Zhang, P.; Sun, Q.; Bai, S.; Hor, T. S.; Liu, X. *Chem. Soc. Rev.*, 2015, **44**, 291-314.
- 34 Chen, X.; Hao, X.-S.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 6790.
- 35 a) Yang, Y.-X.; Hou, W.; Qin, L.-H.; Du, J.-J.; Feng, H.-J.; Zhou, B.; Li, Y.-C. *Chem. Eur. J.* **2014**, *20*, 416; b) Iwasaki, M.; Iyanaga, M.; Tsuchiya, Y.; Nishimura, Y.; Li, W.; Li, Z.; Nishihara, Y. *Chem. Eur. J.* **2014**, *20*, 2459.

-
- 36 Dieu. T. Ly; Popov. I.; Daugulis. O. *J. Am. Chem. Soc.*, 2012, **134**, 18237-18240
- 37 During the preparation of this manuscript of this project, similar work was reported by Zhang's group. Nickel catalysts, TBAI (4 eq.) and ligands were required to achieve for sp^3 C-H sulfenylation. See: Lin. C.; Yu. W.; Yao. J.; Wang. B.; Liu. Z.; Zhang. Y. *Org. Lett.*, **2015**, *17*, 1340. sp^2 C-H sulfenylation was also reported by same group. See: Lin. C.; Li. D.; Wang. B.; Yao. J.; Zhang. Y. *Org. Lett.*, **2015**, *17*, 1328.
- 38 (a) Hu. X. *Chem. Sci*, 2011, **2**, 1867; (b) Tasker. S. Z.; Standley. E. A.; Jamison. T. F. *Nature*, 2014, **509**, 299.
- 39 For examples of Yu-Wasa amide directed sp^3 C-H functionalization, see: (a) M. Wasa, K. S. L. Chan, X.-G. Zhang, J. He, M. Miura and J.-Q. Yu, *J. Am. Chem. Soc.*, **2012**, *134*, 18570; (b) He. J.; Li. S.; Deng. Y.; Fu. H.; Laforteza. B. N.; Spangler. J. E.; Homs. A. Yu. J.-Q. *Science*, **2014**, *343*, 1216; (c) Zhu. R.-Y.; He. J.; Wang. X.-C.; Yu. J.-Q. *J. Am. Chem. Soc.*, **2014**, *136*, 13194.
- 40 Wallace. T. J. *J. Am. Chem. Soc.* **1964**, *86*, 2018.
- 41 Ni(IV) was rarely reported and one recently example, see: Camasso, N. M.; Sanford, M. S. *Science* **2015**, *347*, 1218-1220.

Appendix

Publications during Ph.D. work at West Virginia University:

- 1) Ye, X.; Petersen, J. L.; Shi, X.* "Nickel-Catalyzed Directed Sulfenylation of sp^2 and sp^3 C-H Bonds" *Chem. Commun.* **2015**, 51, 7863-7866.
- 2) Shi, Y.; Ye, X.; Gu, Q.; Shi, X.*; Song, Z.* "Facile Synthesis and Stereo-Resolution of Chiral 1,2,3-Triazole" *Org. Biomol. Chem.* **2015**, 13, 5407-5411.
- 3) Zhang, Y.; Ye, X.; Petersen, J. L.; Li, M.*; Shi, X.* "Synthesis and Characterization of Bis-N-2-Aryl Triazole as Fluorophore" *J. Org. Chem.* **2015**, 80, 3664-3669.
- 4) Motika, S. E.; Wang, Q.; Ye, X.; Shi, X.* "Ambient Synthesis of Dienals via Triazole-Au and Amine Catalysis Relay" *Org. Lett.* **2015**, 17, 290-293.
- 5) Ye, X.; Shi, X.* "Palladium Catalyzed Aerobic Oxidative C-H Olefination with Removable 1, 2, 3-Triazole Directing Group" *Org. Lett.* **2014**, 16, 4448-4451.
- 6) Xi, Y.; Wang, D.; Ye, X.; Akhmedov, N. G.; Petersen, J. L.; Shi, X.* "Synergistic Au/Ga Catalysis in Ambient Nakamura Reaction" *Org. Lett.* **2014**, 16, 306-309.
- 7) Ye, X.; He, Z.; Ahmed, T.; Weise, K.; Akhmedov, N. G.; Petersen, J. L.; Shi, X.* "1,2,3-Triazoles as versatile directing group for selective sp^2 and sp^3 C-H activation: cyclization vs substitution" *Chem. Sci.* **2013**, 4, 3712-3716.
- 8) Yan, W.; Ye, X.; Akhmedov, N. G.; Petersen, J. L.; Shi, X.* "1,2,3-Triazole: Unique Ligand in Promoting Iron-Catalyzed Propargyl Alcohol Dehydration" *Org. Lett.* **2012**, 14, 2358-2361.
- 9) Yan, W.; Ye, X.; Weise, K.; Petersen, J. L.; Shi, X.* "Synthesis of allene triazole through iron catalyzed regioselective addition to propargyl alcohols" *Chem. Commun.* **2012**, 48, 3521-3523.
- 10) Wang, D.; Ye, X.; Shi, X.* "Efficient Synthesis of E- α -Haloenones Through Chemoselective Alkyne Activation Over Allene with Triazole-Au Catalysts" *Org. Lett.* **2010**, 12, 2088-2091.

Part V.

Experiment Section

Section A: General Methods and Materials

All of the reactions dealing with air and/or moisture-sensitive reactions were carried out under an atmosphere of nitrogen using oven/flame-dried glassware and standard syringe/septa techniques. Unless otherwise noted, all commercial reagents and solvents were obtained from the commercial provider and used without further purification. ^1H NMR and ^{13}C NMR spectra were recorded on Varian 600 MHz spectrometers and Agilent 400 MHz spectrometers. Chemical shifts were reported relative to internal tetramethylsilane (δ 0.00 ppm) or CDCl_3 (δ 7.26 ppm) for ^1H and CDCl_3 (δ 77.16 ppm/77.00 ppm) for ^{13}C . Flash column chromatography was performed on 230-430 mesh silica gel. Analytical thin layer chromatography was performed with precoated glass baked plates (250 μ) and visualized by fluorescence and by charring after treatment with potassium permanganate stain. HRMS were recorded on LTQ-FTUHRA spectrometer and Thermo Q-Exactive MS.

Section B: General Experiment and Procedures

Part I. 1,2,3-Triazoles as versatile directing group for selective sp^2 and sp^3 C–H activation: cyclization vs substitution

Preparation of Triazole/Triazole-Pyridine acid

General procedure for the preparation of Triazole acid (TAA-1)

Synthesis of triazole ester TAE-1: A mixture of 1-azido-4-benzylbenzene (1.0 equiv.), methyl propiolate (1.05 equiv.), CuSO₄ (0.05 equiv.) and sodium ascorbate (0.1 equiv.) were stirred in *t*-BuOH/H₂O (1:1, 0.2 M) at room temperature and monitored by TLC. After the reaction was completed (about 12 h), the saturated NH₄Cl was added. The mixture was extracted with EtOAc (3 x 20 mL), and the combined organic phases were washed with water and brine, dried with anhydrous MgSO₄, and filtered. The filtrate was concentrated, and the residue was purified through silica gel flash column chromatography (hexanes/ethyl acetate = 4/1) to give triazole ester **TAE-1** (yield: 95%) as white solid.

Synthesis of triazole acid TAA-1: To a solution of triazole ester (1.0 equiv.) in THF/MeOH/H₂O (1:1:1 mixture, 0.2 M), was added LiOH (2 equiv., 2M) at room temperature. and monitored by TLC. After the reaction was completed (6 h), HCl (1M) was added to acidify the solution. The white participation was then collected by Büchner funnel and washed by water to afford Triazole acid **TAA-1** (yield: 97%).

General procedure for the preparation of Triazole acid(TAA-2)

The syntheses of 1-azido-4-methoxybenzene were followed according to procedures described in literature: Zhu, W.; Ma, D., *Chem. Comm.* **2004**, 7, 888.

Synthesis of triazole ester TAE-2: A mixture of 1-azido-4-methoxybenzene (1.0 equiv.), methyl propiolate (1.05 equiv.), CuSO_4 (5 mol%) and sodium ascorbate (10 mol%) were stirred in $t\text{-BuOH}/\text{H}_2\text{O}$ (1:1, 0.2 M) at room temperature and monitored by TLC. After the reaction was completed (about 12 h), the saturated NH_4Cl was added. The mixture was extracted with EtOAc (3 x 20 mL), and the combined organic phases were washed with water and brine, dried with anhydrous MgSO_4 , and filtered. The filtrate was concentrated, and the residue was purified through silica gel flash column chromatography (hexanes/ethyl acetate = 3/1) to give triazole ester **TAE-2** (yield: 94%) as yellow oil.

Synthesis of triazole acid TAA-2: To a solution of triazole ester (1.0 equiv.) in $\text{THF}/\text{MeOH}/\text{H}_2\text{O}$ (1:1:1 mixture, 0.2 M), was added LiOH (2 equiv., 2M) at room temperature and monitored by TLC. After the reaction was completed (6 h), HCl (1M) was added to acidify the solution. The mixture was extracted with DCM , and the combined organic phases were washed with water and brine, dried with anhydrous MgSO_4 , and filtered. The filtrate was concentrated. The obtained brown solid was then recrystallized using DCM/Hexane to afford Triazole acid **TAA-2** (yield: 90%).

General procedure for the preparation of 5-phenyl-2-(pyridin-2-yl)-2H-1,2,3-triazole-4-carboxylic acid(TA-Py)

Synthesis of triazole ester E: To a solution of methyl 3-phenylpropiolate (1.0 equiv.) in DMSO(0.2 M), was added NaN_3 at room temperature. The reaction mixture was stirred at $80\text{ }^\circ\text{C}$ and monitored by TLC. After the reaction was completed (6 h), HCl (1M) was added to acidify the PH to 4. The mixture was extracted with EtOAc (3 x 20 mL), and the combined organic phases were washed with water and brine, dried with anhydrous MgSO_4 , and filtered. The filtrate was concentrated, and the residue was recrystallized using DCM/Hexane to afford **TAE** (yield: 90%) as white solid.

The syntheses of Triazole Pyridine ester **TAPyE** were followed according to procedures described in literature: Yan, W.; Wang, Q.; Lin, Q.; Li, M.; Petersen, J. L.; Shi, X. *Chem. Eur. J.* **2011**, *17*, 5011. (Yield: 50%, 80% brsm, yellow solid)

The hydrolysis of Triazole Pyridine ester **TAPyE** were followed **General procedure A** to afford Triazole Pyridine acid **TA-Py** (yield: 90%) as white solid.

General procedure for the preparation of Triazole-Pyridine acid TAPyA

The syntheses of Triazole Pyridine ester **TAPyE** were followed according to procedures described in literature: Yan, W.; Wang, Q.; Lin, Q.; Li, M.; Petersen, J. L.; Shi, X. *Chem. Eur. J.* **2011**, *17*, 5011. (N2: N1 isomer: 1: 3, Yield of N2 isomer **TAPyE**: 30% as white solid)

The hydrolysis of Triazole Pyridine ester **PyTAE** were followed **General procedure A** to afford Triazole Pyridine acid **Py-TA** (yield: 94%) as white solid.

Preparation of Triazole/Triazole-Pyridine amide substrates

The syntheses of corresponding amine **4d**, **4e**, **4n**, **7d**, **7e**, and **7n** were followed according to procedures described in literature as below

1. He, G., Lu, C., Zhao, Y., Nack, W. A., Chen, G. *Org. Lett.* **2012**, *12*, 2944-2947.
2. He, G., Zhao, Y., Zhang, S., Lu, C., Chen, G. *J. Am. Chem. Soc.* **2012**, *1*, 3-6.

General procedure for the preparation of Triazole/Trizaole-Pyridine acid based amide substrates.

A mixture of triazole/triazole-pyridine acid (1.0 equiv.), amine (1.2 equiv.), EDC·HCl (1.2 equiv.), HOBT (1.2 equiv.) and Et₃N (1.2 equiv.) were stirred in anhydrous DCM (0.1M) at room temperature and monitored by TLC. After the reaction was completed (about 12-24 h), the water was added. The mixture was extracted with EtOAc (3 x 20 mL), and the combined organic phases were washed with water and brine, dried with anhydrous MgSO₄, and filtered. The filtrate was concentrated, and the residue was purified through silica gel flash column chromatography (ethyl acetate/hexane = 1:2, V/V) to give desired amide product in 80-95%.

General procedure for Pd-catalyzed intramolecular amidation

Procedure A: Synthesis of indolines via Pd-catalyzed intramolecular amidation.

A 20 mL screw-cap vial was charged with the triazole amide (0.3 mmol, 1.0 equiv.), Pd(OAc)₂ (0.015mmol, 5 mol%) , PhI(OAc)₂ (0.6 mmol, 2.0 equiv) in 3 mL anhydrous DCE. The vial was purged with Ar and placed in a preheated metal block at 80 °C. After

the reaction was completed (24 h), the solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel (ethyl acetate/hexane = 4:1, V/V) to give desired product.

Procedure B: Synthesis of Azetidines via Pd-catalyzed intramolecular amidation.

A 20 mL sealed tube was charged with the triazole amide (0.3 mmol, 1.0 equiv.), Pd(OAc)₂ (0.015mmol, 5 mol%), PhI(OAc)₂ (0.6 mmol, 2.0 equiv) and AcOH(0.6 mmol, 2.0 equiv.) in 3 mL anhydrous DCE. The vial was purged with Ar and placed in a preheated metal block at 120 °C. After the reaction was completed (24 h), the solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel (ethyl acetate/hexane = 2:1, V/V) to give desired product.

General procedure for Pd-catalyzed Acetoxylation.

Procedure C: Pd-catalyzed acetoxylation of δ -C(sp²)-H bonds

A 20 mL screw-cap vial was charged with the triazole-pyridine amide (0.3 mmol, 1.0 equiv.), Pd(OAc)₂ (0.03mmol, 10 mol%) , PhI(OAc)₂ (0.75 mmol, 2.5 equiv) and AgOAc (0.15 mmol, 0.5 equiv.) in 6 mL anhydrous DCE. The tube was stirred at 80 °C. After the reaction was completed (24 h), the solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel (ethyl acetate/hexane = 2 : 1, V/V) to give desired acetoxylation product.

Procedure D: Pd-catalyzed acetoxylation of γ -C(sp³)-H bond

A 20 mL sealed tube was charged with the triazole- pyridine amide (0.30 mmol, 1.0 equiv.), Pd(OAc)₂ (0.03mmol, 10 mol%) , PhI(OAc)₂ (0.75 mmol, 2.5 equiv) and AcOH(0.45 mmol, 1.5 equiv.) in 8 mL anhydrous DCE. The tube The tube was stirred at 140 °C. After the reaction was completed (24 h), the solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel (ethyl acetate/hexane = 2:1, V/V) to give desired acetoxylation product.

Part II. Palladium-Catalyzed Aerobic Oxidative C–H Olefination with Removable 1,2,3-Triazole Directing Group

Preparation of Triazole acid

General procedure for the preparation of Triazole acid

Synthesis of triazole ester TAN1: A mixture of methyl 3-phenylpropiolate (1.0 equiv.), Benzyl azide (1.5 equiv.) were stirred in DMSO (0.2 M) at 80 °C and monitored by TLC. After the reaction was completed (about 12 h), the saturated NH_4Cl was added. The mixture was extracted with EtOAc (3 x 20 mL), and the combined organic phases were washed with brine, dried with anhydrous MgSO_4 , and filtered. The filtrate was concentrated, and the residue was purified through silica gel flash column chromatography (hexanes/ethyl acetate = 4/1) to give triazole ester **TAN1**: **TAN3** = 1.5: 1 (yield: 85%).

Synthesis of triazole acid TAAN1: To a solution of triazole ester (1.0 equiv.) in THF/MeOH/ H_2O (1:1:1 mixture, 0.2 M), was added LiOH (2 equiv., 2M) at room temperature. and monitored by TLC. After the reaction was completed (6 h), HCl (2M) was added to acidify the solution. The white participation was then collected by Büchner funnel and washed by water to afford Triazole acid **TAAN1** (yield: 97%) without further purification.

Preparation of Triazole amide substrates

General procedure for the preparation of Triazole acid based amide substrates.

A mixture of triazole acid TAAN1 (1.0 equiv.), amine (1.2 equiv.), EDC·HCl (1.2 equiv.), HOBT (1.2 equiv.) and DMAP (10 mol%) were stirred in anhydrous DCM (0.1M) at room temperature and monitored by TLC. After the reaction was completed (about 12-24 h), the water was added. The mixture was extracted with DCM (3 x 20 mL), and the combined organic phases were washed with water and brine, dried with anhydrous MgSO_4 , and filtered. The filtrate was concentrated, and the residue was purified through silica gel flash column chromatography (ethyl acetate/hexane = 1:2, V/V) to give desired amide product in 80-95%.

General procedure for Pd-catalyzed Olefination

Condition A: A 20 mL schlenk tube was charged with the triazole amide (0.2 mmol, 1.0 equiv), alkene (0.8 mmol, 4.0 equiv), $\text{Pd}(\text{OAc})_2$ (0.015 mmol, 7.5 mol %), $\text{Cu}(\text{OTf})_2$ (0.02 mmol, 10 mol %) and HOAc (0.5 mmol, 2.5 equiv) in 1 mL anhydrous 1,4-Dioxane. The tube was placed under vacuum and purged with O_2 balloon. The reaction was run at 105 °C for 20 h. After the reaction was completed, the solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel to give desired olefination product.

Condition B: A 20 mL seal tube was charged with the triazole amide (0.2 mmol, 1.0 equiv), alkene (0.8 mmol, 4.0 equiv), Pd(OAc)₂ (0.02 mmol, 10 mol %), Cu(OTf)₂ (0.02 mmol, 10 mol %) and HOAc (0.5 mmol, 2.5 equiv) in 1 mL anhydrous 1,4-Dioxane. The tube was placed under vacuum and purged with O₂ twice. The reaction was run at 115 °C for 20 h. After the reaction was completed (20 h), the solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel to give desired olefination product.

Condition C: A 20 mL seal tube was charged with the triazole amide (0.2 mmol, 1.0 equiv), alkene (2.4 mmol, 12 equiv), Pd(OAc)₂ (0.03 mmol, 15 mol %), Cu(OTf)₂ (0.02 mmol, 10 mol %) and HOAc (0.5 mmol, 2.5 equiv) in 1 mL anhydrous 1,4-Dioxane. The tube was placed under vacuum and purged with O₂ twice. The reaction was run at 115 °C for 20h. After the reaction was completed (20 h), the solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel to give desired olefination product.

Kinetic Isotope Effect Experiments

KIE (K_H/K_D) was determined based on parallel reactions of compound **11ba** and compound **11bd** with butylacrylate under the general condition A. The reaction mixture was quenched after 3h and analyzed by ¹H NMR. The K_H/K_D was determined by the ratio of ¹H NMR yield of **13b**. $k_H/k_D \sim 2.1$.

General procedure for the synthesis of tetrahydroisoquinoline

To the solution of **13a** (0.4 mmol) in dry THF (4 mL) at 0 °C, NaH (0.8 mmol) was added slowly. The mixture was initially stirred at 0 °C for another 15min and then at ambient temperature, monitored by TLC. After the reaction was completed (about 3 h), the water was added. The mixture was extracted with DCM (2 x 10 mL), and the combined organic phases were washed with water and brine, dried with anhydrous MgSO₄, and filtered. The filtrate was concentrated, and the residue was purified through silica gel flash column chromatography (ethyl acetate/hexane = 1:2, V/V) to give desired amide product in 90%.

Part III. Nickel-catalyzed directed sulfenylation of sp^2 and sp^3 C–H bonds

General Procedure for preparation of sp^2 starting materials

To the solution of carboxylic acid (10 mmol) and 10 drops of DMF in 30mL dry DCM at 0 °C, oxalyl chloride (20 mmol) was added dropwise under Ar. The mixture was then warm to r.t and stirred for another 5h. The solvent was removed under vacuum to give crude acid chloride, which was used directly for next step without further purification.

To the mixture of 8-aminoquinoline (10 mmol) and Et_3N (12 mmol) in dry DCM (30 mL) at 0 °C, the crude acid chloride obtained from previous step in 20 mL dry DCM was added dropwise. The mixture was then warm to r.t and stirred overnight. The reaction was quenched with H_2O . The mixture was extracted, washed with saturated NaHCO_3 solution. The combined organic layers were dried (MgSO_4), and concentrated in vacuum and then purified by silica gel chromatography with a mixture of hexanes and ethyl acetate as the eluent to afford the corresponding amide products.

General Procedure for preparation of sp^3 starting materials

The LDA solution was prepared freshly, by adding 2.5 M $n\text{-BuLi}$ in hexane (10 mmol) into the THF solution (30 mL) of diisopropylamine (10 mmol) at -78 °C under Ar

atmosphere. The ester (10 mmol) was then added at -78 °C. After stirring at same temperature for another 1h, Alkyl halide (15mmol) was then added. The mixture was warmed to r.t. and stirred overnight. The reaction was carefully quenched with the NH₄Cl solution. The aqueous phase was extracted with ether and the combined organic layers were dried (MgSO₄), and concentrated in vacuum, affording the crude ester. The crude ester used directly for next step without further purification.

NaOH (4M, 10 mL) was then adding into a solution of crude ester in 20mL MeOH. The mixture was then stirred at 60 °C overnight. The reaction was carefully acidified with 2M HCl. The aqueous phase was extracted with ether and the combined organic layers were dried (MgSO₄), and concentrated in vacuum, affording the crude acid. The crude acid used directly for next step without further purification.

To the solution of carboxylic acid (10 mmol) and 10 drops of DMF in 30mL dry DCM at 0 °C, oxalyl chloride (20 mmol) was added dropwise under Ar. The mixture was then warm to r.t and stired for another 5h. The solvent was removed under vacuum to give crude acid cholid, which was used directly for next step without further purification.

To the mixture of 8-aminoquinoline (10 mmol) and Et₃N (12 mmol) in dry DCM (30 mL) at 0 °C, the crude acid chloride obtained from previous step in 20 mL dry DCM was added dropwise. The mixture was then warm to r.t and stirred overnight. The reaction was quenched with H₂O. The mixture was extracted, washed with saturated NaHCO₃ solution. The combined organic layers were dried (MgSO₄), and concentrated in vacuum and then purified by silica gel chromatography with a mixture of hexanes and ethyl acetate as the eluent to afford the corresponding amide products.

General Procedure for sp² C-H Sulfenylation.

A 10 mL tube was charged with the amides (0.3 mmol, 1.0 equiv.), LiOtBu (1.5 mmol, 5.0 equiv.) and NiCl₂(DME) (0.03 mmol, 10 mol%) in 0.6 mL anhydrous DMF. The benzenethiol (0.66 mmol, 2.2 equiv.) was then added into mixture slowly. After stirring

at r.t for 15 min, the mixture was then heated at 100 °C. The reaction was monitored by TLC. After the reaction was completed, the solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel (ethyl acetate/hexane = 15 : 1, V/V) to give desired sulfenylation product.

General Procedure for Sp³ C-H Sulfenylation.

Condition A: A 10 mL sealed tube was charged with the amides (0.3 mmol, 1.0 equiv.), LiOtBu (1.5 mmol, 5.0 equiv.) and Ni(OTf)₂ (0.06 mmol, 20 mol%) in 0.6 mL anhydrous DMF. The disulfide (0.75 mmol, 2.5 equiv.) was then added into mixture slowly. The mixture was purged, protected under Ar, and then heated under 120 °C. After the reaction was completed (20h), the solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel (ethyl acetate/hexane = 15 : 1, V/V) to give desired sulfenylation product.

Condition B: A 10 mL sealed tube was charged with the amides (0.3 mmol, 1.0 equiv.), LiOtBu (2.1 mmol, 7.0 equiv.) and NiCl₂(DME) (0.06 mmol, 20 mol%) in 0.6 mL anhydrous DMF. The disulfide (1.2 mmol, 4 equiv.) was then added into mixture dropwise. The mixture was first stirred at r.t for 15min, and then heated under 120 °C. The reaction was monitored by TLC. After the completion of the reaction (5-6 h), the solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel (ethyl acetate/hexane = 15 : 1, V/V) to give desired sulfenylation product.

Competition experiment.

To a mixture of benzamide **22ca** (0.20 mmol), **22fa** (0.20 mmol), phenyldisulfide (0.10 mmol), NiCl₂(DME) (10.0 mol %) and LiOt-Bu (1.00 mmol) was added DMF (0.4 mL). The reaction mixture was stirred at 100 °C for 4 h. After cooling to room temperature, the reaction mixture was passed through a silica pad and washed by EtOAc. 1, 3, 5 trimethoxybenzene was then added as internal standard. The mixture was concentrated under vacuum and analyzed by ¹HNMR

Section C: Compound Characterization

Part I. 1,2,3-Triazoles as versatile directing group for selective sp^2 and sp^3 C–H activation: cyclization vs substitution

1-benzyl-N-phenethyl-1H-1,2,3-triazole-4-carboxamide (2a) was purified by flash chromatography (Hexane-EtOAc, v/v 2/1) as white solid; ^1H -NMR (600 MHz, CDCl_3) δ 7.94 (s, 1H), 7.41-7.37 (m, 3H), 7.32-7.27 (m, 4H), 7.24-7.20 (m, 3H), 7.18-7.17 (m, br, 1H), 5.54 (s, 2H), 3.71-3.68 (q, $J = 7.5$ Hz, 2H), 2.92-2.90 (t, $J = 7.2$ Hz, 2H); ^{13}C -NMR (150 MHz, CDCl_3) δ 160.1, 140.5, 138.8, 133.9, 129.4, 129.3, 128.9, 128.8, 128.4, 126.7, 125.3, 54.7, 40.5, 36.0; HRMS Calculated for $\text{C}_{18}\text{H}_{17}\text{N}_4\text{O}$ $[\text{M}+\text{H}]^+$: 307.1554, Found: 307.1553.

(1-benzyl-1H-1,2,3-triazol-4-yl)(indolin-1-yl)methanone (3a) was prepared following the general procedure A, and purified by flash chromatography (Hexane-EtOAc, v/v 3/1) as white solid; Isolated yield 83%; ^1H -NMR (600 MHz, CDCl_3) δ 8.30-8.28 (d, $J = 7.8$ Hz, 1H), 8.12 (s, 1H), 7.42-7.39 (m, 3H), 7.33-7.31 (m, 2H), 7.24-7.21 (m, 2H), 7.08-7.06 (t, $J = 7.5$ Hz, 1H), 5.57 (s, 1H), 4.81-4.78 (t, $J = 8.4$ Hz, 2H), 3.25-3.23 (t, $J = 8.4$ Hz, 2H); ^{13}C -NMR (150 MHz, CDCl_3) δ 159.1, 145.9, 143.4, 133.9, 132.4, 129.4, 129.2,

128.6, 128.5, 127.5, 124.8, 124.6, 118.0, 55.6, 50.3, 28.8; HRMS Calculated for $C_{18}H_{15}N_4O [M+H]^+$: 305.1397, Found: 305.1397.

(S)-methyl-2-(1-benzyl-1H-1,2,3-triazole-4-carboxamido)-3-phenylpropanoate (4a') was purified by flash chromatography (Hexane-EtOAc, v/v 2/1) as white solid; ^1H -NMR (600 MHz, CDCl_3) δ 7.92 (s, 1H), 7.53-7.51 (d, $J = 8.4$ Hz, 1H), 7.41-7.37 (m, 3H), 7.30-7.26 (m, 4H), 7.25-7.22 (m, 1H), 7.18-7.17 (m, 2H), 5.56-5.51 (ABq, $J = 15, 8.4$ Hz, 2H), 5.05-5.02 (dt, $J = 7.8, 6.6$ Hz, 1H), 3.72 (s, 3H), 3.24-3.16 (ddd, $J = 31.8, 14.4, 6.3$ Hz); ^{13}C -NMR (150 MHz, CDCl_3) δ 171.6, 159.7, 143.1, 135.9, 133.8, 129.6, 129.4, 129.3, 128.8, 128.5, 127.3, 125.5, 54.7, 53.1, 52.5, 38.4; HRMS Calculated for $C_{20}H_{20}N_4O_3 [M+H]^+$: 365.1609, Found: 365.1613.

(S)-methyl-1-(1-benzyl-1H-1,2,3-triazole-4-carbonyl)indoline-2-carboxylate (4a) was prepared following the general procedure A and purified by flash chromatography (Hexane-EtOAc, v/v 3/1) as colorless oil; Isolated yield 70%; ^1H -NMR (600 MHz, CDCl_3) δ 8.36-8.35 (d, $J = 8.4$ Hz, 1H), 8.13 (s, 1H), 7.42-7.38 (m, 3H), 7.31-7.29 (m, 2H), 7.27-7.24 (m, br, 1H), 7.21-7.20 (d, $J = 7.2$ Hz, 1H), 7.09-7.07 (t, $J = 7.2$ Hz, 1H), 6.27-6.25 (d, $J = 10.2$ Hz, 1H), 5.57-5.50 (ABq, $J = 14.4, 26.4$ Hz, 2H), 3.69-3.66 (m, 4H), 3.37-3.34 (d, $J = 17.4$ Hz); ^{13}C -NMR (150 MHz, CDCl_3) δ 172.7, 159.4, 142.3, 133.7,

129.5, 129.3, 128.81, 128.80, 128.79, 128.6, 128.0, 124.8, 124.5, 118.1, 61.9, 54.6, 52.8, 33.9; HRMS Calculated for C₂₀H₁₈N₄O₃ [M+H]⁺: 363.1452, Found: 363.1452.

1-benzyl-N-(2-phenylpropyl)-1H-1,2,3-triazole-4-carboxamide (4b') was purified by flash chromatography (Hexane-EtOAc, v/v 2/1) as white solid; ¹H-NMR (600 MHz, CDCl₃) δ 7.93(s, 1H), 7.40-7.36(m, 3H), 7.33-7.31(m, 2H), 7.28-7.27(m, 2H), 7.25-7.21(m, 3H), 7.10-7.08(m, br, 1H), 5.52(s, 2H), 3.74-3.69(m, 1H) 3.53-3.48(qd, *J* = 7.8, 5.4 Hz, 1H), 3.07-3.01(dq, *J* = 14.4, 7.2 Hz, 1H), 1.34-1.32(d, *J* = 6.6 Hz, 3H); ¹³C-NMR (150 MHz, CDCl₃) δ 160.1, 144.0, 143.7, 133.9, 129.4, 129.2, 128.9, 128.4, 127.3, 126.9, 125.3, 54.7, 45.9, 40.1, 19.4; HRMS Calculated for C₁₉H₂₀N₄O [M+H]⁺: 321.1710, Found: 321.1709.

(1-benzyl-1H-1,2,3-triazol-4-yl)(3-methylindolin-1-yl)methanone (4b) was prepared following the general procedure A and purified by flash chromatography (Hexane-EtOAc, v/v 3/1) as white solid; Isolated yield 80%; ¹H-NMR (600 MHz, CDCl₃) δ 8.29-8.27 (d, *J* = 7.8, 1H), 8.13(s, 1H), 7.41-7.37(m, 3H), 7.32-7.31(m, 2H), 7.25-7.21(m, 2H), 7.11-7.09(t, *J* = 7.5 Hz, 1H), 5.57(s, 2H), 5.02-4.99(dd, *J* = 10.5, 10.5 Hz, 1H), 4.30-4.27(dd, *J* = 11.4, 6.6 Hz, 1H), 3.57-3.51(tq, *J* = 7.2, 7.2 Hz, 1H), 1.38-1.37(d, *J* = 11.4, 6.6 Hz, 3H); ¹³C-NMR (150 MHz, CDCl₃) δ 159.0, 145.9, 142.9, 137.5, 133.9, 129.25,

129.20, 128.6, 127.7, 124.7, 123.6, 117.8, 58.2, 54.5, 35.5, 20.1; HRMS Calculated for $C_{19}H_{18}N_4O$ $[M+H]^+$: 319.1554, Found: 319.1553.

1-benzyl-N-(2-bromophenethyl)-1H-1,2,3-triazole-4-carboxamide (4c') was purified by flash chromatography (Hexane-EtOAc, v/v 2/1) as white solid. 1H -NMR (600 MHz, $CDCl_3$) δ 7.95(s, 1H), 7.55-7.54(m, 2H), 7.41-7.37(m, 3H), 7.29-7.27(m, 2H), 7.25-7.22(m, 2H), 7.10-7.08(m, 1H), 5.54(s, 2H), 3.73-3.69(q, J = 7.2 Hz, 2H), 3.07-3.05(t, J = 7.2 Hz, 2H); ^{13}C -NMR (150 MHz, $CDCl_3$) δ 160.2, 143.7, 138.2, 133.9, 133.1, 131.0, 131.0, 129.4, 129.3, 128.5, 127.8, 125.3, 124.7, 54.7, 39.0, 36.2; HRMS Calculated for $C_{18}H_{17}BrN_4O$ $[M+H]^+$: 385.0659, Found: 385.0664.

(1-benzyl-1H-1,2,3-triazol-4-yl)(4-bromoindolin-1-yl)methanone (4c) was prepared following the general procedure A at 100 °C and purified by flash chromatography (Hexane-EtOAc, v/v 3/1) as white solid; Isolated yield 87%; 1H -NMR (600 MHz, $CDCl_3$) δ 8.25-8.23 (d, J = 7.8 Hz, 1H), 8.11(s, 1H), 7.42-7.39(m, 3H), 7.29-7.31(m, 2H), 7.23-7.21(d, J = 8.4 Hz, 1H), 7.12-7.09(t, J = 7.8 Hz, 1H), 5.58(s, 2H), 4.84-4.81(t, J = 8.4 Hz, 2H), 3.25-3.22(t, J = 8.4 Hz, 2H); ^{13}C -NMR (150 MHz, $CDCl_3$) δ 159.46, 145.6, 144.5, 133.8, 133.0, 129.5, 129.31, 129.29, 128.7, 127.3, 119.6, 116.6, 54.6, 49.8, 30.4; HRMS Calculated for $C_{18}H_{15}BrN_4O$ $[M+H]^+$: 383.0502, Found: 383.0507.

1-benzyl-N-(2-fluorophenethyl)-1H-1,2,3-triazole-4-carboxamide (4d') was purified by flash chromatography (Hexane-EtOAc, v/v 2/1) as white solid; ^1H -NMR (600 MHz, CDCl_3) δ 7.94(s, 1H), 7.40-7.37(m, 3H), 7.29-7.27(m, 2H), 7.23-7.19(m, 3H), 7.08-7.02(m, 2H), 5.54(s, 2H), 3.72-3.68(q, $J = 7.2$ Hz, 2H) 2.97-2.95(t, $J = 7.2$ Hz, 2H); ^{13}C -NMR (150 MHz, CDCl_3) δ 160.6, 160.1, 143.7, 133.9, 131.21, 131.18, 129.4, 129.3, 128.57, 128.51, 128.4, 125.8, 125.7, 125.3, 124.37, 124.35, 115.6, 115.5, 54.7, 39.3, 29.5; HRMS Calculated for $\text{C}_{18}\text{H}_{17}\text{FN}_4\text{O}$ $[\text{M}+\text{H}]^+$: 325.1460, Found: 325.1459.

(1-benzyl-1H-1,2,3-triazol-4-yl)(4-fluoroindolin-1-yl)methanone (4d) was prepared following the general procedure A at 100 °C and purified by flash chromatography (Hexane-EtOAc, v/v 3/1) as white solid; Isolated yield 60%; ^1H -NMR (600 MHz, CDCl_3) δ 8.11(s, 1H), 8.08-8.06(d, $J = 7.8$, 1H), 7.42-7.38(m, 3H), 7.33-7.31(m, 2H), 7.22-7.18(dd, $J = 14.4$, 8.4 Hz, 2H), 6.80-6.78(dd, $J = 8.4$ Hz, 1H), 5.58(s, 2H), 4.87-4.84(t, $J = 8.4$ Hz, 2H), 3.28-3.25(dd, $J = 8.4$ Hz, 2H); ^{13}C -NMR (150 MHz, CDCl_3) δ 160.0, 159.25, 158.4, 145.7, 133.9, 129.47, 129.44, 129.39, 129.31, 128.7, 128.5, 118.5, 113.76, 113.75, 111.42, 111.28, 54.63, 50.84, 25.07; HRMS Calculated for $\text{C}_{18}\text{H}_{15}\text{FN}_4\text{O}$ $[\text{M}+\text{H}]^+$: 323.1303, Found: 323.1306.

1-benzyl-N-(2-iodophenethyl)-1H-1,2,3-triazole-4-carboxamide (4e') was purified by flash chromatography (Hexane-EtOAc, v/v 2/1) as white solid; $^1\text{H-NMR}$ (600 MHz, CDCl_3) δ 7.95(s, 1H), 7.84-7.82(dd, $J = 7.8, 1.2$ Hz, 1H), 7.40-7.37(m, 3H), 7.29-7.28(m, 3H), 7.27-7.24(td, $J = 7.2, 1.8$ Hz, 1H), 7.24-7.22(m, br, 1H), 6.93-6.90(td, $J = 7.8, 1.8$ Hz, 1H), 5.55(s, 1H), 3.72-3.68(q, $J = 7.2$ Hz, 2H), 2.97-2.95(t, $J = 7.2$ Hz, 2H); $^{13}\text{C-NMR}$ (150 MHz, CDCl_3) δ 160.2, 143.8, 141.5, 139.8, 133.9, 130.2, 129.5, 129.3, 128.7, 128.6, 128.4, 125.3, 100.6, 54.7, 40.7, 39.2; HRMS Calculated for $\text{C}_{18}\text{H}_{17}\text{IN}_4\text{O}$ $[\text{M}+\text{H}]^+$: 433.0520, Found: 433.0526.

(1-benzyl-1H-1,2,3-triazol-4-yl)(4-iodoindolin-1-yl)methanone (4e) was prepared following the general procedure A at 100 °C and purified by flash chromatography (Hexane-EtOAc, v/v 3/1) as white solid; Isolated yield 62%; $^1\text{H-NMR}$ (600 MHz, CDCl_3) δ 8.29-8.27 (d, $J = 7.8$ Hz, 1H), 8.11(s, 1H), 7.45-7.44(d, $J = 7.8$ Hz, 1H), 7.42-7.38(m, 3H), 7.33-7.31(m, 2H), 6.96-6.94(t, $J = 7.8$ Hz, 1H), 5.57(s, 2H), 4.82-4.80(t, $J = 8.1$ Hz, 2H), 3.19-3.16(t, $J = 8.4$ Hz, 2H); $^{13}\text{C-NMR}$ (150 MHz, CDCl_3) δ 159.6, 143.5, 137.0, 133.8, 133.4, 129.5, 129.47, 129.34, 129.31, 128.7, 128.5, 117.5, 93.1, 54.6, 49.3, 34.2; HRMS Calculated for $\text{C}_{18}\text{H}_{15}\text{IN}_4\text{O}$ $[\text{M}+\text{H}]^+$: 431.0364, Found: 431.0370.

1-benzyl-N-(2-methylphenethyl)-1H-1,2,3-triazole-4-carboxamide (4f') was purified by flash chromatography (Hexane-EtOAc, v/v 2/1) as white solid; ^1H -NMR (600 MHz, CDCl_3) δ 7.95(s, 1H), 7.40-7.37(m, 3H), 7.29-7.28(m, 3H), 7.29-7.27(m, 2H), 7.26-7.13(m, br, 1H), 7.18-7.13(m, 4H), 5.54(s, 1H), 3.67-3.64(q, J = 6.3 Hz, 2H), 2.94-2.91(t, J = 7.5 Hz, 2H), 3.56(s, 3H); ^{13}C -NMR (150 MHz, CDCl_3) δ 160.2, 143.8, 136.9, 136.5, 133.9, 130.6, 129.44, 129.39, 129.27, 128.4, 126.8, 126.3, 125.3, 54.7, 39.5, 33.4, 19.5; HRMS Calculated for $\text{C}_{19}\text{H}_{20}\text{N}_4\text{O}$ $[\text{M}+\text{H}]^+$: 321.1710, Found: 321.1714.

(1-benzyl-1H-1,2,3-triazol-4-yl)(4-methylindolin-1-yl)methanone (4f) was prepared following the general procedure A and purified by flash chromatography (Hexane-EtOAc, v/v 3/1) as yellow solid; Isolated yield 53%; ^1H -NMR (600 MHz, CDCl_3) δ 8.15-8.14 (d, J = 7.8 Hz, 1H), 8.11(s, 1H), 7.42-7.26(m, 3H), 7.33-7.26(m, 2H), 7.16-7.14(t, J = 7.5 Hz, 1H), 6.91-6.90(t, J = 7.2 Hz, 1H), 5.57(s, 2H), 4.82-4.79(t, J = 8.4 Hz, 2H), 3.15-3.13(t, J = 8.4 Hz, 2H), 2.27(s, 3H); ^{13}C -NMR (150 MHz, CDCl_3) δ 159.1, 146.1, 143.1, 134.2, 133.9, 131.1, 129.5, 129.2, 128.55, 128.51, 127.7, 125.6, 115.4, 54.6, 50.3, 27.7, 18.8; HRMS Calculated for $\text{C}_{19}\text{H}_{18}\text{N}_4\text{O}$ $[\text{M}+\text{H}]^+$: 319.1554, Found: 319.1557.

1-benzyl-N-(2-methoxyphenethyl)-1H-1,2,3-triazole-4-carboxamide (4g') was purified by flash chromatography (Hexane-EtOAc, v/v 2/1) as white solid.; $^1\text{H-NMR}$ (600 MHz, CDCl_3) δ 7.93(s, 1H), 7.52-7.49(m, br, 1H), 7.40-7.36(m, 3H), 7.28-7.26(m, 2H), 7.23-7.20(td, $J = 7.8, 1.8$ Hz, 1H), 7.17-7.15(dd, $J = 7.5, 1.5$ Hz, 1H), 6.91-6.86(m, 2H), 5.53(s, 1H), 3.88(s, 3H), 3.67-3.64(q, $J = 6.6$ Hz, 2H), 2.95-2.93(t, $J = 6.9$ Hz, 2H); $^{13}\text{C-NMR}$ (150 MHz, CDCl_3) δ 160.1, 157.6, 144.0, 133.9, 120.8, 129.4, 129.2, 128.4, 128.1, 127.5, 125.1, 120.8, 110.4, 55.5, 54.6, 40.0, 30.3; HRMS Calculated for $\text{C}_{19}\text{H}_{20}\text{N}_4\text{O}_2$ $[\text{M}+\text{H}]^+$: 337.1660, Found: 337.1662

(1-benzyl-1H-1,2,3-triazol-4-yl)(4-methoxyindolin-1-yl)methanone (4g) was prepared following the general procedure A and purified by flash chromatography (Hexane-EtOAc, v/v 3/1) as yellow solid; Isolated yield 67%; $^1\text{H-NMR}$ (600 MHz, CDCl_3) δ 8.11(s, 1H), 7.93-7.92(d, $J = 7.8$ Hz, 1H), 7.41-7.38(m, 3H), 7.32-7.31(m, 2H), 7.22-7.19(t, $J = 8.1$ Hz, 1H), 6.64-6.63(d, $J = 8.4$ Hz, 1H), 5.57(s, 2H), 4.82-4.78(t, $J = 8.4$ Hz, 2H), 3.85(s, 3H), 3.17-3.14(t, $J = 8.4$ Hz, 2H); $^{13}\text{C-NMR}$ (150 MHz, CDCl_3) δ 159.1, 155.9, 145.9, 144.8, 133.9, 149.4, 129.2, 128.9, 128.52, 128.49, 119.7, 110.9, 106.8, 55.5, 54.6, 50.8, 25.8; HRMS Calculated for $\text{C}_{19}\text{H}_{18}\text{N}_4\text{O}_2$ $[\text{M}+\text{H}]^+$: 335.1503, Found: 335.1507.

1-benzyl-N-(3-methylphenethyl)-1H-1,2,3-triazole-4-carboxamide (4h') was purified by flash chromatography (Hexane-EtOAc, v/v 2/1) as white solid; ^1H -NMR (600 MHz, CDCl_3) δ 7.94(s, 1H), 7.41-7.37(m, 3H), 7.29-7.27(m, 2H), 7.20-7.18(dd, $J = 7.5$, 7.5 Hz, 2H), 7.05-7.02(m, $J = 3$ H), 5.54(s, 1H), 3.88(s, 3H), 3.70-3.67(q, $J = 6.6$ Hz, 2H), 2.88-2.86(t, $J = 7.2$ Hz, 2H), 2.33(s, 3H); ^{13}C -NMR (150 MHz, CDCl_3) δ 160.1, 143.8, 138.7, 138.4, 133.9, 129.7, 129.4, 129.3, 128.7, 126.4, 127.5, 125.9, 125.3, 54.7, 40.5, 35.9, 21.5; HRMS Calculated for $\text{C}_{19}\text{H}_{20}\text{N}_4\text{O}$ $[\text{M}+\text{H}]^+$: 321.1710, Found: 321.1713.

(1-benzyl-1H-1,2,3-triazol-4-yl)(5-methylindolin-1-yl)methanone (4h) was prepared following the general procedure A and purified by flash chromatography (Hexane-EtOAc, v/v 2/1) as white solid; Isolated yield 88%; ^1H -NMR (600 MHz, CDCl_3) δ 8.18-8.16(d, $J = 8.4$ Hz, 1H), 8.10(s, 1H), 7.41-7.38(m, 3H), 7.32-7.31(m, 2H), 7.05(s, 1H), 7.04-7.02(d, $J = 7.8$ Hz, 1H), 5.57(s, 2H), 4.79-4.77(t, $J = 8.4$ Hz, 2H), 3.21-3.18(t, $J = 8.4$ Hz, 2H), 3.85(s, 3H); ^{13}C -NMR (150 MHz, CDCl_3) δ 158.8, 146.1, 141.1, 134.3, 133.9, 132.5, 129.5, 129.2, 128.50, 128.45, 127.99, 125.5, 117.6, 54.6, 50.4, 28.8, 21.2 ; HRMS Calculated for $\text{C}_{19}\text{H}_{18}\text{N}_4\text{O}$ $[\text{M}+\text{H}]^+$: 319.1554, Found: 319.1557.

1-benzyl-N-(3-fluorophenethyl)-1H-1,2,3-triazole-4-carboxamide (4i') was purified by flash chromatography (Hexane-EtOAc, v/v 2/1) as white solid; ^1H -NMR (600 MHz, CDCl_3) δ 7.94(s, 1H), 7.40-7.37(m, 3H), 7.29-7.21(m, 3H), 7.21-7.18(m, br, 1H), 7.01-7.00(d, $J = 7.8$ Hz, 2H), 6.94-6.92(m, 2H), 5.54(s, 1H), 3.88(s, 3H), 3.71-3.68(q, $J = 7.2$ Hz, 2H), 2.92-2.90(t, $J = 7.2$ Hz, 2H); ^{13}C -NMR (150 MHz, CDCl_3) δ 163.94, 162.3, 160.1, 143.7, 141.37, 141.32, 133.9, 130.28, 130.22, 129.5, 129.3, 128.4, 125.3, 125.54, 124.52, 115.84, 115.70, 113.7, 113.6, 54.7, 40.2, 35.78, 35.77; HRMS Calculated for $\text{C}_{18}\text{H}_{17}\text{FN}_4\text{O}$ $[\text{M}+\text{H}]^+$: 325.1460, Found: 325.1462.

(1-benzyl-1H-1,2,3-triazol-4-yl)(5-fluoroindolin-1-yl)methanone (4i) was prepared following the general procedure A at 100 °C and purified by flash chromatography (Hexane-EtOAc, v/v 3/1) as white solid; Isolated yield 55%; ^1H -NMR (600 MHz, CDCl_3) δ 8.26-8.24(dd, $J = 8.4, 5.1$ Hz, 1H), 8.11(s, 1H), 7.41-7.38(m, 3H), 7.32-7.31(m, 2H), 6.94-6.88(m, 2H), 5.57(s, 2H), 4.83-4.80(t, $J = 8.4$ Hz, 2H), 3.24-3.21(t, $J = 8.4$ Hz, 2H); ^{13}C -NMR (150 MHz, CDCl_3) δ 160.7, 159.0, 158.8, 145.7, 139.5, 134.42, 134.36, 133.9, 129.3, 128.5, 118.72, 118.67, 113.8, 113.7, 112.1, 111.9, 54.6, 50.5, 28.8; HRMS Calculated for $\text{C}_{18}\text{H}_{15}\text{FN}_4\text{O}$ $[\text{M}+\text{H}]^+$: 323.1303, Found: 323.1307.

1-benzyl-N-(4-methoxyphenethyl)-1H-1,2,3-triazole-4-carboxamide (4j') was purified by flash chromatography (Hexane-EtOAc, v/v 2/1) as white solid.; $^1\text{H-NMR}$ (600 MHz, CDCl_3) δ 7.94(s, 1H), 7.41-7.38(m, 3H), 7.29-7.27(m, 2H), 7.19-7.18(m, br, 1H), 7.15-7.14(d, $J = 8.4$ Hz, 2H), 6.85-6.84(d, $J = 8.4$ Hz, 2H), 5.54(s, 1H), 3.79(s, 3H), 3.67-3.64(q, $J = 6.6$ Hz, 2H), 2.86-2.84(t, $J = 7.2$ Hz, 2H); $^{13}\text{C-NMR}$ (150 MHz, CDCl_3) δ 160.0, 158.4, 143.8, 133.9, 130.8, 129.8, 129.4, 128.4, 125.2, 114.2, 55.4, 54.7, 40.7, 35.1; HRMS Calculated for $\text{C}_{19}\text{H}_{20}\text{N}_4\text{O}_2$ $[\text{M}+\text{H}]^+$: 337.1660, Found: 337.1663.

(1-benzyl-1H-1,2,3-triazol-4-yl)(6-methoxyindolin-1-yl)methanone (4j) was prepared following the general procedure A and purified by flash chromatography (Hexane-EtOAc, v/v 3/1) as colorless oil; Isolated yield 67%; $^1\text{H-NMR}$ (600 MHz, CDCl_3) δ 8.11(s, 1H), 7.99(s, 1H), 7.41-7.36(m, 3H), 7.32-7.31(m, 2H), 7.10-7.09(d, $J = 8.4$ Hz, 1H), 6.64-6.62(dd, $J = 8.1, 2.1$ Hz, 1H), 5.56(s, 2H), 4.81-4.78(t, $J = 8.4$ Hz, 2H), 3.80(s, 3H), 3.17-3.14(t, $J = 8.4$ Hz, 2H); $^{13}\text{C-NMR}$ (150 MHz, CDCl_3) δ 159.3, 159.2, 145.9, 144.5, 133.9, 129.4, 129.2, 128.54, 128.47, 124.8, 124.2, 111.0, 103.8, 55.7, 54.5, 51.2, 28.0; HRMS Calculated for $\text{C}_{19}\text{H}_{18}\text{N}_4\text{O}_2$ $[\text{M}+\text{H}]^+$: 335.1503, Found: 335.1506.

1-benzyl-N-(4-methylphenethyl)-1H-1,2,3-triazole-4-carboxamide (4k') was purified by flash chromatography (Hexane-EtOAc, v/v 2/1) as white solid. ; $^1\text{H-NMR}$ (600 MHz, CDCl_3) δ 7.94(s, 1H), 7.41-7.37(m, 3H), 7.29-7.27(m, 2H), 7.20-7.17(m, br, 1H), 7.12(s, 4H), 5.54(s, 1H), 3.88(s, 3H), 3.69-3.65(q, $J = 7.2$ Hz, 2H), 2.88-2.86(t, $J = 7.2$ Hz, 2H), 2.32(s, 1H); $^{13}\text{C-NMR}$ (150 MHz, CDCl_3) δ 160.1, 143.8, 136.2, 135.7, 133.9, 129.5, 129.4, 129.3, 128.7, 128.4, 125.3, 54.7, 40.6, 35.6, 21.2; HRMS Calculated for $\text{C}_{19}\text{H}_{20}\text{N}_4\text{O}$ $[\text{M}+\text{H}]^+$: 321.1710, Found: 321.1713.

(1-benzyl-1H-1,2,3-triazol-4-yl)(6-methylindolin-1-yl)methanone (4k) was purified by flash chromatography (Hexane-EtOAc, v/v 3/1) as white solid; Isolated yield 70%; $^1\text{H-NMR}$ (600 MHz, CDCl_3) δ 8.15(s, 1H), 8.11(s, 1H), 7.41-7.36(m, 3H), 7.33-7.31(m, 2H), 7.12-7.11(d, $J = 7.8$ Hz, 1H), 6.90-6.88(d, $J = 7.8$ Hz, 1H), 5.57(s, 2H), 4.79-4.77(t, $J = 8.1$ Hz, 2H), 3.20-3.17(t, $J = 8.4$ Hz, 2H), 2.36(s, 3H); $^{13}\text{C-NMR}$ (150 MHz, CDCl_3) δ 159.1, 146.1, 143.6, 137.4, 134.0, 129.4, 129.3, 128.51, 128.50, 128.47, 125.3, 124.4, 118.6, 54.6, 50.7, 28.5, 21.8; HRMS Calculated for $\text{C}_{19}\text{H}_{18}\text{N}_4\text{O}$ $[\text{M}+\text{H}]^+$: 319.1554, Found: 319.1558.

1-benzyl-N-(4-fluorophenethyl)-1H-1,2,3-triazole-4-carboxamide (4I') was purified by flash chromatography (Hexane-EtOAc, v/v 2/1) as white solid; ^1H -NMR (600 MHz, CDCl_3) δ 7.94(s, 1H), 7.40-7.38(m, 3H), 7.29-7.28(m, 2H), 7.20-7.17(m, 3H), 7.00-6.97(m, 2H), 5.54(s, 1H), 3.88(s, 3H), 3.69-3.65(q, $J = 7.2$ Hz, 2H), 2.88-2.86(t, $J = 7.2$ Hz, 2H), 2.32(s, 1H); ^{13}C -NMR (150 MHz, CDCl_3) δ 162.6, 161.02, 160.09, 143.7, 134.45, 134.33, 133.8, 130.33, 130.27, 129.5, 129.3, 128.4, 125.3, 115.7, 115.5, 54.7, 40.5, 35.2; HRMS Calculated for $\text{C}_{18}\text{H}_{17}\text{FN}_4\text{O}$ $[\text{M}+\text{H}]^+$: 325.1460, Found: 325.1462.

(1-benzyl-1H-1,2,3-triazol-4-yl)(6-fluoroindolin-1-yl)methanone (4I) was prepared following the general procedure A at 100 °C and purified by flash chromatography (Hexane-EtOAc, v/v 3/1) as white solid; Isolated yield 85%; ^1H -NMR (600 MHz, CDCl_3) δ 8.13(s, 1H), 8.06-8.04(d, $J = 10.8$, 1H), 7.41-7.38(m, 3H), 7.33-7.31(m, 2H), 7.15-7.12(dd, $J = 8.4$, 6 Hz, 1H), 6.78-6.74(td, $J = 8.4$, 2.4Hz, 1H), 5.57(s, 2H), 4.85-4.82(t, $J = 8.4$ Hz, 2H), 3.20-3.17(t, $J = 8.4$ Hz, 2H); ^{13}C -NMR (150 MHz, CDCl_3) δ 163.1, 161.5, 159.3, 145.6, 144.6, 133.8, 129.45, 129.42, 129.3, 128.71, 128.70, 128.5, 127.55, 127.54, 125.1, 125.0, 111.0, 110.9, 106.1, 105.9, 64.6, 51.2, 28.1; HRMS Calculated for $\text{C}_{18}\text{H}_{15}\text{FN}_4\text{O}$ $[\text{M}+\text{H}]^+$: 323.1303, Found: 323.1306.

4m'

(S)-methyl-2-(1-(4-methoxyphenyl)-1H-1,2,3-triazole-4-carboxamido)-3-

methylbutanoate (4m') was purified by flash chromatography (Hexane-EtOAc, v/v 2/1) as white solid; $^1\text{H-NMR}$ (600 MHz, CDCl_3) δ 8.40(s, 1H), 7.64-7.60(m, 3H), 7.05-7.03(d, $J = 9.0$ Hz, 2H), 4.77-4.74(dd, $J = 9.0, 4.8$ Hz, 1H), 3.87(s, 3H), 3.77(s, 3H), 2.35-2.27(m, 1H), 1.04-1.01(dd, $J = 9.0, 6.6$ Hz, 6H); $^{13}\text{C-NMR}$ (150 MHz, CDCl_3) δ 172.0, 160.4, 160.0, 143.4, 130.0, 123.9, 122.5, 115.1, 57.2, 55.8, 52.3, 31.6, 19.2, 18.0; HRMS Calculated for $\text{C}_{16}\text{H}_{20}\text{N}_4\text{O}_4$ $[\text{M}+\text{H}]^+$: 333.1558, Found: 333.1562.

4m

(2S,3R)-methyl-1-(1-(4-methoxyphenyl)-1H-1,2,3-triazole-4-carbonyl)-3-

methylazetidine-2-carboxylate (4m) was prepared following the general procedure B and purified by flash chromatography (Hexane-EtOAc, v/v 1/1) as colorless oil; Isolated yield 81%; $^1\text{H-NMR}$ (600 MHz, CDCl_3 , ratio of rotamers: $\sim 1.2/1$) δ 8.44-8.43(m, 1H), 7.64-7.61(m, 2H), 7.04-7.02(m, 2H), 5.16-5.15(d, $J = 4.8$ Hz, 0.55H), 4.97-4.95(t, $J = 8.7$ Hz, 0.45H), 4.53-4.52(d, $J = 4.8$ Hz, 0.45H), 4.42-4.39(t, $J = 8.4$ Hz, 0.55H), 4.34-4.32(dd, $J = 9.6, 5.4$ Hz, 0.55H), 3.88-3.87(m, 3H), 3.81(s, 1.35H), 3.76-3.37(m, 2H), 2.81-2.72(m, 1H), 1.47-1.46(d, $J = 7.2$ Hz, 1.65H), 1.44-1.43(d, $J = 6.6$ Hz, 1.35H); $^{13}\text{C-NMR}$ (150 MHz, CDCl_3) δ 171.5, 160.6, 160.4, 160.3, 129.99, 129.98, 125.2, 124.7, 122.5, 122.4, 115.11, 115.07, 70.65, 70.63, 66.4, 59.0, 55.81, 55.80, 53.8, 52.53, 52.52,

52.51, 31.31, 31.29, 30.9; HRMS Calculated for C₁₆H₁₈N₄O₄ [M+H]⁺: 331.1401, Found: 331.1405.

(S)-2-(1-(4-methoxyphenyl)-1H-1,2,3-triazole-4-carboxamido)-3-methylbutyl acetate (4n') was purified by flash chromatography (Hexane-EtOAc, v/v 2/1) as white solid; ¹H-NMR (600 MHz, CDCl₃) δ8.40(s, 1H), 7.64-7.63(d, *J* = 9.0 Hz, 2H), 7.25-7.23(m, br, 1H), 7.06-7.04(d, *J* = 9 Hz, 2H), 4.29-4.21(m, 3H), 3.88(s, 3H), 2.08(s, 3H), 2.02-1.96(m, 1H), 1.04-1.03(dd, *J* = 7.7, 1.2 Hz, 6H); ¹³C-NMR (150 MHz, CDCl₃) δ171.1, 160.5, 160.0, 143.7, 123.8, 122.5, 115.1, 64.7, 55.8, 53.3, 29.8, 21.0, 19.6, 18.8; HRMS Calculated for C₁₇H₂₂N₄O₄ [M+H]⁺: 347.1714, Found: 347.1718

((2S,3R)-1-(1-(4-methoxyphenyl)-1H-1,2,3-triazole-4-carbonyl)-3-methylazetidin-2-yl)methyl acetate (4n) was prepared following the general procedure B and purified by flash chromatography (Hexane-EtOAc, v/v 1/1) as colorless oil; Isolated yield 69%; ¹H-NMR (600 MHz, CDCl₃, ratio of rotamers: ~1.8/1) δ8.44(s, 1H), 7.64-7.62(d, *J* = 9 Hz, 2H), 7.04-7.02(d, *J* = 9 Hz, 2H), 4.90-4.88(dd, *J* = 6.6, 3.6 Hz, 0.35H), 4.85-4.82(t, *J* = 9 Hz, 0.65H), 4.75-4.73(dd, *J* = 11.7, 4.5 Hz, 0.35H), 4.57-4.54(dd, *J* = 11.7, 4.8 Hz,

0.65H), 4.47-4.43(m, 1H), 4.34-4.22(dd, $J = 9$, 4.2 Hz, 0.65H), 4.26-4.23(t, $J = 9$ Hz, 0.35H), 4.22-4.19(dd, $J = 9.9$, 6 Hz, 0.65), 3.87(s, 3H), 3.70-3.67(dd, $J = 10.5$, 4.5 Hz, 0.35H), 2.67-2.60(m, 1H), 2.10-2.07(m, 3H); ^{13}C -NMR (150 MHz, CDCl_3) δ 170.03, 169.98, 163.2, 161.0, 160.4, 144.3, 143.9, 130.01, 129.98, 125.1, 125.0, 122.38, 122.35, 115.11, 115.08, 69.8, 66.8, 64.9, 63.7, 58.7, 55.8, 53.7, 29.8, 28.8, 28.5, 21.02, 20.99, 19.3, 18.9; HRMS Calculated for $\text{C}_{17}\text{H}_{20}\text{N}_4\text{O}_4$ $[\text{M}+\text{H}]^+$: 345.1558, Found: 345.1563.

(2S)-methyl-2-(1-(4-methoxyphenyl)-1H-1,2,3-triazole-4-carboxamido)-3-

methylpentanoate (4o') was purified by flash chromatography (Hexane-EtOAc, v/v 2/1) as white solid; ^1H -NMR (600 MHz, CDCl_3) δ 8.40(s, 1H), 7.64-7.60(m, 3H), 7.04-7.03(d, $J = 9$ Hz, 2H), 4.79-4.77(dd, $J = 9$, 4.8 Hz, 1H), 3.87(s, 3H), 3.77(s, 3H), 2.06-2.00(m, 1H), 1.58-1.52(m, 1H), 1.33-1.25(m, 1H), 1.00-0.99(d, $J = 6.6$ Hz, 3H), 0.97-0.95(t, $J = 7.5$ Hz, 3H); ^{13}C -NMR (150 MHz, CDCl_3) δ 171.9, 160.4, 159.8, 143.4, 130.0, 123.8, 122.5, 115.1, 56.5, 55.8, 52.3, 38.2, 25.3, 15.7, 11.7; HRMS Calculated for $\text{C}_{17}\text{H}_{22}\text{N}_4\text{O}_4$ $[\text{M}+\text{H}]^+$: 347.1714, Found: 247.1718.

(2S,3R)-methyl-3-ethyl-1-(1-(4-methoxyphenyl)-1H-1,2,3-triazole-4-

carbonyl)azetidine-2-carboxylate (4o) was prepared following the general procedure B and purified by flash chromatography (Hexane-EtOAc, v/v 1/1) as colorless oil; Isolated

yield 56%; $^1\text{H-NMR}$ (600 MHz, CDCl_3 , ratio of rotamers: $\sim 1.5/1$) δ 8.44-8.43(m, 1H), 7.64-7.61(m, 2H), 7.05-7.02(m, 2H), 5.66-5.65(d, $J = 9.6$ Hz, 0.60H), 5.04-5.03(d, $J = 9.6$ Hz, 0.40H), 4.88-4.85(d, $J = 9$ Hz, 0.40H), 4.47-4.44(dd, $J = 9.3, 6.9$ Hz, 0.40H), 4.28-4.25(t, $J = 9$ Hz, 0.60H), 3.91-3.88(dd, $J = 9.6, 7.8$ Hz, 0.60H), 3.88-3.87(m, 3H), 3.80(s, 1.2), 3.75(s, 1.8), 3.03-2.95(m, 1H), 1.67-1.60(m, 1H), 1.55-1.42(m, 1H), 0.92-0.89(t, $J = 7.5$ Hz, 3H); $^{13}\text{C-NMR}$ (150 MHz, CDCl_3) δ 170.2, 160.4, 160.33, 160.28, 159.9, 144.1, 143.9, 130.0, 124.7, 122.5, 122.3, 115.1, 115.06, 67.8, 55.84, 55.82, 52.84, 52.83, 52.1, 35.4, 35.1, 23.3, 23.0, 11.3, 11.09, 11.07; HRMS Calculated for $\text{C}_{17}\text{H}_{20}\text{N}_4\text{O}_4$ $[\text{M}+\text{H}]^+$: 345.1558, Found: 345.1561.

(2S)-methyl-3-(acetoxymethyl)-2-(1-(4-methoxyphenyl)-1H-1,2,3-triazole-4-carboxamido)pentanoate (4oa) was prepared following the general procedure B and purified by flash chromatography (Hexane-EtOAc, v/v 1/1) as colorless oil, Isolated yield 30%; $^1\text{H-NMR}$ (600 MHz, CDCl_3) δ 8.39(s, 1H), 7.81-7.79(d, $J = 9.6$ Hz, 1H), 7.64-7.62(d, $J = 9$ Hz, 2H), 7.05-7.04(d, $J = 9$ Hz, 2H), 5.08-5.06(dd, $J = 9.0, 4.2$ Hz, 1H), 4.21-4.19(dd, $J = 11.7, 3.9$ Hz, 3H), 4.02-3.99(dd, $J = 11.4, 9$ Hz, 1H), 3.88(s, 3H), 3.79(s, 3H), 3.36-2.30(m, 1H), 2.13(s, 3H), 1.60-1.53(m, 3H), 1.56-1.42(m, 1H), 1.04-1.02(t, $J = 7.2$ Hz, 3H); $^{13}\text{C-NMR}$ (150 MHz, CDCl_3) δ 171.6, 171.0, 160.5, 159.9, 143.2, 130.0, 123.9, 122.6, 115.1, 64.0, 55.85, 55.84, 52.9, 52.63, 52.62, 42.6, 21.1, 20.7, 11.9 ; HRMS Calculated for $\text{C}_{19}\text{H}_{24}\text{N}_4\text{O}_6$ $[\text{M}+\text{H}]^+$: 405.1769, Found: 405.1773.

1-(4-methoxyphenyl)-N-(3-methylbutan-2-yl)-1H-1,2,3-triazole-4-carboxamide (4p') was purified by flash chromatography (Hexane-EtOAc, v/v 2/1) as white solid; ^1H -NMR (600 MHz, CDCl_3) δ 8.38(s, 1H), 7.64-7.63(d, J = 8.4 Hz, 2H), 7.05-7.03(m, 3H), 4.11-4.07(m, 1H), 3.88(s, 3H), 1.86-1.81(m, 1H), 7.06-7.04(d, J = 9 Hz, 2H), 4.29-4.21(m, 3H), 3.88(s, 3H), 2.08(s, 3H), 2.02-1.96(m, 1H), 1.04-1.03(dd, J = 7.7, 1.2 Hz, 6H); ^{13}C -NMR (150 MHz, CDCl_3) δ 160.4, 159.4, 144.1, 123.5, 122.5, 115.1, 55.8, 50.1, 33.4, 31.1, 18.79, 18.71, 17.9; HRMS Calculated for $\text{C}_{15}\text{H}_{20}\text{N}_4\text{O}_2$ $[\text{M}+\text{H}]^+$: 289.1660, Found: 289.1663.

((2R,3R)-2,3-dimethylazetidin-1-yl)(1-(4-methoxyphenyl)-1H-1,2,3-triazol-4-yl)methanone (4pa) was prepared following the general procedure B and purified by flash chromatography (Hexane-EtOAc, v/v 1/1) as colorless oil; Isolated yield 74%; ^1H -NMR (600 MHz, CDCl_3 , ratio of rotamers: $\sim$ 1.5/1) δ 8.43-8.41(s, 1H), 7.66-7.63(m, 2H), 7.04-7.03(m, 2H), 4.90-4.87(t, J = 9.3 Hz, 0.60H), 4.77-4.73(m, 0.40H), 4.32-4.29(t, J = 9.0 Hz, 0.4H), 4.21-4.17(m, 1H), 3.87(s, 3H), 3.69-3.66(dd, J = 10.8, 4.8 Hz, 0.4H), 2.37-2.23(m, 1H), 1.61-1.60(d, J = 6.6 Hz, 1.20H), 1.57-1.56(d, J = 6.6 Hz, 1.80H); ^{13}C -NMR (150 MHz, CDCl_3) δ 160.5, 160.1, 144.7, 144.1, 129.9, 124.766, 124.762, 124.6, 122.2, 122.1, 114.9, 65.1, 57.8, 55.7, 55.65, 55.63, 52.4, 33.4, 32.8, 21.4, 19.9, 19.1, 18.7; HRMS Calculated for $\text{C}_{15}\text{H}_{18}\text{N}_4\text{O}_2$ $[\text{M}+\text{H}]^+$: 287.1503, Found: 287.1505.

((2R,3S)-2,3-dimethylazetidin-1-yl)(1-(4-methoxyphenyl)-1H-1,2,3-triazol-4-yl)methanone (4pb) was prepared following the general procedure B and purified by flash chromatography (Hexane-EtOAc, v/v 1/1) as colorless oil; Isolated yield 15%; ^1H -NMR (600 MHz, CDCl_3 , ratio of rotamers: $\sim 1.5/1$) δ 8.42-8.40(s, 1H), 7.66-7.63(m, 2H), 7.05-7.03(m, 2H), 5.32-5.27(m, 0.60H), 4.81-4.74(m, 1.20H), 4.34-4.28(m, 1H), 3.87(s, 3H), 3.78-3.75(ddd, $J = 10.2, 7.2, 0.6\text{ Hz}$, 0.40H), 3.05-3.29(m, 1H), 1.53-1.52(d, $J = 6.6\text{ Hz}$, 1.20H), 1.49-1.48(d, $J = 7.2\text{ Hz}$, 1.80H), 1.21-1.19(d, $J = 7.2\text{ Hz}$, 1.80H), 1.18-1.16(d, $J = 7.2\text{ Hz}$, 1.20H),; ^{13}C -NMR (150 MHz, CDCl_3) δ 163.2, 160.3, 130.1, 124.9, 124.7, 122.4, 115.1, 60.2, 59.1, 55.82, 55.81, 53.97, 28.2, 15.8, 14.4, 13.98, 13.96; HRMS Calculated for $\text{C}_{15}\text{H}_{18}\text{N}_4\text{O}_2$ $[\text{M}+\text{H}]^+$: 287.1503, Found: 287.1505.

(1-(4-methoxyphenyl)-1H-1,2,3-triazol-4-yl)(2,2,4,4-tetramethylpyrrolidin-1-yl)methanone was prepared following the general procedure B and purified by flash chromatography (Hexane-EtOAc, v/v 1/1) as colorless soild; Isolated yield 84%; ^1H -NMR (400 MHz, CDCl_3) δ 8.41(s, 1H), 7.64-7.62(d, $J = 9.2\text{ Hz}$, 2H), 7.04-7.02(d, $J = 9.2\text{ Hz}$, 2H), 4.08(s, 2H), 3.87(s, 3H), 1.81(s, 2H), 1.65(m, 6H), 1.18(s, 6H),; ^{13}C -NMR (150 MHz, CDCl_3) δ 160.2, 159.6, 147.2, 130.2, 126.0, 122.4, 115.0, 64.5, 62.6, 55.9, 55.8, 55.77, 36.97, 27.9; HRMS Calculated for $\text{C}_{18}\text{H}_{24}\text{N}_4\text{O}_2$ $[\text{M}+\text{H}]^+$: 329.1972, Found:329.1972.

5a

N-phenethyl-5-phenyl-2-(pyridin-2-yl)-2H-1,2,3-triazole-4-carboxamide(5a) was purified by flash chromatography (Hexane-EtOAc, v/v 2/1) as white solid; ^1H -NMR (600 MHz, CDCl_3) δ 8.65-8.63(d, J = 4.8 Hz, 1H), 8.16-8.14(d, J = 8.4 Hz, 1H), 8.12-8.10(m, 2H), 7.95-7.92(td, J = 7.8, 1.8 Hz, 1H), 7.48-7.40(m, 3H), 7.38-7.36(ddd, J = 7.2, 1.8, 0.6 Hz, 1H), 7.31-7.29(m, 2H), 7.25-7.21(m, 4H), 3.72-3.69(q, J = 6.6 Hz, 2H), 2.96-2.94(t, J = 7.2 Hz, 2H); ^{13}C -NMR (150 MHz, CDCl_3) δ 160.3, 150.5, 150.2, 149.1, 140.8, 139.3, 128.9, 129.65, 129.60, 129.1, 128.9, 128.74, 128.71, 128.3, 126.6, 123.8, 114.6, 41.0, 36.0; HRMS Calculated for $\text{C}_{22}\text{H}_{19}\text{N}_5\text{O}$ $[\text{M}+\text{H}]^+$: 370.1663, Found: 370.1668.

6a

2-(2-(5-phenyl-2-(pyridin-2-yl)-2H-1,2,3-triazole-4-carboxamido)ethyl)phenyl acetate (6b) was prepared following the general procedure C and purified by flash chromatography (Hexane-EtOAc, v/v 1/1) as colorless oil; Isolated yield 47%; ^1H -NMR (600 MHz, CDCl_3) δ 8.66-8.65(d, J = 4.8 Hz, 1H), 8.19-8.18(d, J = 7.8 Hz, 1H), 8.14-8.12(m, 2H), 7.96-7.93(td, J = 7.2, 1.8 Hz, 1H), 7.49-7.45(m, 3H), 7.41-7.39(m, 1H), 7.32-7.24(m, 3H), 7.20-7.17(td, J = 7.8, 1.2 Hz, 1H), 7.07-7.04(d, J = 7.2, 1.2 Hz, 1H), 3.58-3.55(q, J = 6.0 Hz, 2H), 2.90-2.88(t, J = 7.8 Hz, 2H), 2.33(s, 3H); ^{13}C -NMR (150 MHz, CDCl_3) δ 169.9, 160.4, 150.5, 150.2, 149.4, 149.1, 140.8, 139.4, 130.89, 130.84, 128.0, 126.5, 123.9, 122.7, 114.6, 39.9, 30.4, 21.1; HRMS Calculated for $\text{C}_{24}\text{H}_{21}\text{N}_5\text{O}_3$ $[\text{M}+\text{H}]^+$: 428.1718, Found: 428.1716.

7a'

5-phenyl-N-(2-phenylpropyl)-2-(pyridin-2-yl)-2H-1,2,3-triazole-4-carboxamide (7a') was purified by flash chromatography (Hexane-EtOAc, v/v 2/1) as white solid; $^1\text{H-NMR}$ (600 MHz, CDCl_3) δ 8.58-8.57(d, $J = 4.8$ Hz, 1H), 8.08-8.04(m, 3H), 7.86-7.83(td, $J = 7.8, 1.8$ Hz, 1H), 7.46-7.40(m, 3H), 7.32-7.28(m, 3H), 7.25-7.23(m, 2H), 7.21-7.18(m, 1H), 7.14-7.12(t, $J = 6.6$ Hz, 1H), 3.74-3.70(m, 1H), 3.53-3.48(m, 1H), (ddd, $J = 7.2, 1.8, 0.6$ Hz, 1H), 7.31-7.29(m, 2H), 7.25-7.21(m, 4H), 3.72-3.69(q, $J = 6.6$ Hz, 2H), 2.96-2.94(t, $J = 7.2$ Hz, 2H); $^{13}\text{C-NMR}$ (150 MHz, CDCl_3) δ 160.2, 150.2, 149.9, 148.9, 144.0, 139.1, 129.45, 129.41, 129.0, 128.6, 128.1, 127.2, 126.6, 123.6, 114.3, 46.3, 39.8, 19.2; HRMS Calculated for $\text{C}_{23}\text{H}_{21}\text{N}_5\text{O}$ $[\text{M}+\text{H}]^+$: 384.1819, Found: 384.1825.

7aa

2-(1-(5-phenyl-2-(pyridin-2-yl)-2H-1,2,3-triazole-4-carboxamido)propan-2-yl)phenyl acetate (7aa) was prepared following the general procedure C and purified by flash chromatography (Hexane-EtOAc, v/v 1/1) as colorless oil; Isolated yield 68%; $^1\text{H-NMR}$ (600 MHz, CDCl_3) δ 8.63-8.62(d, $J = 4.8$ Hz, 1H), 8.15-8.14(d, $J = 8.4$ Hz, 1H), 8.11-8.10(m, 2H), 7.93-7.91(td, $J = 8.4, 1.2$ Hz, 1H), 7.47-7.43(m, 3H), 7.39-7.35(m, 2H), 7.25-7.23(m, 2H), 7.13-7.11(m, br, 1H), 7.01-6.99(m, 1H), 3.74-3.70(m, 1H), 3.50-3.46(m, 1H), 3.67-3.31(m, 1H), 2.26(s, 3H), 1.30-1.29(d, $J = 6.6$ Hz, 3H); $^{13}\text{C-NMR}$ (150 MHz, CDCl_3) δ 170.0, 160.6, 149.1, 149.0, 139.3, 136.0, 129.7, 129.6, 129.2, 128.2,

127.6, 127.4, 126.7, 122.8, 45.8, 32.9, 21.0, 18.7 ; HRMS Calculated for $C_{25}H_{23}N_5O_3$ $[M+H]^+$: 442.1874, Found: 442.1880.

7ab

2-(1-(5-phenyl-2-(pyridin-2-yl)-2H-1,2,3-triazole-4-carboxamido)propan-2-yl)-1,3-phenylene diacetate (7ab) was prepared following the general procedure C and purified by flash chromatography (Hexane-EtOAc, v/v 1/1) as colorless oil; Isolated yield 13%; 1H -NMR (600 MHz, $CDCl_3$) δ 8.63-8.62(d, J = 4.8 Hz, 1H), 8.14-8.11(m, 3H), 7.93-7.91(td, J = 8.4, 1.2 Hz, 1H), 7.47-7.42(m, 3H), 7.38-7.36(m, 2H), 7.24-7.21(t, J = 7.8 Hz, 1H), 7.15-7.13(m, br, 1H), 6.93-6.91(d, J = 7.8 Hz, 2H), 3.93-3.88(m, 1H), 3.55-3.43(m, 2H), 2.27(s, 6H), 1.30-1.28(d, J = 6.6 Hz, 3H); ^{13}C -NMR (150 MHz, $CDCl_3$) δ 169.5, 160.7, 150.6, 150.3, 150.2, 149.1, 140.8, 139.2, 129.8, 129.5, 129.4, 128.2, 128.0, 127.5, 123.7, 121.07, 121.06, 121.05, 114.6, 43.89, 43.87, 31.3, 21.179, 21.172, 16.97; HRMS Calculated for $C_{27}H_{25}N_5O_5$ $[M+H]^+$: 500.1929, Found: 500.1936.

7b'

N-(2-methylphenethyl)-5-phenyl-2-(pyridin-2-yl)-2H-1,2,3-triazole-4-carboxamide (7b') was purified by flash chromatography (Hexane-EtOAc, v/v 2/1) as white solid; 1H -NMR (600 MHz, $CDCl_3$) δ 8.65-8.64(d, J = 4.8 Hz, 1H), 8.17-8.16(d, J = 7.8 Hz, 1H), 8.13-8.11(m, 2H), 7.95-7.92(t, J = 7.8 Hz, 1H), 7.49-7.43(m, 3H), 7.41-7.38(ddd, J = 7.2, 4.8, 0.6 Hz, 1H), 7.28(m, br, 1H), 7.19-7.13(m, 4H), 3.69-3.66(q, J = 6.6 Hz, 2H),

2.98-2.95(t, $J = 7.5$ Hz, 2H). 2.37(s, 3H); ^{13}C -NMR (150 MHz, CDCl_3) δ 160.3, 150.2, 149.1, 140.8, 139.3, 137.0, 136.5, 130.5, 129.65, 129.62, 129.5, 128.3, 126.8, 126.2, 123.9, 114.6, 39.8, 33.4, 19.5; HRMS Calculated for $\text{C}_{23}\text{H}_{21}\text{N}_5\text{O}$ $[\text{M}+\text{H}]^+$: 384.1819, Found: 384.1818.

3-methyl-2-(2-(5-phenyl-2-(pyridin-2-yl)-2H-1,2,3-triazole-4-

carboxamido)ethyl)phenyl acetate (7b) was prepared following the general procedure C at 100 °C and purified by flash chromatography (Hexane-EtOAc, v/v 1/1) as colorless oil; Isolated yield 85%; ^1H -NMR (600 MHz, CDCl_3) δ 8.65-8.64(d, $J = 4.8$ Hz, 1H), 8.19-8.18(d, $J = 7.8$ Hz, 1H), 8.15-8.14(m, 2H), 7.95-7.93(t, $J = 7.2$ Hz, 1H), 7.49-7.41(m, 3H), 7.41-7.39(m, 1H), 7.32(m, br, 1H), 7.16-7.13(t, $J = 7.8$ Hz, 1H), 7.07-7.06(d, $J = 7.2$ Hz, 1H), 6.89-6.88(d, $J = 7.8$ Hz, 1H) 3.58-3.55(q, $J = 7.2$ Hz, 2H), 2.93-2.90(t, $J = 7.8$ Hz, 2H). 2.40(s, 3H), 2.33(s, 3H); ^{13}C -NMR (150 MHz, CDCl_3) δ 170.2, 160.5, 150.6, 150.2, 149.8, 149.2, 140.9, 139.3, 138.8, 129.7, 129.6, 129.3, 129.2, 128.30, 128.27, 127.3, 123.9, 120.2, 114.6, 38.9, 27.4, 21.2, 19.7; HRMS Calculated for $\text{C}_{25}\text{H}_{23}\text{N}_5\text{O}_3$ $[\text{M}+\text{H}]^+$: 442.1874, Found: 442.1873

N-(2-bromophenethyl)-5-phenyl-2-(pyridin-2-yl)-2H-1,2,3-triazole-4-carboxamide (7c') was purified by flash chromatography (Hexane-EtOAc, v/v 2/1) as white solid; ^1H -NMR (600 MHz, CDCl_3) δ 8.66-8.65(d, J = 4.8 Hz, 1H), 8.19-8.17(d, J = 8.4 Hz, 1H), 8.12-8.11(m, 2H), 7.96-7.93(td, J = 8.4, 1.8 Hz, 1H), 7.56-7.54(dd, J = 8.4, 1.2 Hz, 1H), 7.50-7.45(m, 3H), 7.42-7.39(ddd, J = 7.2, 4.8, 0.6 Hz, 1H), 7.29-7.22(m, 3H), 7.11-7.08(td, J = 7.8, 1.8 Hz, 1H), 3.75-3.71(q, J = 6.3 Hz, 2H), 3.12-3.10(t, J = 7.2 Hz, 2H); ^{13}C -NMR (150 MHz, CDCl_3) δ 160.4, 150.6, 150.3, 149.2, 140.8, 139.3, 188.3, 122.1, 129.75, 129.73, 129.72, 129.6, 129.2, 128.5, 127.8, 124.8, 123.9, 114.6, 39.5, 36.2; HRMS Calculated for $\text{C}_{22}\text{H}_{18}\text{BrN}_5\text{O}$ $[\text{M}+\text{H}]^+$: 448.0768, Found: 448.0767.

3-methyl-2-(2-(5-phenyl-2-(pyridin-2-yl)-2H-1,2,3-triazole-4-carboxamido)ethyl)phenyl acetate (7c) was prepared following the general procedure C at 100 °C and purified by flash chromatography (Hexane-EtOAc, v/v 1/1) as white solid; Isolated yield 73%; ^1H -NMR (600 MHz, CDCl_3) δ 8.65-8.64(dd, J = 4.8 1.2 Hz, 1H), 8.19-8.18(d, J = 8.4 Hz, 1H), 8.16-8.14(m, 2H), 7.95-7.93(td, J = 7.8, 2.4 Hz, 1H), 7.48-7.43(m, 3H), 7.41-7.38(ddd, J = 7.2, 4.8, 0.6 Hz, 1H), 7.32-7.30(t, J = 6 Hz, 1H), 7.13-7.10(t, J = 8.1 Hz, 1H), 7.01-7.00(dd, J = 8.1, 0.6 Hz, 1H), 3.65-3.62(q, J = 6.6 Hz, 2H), 3.10-3.08(t, J = 7.5 Hz, 2H), 2.29(s, 3H); ^{13}C -NMR (150 MHz, CDCl_3) δ 160.5, 150.5, 150.3, 150.1, 149.1, 140.8, 139.3, 131.3, 130.6, 129.7, 129.6, 129.2, 128.6, 128.2, 125.7, 123.9, 122.2, 114.6, 38.4, 30.5, 20.9; HRMS Calculated for $\text{C}_{24}\text{H}_{20}\text{BrN}_5\text{O}_3$ $[\text{M}+\text{H}]^+$: 506.0823, Found: 506.0822.

N-(2-bromophenethyl)-5-phenyl-2-(pyridin-2-yl)-2H-1,2,3-triazole-4-carboxamide (7d') was purified by flash chromatography (Hexane-EtOAc, v/v 2/1) as white solid; ^1H -NMR (600 MHz, CDCl_3) δ 8.66-8.65(dd, J = 4.8, 1.8 Hz, 1H), 8.18-8.16(d, J = 7.8 Hz, 1H), 8.12-8.11(m, 2H), 7.96-7.93(td, J = 7.8, 1.8 Hz, 1H), 7.49-7.43 (m, 3H), 7.41-7.39(ddd, J = 7.2, 4.8, 0.6 Hz, 1H), 7.26-7.19(m, 4H), 7.08-7.05(td, J = 7.8, 1.2 Hz, 1H), 7.05-7.02(t, J = 7.8 Hz, 1H), 3.74-3.70(q, J = 6.6 Hz, 2H), 3.12-3.10(t, J = 7.2 Hz, 2H); ^{13}C -NMR (150 MHz, CDCl_3) δ 160.3, 160.4, 150.6, 150.3, 149.2, 140.8, 139.30, 139.28, 131.33, 131.30, 129.7, 129.6, 129.1, 128.51, 128.46, 125.9, 125.8, 124.34, 124.32, 123.9, 115.6, 115.5, 114.6, 39.8, 29.52, 29.51; HRMS Calculated for $\text{C}_{22}\text{H}_{18}\text{FN}_5\text{O}$ $[\text{M}+\text{H}]^+$: 388.1569, Found: 388.1566.

3-fluoro-2-(2-(5-phenyl-2-(pyridin-2-yl)-2H-1,2,3-triazole-4-carboxamido)ethyl)phenyl acetate (7d) was prepared following the general procedure C at 100 °C and purified by flash chromatography (Hexane-EtOAc, v/v 1/1) as colorless oil; Isolated yield 60%; ^1H -NMR (600 MHz, CDCl_3) δ 8.65-8.64(d, J = 4.2 Hz, 1H), 8.19-8.18(d, J = 8.4 Hz, 1H), 8.14-8.13(m, 2H), 7.95-7.93(td, J = 8.4, 1.2 Hz, 1H), 7.48-7.44(m, 3H), 7.41-7.39(dd, J = 7.2, 4.8 Hz, 1H), 7.27(s, br, 1H), 7.23-7.19(td, J = 8.4, 6.0 Hz, 1H), 6.97-6.94(t, J = 8.7 Hz, 1H), 6.87-6.86(d, J = 7.8 Hz, 1H), 3.65-3.61(q, J = 7.2 Hz, 2H), 2.96-2.94(t, J = 7.2 Hz, 2H), 2.28(s, 3H); ^{13}C -NMR (150 MHz, CDCl_3) δ 169.6, 162.8, 161.1, 160.5, 150.52, 150.47, 150.2, 149.1, 140.8, 139.4, 129.7, 129.6,

129.1, 128.2, 128.1, 127.99, 123.9, 119.5, 119.4, 118.54, 118.52, 114.6, 113.2, 113.10, 39.1, 23.94, 23.92, 20.9; HRMS Calculated for $C_{24}H_{20}FN_5O_3$ $[M+H]^+$: 446.1623, Found: 446.1623.

N-(2-methoxyphenethyl)-5-phenyl-2-(pyridin-2-yl)-2H-1,2,3-triazole-4-carboxamide (7e') was purified by flash chromatography (Hexane-EtOAc, v/v 2/1) as white solid; 1H -NMR (600 MHz, $CDCl_3$) δ 8.64-8.63(dd, J = 4.8, 0.6 Hz, 1H), 8.15-8.14(d, J = 7.8 Hz, 1H), 8.12-8.11(m, 2H), 7.93-7.90(td, J = 7.8, 1.8 Hz, 1H), 7.47-7.42 (m, 3H), 7.39-7.36(m, 2H), 7.22-7.19(m, 2H), 7.18-7.166(dd, J = 7.8, 1.2 Hz, 1H), 6.89-6.85(m, 2H), 3.84(s, 1H), 3.71-3.67(q, J = 6.6 Hz, 2H), 2.98-2.96(t, J = 7.2 Hz, 2H); ^{13}C -NMR (150 MHz, $CDCl_3$) δ 160.3, 157.6, 150.5, 120.0, 149.1, 141.0, 139.2, 130.7, 129.6, 129.5, 129.2, 128.2, 127.9, 127.4, 123.7, 120.7, 114.5, 110.4, 55.4, 40.0, 30.5; HRMS Calculated for $C_{23}H_{21}N_5O_2$ $[M+H]^+$: 400.1768, Found: 400.1768.

3-methoxy-2-(2-(5-phenyl-2-(pyridin-2-yl)-2H-1,2,3-triazole-4-carboxamido)ethyl)phenyl acetate (7e) was prepared following the general procedure C at 100 °C and purified by flash chromatography (Hexane-EtOAc, v/v 1/1) as colorless oil; Isolated yield 74%(82% brsm); 1H -NMR (600 MHz, $CDCl_3$) δ 8.63(s, 1H), 8.17-8.14(m, 3H), 7.94-7.91(td, J = 8.4, 1.5 Hz, 1H), 7.48-7.37(m, 3H), 7.39-7.37(dd, J = 6.6, 4.8 Hz,

1H), 7.35-7.33(m, br, 1H), 7.21-7.18(t, $J = 8.4$ Hz, 1H), 6.76-6.74(d, $J = 8.4$ Hz, 1H), 6.67-6.66(d, $J = 8.4$ Hz, 1H), 3.84(s, 3H), 3.62-3.59(q, $J = 7.2$ Hz, 2H), 2.93-2.91(t, $J = 7.2$ Hz, 2H). 2.26(s, 3H); ^{13}C -NMR (150 MHz, CDCl_3) δ 169.8, 160.4, 158.8, 150.3, 150.0, 149.09, 149.08, 141.0, 139.2, 129.7, 129.5, 129.2, 128.2, 127.7, 123.7, 120.0, 114.9, 114.5, 108.1, 55.9, 39.1, 24.0, 20.9; HRMS Calculated for $\text{C}_{25}\text{H}_{23}\text{N}_5\text{O}_4$ $[\text{M}+\text{H}]^+$: 458.1823, Found: 458.1822

N-(2-iodophenethyl)-5-phenyl-2-(pyridin-2-yl)-2H-1,2,3-triazole-4-carboxamide (7f) was purified by flash chromatography (Hexane-EtOAc, v/v 2/1) as white solid; ^1H -NMR (600 MHz, CDCl_3) δ 8.67-8.66(dd, $J = 4.8, 1.2$ Hz, 1H), 8.20-8.18(d, $J = 7.8$ Hz, 1H), 8.13-8.11(m, 3H), 7.97-7.94(td, $J = 7.8, 1.8$ Hz, 1H), 7.84-7.83(d, $J = 7.2$ Hz, 1H), 7.49-7.45 (m, 3H), (ddd, $J = 7.2, 4.8, 0.6$ Hz, 1H), 7.29-7.24(m, 2H), 7.25-7.23(m, br, 1H), 6.92-6.91(m, 1H), 3.73-3.69(q, $J = 6.6$ Hz, 2H), 3.11-3.08(t, $J = 7.5$ Hz, 2H); ^{13}C -NMR (150 MHz, CDCl_3) δ 160.5, 150.6, 150.3, 149.2, 141.6, 140.8, 139.8, 139.3, 130.3, 129.71, 129.66, 129.2, 128.7, 128.6, 128.3, 123.9, 114.7, 100.7, 40.6, 39.7; HRMS Calculated for $\text{C}_{22}\text{H}_{18}\text{IN}_5\text{O}$ $[\text{M}+\text{H}]^+$: 496.0629, Found: 496.0635.

3-iodo-2-(2-(5-phenyl-2-(pyridin-2-yl)-2H-1,2,3-triazole-4-carboxamido)ethyl)phenyl acetate (7f) was prepared following the general procedure C and purified by flash

chromatography (Hexane-EtOAc, v/v 1/1) as colorless oil; Isolated yield 68%; ^1H -NMR (600 MHz, CDCl_3) δ 8.65-8.64(d, $J = 3.6$ Hz, 1H), 8.20-8.19(d, $J = 8.4$ Hz, 1H), 8.17-8.15(m, 2H), 7.96-7.93(td, $J = 7.8, 1.5$ Hz, 1H), 7.72-7.01(d, $J = 7.8$, 1H), 7.48-7.44(m, 3H), 7.41-7.39(dd, $J = 7.2, 4.8$ Hz, 1H), 7.24-7.04 (t, $J = 6$ Hz, 1H), 7.04-7.02(d, $J = 7.8$ Hz, 1H), 6.97-6.94(t, $J = 7.8$ Hz, 1H), 3.63-3.59(q, $J = 6.6$ Hz, 2H), 3.10-3.08(t, $J = 7.5$ Hz, 2H). 2.30(s, 3H); ^{13}C -NMR (150 MHz, CDCl_3) δ 169.9, 160.5, 150.5, 150.2, 149.3, 149.2, 140.8, 139.3, 137.4, 134.2, 129.8, 129.6, 129.23, 129.17, 128.2, 123.9, 123.21, 114.6, 101.5, 38.5, 35.1, 20.9; HRMS Calculated for $\text{C}_{24}\text{H}_{20}\text{IN}_5\text{O}_3$ $[\text{M}+\text{H}]^+$: 554.0684, Found: 554.0692.

N-(3-fluorophenethyl)-5-phenyl-2-(pyridin-2-yl)-2H-1,2,3-triazole-4-carboxamide (7g') was purified by flash chromatography (Hexane-EtOAc, v/v 2/1) as white solid; ^1H -NMR (600 MHz, CDCl_3) δ 8.67-8.65(dd, $J = 4.8, 1.2$ Hz, 1H), 8.18-8.16(d, $J = 7.8$ Hz, 1H), 8.11-8.09(m, 2H), 7.97-7.94(ddd, $J = 8.4, 7.8, 1.8$ Hz, 1H), 7.49-7.44 (m, 3H), 7.42-7.39(ddd, $J = 7.2, 4.8, 0.6$ Hz, 1H), 7.29-7.25(m, 1H), 7.21-7.19(m, br, 1H), 7.03-7.02(m, 1H), 6.97-6.95(m, 1H), 6.94-6.91(m, 1H), 3.73-3.69(q, $J = 6.6$ Hz, 2H), 2.97-2.94(t, $J = 7.5$ Hz, 2H); ^{13}C -NMR (150 MHz, CDCl_3) δ 162.3, 160.4, 150.6, 150.3, 149.2, 141.5, 140.8, 139.3, 130.3, 130.2, 129.1, 128.4, 124.63, 124.61, 123.9, 115.9, 115.8, 114.6, 113.7, 113.5, 40.8, 35.80, 35.79; HRMS Calculated for $\text{C}_{22}\text{H}_{18}\text{FN}_5\text{O}$ $[\text{M}+\text{H}]^+$: 388.1569, Found: 487.1573.

7g

4-fluoro-2-(2-(5-phenyl-2-(pyridin-2-yl)-2H-1,2,3-triazole-4-

carboxamido)ethyl)phenyl acetate (7g) was prepared following the general procedure C at 100 °C and purified by flash chromatography (Hexane-EtOAc, v/v 2/1) as white solid; Isolated yield 64%; ¹H-NMR (600 MHz, CDCl₃) δ8.65-8.64(d, *J* = 4.2 Hz, 1H), 8.19-8.17(d, *J* = 8.4 Hz, 1H), 8.13-8.12(m, 2H), 7.96-7.93(td, *J* = 7.8, 1.8 Hz, 1H), 7.49-7.45(m, 3H), 7.41-7.39(dd, *J* = 7.2, 4.8 Hz, 1H), 7.26-7.25(m, br, 1H), 7.03-6.99(m, *J* = 2H), 7.96-6.92(m, 1H), 3.67-3.63(q, *J* = 6.6 Hz, 2H), 2.93-2.91(t, *J* = 7.2 Hz, 2H). 2.32(s, 3H); ¹³C-NMR (150 MHz, CDCl₃) δ169.8, 161.2, 160.5, 160.5, 159.6, 150.5, 150.2, 149.1, 145.22, 145.20, 140.6, 139.2, 132.99, 123.94, 129.8, 129.66, 129.64, 129.14, 129.09, 128.3, 128.2, 126.6, 124.0, 123.9, 120.8, 117.2, 117.1, 114.65, 114.63, 114.61, 114.5, 39.6, 30.5, 20.9; HRMS Calculated for C₂₄H₂₀FN₅O₃ [M+H]⁺: 446.1623, Found: 446.1630.

7h'

N-(3-methylphenethyl)-5-phenyl-2-(pyridin-2-yl)-2H-1,2,3-triazole-4-carboxamide

(7h') was purified by flash chromatography (Hexane-EtOAc, v/v 2/1) as white solid; ¹H-NMR (600 MHz, CDCl₃) δ8.61-8.60(d, *J* = 4.2 Hz, 1H), 8.13-8.09(m, 3H), 7.89-7.86(td, *J* = 7.2, 1.8 Hz, 1H), 7.47-7.42(m, 3H), 7.35-7.33(m, 1H), 7.26-7.224(m, br, H), 7.19-7.17(t, *J* = 7.8 Hz, 1H), 7.06(s, 1H), 7.04-7.02(m, 2H), 3.71-3.67(q, *J* = 6.6 Hz, 2H), 2.92-2.89(t, *J* = 7.5 Hz, 2H). 2.31(s, 3H); ¹³C-NMR (150 MHz, CDCl₃) δ160.2, 150.3,

149.9, 149.0, 140.7, 139.0, 138.6, 128.1, 129.6, 129.5, 129.4, 129.0, 128.5, 128.1, 127.2, 125.8, 123.7, 114.3, 40.9, 35.8, 21.3; HRMS Calculated for $C_{23}H_{21}N_5O$ $[M+H]^+$: 384.1819, Found: 384.1824.

4-methyl-2-(2-(5-phenyl-2-(pyridin-2-yl)-2H-1,2,3-triazole-4-carboxamido)ethyl)phenyl acetate (7h) was prepared following the general procedure C and purified by flash chromatography (Hexane-EtOAc, v/v 1/1) as colorless oil; Isolated yield 78%; 1H -NMR (600 MHz, $CDCl_3$) δ 8.65-8.64(d, J = 4.2 Hz, 1H), 8.19-8.17(d, J = 8.4 Hz, 1H), 8.14-8.13(d, J = 7.8 Hz, 2H), 7.96-7.93(td, J = 8.4, 1.8 Hz, 1H), 7.49-7.45(m, 3H), 7.41-7.39(dd, J = 7.2, 4.8 Hz, 1H), 7.26-7.25(m, br, 1H), 7.11(s, 1H), 7.06-7.04(d, J = 8.4 Hz, 1H), 6.92-6.91(d, J = 8.4 Hz, 1H), 3.67-3.63(q, J = 6.6 Hz, 2H), 2.85-2.82(t, J = 7.5 Hz, 2H), 2.31(s, 3H), 2.30(s, 3H); ^{13}C -NMR (150 MHz, $CDCl_3$) δ 170.1, 160.4, 150.5, 150.2, 149.1, 147.1, 140.8, 139.3, 136.1, 131.4, 130.4, 129.7, 129.6, 129.2, 128.6, 128.32, 128.29, 123.9, 122.3, 114.6, 39.9, 30.8, 21.1, 20.9; HRMS Calculated for $C_{25}H_{23}N_5O_3$ $[M+H]^+$: 442.1874, Found: 442.1880.

N-(3-methoxyphenethyl)-5-phenyl-2-(pyridin-2-yl)-2H-1,2,3-triazole-4-carboxamide (7i') was purified by flash chromatography (Hexane-EtOAc, v/v 2/1) as white solid; 1H -NMR (600 MHz, $CDCl_3$) δ 8.64-8.63(d, J = 4.2 Hz, 1H), 8.15-8.14(d, J = 8.4 Hz, 1H),

8.12-8.10(m, 2H), 7.94-7.91(t, $J = 7.8, 1.8$ Hz, 1H), 7.49-7.44(m, 3H), 7.39-7.37(dd, $J = 6.6, 4.8$ Hz, 1H), 7.23-7.20(m, 2H), 6.84-6.83(d, $J = 7.2$, 2H), 6.79(s, 1H), 6.78-6.76(dd, $J = 8.4, 2.4$ Hz, 1H), 3.77(s, 3H), 3.73-3.69(q, $J = 6.6$ Hz, 2H), 2.94-2.92(t, $J = 7.2$ Hz, 2H); ^{13}C -NMR (150 MHz, CDCl_3) δ 160.3, 159.9, 150.5, 150.2, 149.1, 140.8, 140.5, 139.2, 129.7, 129.6, 129.1, 123.83, 123.82, 121.26, 121.24, 114.6, 114.55, 114.54, 114.48, 112.2, 55.3, 40.9, 36.0; HRMS Calculated for $\text{C}_{23}\text{H}_{21}\text{N}_5\text{O}_2$ $[\text{M}+\text{H}]^+$: 400.1768, Found: 400.1768.

7i

4-methoxy-2-(2-(5-phenyl-2-(pyridin-2-yl)-2H-1,2,3-triazole-4-

carboxamido)ethyl)phenyl acetate (7i) was prepared following the general procedure C and purified by flash chromatography (Hexane-EtOAc, v/v 1/1) as colorless oil; Isolated yield 75%; ^1H -NMR (600 MHz, CDCl_3) δ 8.65-8.64(d, $J = 4.2$ Hz, 1H), 8.19-8.17(d, $J = 8.4$ Hz, 1H), 8.13-8.12(m, 2H), 7.96-7.93(td, $J = 8.4, 1.8$ Hz, 1H), 7.49-7.45(m, 3H), 7.41-7.39(dd, $J = 7.2, 4.8$ Hz, 1H), 7.26-7.25(m, br, 1H), 6.96-6.94(d, $J = 9.0$ Hz, 1H), 6.83-6.82(d, $J = 3.6$ Hz, 1H), 6.79-6.77(dd, $J = 9, 3.6$ Hz, 1H), 3.76(s, 3H), 3.68-3.64(q, $J = 6.6$ Hz, 2H), 2.86-2.83(t, $J = 7.5$ Hz, 2H), 2.31(s, 3H); ^{13}C -NMR (150 MHz, CDCl_3) δ 170.3, 160.5, 157.6, 150.6, 150.2, 149.2, 142.9, 140.8, 139.3, 131.8, 129.8, 129.7, 129.6, 129.2, 128.3, 128.2, 123.9, 123.4, 115.6, 114.6, 113.2, 55.7, 39.8, 30.7, 21.0; HRMS Calculated for $\text{C}_{25}\text{H}_{23}\text{N}_5\text{O}_4$ $[\text{M}+\text{H}]^+$: 458.1823, Found: 458.1829.

7j'

N-(4-methylphenethyl)-5-phenyl-2-(pyridin-2-yl)-2H-1,2,3-triazole-4-carboxamide (7j') was purified by flash chromatography (Hexane-EtOAc, v/v 2/1) as white solid.; ¹H-NMR (600 MHz, CDCl₃) δ8.65-8.64(d, *J* = 4.2 Hz, 1H), 8.16-8.15(d, *J* = 8.4 Hz, 1H), 8.12-8.10(d, *J* = 7.2 Hz, 2H), 7.95-7.92(t, *J* = 7.8 Hz, 1H), 7.49-7.43(m, 3H), 7.39-7.37(dd, *J* = 7.2, 5.4 Hz, 1H), 7.18(s, br, 1H), 7.14-7.11(dd, *J* = 14.4, 7.8 Hz, 4H), 3.71-3.67(q, *J* = 6.6 Hz, 2H), 2.93-2.91(t, *J* = 7.2 Hz, 2H), 2.32(s, 3H); ¹³C-NMR (150 MHz, CDCl₃) δ160.3, 150.6, 150.2, 149.2, 140.9, 139.3, 136.1, 135.8, 129.67, 129.61, 129.4, 129.2, 128.8, 128.3, 123.8, 114.6, 41.1, 35.6, 21.2; HRMS Calculated for C₂₃H₂₁N₅O [M+H]⁺: 384.1819, Found: 384.1824.

7j

5-methyl-2-(2-(5-phenyl-2-(pyridin-2-yl)-2H-1,2,3-triazole-4-carboxamido)ethyl)phenyl acetate (7j) was prepared following the general procedure C and purified by flash chromatography (Hexane-EtOAc, v/v 1/1) as white solid; Isolated yield 37%; ¹H-NMR (600 MHz, CDCl₃) δ8.65-8.64(m, 1H), 8.19-8.17(d, *J* = 7.8 Hz, 1H), 8.13-8.11(m, 2H), 7.95-7.93(m, 1H), 7.49-7.44(m, 3H), 7.41-7.39(dd, *J* = 7.2, 5.4 Hz, 1H), 7.25-7.23(m, br, 1H), 7.18-7.17(d, *J* = 7.8 Hz, 1H), 7.00-6.99(d, *J* = 7.8 Hz, 1H), 6.86(s, 1H), 3.65-3.62(q, *J* = 6.6 Hz, 2H), 2.85-2.82(t, *J* = 7.2 Hz, 2H), 2.32(m, 6H); ¹³C-NMR (150 MHz, CDCl₃) δ169.9, 160.4, 150.6, 120.2, 149.3, 149.2, 140.8, 139.3, 138.0, 130.5, 129.6, 129.2, 128.3, 127.6, 127.3, 123.9, 123.1, 114.6, 40.0, 30.1, 21.11, 21.10; HRMS Calculated for C₂₅H₂₃N₅O₃ [M+H]⁺: 442.1874, Found: 442.1880.

5-methyl-2-(2-(5-phenyl-2-(pyridin-2-yl)-2H-1,2,3-triazole-4-carboxamido)ethyl)-1,3-phenylene diacetate (7n) was prepared following the general procedure C with 3 equiv. $\text{PhI}(\text{OAc})_2$ at 100 °C and purified by flash chromatography (Hexane-EtOAc, v/v 1/1) as colorless oil; Isolated yield 70%; ^1H -NMR (600 MHz, CDCl_3) δ 8.65-8.64(d, J = 4.2 Hz, 1H), 8.19-8.18(d, J = 7.8 Hz, 1H), 8.17-8.15(m, 2H), 7.96-7.93(td, J = 8.4, 1.8 Hz, 1H), 7.48-7.44(m, 3H), 7.41-7.39(dd, J = 7.2, 4.8 Hz, 1H), 7.28-7.26(m, br, 1H), 6.79(s, 2H), 3.55-3.51(q, J = 6.6 Hz, 2H), 2.80-2.78(t, J = 7.5 Hz, 2H), 2.315(s, 3H), 2.306(s, 6H); ^{13}C -NMR (150 MHz, CDCl_3) δ 169.7, 160.5, 150.5, 150.2, 150.1, 149.1, 140.8, 139.3, 138.2, 129.8, 129.6, 129.2, 128.2, 123.9, 121.0, 120.9, 114.6, 39.1, 24.9, 21.2, 21.0; HRMS Calculated for $\text{C}_{27}\text{H}_{25}\text{N}_5\text{O}_5$ $[\text{M}+\text{H}]^+$: 500.1929, Found: 500.1936.

N-(4-methoxyphenethyl)-5-phenyl-2-(pyridin-2-yl)-2H-1,2,3-triazole-4-carboxamide (7k') was purified by flash chromatography (Hexane-EtOAc, v/v 2/1) as white solid; ^1H -NMR (600 MHz, CDCl_3) δ 8.65(s, 1H), 8.16-8.15(d, J = 7.8 Hz, 1H), 8.11-8.10(d, 2H), 7.95-7.92(m, 1H), 7.49-7.44(m, 3H), 7.40-7.39(m, 1H), 7.17-7.15(m, br, 1H), 7.17-7.15(d, J = 8.4 Hz, 2H), 6.85-6.84(d, J = 8.4 Hz, 2H), 3.79(s, 3H), 3.69-3.66(q, J = 6.6 Hz, 2H), 2.91-2.88(t, J = 7.5 Hz, 2H); ^{13}C -NMR (150 MHz, CDCl_3) δ 160.3, 158.4, 150.6, 150.2, 149.2, 140.9, 139.3, 129.9, 129.77, 129.75, 127.74, 129.73, 129.2, 128.3,

114.6, 114.2, 55.4, 41.2, 35.12, 35.14; HRMS Calculated for $C_{23}H_{21}N_5O_2$ $[M+H]^+$: 400.1768, Found: 400.1773.

5-methoxy-2-(2-(5-phenyl-2-(pyridin-2-yl)-2H-1,2,3-triazole-4-carboxamido)ethyl)phenyl acetate (7k) was prepared following the general procedure C and purified by flash chromatography (Hexane-EtOAc, v/v 1/1) as colorless oil; Isolated yield 30%; 1H -NMR (600 MHz, $CDCl_3$) δ 8.66-8.65(m, 1H), 8.19-8.17(d, J = 8.4 Hz, 1H), 8.13-8.11(m, 2H), 7.96-7.93(m, 1H), 7.49-7.44(m, 3H), 7.41-7.39(m, 1H), 7.24-7.22(m, br, 1H), 7.20-7.19(d, J = 8.4 Hz, 1H), 6.76-6.74(dd, J = 8.4, 2.4 Hz, 2H), 6.61-6.60(d, J = 2.4 Hz), 3.77(s, 3H), 3.64-3.60(q, J = 6.6 Hz, 2H), 2.82-2.79(t, J = 7.5 Hz, 2H), 2.32(s, 3H); ^{13}C -NMR (150 MHz, $CDCl_3$) δ 169.7, 160.4, 159.3, 150.0, 149.187, 149.181, 140.8, 139.3, 131.2, 129.7, 129.6, 129.2, 123.9, 122.8, 114.6, 112.3, 108.4, 99.9, 55.6, 40.1, 29.8, 21.1; HRMS Calculated for $C_{25}H_{23}N_5O_4$ $[M+H]^+$: 458.1823, Found: 458.1830.

2-(2-(5-phenyl-2-(pyridin-2-yl)-2H-1,2,3-triazole-4-carboxamido)ethyl)-1,3-phenylene diacetate (7m) was prepared following the general procedure C with 3 equiv. $PhI(OAc)_2$ at 100 °C and purified by flash chromatography (Hexane-EtOAc, v/v 1/1) as colorless oil; Isolated yield 62%; 1H -NMR (600 MHz, $CDCl_3$) δ 8.65-8.64(d, J = 4.2 Hz,

1H), 8.19-8.18(d, J = 8.4 Hz, 1H), 8.17-8.15(m, 2H), 7.96-7.93(td, J = 8.4, 1.8 Hz, 1H), 7.48-7.44(m, 3H), 7.41-7.39(dd, J = 7.2, 4.8 Hz, 1H), 7.28-7.26(m, br, 1H), 6.55(s, 2H), 3.75(s, 3H), 3.53-3.49(q, J = 6.6 Hz, 2H), 2.76-2.74(t, J = 7.5 Hz, 2H), 2.31(s, 6H); ^{13}C -NMR (150 MHz, CDCl_3) δ 169.5, 160.5, 158.9, 150.8, 150.5, 150.1, 149.1, 140.8, 139.3, 129.8, 129.6, 129.2, 128.2, 123.9, 116.0, 114.6, 106.8, 55.7, 39.1; HRMS Calculated for $\text{C}_{27}\text{H}_{25}\text{N}_5\text{O}_6$ $[\text{M}+\text{H}]^+$: 516.1878, Found: 516.1885

N-(4-fluorophenethyl)-5-phenyl-2-(pyridin-2-yl)-2H-1,2,3-triazole-4-carboxamide (7l') was purified by flash chromatography (Hexane-EtOAc, v/v 2/1) as white solid; ^1H -NMR (600 MHz, CDCl_3) δ 8.67-8.65(d, J = 4.8 Hz, 1H), 8.17-8.16(d, J = 8.4 Hz, 1H), 8.11-8.10(m, 2H), 7.97-7.94(td, J = 7.8, 2.4 Hz, 1H), 7.49-7.45(m, 3H), 7.42-7.40(dd, J = 7.2, 5.4 Hz, 1H), 7.21-7.19(m, 3H), 7.00-6.98 (t, J = 8.7 Hz, 2H), 3.70-3.67(q, J = 6.0 Hz, 2H), 2.94-2.92(t, J = 7.2 Hz, 2H); ^{13}C -NMR (150 MHz, CDCl_3) δ 162.6, 161.0, 160.4, 150.6, 150.3, 149.2, 140.8, 139.3, 134.58, 134.56, 130.41, 130.36, 129.1, 123.9, 115.6, 115.5, 114.6, 41.088, 41.084, 35.2, ; HRMS Calculated for $\text{C}_{22}\text{H}_{18}\text{FN}_5\text{O}$ $[\text{M}+\text{H}]^+$: 388.1569, Found: 388.1573.

7k was prepared following the general procedure C and purified by flash chromatography (Hexane-EtOAc, v/v 1/1) to get mono- and di-substitution product as inseparable mixture (ratio of mono-: di ~1: 0.2); Isolated yield of mixture 68%; ^1H -NMR

(600 MHz, CDCl₃) δ 8.65-8.64(m, 1H), 8.19-8.17(m, 1H), 8.18-8.11(m, 2H), 7.96-7.93(m, 1H), 7.48-7.44(m, 3H), 7.41-7.39(m, 1H), 7.27-7.24(m, 0.77H), 6.93-6.89(td, J = 8.4, 3.0 Hz, 0.77H), 6.84-6.82(dd, J = 9.0, 2.4 Hz, 0.77H), 6.78-6.77(d, J = 9.0 Hz, 0.35H), 3.64-3.61(q, J = 6.6 Hz, 1.54H), 3.53-3.49(q, J = 6.6 Hz, 1.54H), 2.86-2.84(t, J = 7.5 Hz, 1.54H), 2.81-2.79(t, J = 7.5 Hz, 0.35H), 2.33(s, 2.31H), 2.32(s, 0.53H).

7o

5-methoxy-2-(2-(5-phenyl-2-(pyridin-2-yl)-2H-1,2,3-triazole-4-carboxamido)ethyl)-1,3-phenylene diacetate (7m) was prepared following the general procedure C with 3 equiv. at 100 °C and purified by flash chromatography (Hexane-EtOAc, v/v 1/1) as colorless oil; Isolated yield 80%; ¹H-NMR (600 MHz, CDCl₃) δ 8.65-8.64(d, J = 4.2 Hz, 1H), 8.19-8.18(d, J = 8.4 Hz, 1H), 8.17-8.15(m, 2H), 7.96-7.93(td, J = 8.4, 1.8 Hz, 1H), 7.48-7.44(m, 3H), 7.41-7.39(dd, J = 7.2, 4.8 Hz, 1H), 7.28-7.26(m, br, 1H), 6.55(s, 2H), 3.75(s, 3H), 3.53-3.49(q, J = 6.6 Hz, 2H), 2.76-2.74(t, J = 7.5 Hz, 2H), 2.31(s, 6H); ¹³C-NMR (150 MHz, CDCl₃) δ 169.5, 160.5, 158.9, 150.8, 150.5, 150.1, 149.1, 140.8, 139.3, 129.8, 129.6, 129.2, 128.2, 123.9, 116.0, 114.6, 106.8, 55.7, 39.1; HRMS Calculated for C₂₇H₂₅N₅O₆ [M+H]⁺: 516.1878, Found:516.1880.

7p'

(S)-methyl-3-methyl-2-(5-phenyl-2-(pyridin-2-yl)-2H-1,2,3-triazole-4-carboxamido)butanoate (7p') was purified by flash chromatography (Hexane-EtOAc, v/v 2/1) as white solid; ¹H-NMR (600 MHz, CDCl₃) δ 8.68-8.66(dd, J = 4.8, 1.2 Hz, 1H), 8.20-8.18(d, J = 6.4 Hz, 1H), 8.09-8.08(m, 2H), 7.98-7.95(td, J = 7.8, 1.8 Hz, 1H), 7.49-7.41(m, 5H), 4.76-4.74(q, J = 5.4 Hz, 1H), 3.77(s, 3H), 2.32-2.67(m, 1H), 1.040-1.036(d,

$J = 2.4$ Hz, 3H), 1.029-1.025(d, $J = 2.4$ Hz, 3H); ^{13}C -NMR (150 MHz, CDCl_3) δ 172.3, 160.2, 150.5, 149.2, 140.3, 139.3, 129.8, 129.7, 129.1, 128.3, 123.9, 114.8, 57.5, 52.4, 31.6, 19.2, 18.4; HRMS Calculated for $\text{C}_{20}\text{H}_{21}\text{N}_5\text{O}_3$ $[\text{M}+\text{H}]^+$: 380.1717, Found: 380.1722.

(2S,3R)-methyl-4-acetoxy-3-methyl-2-(5-phenyl-2-(pyridin-2-yl)-2H-1,2,3-triazole-4-carboxamido)butanoate (7pa) was prepared following the general procedure D and purified by flash chromatography (Hexane-EtOAc, v/v 1/1) as colorless oil; Isolated yield 57%; ^1H -NMR (600 MHz, CDCl_3) δ 8.65-8.64(m, 1H), 8.20-8.19(d, $J = 6.4$ Hz, 1H), 8.09-8.08(m, 2H), 7.98-7.94(td, $J = 7.8, 1.8$ Hz, 1H), 7.76-7.75(d, $J = 6.4$ Hz, 1H), 7.48-7.41(m, 4H), 4.95-4.93(q, $J = 4.8$ Hz, 1H), 4.02-4.17(m, 1H), 4.08-4.05(m, 1H), 3.78(s, 3H), 2.62-2.59(m, 1H), 2.12(s, 3H), 1.09-1.08(d, $J = 7.2$ Hz, 3H).; ^{13}C -NMR (150 MHz, CDCl_3) δ 171.5, 171.0, 160.4, 150.5, 150.4, 149.1, 140.0, 139.2, 129.7, 129.6, 129.0, 128.5, 124.0, 114.7, 65.6, 54.4, 52.5, 35.5, 20.9, 14.2; HRMS Calculated for $\text{C}_{23}\text{H}_{25}\text{N}_5\text{O}_5$ $[\text{M}+\text{H}]^+$: 452.1929, Found: 452.1936.

(S)-2-(2-methoxy-2-oxo-1-(5-phenyl-2-(pyridin-2-yl)-2H-1,2,3-triazole-4-carboxamido)ethyl)propane-1,3-diyl diacetate (7pb) was prepared following the general procedure D and purified by flash chromatography (Hexane-EtOAc, v/v 1/1) as colorless oil; Isolated yield 19%; ^1H -NMR (600 MHz, CDCl_3) δ 8.64-8.62(m, 1H), 8.20-8.18(d, $J = 7.8$ Hz, 1H), 8.09-8.08(m, 2H), 7.98-7.94(td, $J = 7.8, 1.8$ Hz, 1H), 7.87-7.85(m, 1H), 7.48-7.41(m, 4H), 5.14-5.12(q, $J = 4.8$ Hz, 1H), 4.35-4.32(m, 1H), 4.22-4.18(m, 2H), 3.79(s, 3H), 2.84-2.81(m, 1H), 2.16(s, 3H), 2.08(s, 3H); ^{13}C -NMR (150

MHz, CDCl₃) δ171.1, 171.7, 160.4, 150.6, 150.5, 149.1, 139.8, 139.2, 129.8, 129.7, 129.0, 128.4, 124.1, 114.8, 61.95, 61.93, 51.9, 51.4, 40.0, 20.97, 20.95; HRMS Calculated for C₂₄H₂₅N₅O₇ [M+H]⁺: 496.1827, Found: 496.1832.

(S)-3-methyl-2-(5-phenyl-2-(pyridin-2-yl)-2H-1,2,3-triazole-4-carboxamido)butyl acetate (7q') was purified by flash chromatography (Hexane-EtOAc, v/v 2/1) as white solid; ¹H-NMR (600 MHz, CDCl₃) δ8.68-8.67(m, 1H), 8.20-8.19(d, *J* = 7.8 Hz, 1H), 8.10-8.08(m, 2H), 7.98-7.95(t, *J* = 7.8 Hz, 1H), 7.48-7.42(m, 4H), 7.09-7.08(m, br, 1H), 4.30-4.21(m, 2H), 2.06(s, 3H), 2.01-2.97(m, 1H), 1.04-1.02(t, *J* = 5.4 Hz, 6H); ¹³C-NMR (150 MHz, CDCl₃) δ171.2, 160.3, 150.5, 149.2, 140.7, 139.4, 129.8, 129.8, 129.2, 128.3, 123.9, 114.9, 64.7, 53.8, 29.7, 21.1, 19.6, 19.2; HRMS Calculated for C₂₁H₂₃N₅O₃ [M+H]⁺: 394.1874, Found: 394.1880.

(3S)-2-methyl-3-(5-phenyl-2-(pyridin-2-yl)-2H-1,2,3-triazole-4-carboxamido)butane-1,4-diyl diacetate (7qa) was prepared following the general procedure D and purified by flash chromatography (Hexane-EtOAc, v/v 1/1) as colorless oil; Isolated yield 61%; ¹H-NMR (600 MHz, CDCl₃) δ8.65-8.64(d, *J* = 4.8 Hz, 1H), 8.20-8.18(d, *J* = 7.8 Hz, 1H), 8.09-8.08(m, 2H), 7.98-7.95(td, *J* = 7.8, 1.8 Hz, 1H), 7.48-7.41(m, 4H), 7.38-7.26(d, *J* = 8.4 Hz, 1H), 4.46-4.41(m, 1H), 4.33-4.25(m, 2H), 4.18-4.11(m, 2H), 2.25-2.22(m, 1H), 2.10(s, 3H), 2.07(s, 3H), 2.48-2.44 (m, 1H), 2.14(s, 3H), 2.087(s, 3H), 2.081(s, 3H); ¹³C-NMR (150 MHz, CDCl₃) δ170.9, 170.87, 170.82, 160.2, 150.6, 149.1, 140.1, 139.3, 129.8, 129.0, 128.3, 114.8, 64.1, 62.12, 62.089, 62.083, 41.4, 38.7, 21.04, 20.99; HRMS Calculated for C₂₃H₂₅N₅O₅ [M+H]⁺: 452.1929, Found: 452.1936.

(S)-2-(acetoxymethyl)-3-(5-phenyl-2-(pyridin-2-yl)-2H-1,2,3-triazole-4-carboxamido)butane-1,4-diyl diacetate (7qb) was prepared following the general procedure D and purified by flash chromatography (Hexane-EtOAc, v/v 1/1) as colorless oil; Isolated yield 13%; $^1\text{H-NMR}$ (600 MHz, CDCl_3) δ 8.63-8.62(d, $J = 4.8$ Hz, 1H), 8.20-8.18(d, $J = 7.8$ Hz, 1H), 8.09-8.08(m, 2H), 7.98-7.95(td, $J = 7.8, 1.8$ Hz, 1H), 7.51-7.41(m, 5H), 4.70-4.65(m, 1H), 4.33-4.17(m, 6H), 2.48-2.44 (m, 1H), 2.14(s, 3H), 2.087(s, 3H), 2.081(s, 3H); $^{13}\text{C-NMR}$ (150 MHz, CDCl_3) δ 170.9, 170.87, 170.82, 160.2, 150.6, 149.1, 140.1, 139.3, 129.8, 129.0, 128.3, 114.8, 64.1, 62.12, 62.089, 62.083, 41.4, 38.7, 21.04, 20.99; HRMS Calculated for $\text{C}_{25}\text{H}_{27}\text{N}_5\text{O}_7$ $[\text{M}+\text{H}]^+$: 510.1984, Found: 510.1987.

(2S)-methyl-3-methyl-2-(5-phenyl-2-(pyridin-2-yl)-2H-1,2,3-triazole-4-carboxamido)pentanoate (7r') was purified by flash chromatography (Hexane-EtOAc, v/v 2/1) as white liquid; $^1\text{H-NMR}$ (600 MHz, CDCl_3) δ 8.68-8.66(d, $J = 4.8$ Hz, 1H), 8.19-8.18(d, $J = 8.4$ Hz, 1H), 8.09-8.08(m, 2H), 7.97-7.94(td, $J = 8.7, 1.5$ Hz, 1H), 7.49-7.41(m, 5H), 4.81-4.79 (dd, $J = 8.4, 5.4$ Hz, 1H), 3.77(m, 3H), 2.04-2.01(m, 1H), 1.588-1.54(m, 1H), 1.32-1.27(m, 1H), 1.00-0.99 (d, $J = 7.2$ Hz, 3H), 0.97-0.95(t, $J = 7.2$ Hz, 3H); $^{13}\text{C-NMR}$ (150 MHz, CDCl_3) δ 172.2, 160.1, 150.6, 150.5, 149.2, 140.3, 139.2, 129.8, 129.6, 129.1, 128.3, 140.0, 114.8, 56.8, 52.33, 52.32, 38.2, 25.6, 15.7, 11.7; HRMS Calculated for $\text{C}_{21}\text{H}_{23}\text{N}_5\text{O}_3$ $[\text{M}+\text{H}]^+$: 394.1874, Found: 394.1880.

(2S)-methyl-3-(acetoxymethyl)-2-(5-phenyl-2-(pyridin-2-yl)-2H-1,2,3-triazole-4-carboxamido)pentanoate (7r) was prepared following the general procedure D and purified by flash chromatography (Hexane-EtOAc, v/v 1/1) as colorless oil; Isolated yield 58%(72% brsm); ¹H-NMR (600 MHz, CDCl₃) δ8.65-8.64(d, *J* = 4.8 Hz, 1H), 8.19-8.18(d, *J* = 8.4 Hz, 1H), 8.11-8.07(m, 2H), 7.96-7.94(td, *J* = 7.8, 1.8 Hz, 1H), 7.69-7.67(d, *J* = 9.0 Hz, 1H), 7.48-7.41(m, 4H), 5.05-5.03(q, *J* = 4.5 Hz, 1H), 4.22-4.19 (m, 1H), 4.06-4.03(m, 1H), 3.77(s, 3H), 2.31-2.27(m, 1H), 2.11(s, 3H), 1.60-1.56(m, 1H), 1.49-1.12(m, 1H), 1.04-1.01(t, *J* = 7.5 Hz, 3H); ¹³C-NMR (150 MHz, CDCl₃) δ171.7, 171.0, 160.2, 150.56, 150.54, 149.2, 140.1, 139.2, 129.75, 129.68, 129.0, 128.3, 124.0, 114.7, 63.8, 53.3, 52.598, 52.593, 42.6, 21.06, 21.00, 17.6, 11.9.; HRMS Calculated for C₂₃H₂₅N₅O₅ [M+H]⁺: 452.1929, Found: 452.1936

N-(3-methylbutan-2-yl)-5-phenyl-2-(pyridin-2-yl)-2H-1,2,3-triazole-4-carboxamide (7s') was purified by flash chromatography (Hexane-EtOAc, v/v 2/1) as white solid; ¹H-NMR (600 MHz, CDCl₃) δ8.66-8.65(d, *J* = 4.8 Hz, 1H), 8.18-8.17(d, *J* = 8.4 Hz, 1H), 8.11-8.10(m, 2H), 7.95-7.92(td, *J* = 8.7, 1.5 Hz, 1H), 7.47-7.43(m, 3H), 7.41-7.39(dd, *J* = 7.2, 5.4 Hz, 1H), 6.91-6.90(d, *J* = 8.4 Hz, 1H), 4.01-4.04 (m, 1H), 1.87-1.79(m, 1H), 1.22-1.21(d, *J* = 6.6 Hz, 3H), 0.98-0.96(dd, *J* = 9.0, 7.2 Hz, 3H); ¹³C-NMR (150 MHz, CDCl₃) δ159.7, 150.6, 150.3, 149.2, 141.1, 139.2, 129.7, 129.5, 129.3, 128.2, 123.8, 114.7, 50.6, 33.3, 19.2, 18.8, 17.8; HRMS Calculated for C₁₉H₂₁N₅O [M+H]⁺: 336.1819, Found: 336.1823

2-methyl-3-(5-phenyl-2-(pyridin-2-yl)-2H-1,2,3-triazole-4-carboxamido)butyl

acetate (7s) was prepared following the general procedure D and purified by flash chromatography (Hexane-EtOAc, v/v 1/1) as colorless oil; Isolated yield 68%; $^1\text{H-NMR}$ (600 MHz, CDCl_3) δ 8.65-8.64(d, $J = 4.8$ Hz, 1H), 8.19-8.18(d, $J = 8.4$ Hz, 1H), 8.11-8.10(m, 2H), 7.96-7.93(td, $J = 7.8, 1.8$ Hz, 1H), 7.48-7.44(m, 3H), 7.42-7.39(dd, $J = 7.2, 5.4$ Hz, 1H), 7.19-7.18(d, $J = 9.0$ Hz, 1H), 4.30-4.26 (m, 1H), 4.15-4.02(m, 1H), 4.09-4.06(m, 1H), 1.87-1.79(m, 1H), 2.11-2.07(m, 4H), 1.28-1.27(d, $J = 6.6$ Hz, 3H), 1.04-1.03(d, $J = 6.6$ Hz, 3H); $^{13}\text{C-NMR}$ (150 MHz, CDCl_3) δ 171.3, 159.7, 150.4, 149.1, 140.8, 139.3, 129.8, 129.6, 129.2, 128.3, 123.9, 114.8, 66.7, 47.4, 37.4, 21.1, 17.9, 13.9; HRMS Calculated for $\text{C}_{21}\text{H}_{23}\text{N}_5\text{O}_3$ $[\text{M}+\text{H}]^+$: 394.1874, Found: 394.1879.

N-phenethyl-6-(4-phenyl-2H-1,2,3-triazol-2-yl)picolinamide (PyTAA) was purified by flash chromatography (Hexane-EtOAc, v/v 2/1) as white solid; $^1\text{H-NMR}$ (600 MHz, CDCl_3) δ 8.44(s, 1H), 8.39-8.38(d, $J = 7.8$ Hz, 1H), 8.27-8.26(d, $J = 7.2$ Hz, 1H), 8.12-8.09(t, $J = 7.8$ Hz, 1H), 7.95-7.94(d, $J = 7.8$ Hz, 1H), 7.95-7.94(d, $J = 8.4$ Hz, 1H), 7.79-7.78(m, br, 1s), 7.54-7.51(t, $J = 7.8$ Hz, 1H), 7.45-7.74(t, $J = 7.8$ Hz, 1H), 7.0-7.37(t, $J = 7.8$ Hz, 2H), 7.33-7.30(m, 3H), 8.19-8.18(d, $J = 8.4$ Hz, 1H), 8.11-8.10(m, 2H), 7.96-7.93(td, $J = 7.8, 1.8$ Hz, 1H), 7.48-7.44(m, 3H), 3.84-3.81(q, $J = 6.0$ Hz, 2H), 3.00-2.98(t, $J = 6.6$ Hz, 2H); $^{13}\text{C-NMR}$ (150 MHz, CDCl_3) δ 163.2, 162.8, 149.2, 148.5, 147.8, 141.0, 139.0, 130.0, 129.2, 129.1, 192.0, 128.9, 126.9, 126.2, 122.3, 116.6, 116.5, 40.5, 35.9; HRMS Calculated for $\text{C}_{22}\text{H}_{19}\text{N}_5\text{O}$ $[\text{M}+\text{H}]^+$: 370.1662, Found: 370.1666.

Figure 1. ORTEP Drawing of the X-ray Crystal Structure **3a** ($C_{18}H_{16}N_4O$)
CCDC Number: 932446

Part II. Palladium-Catalyzed Aerobic Oxidative C–H Olefination with Removable 1,2,3-Triazole Directing Group

11a (1-benzyl-N-(2-methylphenethyl)-5-phenyl-1H-1,2,3-triazole-4-carboxamide)

was purified by flash chromatography (Hexane-EtOAc, v/v 2/1) as white solid;

¹H-NMR (400 MHz; CDCl₃): δ 7.47-7.41 (m, 3H), 7.37 (s, 1H), 7.28-7.25 (m, 4H), 7.17-7.12 (m, 3H), 7.02-7.00 (m, 2H), 5.41 (s, 2H), 3.60 (q, *J* = 7.2 Hz, 2H), 2.90 (t, *J* = 7.5 Hz, 2H), 2.33 (s, 3H);

¹³C-NMR (100 MHz, CDCl₃): δ 160.2, 139.17, 139.00, 136.9, 136.3, 134.7, 130.4, 129.96, 129.90, 129.3, 128.8, 128.50, 128.36, 127.5, 126.6, 126.14, 125.94, 52.0, 39.1, 33.3, 19.4;

HRMS Calculated for C₂₅H₂₄N₄O [M+H]⁺: 397.2023, Found: 397.2015.

11b (1-benzyl-N-(2-methoxyphenethyl)-5-phenyl-1H-1,2,3-triazole-4-carboxamide)

was purified by flash chromatography (Hexane-EtOAc, v/v 2/1) as white solid;

¹H-NMR (400 MHz, CDCl₃) δ 7.60-7.58 (t, *J* = 5.4 Hz, 1H), 7.47-7.39 (m, 3H), 7.27-7.24 (m, 5H), 7.23-7.19 (td, *J* = 8.0, 1.6Hz, 1H), 7.17-7.14 (dd, *J* = 7.6, 1.6Hz, 1H), 7.02-6.99 (m, 2H), 6.91-6.86(m, 2H), 5.41 (s, 2H), 3.87 (s, 3H), 3.63-3.58 (q, *J* = 7.2 Hz, 2H), 2.94-2.90 (t, *J* = 6.8 Hz, 2H);

¹³C-NMR (100 MHz, CDCl₃) δ 160.21, 157.47, 139.16, 139.04, 134.81, 130.57, 129.97, 129.78, 128.76, 128.41, 128.30, 127.80, 127.45, 127.42, 126.03, 120.62, 110.19, 55.27, 51.93, 39.64, 30.23;

HRMS Calculated for C₂₅H₂₄N₄O₂ [M+H]⁺: 413.1972, Found: 413.1970.

11c (1-benzyl-N-(2-fluorophenethyl)-5-phenyl-1H-1,2,3-triazole-4-carboxamide) was purified by flash chromatography (Hexane-EtOAc, v/v 2/1) as white solid;

¹H-NMR (400 MHz; CDCl₃): δ 7.47-7.41 (m, 3H), 7.38-7.35 (m, 1H), 7.28-7.25 (m, 5H), 7.25-7.17 (m, 2H), 7.08-7.04 (m, 1H), 7.02-7.00 (m, 2H), 5.41 (s, 2H), 3.67-3.62 (m, 2H), 2.94 (t, *J* = 7.2 Hz, 2H);

¹³C-NMR (100 MHz, CDCl₃) δ 162.48, 160.26, 160.03, 139.20, 138.92, 134.73, 131.07, 131.02, 129.96, 129.90, 128.79, 128.48, 128.36, 128.29, 128.21, 127.49, 125.93, 125.82, 125.66, 124.17, 124.14, 115.47, 115.25, 52.00, 39.05, 39.03, 29.37;

HRMS Calculated for C₂₄H₂₁FN₄O [M+H]⁺: 401.1772, Found: 401.1769.

11d (1-benzyl-N-(2-bromophenethyl)-5-phenyl-1H-1,2,3-triazole-4-carboxamide) was purified by flash chromatography (Hexane-EtOAc, v/v 2/1) as white solid;

¹H-NMR (400 MHz; CDCl₃): δ 7.55-7.52 (dd, *J* = 7.9, 0.9 Hz, 1H), 7.49-7.38 (m, 4H), 7.29-7.20 (m, 7H), 7.10-7.05 (ddd, *J* = 8.0, 6.7, 2.4 Hz, 1H), 7.02-7.00 (m, 2H), 5.41 (s, 2H), 3.65 (dt, *J* = 7.9, 6.5 Hz, 2H), 3.06-3.02 (t, *J* = 7.3 Hz, 2H);

¹³C-NMR (100 MHz, CDCl₃) δ 160.26, 139.18, 138.91, 138.18, 134.71, 132.88, 130.89, 129.94, 129.88, 128.76, 128.46, 128.33, 128.19, 127.58, 127.44, 125.90, 124.53, 51.98, 38.67, 36.07;

HRMS Calculated for $C_{24}H_{21}BrN_4O$ $[M+H]^+$: 461.0972, Found: 461.0968.

11e (1-benzyl-N-(3-methylphenethyl)-5-phenyl-1H-1,2,3-triazole-4-carboxamide)

was purified by flash chromatography (Hexane-EtOAc, v/v 2/1) as white solid;

1H -NMR (400 MHz; $CDCl_3$): δ 7.49-7.41 (m, 3H), 7.35-7.32 (m, 1H), 7.29-7.24 (m, 5H), 7.20-7.17 (m, 1H), 7.04-7.00 (m, 5H), 5.41 (s, 2H), 3.62 (dt, $J = 7.9, 6.5$ Hz, 2H), 2.85 (t, $J = 7.3$ Hz, 2H), 2.32 (s, 3H);

^{13}C -NMR (100 MHz, $CDCl_3$) δ 160.2, 139.19, 139.00, 138.7, 138.2, 134.7, 129.97, 129.89, 129.5, 128.8, 128.4, 127.5, 127.2, 126.0, 125.7, 77.3, 77.0, 76.7, 52.0, 40.3, 35.9, 21.3;

HRMS Calculated for $C_{25}H_{24}N_4O$ $[M+H]^+$: 397.2023, Found: 397.2021.

11f (1-benzyl-N-(3-methoxyphenethyl)-5-phenyl-1H-1,2,3-triazole-4-carboxamide) was purified by flash chromatography (Hexane-EtOAc, v/v 2/1) as white solid;

1H -NMR (400 MHz, $CDCl_3$) δ 7.48-7.39 (m, 3H), 7.36 (t, $J = 5.9$ Hz, 1H), 7.28-7.23 (m, 5H), 7.22-7.18 (m, 1H), 7.01-6.98 (m, 2H), 6.81-6.79 (m, 1H), 6.77-6.74 (m, 2H), 5.40 (s, 2H), 3.76 (s, 3H), 3.65-3.60 (m, 2H), 2.86 (t, $J = 7.3$ Hz, 2H);

^{13}C -NMR (100 MHz, $CDCl_3$) δ 160.2, 159.7, 140.4, 139.2, 138.9, 134.7, 129.93, 129.87, 129.6, 128.8, 128.45, 128.33, 127.4, 125.9, 121.0, 114.2, 112.1, 55.1, 52.0, 40.2, 36.0;

HRMS Calculated for $C_{25}H_{24}N_4O_2$ $[M+H]^+$: 413.1972, Found: 413.1970.

11g (1-benzyl-N-(3-fluorophenethyl)-5-phenyl-1H-1,2,3-triazole-4-carboxamide) was purified by flash chromatography (Hexane-EtOAc, v/v 2/1) as white solid;

1H -NMR (400 MHz, $CDCl_3$) δ 7.47-7.38 (m, 4H), 7.28-7.22 (m, 6H), 7.02-6.98 (m, 3H), 6.93-6.89 (m, 2H), 5.41 (s, 2H), 3.66-3.61 (m, 2H), 2.89 (t, $J = 7.3$ Hz, 2H);

^{13}C -NMR (100 MHz, $CDCl_3$) δ 164.1, 161.7, 160.2, 141.40, 141.34, 139.2, 138.9, 134.7, 130.04, 129.95, 129.93, 128.8, 128.48, 128.36, 127.5, 125.9, 124.37, 124.34, 115.7, 115.5, 113.4, 113.2, 77.3, 77.0, 76.7, 52.0, 40.0, 35.67, 35.65;

HRMS Calculated for $C_{24}H_{21}FN_4O$ $[M+H]^+$: 401.1772, Found: 401.1770.

11h (1-benzyl-N-phenethyl-5-phenyl-1H-1,2,3-triazole-4-carboxamide) was purified by flash chromatography (Hexane-EtOAc, v/v 2/1) as white solid;

1H -NMR (400 MHz; $CDCl_3$): δ 7.47-7.41 (m, 3H), 7.32-7.22 (m, 9H), 7.02-7.00 (m, 2H), 5.41 (s, 2H), 3.64 (q, $J = 6.9$ Hz, 2H), 2.89 (t, $J = 7.3$ Hz, 2H);

^{13}C -NMR (100 MHz, $CDCl_3$): δ 160.2, 138.8, 134.7, 129.97, 129.90, 128.79, 128.72, 128.59, 128.48, 128.36, 127.5, 126.4, 125.9, 52.0, 40.3, 36.0;

HRMS Calculated for $C_{24}H_{22}N_4O$ $[M+H]^+$: 383.1866, Found: 383.1863

11i (1-benzyl-N-(4-methylphenethyl)-5-phenyl-1H-1,2,3-triazole-4-carboxamide) was purified by flash chromatography (Hexane-EtOAc, v/v 2/1) as white solid;

¹H-NMR (400 MHz; CDCl₃): δ 7.46-7.40 (m, 3H), 7.34 (s, 1H), 7.28-7.25 (m, 5H), 7.11 (s, 4H), 7.01 (dd, *J* = 6.2, 2.8 Hz, 2H), 5.41 (s, 2H), 3.61 (q, *J* = 6.8 Hz, 2H), 2.84 (t, *J* = 7.3 Hz, 2H), 2.31 (s, 3H);

¹³C-NMR (100 MHz, CDCl₃): δ 160.2, 139.15, 138.98, 135.9, 135.7, 134.7, 129.94, 129.86, 129.3, 128.76, 128.57, 128.45, 128.33, 127.5, 125.9, 52.0, 40.4, 35.5, 21.0;

HRMS Calculated for C₂₅H₂₄N₄O [M+H]⁺: 397.2023, Found: 397.2018.

11j (1-benzyl-N-(4-methoxyphenethyl)-5-phenyl-1H-1,2,3-triazole-4-carboxamide) was purified by flash chromatography (Hexane-EtOAc, v/v 2/1) as white solid;

¹H-NMR (400 MHz; CDCl₃): δ 7.47-7.41 (m, 3H), 7.32 (t, *J* = 5.8 Hz, 1H), 7.28-7.25 (m, 5H), 7.14 (d, *J* = 8.6 Hz, 2H), 7.02-7.00 (m, 2H), 6.86-6.83 (m, 2H), 5.41 (s, 2H), 3.79 (s, 3H), 3.60 (q, *J* = 6.9 Hz, 2H), 2.83 (t, *J* = 7.2 Hz, 2H);

¹³C-NMR (100 MHz, CDCl₃): δ 160.2, 158.2, 139.17, 138.99, 134.7, 130.8, 129.96, 129.89, 129.7, 128.8, 128.48, 128.36, 127.5, 125.9, 114.0, 55.2, 52.0, 40.5, 35.0;

HRMS Calculated for C₂₅H₂₄N₄O₂ [M+H]⁺: 413.1972, Found: 413.1966.

11k (1-benzyl-N-(4-fluorophenethyl)-5-phenyl-1H-1,2,3-triazole-4-carboxamide) was purified by flash chromatography (Hexane-EtOAc, v/v 2/1) as white solid;

¹H-NMR (400 MHz; CDCl₃): δ 7.49-7.41 (m, 3H), 7.36-7.33 (m, 1H), 7.28-7.24 (m, 5H), 7.19-7.15 (m, 2H), 7.02-6.95 (m, 4H), 5.41 (s, 2H), 3.63-3.58 (m, 2H), 2.86 (t, *J* = 7.3 Hz, 2H);

¹³C-NMR (100 MHz, CDCl₃): δ 162.80, 162.80, 160.37, 160.37, 160.21, 160.21, 139.21, 139.21, 138.88, 138.88, 134.68, 134.68, 134.47, 134.47, 134.44, 134.44, 130.15, 130.15, 130.07, 130.07, 129.93, 129.93, 129.91, 129.91, 128.48, 128.48, 128.37, 128.37, 125.88, 125.88, 115.45, 115.45, 115.24, 115.24, 51.99, 51.99, 40.31, 40.31, 40.30, 40.30, 35.12, 35.12

HRMS Calculated for C₂₄H₂₁FN₄O [M+H]⁺: 401.1772, Found: 401.1770

11l (1-benzyl-5-phenyl-N-(2-phenylpropyl)-1H-1,2,3-triazole-4-carboxamide) was purified by flash chromatography (Hexane-EtOAc, v/v 2/1) as white solid;

¹H-NMR (400 MHz; CDCl₃): δ 7.48-7.39 (m, 3H), 7.33-7.29 (m, 2H), 7.27-7.19 (m, 7H), 7.01-6.99 (m, 2H), 5.39 (s, 2H), 3.66 (dt, *J* = 13.5, 6.8 Hz, 1H), 3.44 (ddd, *J* = 13.4, 7.9, 5.5 Hz, 1H), 3.03 (sextet, *J* = 7.1 Hz, 1H), 1.30 (d, *J* = 7.0 Hz, 3H);

$^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 160.2, 144.0, 139.1, 138.9, 134.7, 129.92, 129.82, 128.72, 128.60, 128.42, 128.30, 127.4, 127.1, 126.6, 125.9, 51.9, 45.7, 39.8, 19.2;

HRMS Calculated for $\text{C}_{25}\text{H}_{24}\text{N}_4\text{O}$ $[\text{M}+\text{H}]^+$: 397.2023, Found: 397.2017.

13a ((E)-butyl-3-(2-(2-(1-benzyl-5-phenyl-1H-1,2,3-triazole-4-carboxamido)ethyl)-3-methylphenyl)acrylate) was prepared following the general procedure A and purified by flash chromatography (Hexane-EtOAc, v/v 2/1) as colorless oil; Isolated yield: 99.2 mg, 95%;

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.94 (s, 1H), 7.41-7.37 (m, 3H), 7.32-7.27 (m, 4H), 7.24-7.20 (m, 3H), 7.18-7.17 (m, br, 1H), 5.54 (s, 2H), 3.71-3.68 (q, $J = 7.5$ Hz, 2H), 2.92-2.90 (t, $J = 7.2$ Hz, 2H);

$^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ 166.9, 160.2, 142.4, 139.2, 138.9, 137.6, 136.5, 134.8, 134.1, 132.2, 129.99, 129.89, 128.8, 128.48, 128.34, 127.4, 126.8, 125.9, 124.9, 120.7, 64.4, 52.0, 38.9, 30.7, 29.4, 20.1, 19.2, 13.7;

HRMS Calculated for $\text{C}_{32}\text{H}_{34}\text{N}_4\text{O}_3$ $[\text{M}+\text{H}]^+$: 523.2704, Found: 523.2701.

13b (E)-butyl-3-(2-(2-(1-benzyl-5-phenyl-1H-1,2,3-triazole-4-carboxamido)ethyl)-3-methoxyphenyl)acrylate) was prepared following the general procedure A and purified by flash chromatography (Hexane-EtOAc, v/v 2/1) as colorless oil; Isolated yield: 101.2 mg, 94%;

¹H-NMR (400 MHz; CDCl₃): δ 7.98 (d, *J* = 15.7 Hz, 1H), 7.63 (t, *J* = 5.1 Hz, 1H), 7.47-7.38 (m, 3H), 7.28-7.16 (m, 7H), 7.01-6.98 (m, 2H), 6.91 (dd, *J* = 8.0, 1.1 Hz, 1H), 6.33 (d, *J* = 15.7 Hz, 1H), 5.41 (s, 2H), 4.16 (t, *J* = 6.7 Hz, 2H), 3.91 (s, 3H), 3.55 (q, *J* = 6.0 Hz, 2H), 3.13 (t, *J* = 6.7 Hz, 2H), 1.69-1.62 (m, 3H), 1.45-1.36 (m, 2H), 0.94 (d, *J* = 14.8 Hz, 3H);

¹³C-NMR (100 MHz, CDCl₃): δ 166.7, 160.2, 157.7, 141.6, 139.04, 139.01, 135.02, 134.83, 130.0, 129.8, 128.8, 128.37, 128.29, 127.6, 127.35, 127.27, 126.0, 121.07, 121.05, 119.1, 111.3, 64.4, 55.7, 51.9, 39.7, 30.7, 24.9, 19.2, 13.7;

HRMS Calculated for C₃₂H₃₄N₄O₄ [M+H]⁺: 539.2653, Found: 539.2650.

13c ((E)-butyl-3-(2-(2-(1-benzyl-5-phenyl-1H-1,2,3-triazole-4-carboxamido)ethyl)-3-fluorophenyl)acrylate) was prepared following the general procedure B and purified by flash chromatography (Hexane-EtOAc, v/v 2/1) as colorless oil; Isolated yield: 94.8 mg, 90%;

¹H-NMR (400 MHz; CDCl₃): δ 7.92 (d, *J* = 15.8 Hz, 1H), 7.46-7.40 (m, 3H), 7.36-7.32 (m, 2H), 7.29-7.19 (m, 6H), 7.06 (td, *J* = 8.8, 1.1 Hz, 1H), 7.02-7.00 (m, 2H), 6.35 (d, *J* = 15.7 Hz, 1H), 5.41 (s, 2H), 4.15 (t, *J* = 6.7 Hz, 2H), 3.58 (q, *J* = 6.7 Hz, 2H), 3.10 (td, *J* = 7.0, 1.5 Hz, 2H), 1.68-1.61 (m, 2H), 1.45-1.35 (m, 2H), 0.94 (t, *J* = 7.4 Hz, 3H);

¹³C-NMR (100 MHz, CDCl₃) δ 166.4, 162.8, 160.33, 160.23, 140.37, 140.33, 139.2, 138.8, 136.05, 136.01, 134.8, 130.00, 129.84, 128.8, 128.42, 128.32, 128.12, 128.03, 127.4, 125.93, 125.76, 125.60, 122.53, 122.50, 121.8, 116.6, 116.4, 64.5, 51.9, 39.1, 30.7, 25.34, 25.31, 19.2, 13.7;

HRMS Calculated for C₃₁H₃₁FN₄O₃ [M+H]⁺: 527.2453, Found: 527.2451.

13d ((E)-butyl 3-(2-(2-(1-benzyl-5-phenyl-1H-1,2,3-triazole-4-carboxamido)ethyl)-3-bromophenyl)acrylate) was prepared following the general procedure A and purified by flash chromatography (Hexane-EtOAc, v/v 2/1) as colorless oil; Isolated yield: 94.5 mg, 81%;

¹H-NMR (400 MHz; CDCl₃): δ 7.98 (d, *J* = 15.7 Hz, 1H), 7.59 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.49-7.40 (m, 5H), 7.29-7.25 (m, 6H), 7.11 (t, *J* = 7.9 Hz, 1H), 7.00-1.02 (m, 2H), 6.29 (d, *J* = 15.7 Hz, 1H), 5.42 (s, 2H), 4.13 (d, *J* = 13.5 Hz, 2H), 3.63-3.58 (m, 2H), 3.26 (t, *J* = 7.2 Hz, 2H), 1.65-1.59 (m, 2H), 1.43-1.34 (m, 2H), 0.93 (t, *J* = 7.4 Hz, 3H);

¹³C-NMR (100 MHz, CDCl₃): δ 166.3, 160.2, 141.5, 139.2, 138.8, 137.4, 136.3, 134.8, 134.3, 130.02, 129.96, 129.83, 128.8, 128.41, 128.31, 128.28, 127.47, 127.38, 126.35, 126.33, 125.9, 122.2, 64.5, 51.9, 38.5, 32.6, 30.6, 19.1, 13.7;

HRMS Calculated for C₃₁H₃₁BrN₄O₃ [M+H]⁺: 587.1652, Found: 587.1645.

13e ((E)-butyl-3-(2-(2-(1-benzyl-5-phenyl-1H-1,2,3-triazole-4-carboxamido)ethyl)-4-methylphenyl)acrylate) was prepared following the general procedure A and purified by flash chromatography (Hexane-EtOAc, v/v 2/1) as colorless oil; Isolated yield: 94.5 mg, 91%;

¹H-NMR (400 MHz; CDCl₃): δ 7.96 (d, *J* = 15.8 Hz, 1H), 7.49-7.41 (m, 4H), 7.35 (t, *J* = 6.1 Hz, 1H), 7.30-7.23 (m, 5H), 7.07 (d, *J* = 7.5 Hz, 2H), 7.03-7.00 (m, 2H), 6.34 (d, *J* = 15.7 Hz, 1H), 5.42 (s, 2H), 4.18 (t, *J* = 6.7 Hz, 2H), 3.58-3.55 (m, 2H), 3.01 (t, *J* = 7.4

Hz, 2H), 2.31 (s, 3H), 1.71-1.64 (m, 3H), 1.42 (q, $J = 8.3, 7.3$ Hz, 2H), 0.96 (t, $J = 7.4$ Hz, 3H);

^{13}C -NMR (100 MHz, CDCl_3): δ 167.0, 160.2, 141.3, 140.5, 139.2, 138.9, 138.2, 134.8, 131.2, 130.5, 129.97, 129.88, 128.8, 128.46, 128.33, 128.0, 127.4, 126.7, 125.9, 119.2, 64.3, 52.0, 40.0, 33.1, 30.7, 21.3, 19.2, 13.7;

HRMS Calculated for $\text{C}_{32}\text{H}_{34}\text{N}_4\text{O}_3$ $[\text{M}+\text{H}]^+$: 523.2704, Found: 523.2701.

13f ((E)-butyl-3-(2-(2-(1-benzyl-5-phenyl-1H-1,2,3-triazole-4-carboxamido)ethyl)-4-methoxyphenyl)acrylate) was prepared following the general procedure A and purified by flash chromatography (Hexane-EtOAc, v/v 2/1) as colorless oil; Isolated yield: 85.0 mg, 79%;

^1H -NMR (400 MHz; CDCl_3): δ 7.92 (d, $J = 15.7$ Hz, 1H), 7.55 (d, $J = 8.6$ Hz, 1H), 7.49-7.41 (m, 3H), 7.36-7.33 (m, 1H), 7.30-7.25 (m, 9H), 7.02-6.99 (m, 2H), 6.81-6.76 (m, 2H), 6.28 (d, $J = 15.7$ Hz, 1H), 5.42 (s, 2H), 4.18 (t, $J = 6.7$ Hz, 2H), 3.78 (s, 3H), 3.62-3.57 (m, 2H), 3.04 (t, $J = 7.2$ Hz, 2H), 1.71-1.64 (m, 2H), 1.47-1.38 (m, $J = 7.2$ Hz, 2H), 0.96 (t, $J = 7.4$ Hz, 3H);

^{13}C -NMR (100 MHz, CDCl_3) ^{13}C NMR (101 MHz; cdcl_3): δ 167.2, 161.1, 160.3, 140.8, 140.3, 139.2, 138.9, 134.8, 129.98, 129.92, 128.8, 128.49, 128.37, 127.5, 125.94, 125.81, 117.7, 115.1, 113.5, 64.3, 55.3, 52.0, 39.9, 33.3, 30.8, 19.2, 13.8;

HRMS Calculated for $\text{C}_{32}\text{H}_{34}\text{N}_4\text{O}_4$ $[\text{M}+\text{H}]^+$: 539.2653, Found: 539.2651.

13g ((E)-butyl 3-(2-(2-(1-benzyl-5-phenyl-1H-1,2,3-triazole-4-carboxamido)ethyl)-4-fluorophenyl)acrylate) was prepared following the general procedure B and purified by flash chromatography (Hexane-EtOAc, v/v 2/1) as colorless oil; Isolated yield: 58.8 mg, 56%;

¹H-NMR (400 MHz; CDCl₃): δ 7.74 (d, *J* = 16.2 Hz, 1H), 7.49-7.41 (m, 3H), 7.36-7.32 (m, 1H), 7.28-7.22 (m, 7H), 7.06-6.97 (m, 4H), 6.58 (dd, *J* = 16.1, 0.8 Hz, 1H), 5.42 (s, 2H), 4.20 (t, *J* = 6.7 Hz, 2H), 3.60 (q, *J* = 6.8 Hz, 2H), 3.06 (t, *J* = 7.2 Hz, 2H), 1.67 (dq, *J* = 14.2, 6.8 Hz, 3H), 1.43 (dq, *J* = 15.0, 7.5 Hz, 3H), 0.96 (t, *J* = 7.4 Hz, 3H);

¹³C-NMR (100 MHz, CDCl₃) 13-C NMR (101 MHz; cdcl₃): δ 167.2, 161.1, 160.3, 140.8, 140.3, 139.2, 138.9, 134.8, 129.98, 129.92, 128.8, 128.49, 128.37, 127.5, 125.94, 125.81, 117.7, 115.1, 113.5, 64.3, 55.3, 52.0, 39.9, 33.3, 30.8, 19.2, 13.8;

HRMS Calculated for C₃₁H₃₁FN₄O₃ [M+H]⁺: 527.2453, Found: 527.2452.

13gd (2E,2'E)-dibutyl 3,3'-(2-(2-(1-benzyl-5-phenyl-1H-1,2,3-triazole-4-carboxamido)ethyl)-4-fluoro-1,3-phenylene)diacrylate) was prepared following the general procedure B and purified by flash chromatography (Hexane-EtOAc, v/v 2/1) as colorless oil; Isolated yield: 36.0 mg, 28%;

¹H-NMR (400 MHz; CDCl₃): δ 7.98 (d, *J* = 15.7 Hz, 1H), 7.74 (d, *J* = 16.2 Hz, 1H), 7.52 (dd, *J* = 8.7, 5.4 Hz, 1H), 7.46-7.40 (m, 3H), 7.30-7.25 (m, 6H), 7.07-7.00 (m, 3H), 6.49 (dd, *J* = 16.2, 1.7 Hz, 1H), 6.26 (d, *J* = 15.7 Hz, 1H), 5.41 (s, 2H), 4.14 (q, *J* = 7.1 Hz,

4H), 3.54 (q, $J = 6.7$ Hz, 2H), 3.18 (t, $J = 7.1$ Hz, 2H), 1.64 (td, $J = 7.9, 4.8$ Hz, 6H), 1.43-1.36 (m, 4H), 0.94 (td, $J = 7.4, 1.7$ Hz, 6H);

^{13}C -NMR (100 MHz, CDCl_3): δ 166.6, 166.4, 160.7, 160.2, 140.9, 139.96, 139.93, 139.3, 138.6, 134.91, 134.82, 131.15, 131.11, 129.8, 129.40, 129.30, 128.39, 128.31, 126.28, 126.15, 125.9, 122.99, 122.88, 121.5, 115.3, 115.0, 64.59, 64.49, 51.9, 39.3, 30.7, 29.48, 29.47, 19.2, 13.7;

HRMS Calculated for $\text{C}_{38}\text{H}_{41}\text{FN}_4\text{O}_5$ $[\text{M}+\text{H}]^+$: 653.3134, Found: 653.3128.

13h was prepared following the general procedure A and purified by flash chromatography (Hexane-EtOAc, v/v 2/1) as colorless oil; Isolated yield: 98 mg, 90% (inseparable mixture of mon and di olefination products, ratio =1:0.9);

^1H -NMR (400 MHz; CDCl_3): δ 8.04 (d, $J = 15.7$ Hz, 1.8H), 7.99 (d, $J = 15.8$ Hz, 1H), 7.58-7.56(m, 2.8H), 7.47-7.41 (m, 5H), 7.33-7.24 (m, 14H), 7.02-6.99 (m, 3.8H), 6.37 (d, $J = 15.8$ Hz, 1H), 6.31 (d, $J = 15.7$ Hz, 1.8H), 5.41 (d, $J = 2.3$ Hz, 3.8H), 4.17 (m, 5.6H), 3.62-3.51 (m, 3.8H), 3.19 (t, $J = 7.1$ Hz, 1.8H), 3.05 (t, $J = 7.2$ Hz, 2H), 1.73-1.61 (m, 5.6H), 1.45-1.37 (m, 5.7H), 0.95 (m, 8.4H);

^{13}C -NMR (100 MHz, CDCl_3): δ 166.8, 166.4, 160.23, 160.17, 141.6, 141.4, 139.25, 139.22, 138.85, 138.65, 138.3, 137.3, 135.2, 134.83, 134.74, 133.4, 130.4, 130.16, 130.06, 129.97, 129.89, 129.80, 128.78, 128.63, 128.46, 128.36, 128.34, 128.31, 128.28, 127.45, 127.39, 127.35, 127.1, 126.9, 125.9, 121.8, 120.3, 64.45, 64.42, 51.98, 51.91, 39.9, 39.6, 33.1, 30.71, 30.66, 28.9, 19.18, 19.15, 13.7, 40.5, 36.0.

HRMS Calculated for $\text{C}_{31}\text{H}_{32}\text{N}_4\text{O}_3$ $[\text{M}+\text{H}]^+$: 509.2547, Found: 509.2543

$\text{C}_{38}\text{H}_{42}\text{N}_4\text{O}_5$ $[\text{M}+\text{H}]^+$: 635.3228, Found: 635.3222.

13i was prepared following the general procedure A and purified by flash chromatography (Hexane-EtOAc, v/v 2/1) as colorless oil; Isolated yield: 105.3 mg, 91% (inseparable mixture of mon and di olefination products, ratio = 1:1);

¹H-NMR (400 MHz; CDCl₃): δ 8.02 (d, *J* = 15.7 Hz, 2H), 7.96 (d, *J* = 16.0 Hz, 1H), 7.47-7.39 (m, 8H), 7.35 (q, *J* = 5.7 Hz, 1H), 7.30-7.25 (m, 10H), 7.13-7.11 (m, 2H), 7.02-6.99 (m, 4H), 6.36 (d, *J* = 15.7 Hz, 1H), 6.31 (d, *J* = 15.7 Hz, 2H), 5.41 (d, *J* = 2.3 Hz, 4H), 4.16 (dt, *J* = 17.4, 6.7 Hz, 6H), 3.60-3.49 (m, 4H), 3.15 (t, *J* = 7.1 Hz, 2H), 3.01 (t, *J* = 7.2 Hz, 2H), 2.34 (d, *J* = 8.6 Hz, 6H), 1.70-1.61 (m, 6H), 1.45-1.37 (m, 6H), 0.98-0.92 (m, 8H);

¹³C-NMR (100 MHz, CDCl₃): δ 166.9, 166.5, 160.17, 160.12, 141.8, 141.5, 139.21, 139.18, 138.9, 138.7, 136.79, 136.62, 135.3, 134.93, 134.81, 134.72, 134.5, 133.1, 131.0, 130.4, 130.03, 129.95, 129.85, 129.77, 129.35, 129.25, 128.75, 128.57, 128.43, 128.34, 128.31, 128.25, 127.43, 127.33, 125.9, 121.5, 119.9, 64.38, 64.35, 51.95, 51.88, 40.0, 39.6, 32.7, 30.69, 30.64, 28.5, 20.9, 19.16, 19.13, 13.7.

HRMS Calculated for C₃₂H₃₄N₄O₃ [M+H]⁺: 523.2704, Found: 509.2543

C₃₉H₄₄N₄O₅ [M+H]⁺: 649.3384, Found: 635.3379.

13j was prepared following the general procedure A and purified by flash chromatography (Hexane-EtOAc, v/v 2/1) as colorless oil; Isolated yield: 95.0 mg, 86% (inseparable mixture of mon and di olefination products, ratio =0.8 :1);

¹H-NMR (400 MHz; CDCl₃): δ 8.01 (d, *J* = 15.7 Hz, 2H), 7.95 (d, *J* = 15.7 Hz, 0.8H), 7.47-7.39 (m, 4.6H), 7.35-7.25 (m, 9.5H), 7.16 (d, *J* = 8.5 Hz, 0.8H), 7.08-7.87 (m, 2.8H), 7.02-6.99 (m, 3.6H), 6.89-6.86 (m, 0.8H), 6.35(d, 15.7 Hz, 0.8H), 6.30(d, 15.7 Hz, 2H), 5.412-5.408 (m, 3.6H), 4.20-4.13 (m, 5.6H), 3.84-3.81(m, 5.4H), 3.58-3.47 (m, 3.6H), 3.13 (t, *J* = 7.1 Hz, 2H), 2.99 (t, *J* = 7.1 Hz, 1.6H), 1.71-1.61 (m, 5.6H), 1.45-1.35 (m, 5.6H), 0.98-0.92 (m, 8.4H);

¹³C-NMR (100 MHz, CDCl₃): δ 166.8, 166.4, 160.17, 160.11, 158.4, 158.2, 141.7, 141.4, 139.20, 139.17, 138.85, 138.65, 136.2, 134.80, 134.71, 134.3, 131.5, 130.6, 130.02, 129.94, 129.85, 129.76, 129.63, 128.7, 128.43, 128.33, 128.31, 128.25, 127.42, 127.33, 125.9, 121.8, 120.3, 116.3, 114.0, 111.5, 64.45, 64.43, 55.35, 55.28, 51.95, 51.88, 40.1, 39.8, 32.3, 30.67, 30.62, 28.3, 19.15, 19.12, 13.7 δ 160.1, 140.5, 138.8, 133.9, 129.4, 129.3, 128.9, 128.8, 128.4, 126.7, 125.3, 54.7, 40.5, 36.0.

HRMS Calculated for C₃₂H₃₄N₄O₄ [M+H]⁺: 539.2653, Found: 539.2647

C₃₉H₄₄N₄O₆ [M+H]⁺: 665.3334, Found: 665.3326.

13k ((E)-butyl-3-(2-(2-(1-benzyl-5-phenyl-1H-1,2,3-triazole-4-carboxamido)ethyl)-5-fluorophenyl)acrylate) was prepared following the general procedure B and purified by flash chromatography (Hexane-EtOAc, v/v 2/1) as colorless oil; Isolated yield: 47mg, 44%;

¹H-NMR (400 MHz; CDCl₃): δ 7.91 (dd, *J* = 15.8, 1.5 Hz, 1H), 7.50-7.41 (m, 3H), 7.35-7.31 (m, 1H), 7.30-7.19 (m, 9H), 7.04-6.98 (m, 3H), 6.35 (d, *J* = 15.7 Hz, 1H), 5.42 (s,

2H), 4.19 (t, $J = 6.7$ Hz, 2H), 3.59-3.53 (m, 2H), 3.02 (t, $J = 7.2$ Hz, 2H), 1.71-1.64 (m, 2H), 1.47-1.38 (m, 3H), 0.96 (t, $J = 7.4$ Hz, 3H);

^{13}C -NMR (100 MHz, CDCl_3): δ 166.5, 162.9, 162.1, 160.5, 160.3, 140.34, 140.31, 138.8, 135.21, 135.14, 134.7, 134.10, 134.07, 132.12, 132.04, 129.97, 129.95, 128.8, 128.50, 128.39, 127.5, 125.9, 121.4, 117.2, 117.0, 113.3, 113.1, 77.3, 77.0, 76.7, 64.6, 52.0, 40.0, 32.5, 30.7, 19.2, 13.7;

HRMS Calculated for $\text{C}_{31}\text{H}_{31}\text{FN}_4\text{O}_3$ $[\text{M}+\text{H}]^+$: 527.2453, Found: 527.2449.

13kd ((2E,2'E)-dibutyl 3,3'-(2-(2-(1-benzyl-5-phenyl-1H-1,2,3-triazole-4-carboxamido)ethyl)-5-fluoro-1,3-phenylene)diacrylate) was prepared following the general procedure B and purified by flash chromatography (Hexane-EtOAc, v/v 2/1) as colorless oil; Isolated yield 57.0 mg, 43%;

^1H -NMR (400 MHz; CDCl_3): δ 7.99 (dd, $J = 15.7, 1.2$ Hz, 2H), 7.46-7.40 (m, 3H), 7.32-7.25 (m, 8H), 7.02-7.00 (m, 2H), 6.30 (d, $J = 15.7$ Hz, 2H), 5.41 (s, 2H), 4.15 (t, $J = 6.7$ Hz, 4H), 3.51 (q, $J = 6.8$ Hz, 2H), 3.15 (t, $J = 7.1$ Hz, 2H), 1.68-1.61 (m, 4H), 1.40 (quintet, $J = 8.3, 7.3$ Hz, 4H), 0.94 (t, $J = 7.4$ Hz, 6H);

^{13}C -NMR (100 MHz, CDCl_3): ^{13}C NMR (101 MHz; cd_3cn): δ 166.2, 160.2, 140.59, 140.57, 139.3, 138.6, 137.16, 137.09, 134.8, 133.30, 133.27, 130.02, 129.85, 128.8, 128.39, 128.31, 127.4, 125.8, 122.8, 115.2, 115.0, 64.6, 51.9, 39.5, 30.6, 28.5, 19.1, 13.8;

HRMS Calculated for $\text{C}_{38}\text{H}_{41}\text{FN}_4\text{O}_5$ $[\text{M}+\text{H}]^+$: 653.3134, Found: 653.3130

13l ((E)-butyl 3-(2-(1-(1-benzyl-5-phenyl-1H-1,2,3-triazole-4-carboxamido)propan-2-yl)phenyl)acrylate) was prepared following the general procedure A and purified by flash chromatography (Hexane-EtOAc, v/v 2/1) as colorless oil; Isolated yield: 90.1 mg, 86%;

¹H-NMR (400 MHz; CDCl₃): δ 8.05 (d, *J* = 15.7 Hz, 1H), 7.53 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.46-7.38 (m, 3H), 7.37-7.32 (m, 1H), 7.25 (dd, *J* = 19.7, 1.6 Hz, 6H), 7.18-7.16 (m, 1H), 7.00 (td, *J* = 3.7, 1.7 Hz, 2H), 6.31 (d, *J* = 15.7 Hz, 1H), 5.44-5.36 (m, 2H), 4.18 (t, *J* = 6.7 Hz, 2H), 3.78-3.70 (m, 1H), 3.53-3.44 (m, 2H), 1.71-1.64 (m, 2H), 1.46-1.39 (m, 2H), 1.30 (d, *J* = 6.7 Hz, 3H), 0.95 (t, *J* = 7.4 Hz, 3H);

¹³C-NMR (100 MHz, CDCl₃): δ 166.8, 160.2, 143.1, 141.8, 138.8, 134.7, 133.7, 130.3, 129.99, 129.88, 128.8, 128.44, 128.41, 128.34, 127.46, 127.29, 126.8, 125.98, 125.91, 120.9, 64.4, 52.0, 44.6, 35.0, 30.7, 19.4, 19.2, 13.8;

HRMS Calculated for C₃₂H₃₄N₄O₃ [M+H]⁺: 523.2704, Found: 523.5703.

13m ((2E,2'E)-dibutyl-3,3'-(2-(2-(1-benzyl-5-phenyl-1H-1,2,3-triazole-4-carboxamido)ethyl)-1,3-phenylene)diacrylate) was prepared following the general procedure C and purified by flash chromatography (Hexane-EtOAc, v/v 2/1) as colorless oil; Isolated yield: 104.0 mg, 82%;

¹H-NMR (400 MHz; CDCl₃): δ 8.05 (d, *J* = 15.7 Hz, 2H), 7.57 (d, *J* = 7.8 Hz, 2H), 7.46-7.40 (m, 3H), 7.31-7.26 (m, 8H), 7.02-6.99 (m, 2H), 6.32 (d, *J* = 15.7 Hz, 2H), 5.41 (s, 2H), 4.14 (t, *J* = 6.7 Hz, 4H), 3.53 (q, *J* = 6.8 Hz, 2H), 3.21-3.18 (m, 2H), 1.68-1.61 (m, 4H), 1.44-1.35 (m, 4H), 0.94 (t, *J* = 7.4 Hz, 6H);

¹³C-NMR (100 MHz, CDCl₃): δ 166.5, 160.2, 141.7, 139.3, 138.7, 137.3, 135.1, 134.8, 130.06, 129.97, 129.81, 128.78, 128.64, 128.37, 128.29, 127.4, 125.9, 121.8, 64.5, 51.9, 39.6, 30.7, 28.9, 19.2, 13.7;

HRMS Calculated for C₃₈H₄₂N₄O₅ [M+H]⁺: 635.3228, Found: 635.3225

13n ((2E,2'E)-dibutyl-3,3'-(2-(2-(1-benzyl-5-phenyl-1H-1,2,3-triazole-4-carboxamido)ethyl)-5-methyl-1,3-phenylene)diacrylate) was prepared following the general procedure C and purified by flash chromatography (Hexane-EtOAc, v/v 2/1) as colorless oil; Isolated yield: 110.0 mg, 85%;

¹H-NMR (400 MHz; CDCl₃): δ 8.01 (d, *J* = 15.7 Hz, 2H), 7.46-7.39 (m, 5H), 7.30-7.24 (m, 8H), 7.02-6.99 (m, 2H), 6.30 (d, *J* = 15.7 Hz, 2H), 5.41 (s, 2H), 4.14 (s, 4H), 3.51 (q, *J* = 6.7 Hz, 2H), 3.15 (t, *J* = 7.1 Hz, 2H), 2.35 (s, 3H), 1.68-1.60 (m, 4H), 1.44-1.35 (m, 4H), 0.94 (t, *J* = 7.4 Hz, 6H);

¹³C-NMR (100 MHz, CDCl₃): δ 166.5, 160.1, 141.8, 139.2, 138.7, 136.8, 134.95, 134.83, 134.5, 130.05, 129.97, 129.87, 129.78, 129.4, 128.8, 128.45, 128.35, 128.26, 127.44, 127.37, 127.34, 125.9, 121.5, 64.4, 51.9, 39.7, 30.7, 29.7, 28.5, 21.0, 19.1, 13.7;

HRMS Calculated for C₃₉H₄₄N₄O₅ [M+H]⁺: 649.3384, Found: 649.3380.

13o ((2E,2'E)-dibutyl-3,3'-(2-(2-(1-benzyl-5-phenyl-1H-1,2,3-triazole-4-carboxamido)ethyl)-5-methoxy-1,3-phenylene)diacrylate) was prepared following the general procedure C and purified by flash chromatography (Hexane-EtOAc, v/v 2/1) as colorless oil; Isolated yield: 111.0 mg, 84%;

¹H-NMR (400 MHz; CDCl₃): δ 8.01 (d, *J* = 15.7 Hz, 2H), 7.46-7.39 (m, 3H), 7.29-7.25 (m, 7H), 7.10 (s, 2H), 7.02-6.99 (m, 2H), 6.30 (d, *J* = 15.7 Hz, 2H), 5.41 (s, 2H), 4.15 (t,

$J = 6.7$ Hz, 4H), 3.84 (s, 3H), 3.49 (q, $J = 6.7$ Hz, 2H), 3.12 (dd, $J = 9.4, 4.9$ Hz, 2H), 1.68-1.61 (m, 4H), 1.44-1.35 (m, 5H), 0.94 (t, $J = 7.4$ Hz, 6H);

^{13}C -NMR (100 MHz, CDCl_3): δ 166.4, 160.2, 158.2, 141.7, 139.2, 138.7, 136.3, 134.8, 130.07, 129.88, 129.82, 128.8, 128.38, 128.30, 127.37, 127.33, 125.9, 121.9, 114.0, 64.5, 55.4, 51.9, 39.8, 30.7, 28.3, 19.2, 13.7;

HRMS Calculated for $\text{C}_{39}\text{H}_{44}\text{N}_4\text{O}_6$ $[\text{M}+\text{H}]^+$: 665.3334, Found: 665.3329.

14a ((E)-methyl-3-(2-(2-(1-benzyl-5-phenyl-1H-1,2,3-triazole-4-carboxamido)ethyl)-3-methylphenyl)acrylate) was prepared following the general procedure B and purified by flash chromatography (Hexane-EtOAc, v/v 2/1) as colorless oil; Isolated yield: 87.9 mg, 92%;

^1H -NMR (400 MHz; CDCl_3): δ 8.07 (d, $J = 15.7$ Hz, 1H), 7.46-7.39 (dt, $J = 16.1, 8.2$ Hz, 5H), 7.29-7.26 (m, 5H), 7.17 (dt, $J = 16.9, 8.1$ Hz, 2H), 7.01 (t, $J = 3.6$ Hz, 2H), 6.32 (d, $J = 15.7$ Hz, 1H), 5.42 (s, 2H), 3.74 (d, $J = 0.5$ Hz, 3H), 3.50 (q, $J = 7.3$ Hz, 2H), 3.08 (t, $J = 7.6$ Hz, 2H), 2.39 (s, 3H);

^{13}C -NMR (100 MHz, CDCl_3): δ 167.2, 160.2, 142.7, 139.2, 138.9, 137.6, 136.6, 134.8, 134.1, 133.2, 132.2, 131.1, 130.00, 129.89, 128.8, 128.48, 128.35, 127.4, 126.8, 125.9, 124.9, 120.2, 52.0, 51.6, 38.9, 29.4, 20.1;

HRMS Calculated for $\text{C}_{28}\text{H}_{26}\text{N}_4\text{O}_3$ $[\text{M}+\text{H}]^+$: 481.2234, Found: 481.2233

14b (1-benzyl-N-(2-methyl-6-((E)-3-oxo-3-((1S,2R,4R)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)prop-1-en-1-yl)phenethyl)-5-phenyl-1H-1,2,3-triazole-4-carboxamide) was prepared following the general procedure B and purified by flash chromatography (Hexane-EtOAc, v/v 2/1) as colorless oil; Isolated yield: 103.0 mg, 86%;

¹H-NMR (400 MHz; CDCl₃): δ 8.01 (d, *J* = 15.7 Hz, 1H), 7.47-7.40 (m, 4H), 7.34 (t, *J* = 5.9 Hz, 1H), 7.28-7.26 (m, 5H), 7.20-7.13 (m, 2H), 7.00 (t, *J* = 3.7 Hz, 2H), 6.31 (d, *J* = 15.7 Hz, 1H), 5.42 (s, 2H), 4.78 (t, *J* = 5.8 Hz, 1H), 3.51 (q, *J* = 7.3 Hz, 2H), 3.07 (t, *J* = 7.6 Hz, 2H), 2.38 (s, 3H), 1.84 (d, *J* = 5.6 Hz, 2H), 1.75-1.54 (m, 4H), 1.27-1.10 (m, 3H), 1.07 (d, *J* = 5.0 Hz, 3H), 0.87 (d, *J* = 13.8 Hz, 6H).;

¹³C-NMR (100 MHz, CDCl₃) 13-C NMR (101 MHz; cdcl3): δ 166.2, 160.2, 141.9, 139.2, 138.9, 137.6, 136.4, 134.8, 133.9, 132.2, 129.98, 129.88, 128.8, 128.47, 128.33, 127.4, 126.8, 125.9, 124.8, 121.1, 81.0, 52.0, 48.9, 47.0, 45.0, 38.95, 38.86, 33.7, 29.4, 27.1, 20.13, 20.10, 19.96, 11.5;

HRMS Calculated for C₃₈H₄₂N₄O₃ [M+H]⁺: 603.3330, Found: 603.3327.

14c ((E)-1-benzyl-N-(2-(2-cyanovinyl)-6-methylphenethyl)-5-phenyl-1H-1,2,3-triazole-4-carboxamide) was prepared following the general procedure B and purified by flash chromatography (Hexane-EtOAc, v/v 1/1) as colorless oil; Isolated yield: 71.2 mg, 80%;

¹H-NMR (400 MHz; CDCl₃): δ 7.77 (d, *J* = 16.4 Hz, 1H), 7.48-7.43 (m, 3H), 7.35-7.31 (m, 3H), 7.28-7.25 (m, 5H), 7.18 (t, *J* = 7.6 Hz, 1H), 7.03-7.01 (m, 2H), 5.73 (d, *J* = 16.3 Hz, 1H), 5.43 (s, 2H), 3.52 (q, *J* = 6.9 Hz, 2H), 3.02 (t, *J* = 7.1 Hz, 2H), 2.38 (s, 3H);

¹³C-NMR (100 MHz, CDCl₃): δ 160.4, 148.8, 139.6, 138.6, 137.7, 136.5, 134.7, 133.6, 133.1, 130.0, 128.48, 128.35, 127.0, 125.8, 124.2, 118.0, 98.3, 52.1, 38.8, 29.2, 20.0;

HRMS Calculated for C₂₈H₂₅N₅O [M+H]⁺: 448.2132, Found: 448.2130.

14d ((E)-1-benzyl-N-(2-(3-(dimethylamino)-3-oxoprop-1-en-1-yl)-6-methylphenethyl)-5-phenyl-1H-1,2,3-triazole-4-carboxamide) was prepared following the general procedure B and purified by flash chromatography (Hexane-EtOAc, v/v 1/2) as colorless oil; Isolated yield: 80.8 mg, 82%;

$^1\text{H-NMR}$ (400 MHz; CDCl_3): δ 8.02 (d, J = 15.2 Hz, 1H), 7.47-7.40 (m, 4H), 7.37 (dd, J = 7.3, 1.6 Hz, 1H), 7.29-7.25 (m, 5H), 7.18-7.12 (m, 2H), 7.02-6.99 (m, 2H), 6.76 (d, J = 15.1 Hz, 1H), 5.41 (s, 2H), 3.51 (dt, J = 8.8, 6.5 Hz, 2H), 3.14-3.04 (m, 8H), 2.38 (s, 3H).;

$^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ 166.5, 160.2, 140.5, 139.14, 138.99, 137.6, 136.3, 135.3, 134.8, 131.5, 129.9, 128.48, 128.34, 128.31, 127.5, 126.6, 126.0, 124.8, 120.3, 52.0, 38.9, 37.4, 35.9, 29.4, 20.1;

HRMS Calculated for $\text{C}_{30}\text{H}_{31}\text{N}_5\text{O}_2$ $[\text{M}+\text{H}]^+$: 494.2551, Found: 494.2549.

14e ((E)-diethyl 2-(2-(1-benzyl-5-phenyl-1H-1,2,3-triazole-4-carboxamido)ethyl)-3-methylstyrylphosphonate) was prepared following the general procedure B and purified

by flash chromatography (Hexane-EtOAc, v/v 1/2) as colorless oil; Isolated yield: 100.0 mg, 90%;

¹H-NMR (400 MHz; CDCl₃): δ 7.85 (dd, *J* = 22.4, 17.2 Hz, 1H), 7.49-7.37 (m, 4H), 7.28-7.25 (m, 6H), 7.17 (dt, *J* = 14.9, 7.3 Hz, 2H), 7.02-6.99 (m, 2H), 6.18 (dd, *J* = 18.8, 17.2 Hz, 1H), 5.41 (s, 2H), 4.15-4.07 (m, 4H), 3.52-3.46 (m, 2H), 3.08-3.05 (m, 2H), 2.38 (s, 3H), 1.32 (t, *J* = 7.1 Hz, 6H);

¹³C-NMR (100 MHz, CDCl₃): δ 160.2, 146.49, 146.42, 139.2, 139.0, 137.6, 136.0, 134.81, 134.77, 134.59, 132.2, 129.96, 129.88, 128.55, 128.36, 126.8, 126.0, 124.64, 124.63, 117.8, 115.9, 61.94, 61.88, 52.0, 38.8, 29.7, 29.4, 20.0, 16.44, 16.38;

HRMS Calculated for C₃₁H₃₅N₄O₄P [M+H]⁺: 559.2469, Found: 559.2468.

14f ((E)-1-benzyl-N-(2-methyl-6-(2-(phenylsulfonyl)vinyl)phenethyl)-5-phenyl-1H-1,2,3-triazole-4-carboxamide) was prepared following the general procedure B and purified by flash chromatography (Hexane-EtOAc, v/v 2/1) as colorless oil; Isolated yield: 94.5 mg, 84%;

¹H-NMR (400 MHz; CDCl₃): δ 8.02 (d, *J* = 15.2 Hz, 1H), 7.94-7.91 (m, 2H), 7.57-7.53 (m, 1H), 7.48-7.40 (m, 5H), 7.35-7.21 (m, 7H), 7.12 (t, *J* = 7.6 Hz, 1H), 7.04-7.01 (m, 2H), 6.78 (d, *J* = 15.1 Hz, 1H), 5.43 (s, 2H), 3.51-3.45 (m, 2H), 3.07 (t, *J* = 7.6 Hz, 2H), 2.37 (s, 3H);

¹³C-NMR (100 MHz, CDCl₃): δ 160.3, 140.61, 140.58, 139.4, 138.8, 137.9, 137.1, 134.7, 133.20, 133.04, 132.0, 130.1, 129.8, 129.5, 129.3, 128.8, 128.45, 128.29, 127.7, 127.4, 126.9, 126.0, 125.2, 52.0, 38.8, 29.5, 20.0;

HRMS Calculated for C₃₃H₃₀N₄O₃S [M+H]⁺: 563.2111, Found: 563.2106

14g ((E)-1-benzyl-N-(2-methyl-6-styrylphenethyl)-5-phenyl-1H-1,2,3-triazole-4-carboxamide) was prepared following the general procedure B and purified by flash chromatography (Hexane-EtOAc, v/v 2/1) as colorless oil; Isolated yield: 85.1 mg, 85%; $^1\text{H-NMR}$ (400 MHz; CDCl_3): δ 7.54 (d, $J = 16.0$ Hz, 1H), 7.50-7.40 (m, 7H), 7.28-7.18 (m, 8H), 7.18-7.10 (m, 3H), 7.00-6.98 (m, 2H), 6.92 (d, $J = 16.0$ Hz, 1H), 5.37 (s, 2H), 3.58-3.53 (m, 2H), 3.09 (t, $J = 8.4$ Hz, 2H), 2.39 (s, 3H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ 160.3, 139.1, 138.9, 137.6, 137.4, 136.8, 134.91, 134.75, 131.1, 130.0, 129.83, 129.81, 128.8, 128.51, 128.40, 128.32, 127.43, 127.32, 126.75, 126.63, 125.9, 124.2, 51.9, 38.7, 29.5, 20.0; **HRMS** Calculated for $\text{C}_{33}\text{H}_{30}\text{N}_4\text{O}$ $[\text{M}+\text{H}]^+$: 499.2492, Found: 499.2489.

14h ((E)-1-benzyl-N-(2-(4-chlorostyryl)-6-methylphenethyl)-5-phenyl-1H-1,2,3-triazole-4-carboxamide) was prepared following the general procedure B and purified by flash chromatography (Hexane-EtOAc, v/v 2/1) as white solid; Isolated yield: 94.4 mg, 89%; $^1\text{H-NMR}$ (400 MHz; CDCl_3): δ 7.60 (d, $J = 16.0$ Hz, 1H), 7.56-7.52 (m, 1H), 7.48-7.40 (m, 6H), 7.31-7.25 (m, 4H), 7.23-7.09 (m, 5H), 7.02-6.99 (m, 2H), 6.85 (d, $J = 16.0$ Hz, 1H), 5.39 (s, 2H), 3.57-3.51 (m, 2H), 3.08 (t, $J = 7.8$ Hz, 2H), 2.39 (s, 3H);

¹³C-NMR (100 MHz, CDCl₃): δ 160.4, 139.2, 138.9, 137.1, 136.8, 136.2, 135.0, 134.7, 132.7, 130.06, 129.96, 129.95, 129.5, 128.8, 128.60, 128.50, 128.40, 127.9, 127.52, 127.50, 126.7, 126.0, 124.0, 52.0, 38.8, 29.6, 20.0;

HRMS Calculated for C₃₃H₂₉ClN₄O [M+H]⁺: 533.2103, Found: 533.2100.

14i ((E)-1-benzyl-N-(2-(4-(tert-butyl)styryl)-6-methylphenethyl)-5-phenyl-1H-1,2,3-triazole-4-carboxamide) was prepared following the general procedure B and purified by flash chromatography (Hexane-EtOAc, v/v 2/1) as colorless oil; Isolated yield: 89.5 mg, 81%;

¹H-NMR (400 MHz; CDCl₃): δ 7.53-7.39 (m, 7H), 7.29-7.20 (m, 7H), 7.17-7.09 (m, 2H), 7.02-6.99 (m, 2H), 6.90 (d, *J* = 16.0 Hz, 1H), 5.38 (s, 2H), 3.57-3.52 (m, 2H), 3.08 (t, *J* = 7.7 Hz, 2H), 2.39 (s, 3H), 1.32 (s, 9H);

¹³C-NMR (100 MHz, CDCl₃): δ 160.3, 150.4, 139.1, 138.9, 137.6, 136.8, 134.84, 134.76, 130.9, 130.1, 129.80, 129.65, 128.8, 128.40, 128.35, 127.4, 126.6, 126.4, 126.0, 125.5, 124.2, 51.9, 38.7, 34.6, 31.3, 29.6, 20.1;

HRMS Calculated for C₃₇H₃₈N₄O [M+H]⁺: 555.3118, Found: 555.3114.

14j ((E)-1-benzyl-N-(2-(4-fluorostyryl)-6-methoxyphenethyl)-5-phenyl-1H-1,2,3-triazole-4-carboxamide) was prepared following the general procedure B and purified

by flash chromatography (Hexane-EtOAc, v/v 2/1) as white solid; Isolated yield: 89.5 mg, 84%;

¹H-NMR (400 MHz; CDCl₃): δ 7.59-7.56 (m, 1H), 7.50-7.46 (m, 1H), 7.44-7.38 (m, 5H), 7.28-7.18 (m, 7H), 6.98 (dd, *J* = 7.3, 2.2 Hz, 2H), 6.91-6.86 (m, 3H), 6.82 (t, *J* = 4.6 Hz, 1H), 5.37 (s, 2H), 3.89 (s, 3H), 3.57 (q, *J* = 6.5 Hz, 2H), 3.11 (t, *J* = 7.0 Hz, 2H);

¹³C-NMR (100 MHz, CDCl₃): δ 163.4, 161.0, 160.4, 157.7, 139.02, 139.00, 138.2, 134.8, 133.73, 133.70, 130.04, 130.00, 129.96, 129.80, 128.8, 128.38, 128.34, 128.19, 128.10, 127.43, 127.36, 126.04, 125.99, 125.97, 125.4, 118.4, 115.5, 115.3, 109.3, 55.6, 51.9, 39.3, 25.5;

HRMS Calculated for C₃₃H₂₉FN₄O₂ [M+H]⁺: 533.2347, Found: 533.2342

15 ((E)-tert-butyl 2-(4-fluorostyryl)-6-methoxyphenethylcarbamate) was prepared according to procedures described in literature: Zhao, Y.; Chen, G. *Org. Lett.* **2011**, *13*, 4850. Isolated yield: 70.0 mg, 90% as white solid;

¹H-NMR (400 MHz; CDCl₃): δ 7.55 (q, *J* = 7.3 Hz, 2H), 7.47 (t, *J* = 13.2 Hz, 1H), 7.25-7.15 (m, 2H), 7.07-7.01 (m, 2H), 6.97-6.88 (m, 1H), 6.84-6.79 (m, 1H), 4.72 (s, 1H), 3.83 (s, 3H), 3.31 (t, *J* = 6.4 Hz, 2H), 3.00 (t, *J* = 7.1 Hz, 2H), 1.40 (s, 9H);

¹³C-NMR (100 MHz, CDCl₃): δ 13-C NMR (101 MHz; c6d6): δ 163.6, 161.1, 157.8, 156.0, 138.1, 133.77, 133.74, 133.5, 129.9, 129.04, 128.96, 128.31, 128.23, 127.3, 126.03, 126.01, 125.7, 125.5, 118.2, 115.6, 115.4, 109.3, 55.5, 40.5, 28.4, 26.3, 22.7;

HRMS Calculated for C₂₂H₂₆FNO₃ [M+Na]⁺: 394.1789, Found: 394.1786.

16 (methyl 2-(2-(1-benzyl-5-phenyl-1H-1,2,3-triazole-4-carbonyl)-5-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)acetate) was prepared following the general procedure **1.5** and purified by flash chromatography (Hexane-EtOAc, v/v 2/1) as colorless oil; Isolated yield: 174.5 mg, 90%;

$^1\text{H-NMR}$ (400 MHz; CDCl_3): δ 7.42-7.36 (m, 2H), 7.34-7.22 (m, 6H), 7.11-7.01 (m, 4H), 6.17-6.13 (m, 0.3), 5.99 (t, $J = 7.2$ Hz, 0.7H), 5.44 (d, $J = 2.0$ Hz, 2H), 4.77-4.71 (m, 0.3), 4.62-4.57 (m, 0.7H), 3.61-3.52 (m, 1.6H), 3.39 (s, 2.1H), 3.20 (ddd, $J = 13.6, 11.3, 5.0$ Hz, 0.3), 3.06-2.98 (m, 1.0H), 2.81-2.69 (m, 2.9H), 2.22-2.19 (s, 3H);

$^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ 170.86, 170.83, 161.0, 140.3, 139.5, 136.70, 136.68, 135.6, 134.93, 134.82, 132.7, 132.5, 130.1, 129.70, 129.65, 128.82, 128.75, 128.53, 128.48, 128.42, 128.36, 128.24, 127.58, 127.46, 126.15, 126.07, 125.99, 124.8, 124.5, 54.3, 52.07, 52.01, 51.72, 51.70, 50.5, 42.4, 41.0, 40.6, 35.9, 27.2, 25.6, 21.0, 19.36, 19.28, 14.2;

HRMS Calculated for $\text{C}_{29}\text{H}_{28}\text{N}_4\text{O}_3$ $[\text{M}+\text{H}]^+$: 481.2234, Found: 481.2236.

13bd was prepared according to procedures described in literature (Zhao, Y.; Chen, G. *Org. Lett.* **2011**, *13*, 4850.) in 1mmol scale; isolated yield: 330.0 mg, 81% as white solid; $^1\text{H-NMR}$ (400 MHz; CDCl_3): δ 7.59-7.57 (m, 1H), 7.46-7.39 (m, 3H), 7.27-7.19 (m, 6H), 7.01-6.99 (m, 2H), 6.88 (t, $J = 7.8$ Hz, 2H), 5.41 (s, 2H), 3.87 (s, 3H), 3.61 (q, $J = 6.2$ Hz, 2H), 2.92 (t, $J = 6.8$ Hz, 2H);

$^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ 160.2, 157.5, 139.17, 139.06, 134.8, 130.6, 129.99, 129.80, 128.8, 128.43, 128.32, 128.29, 127.8, 127.43, 127.38, 126.1, 120.63, 120.52, 110.2, 55.3, 51.9, 39.6, 30.25, 30.19;

HRMS Calculated for $\text{C}_{25}\text{H}_{23}\text{DN}_4\text{O}_2$ $[\text{M}+\text{H}]^+$: 414.2035, Found: 414.2033

Part III. Nickel-catalyzed directed sulfenylation of sp^2 and sp^3 C–H bonds

20a: 1-((phenylthio)methyl)-N-(quinolin-8-yl)cyclohexanecarboxamide was prepared following the general procedure **Condition A** and purified by flash chromatography (Hexane-EtOAc, v/v 20/1) as colorless oil; Isolated yield 86%;

^1H NMR (400 MHz; CDCl_3): δ 10.40 (s, 1H), 8.82 (dd, J = 4.2, 1.7 Hz, 1H), 8.71 (dd, J = 5.8, 3.3 Hz, 1H), 8.15 (dd, J = 8.3, 1.7 Hz, 1H), 7.50-7.44 (m, 3H), 7.32-7.29 (m, 2H), 7.08-7.04 (m, 2H), 7.01-6.97 (m, 1H), 3.32 (s, 2H), 2.35-2.30 (m, 2H), 1.74-1.55 (m, 7H), 1.43-1.37 (m, 1H).

^{13}C NMR (101 MHz; CDCl_3): δ 173.4, 148.2, 138.8, 136.7, 136.2, 134.3, 129.9, 128.6, 127.8, 127.3, 125.9, 121.47, 121.29, 116.4, 49.1, 44.5, 33.8, 25.7, 22.8.

HRMS Calculated for $[\text{C}_{23}\text{H}_{25}\text{N}_2\text{OS}]^+$: 377.1682, Found: 377.1687

20b: 2-ethyl-2-((phenylthio)methyl)-N-(quinolin-8-yl)butanamide was prepared following the general procedure **Condition A** and purified by flash chromatography (Hexane-EtOAc, v/v 20/1) as colorless oil; Isolated yield 74%;

^1H NMR (400 MHz; CDCl_3): δ 10.32 (s, 1H), 8.81 (dd, J = 4.3, 1.7 Hz, 1H), 8.76 (dd, J = 7.0, 2.0 Hz, 1H), 8.15 (dd, J = 8.3, 1.7 Hz, 1H), 7.54-7.40 (m, 6H), 7.21-7.17 (m, 2H), 7.12-7.10 (m, 1H), 3.41 (s, 2H), 2.04-1.89 (m, 4H), 0.93 (t, J = 7.4 Hz, 6H).

^{13}C NMR (101 MHz; CDCl_3): δ 173.8, 148.2, 138.8, 136.9, 136.2, 134.3, 132.4, 130.0, 128.7, 127.9, 127.4, 126.0, 121.5, 121.3, 116.3, 52.0, 38.6, 28.0, 8.6.

HRMS Calculated for $[\text{C}_{22}\text{H}_{25}\text{N}_2\text{OS}]^+$: 365.1682, Found: 365.1684.

20c: 2-ethyl-2-((phenylthio)methyl)-N-(quinolin-8-yl)heptanamide was prepared following the general procedure **Condition A** and purified by flash chromatography (Hexane-EtOAc, v/v 20/1) as colorless oil; Isolated yield 87%;

¹H NMR (400 MHz; CDCl₃): δ 10.33 (s, 1H), 8.81 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.75 (dd, *J* = 7.0, 1.9 Hz, 1H), 8.15 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.52-7.41 (m, 5H), 7.22-7.18 (m, 2H), 7.12 (m, 1H), 3.45-3.38 (ABq, *J* = 12.8 Hz, 2H), 2.05-1.78 (m, 5H), 1.31-1.26 (m, 5H), 0.93 (t, *J* = 7.4 Hz, 3H), 0.85 (t, *J* = 6.9 Hz, 3H).

¹³C NMR (101 MHz; CDCl₃): δ 173.9, 148.2, 138.8, 137.0, 136.2, 134.3, 130.0, 128.7, 127.9, 127.4, 126.0, 121.5, 121.3, 116.3, 51.7, 38.9, 35.3, 28.4, 26.3, 23.1, 13.9, 8.6

HRMS Calculated for [C₂₄H₂₉N₂OS]⁺: 393.1995, Found: 393.2000.

20d: 2-benzyl-2-((phenylthio)methyl)-N-(quinolin-8-yl)butanamide was prepared following the general procedure **Condition A** and purified by flash chromatography (Hexane-EtOAc, v/v 20/1) as colorless oil; Isolated yield 75%;

¹H NMR (400 MHz; CDCl₃): δ 10.27 (s, 1H), 8.75-8.73 (m, 2H), 8.15 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.55-7.49 (m, 2H), 7.45-7.39 (m, 3H), 7.25-7.10 (m, 8H), 3.40-3.21 (m, 4H), 1.97 (q, *J* = 7.4 Hz, 2H), 1.02 (t, *J* = 7.4 Hz, 3H).

¹³C NMR (101 MHz; CDCl₃): δ 172.9, 148.2, 138.7, 136.74, 136.68, 136.2, 130.08, 129.93, 128.8, 128.2, 127.98, 127.87, 127.4, 126.6, 126.0, 121.52, 121.41, 116.4, 53.1, 41.0, 38.6, 28.2, 8.8.

HRMS Calculated for [C₂₇H₂₇N₂OS]⁺: 427.1839, Found: 427.1845.

20e: 2-(cyclopropylmethyl)-2-((phenylthio)methyl)-N-(quinolin-8-yl)butanamide was prepared following the general procedure **Condition A** and purified by flash chromatography (Hexane-EtOAc, v/v 20/1) as colorless oil; Isolated yield 71%;

¹H NMR (400 MHz; CDCl₃): δ 10.34 (s, 1H), 8.81 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.76 (dd, *J* = 7.1, 1.9 Hz, 1H), 8.16 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.53-7.50 (m, 2H), 7.47-7.41 (m, 3H), 7.23-7.19 (m, 2H), 7.12 (d, *J* = 7.4 Hz, 1H), 3.54 (d, *J* = 0.9 Hz, 2H), 2.05 (dt, *J* = 17.2, 7.2 Hz, 2H), 1.86 (dd, *J* = 6.8, 3.4 Hz, 2H), 0.95 (t, *J* = 7.4 Hz, 3H), 0.72-0.68 (m, 1H), 0.41-0.38 (m, 2H), 0.21-0.11 (m, 2H).

¹³C NMR (101 MHz; CDCl₃): δ 173.9, 148.2, 138.8, 137.0, 136.3, 134.3, 129.8, 128.7, 127.9, 127.4, 125.9, 121.5, 121.3, 116.4, 52.4, 40.3, 38.8, 28.3, 8.6, 6.4, 4.4, 4.1

HRMS Calculated for [C₂₄H₂₇N₂OS]⁺: 391.1839, Found: 391.1840.

20f: 2-ethyl-5-phenyl-2-((phenylthio)methyl)-N-(quinolin-8-yl)pentanamide was prepared following the general procedure **Condition A** and purified by flash chromatography (Hexane-EtOAc, v/v 20/1) as colorless oil; Isolated yield 75%;

¹H NMR (400 MHz; CDCl₃): δ 10.29 (s, 1H), 8.79 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.72 (dd, *J* = 6.7, 2.3 Hz, 1H), 8.16 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.52-7.40 (m, 5H), 7.19-7.07 (m, 8H), 3.41 (s, 2H), 2.58 (t, *J* = 7.6 Hz, 2H), 2.00-1.96 (m, 1H), 1.92-1.84 (m, 2H), 1.82-1.74 (m, 1H), 1.65-1.60 (m, 2H), 1.32-1.24 (m, 2H), 0.87 (t, *J* = 7.3 Hz, 3H).

¹³C NMR (101 MHz; CDCl₃): δ 173.8, 148.2, 141.9, 138.8, 136.9, 136.2, 134.3, 130.1, 128.8, 128.34, 128.18, 127.9, 127.4, 126.1, 125.7, 121.53, 121.34, 116.4, 51.5, 39.4, 38.2, 36.1, 35.4, 25.9, 17.5, 14.4

HRMS Calculated for [C₃₀H₃₃N₂OS]⁺: 469.2308, Found: 469.2315.

20g: 2-benzyl-2-((phenylthio)methyl)-N-(quinolin-8-yl)pentanamide was prepared following the general procedure **Condition A** and purified by flash chromatography (Hexane-EtOAc, v/v 20/1) as colorless oil; Isolated yield 88%;

¹H NMR (400 MHz; CDCl₃): δ 10.28 (s, 1H), 8.75-8.72 (m, 2H), 8.14 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.55-7.48 (m, 2H), 7.44-7.39 (m, 3H), 7.25-7.09 (m, 8H), 3.38-3.26 (m, 4H), 1.91-1.82 (m, 2H), 1.46-1.40 (m, 2H), 0.90 (t, *J* = 7.3 Hz, 3H).

¹³C NMR (101 MHz; CDCl₃): δ 173.0, 148.2, 138.7, 136.71, 136.70, 136.2, 134.1, 130.07, 129.91, 128.8, 128.2, 127.9, 127.4, 126.6, 126.0, 121.51, 121.39, 116.4, 52.8, 41.4, 38.9, 37.9, 17.7, 14.3

HRMS Calculated for [C₂₈H₂₉N₂OS]⁺: 441.1995, Found: 441.2001.

20h: 2-((phenylthio)methyl)-2-propyl-N-(quinolin-8-yl)heptanamide was prepared following the general procedure **Condition A** and purified by flash chromatography (Hexane-EtOAc, v/v 20/1) as colorless oil; Isolated yield 72%;

¹H NMR (400 MHz; CDCl₃): δ 10.32 (s, 1H), 8.81 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.74 (dd, *J* = 7.0, 2.0 Hz, 1H), 8.15 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.54-7.41 (m, 3H), 7.23-7.19 (m, 2H), 7.14-7.10 (m, 1H), 3.42 (s, 2H), 1.97-1.89 (m, *J* = 5.7 Hz, 2H), 1.85-1.76 (m, *J* = 5.3 Hz, 2H), 1.36-1.24 (m, 8H), 0.89 (t, *J* = 7.3 Hz, 3H), 0.83-0.80 (m, 3H).

¹³C NMR (101 MHz; CDCl₃): δ 174.1, 148.2, 138.8, 137.0, 136.2, 134.4, 130.0, 128.7, 127.9, 127.4, 126.0, 121.5, 121.3, 116.4, 51.5, 39.3, 38.4, 35.9, 32.2, 23.8, 22.4, 17.5, 14.5, 14.0

HRMS Calculated for [C₂₆H₃₃N₂OS]⁺: 421.2308, Found: 421.2315

20i: 1-((phenylthio)methyl)-N-(quinolin-8-yl)cyclobutanecarboxamide was prepared following the general procedure **Condition A** and purified by flash chromatography (Hexane-EtOAc, v/v 20/1) as colorless oil; Isolated yield 63%;

¹H NMR (400 MHz; CDCl₃): δ 10.19 (s, 1H), 8.82 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.69 (dd, *J* = 5.6, 3.4 Hz, 1H), 8.16 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.50-7.44 (m, 3H), 7.35-7.33 (m, 2H), 7.09-7.05 (m, 2H), 7.02-7.00 (m, 1H), 3.56 (s, 2H), 2.67 (ddd, *J* = 12.7, 9.5, 7.5 Hz, 2H), 2.30-2.23 (m, 2H), 2.04 (ddt, *J* = 19.6, 10.7, 5.1 Hz, 2H).

¹³C NMR (101 MHz; CDCl₃): δ 174.2, 148.2, 138.7, 136.2, 134.2, 130.0, 128.6, 127.8, 127.3, 126.0, 121.49, 121.37, 116.3, 50.3, 42.9, 30.3, 15.1

HRMS Calculated for [C₂₁H₂₁N₂OS]⁺: 349.1369, Found: 349.1373.

20j: 2-methyl-2-phenyl-3-(phenylthio)-N-(quinolin-8-yl)propanamide was prepared following the general procedure **Condition A** and purified by flash chromatography (Hexane-EtOAc, v/v 20/1) as colorless oil; Isolated yield 53%;

¹H NMR (400 MHz; CDCl₃): δ 9.91 (s, 1H), 8.75 (dd, *J* = 7.5, 1.5 Hz, 1H), 8.58 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.08 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.54-7.44 (m, 4H), 7.40-7.29 (m, 6H), 7.20-7.16 (m, 2H), 7.12-7.08 (m, 1H), 3.86-3.71 (ABq, *J* = 12.8 Hz, 2H), 1.97 (s, 3H).

¹³C NMR (101 MHz; CDCl₃): δ 173.8, 148.1, 141.7, 138.6, 137.4, 136.1, 134.4, 129.8, 128.80, 128.71, 127.8, 127.6, 127.2, 126.9, 126.0, 121.47, 121.44, 116.1, 52.9, 44.9, 23.2

HRMS Calculated for [C₂₅H₂₃N₂OS]⁺: 399.1526, Found: 399.1530.

20j-di: **2-phenyl-3-(phenylthio)-2-((phenylthio)methyl)-N-(quinolin-8-yl)propanamide** was prepared following the general procedure **Condition A** and purified by flash chromatography (Hexane-EtOAc, v/v 20/1) as colorless oil; Isolated yield 27%;

¹H NMR (400 MHz; CDCl₃): δ 9.93 (s, 1H), 8.64 (dd, *J* = 7.2, 1.8 Hz, 1H), 8.53 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.06 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.50-7.43 (m, 5H), 7.37-7.31 (m, 3H), 7.30 (s, 4H), 7.08-6.98 (m, 5H), 4.03 (s, 4H).

¹³C NMR (101 MHz; CDCl₃): δ 171.4, 148.0, 139.8, 138.5, 136.2, 135.9, 134.1, 130.5, 129.4, 128.79, 128.59, 128.0, 127.22, 127.18, 126.2, 121.47, 121.37, 116.3, 56.7, 41.7

HRMS Calculated for [C₃₁H₂₇N₂OS₂]⁺: 507.1559, Found: 507.1568.

21a: **1-(((2-fluorophenyl)thio)methyl)-N-(quinolin-8-yl)cyclohexanecarboxamide** was prepared following the general procedure **Condition B** and purified by flash chromatography (Hexane-EtOAc, v/v 20/1) as colorless oil; Isolated yield 80%;

¹H NMR (400 MHz; CDCl₃): δ 10.37 (s, 1H), 8.82 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.66 (t, *J* = 4.5 Hz, 1H), 8.15 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.48-7.44 (m, 3H), 7.34-7.30 (m, 1H), 6.99-6.94 (m, 1H), 6.81-6.76 (m, 2H), 3.30 (s, 2H), 2.34-2.30 (m, 2H), 1.75-1.58 (m, 7H), 1.43-1.38 (m, 1H).

¹³C NMR (101 MHz; CDCl₃): δ 173.2, 161.5 (d, *J* = 244.4 Hz), 148.2, 138.8, 136.1, 134.3, 132.93 (d, *J* = 1.9 Hz), 128.26, 128.18, 127.8, 127.3, 124.08 (d, *J* = 3.7 Hz), 123.24, 121.5, 121.3, 116.4, 115.34 (d, *J* = 22.2 Hz), 49.0, 43.6, 33.7, 25.7, 22.8

HRMS Calculated for [C₂₃H₂₄FN₂OS]⁺: 395.1588, Found: 395.2595.

21b: 1-(((2-chlorophenyl)thio)methyl)-N-(quinolin-8-yl)cyclohexanecarboxamide was prepared following the general procedure **Condition B** and purified by flash chromatography (Hexane-EtOAc, v/v 20/1) as colorless oil; Isolated yield 78%;

¹H NMR (400 MHz; CDCl₃): δ 10.40 (s, 1H), 8.81 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.69 (dd, *J* = 5.4, 3.6 Hz, 1H), 8.13 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.48-7.42 (m, 3H), 7.34 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.10 (dd, *J* = 7.9, 1.4 Hz, 1H), 6.99-6.95 (m, 1H), 6.89 (td, *J* = 7.6, 1.6 Hz, 1H), 3.32 (s, 2H), 2.39-2.34 (m, 2H), 1.78-1.58 (m, 7H), 1.45-1.39 (m, 1H).

¹³C NMR (101 MHz; CDCl₃): δ 173.2, 148.2, 138.8, 136.1, 135.5, 134.39, 134.29, 130.3, 129.3, 127.8, 127.3, 126.80, 126.66, 121.47, 121.35, 116.5, 48.8, 43.12, 33.8, 25.7, 22.8.

HRMS Calculated for [C₂₃H₂₄ClN₂OS]⁺: 411.1292, Found: 411.1297.

21c: **N-(quinolin-8-yl)-1-(((2-(trifluoromethyl)phenyl)thio)methyl)cyclohexanecarbox-amide** was prepared following the general procedure **Condition B** and purified by flash chromatography (Hexane-EtOAc, v/v 20/1) as colorless oil; Isolated yield 42%;

¹H-NMR (400 MHz; CDCl₃): δ 10.40 (s, 1H), 8.80 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.71 (dd, *J* = 5.7, 3.3 Hz, 1H), 8.14 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.55 (d, *J* = 7.9 Hz, 1H), 7.52-7.40 (m, 3H), 7.31-7.28 (m, 1H), 7.10-7.05 (m, 1H), 3.36 (s, 2H), 2.37-2.31 (m, 2H), 1.79-1.57 (m, 7H), 1.43-1.36 (m, 1H).

^{13}C NMR (101 MHz; CDCl_3): δ 173.3, 148.3, 138.8, 136.1, 134.3, 132.3, 131.8, 127.8, 127.3, 126.38 (q, $J = 5.8$ Hz), 125.8, 125.0, 123.7 (q, $J = 272.3$ Hz), 121.51, 121.44, 116.5, 49.0, 45.01, 44.99, 33.6, 25.7, 22.8

HRMS Calculated for $[\text{C}_{24}\text{H}_{24}\text{F}_3\text{N}_2\text{OS}]^+$: 445.1556, Found: 455.1559

21d: 1-(((3-fluorophenyl)thio)methyl)-N-(quinolin-8-yl)cyclohexanecarboxamide was prepared following the general procedure **Condition B** and purified by flash chromatography (Hexane-EtOAc, v/v 20/1) as colorless oil; Isolated yield 75%;

^1H -NMR (400 MHz; CDCl_3): δ 10.38 (s, 1H), 8.82 (dd, $J = 4.2, 1.7$ Hz, 1H), 8.70 (dd, $J = 5.2, 3.8$ Hz, 1H), 8.15 (dd, $J = 8.3, 1.7$ Hz, 1H), 7.49-7.43 (m, 3H), 7.05-6.95 (m, 3H), 6.66-6.61 (m, 1H), 3.31 (s, 2H), 2.34 (dd, $J = 12.9, 4.5$ Hz, 2H), 1.72-1.56 (m, 8H).

^{13}C NMR (101 MHz; CDCl_3): δ 173.1, 163.48 (d, $J = 246.6$ Hz), 148.2, 139.00 (d, $J = 7.6$ Hz), 138.796, 136.2, 134.2, 129.72 (d, $J = 8.5$ Hz), 127.9, 127.3, 124.976 (d, $J = 2.8$ Hz), 121.50, 121.38, 116.39, 116.24 (d, $J = 23.2$ Hz), 112.66 (d, $J = 21.2$ Hz), 49.0, 44.1, 33.9, 25.7, 22.8.

HRMS Calculated for $[\text{C}_{23}\text{H}_{24}\text{FN}_2\text{OS}]^+$: 395.1588, Found: 395.1590.

21e: 1-(((3-chlorophenyl)thio)methyl)-N-(quinolin-8-yl)cyclohexanecarboxamide was prepared following the general procedure **Condition B** and purified by flash chromatography (Hexane-EtOAc, v/v 20/1) as colorless oil; Isolated yield 81%;

^1H -NMR (400 MHz; CDCl_3): δ 10.37 (s, 1H), 8.82 (dd, $J = 4.2, 1.7$ Hz, 1H), 8.68 (t, $J = 4.5$ Hz, 1H), 8.14 (dd, $J = 8.3, 1.6$ Hz, 1H), 7.49-7.43 (m, 3H), 7.24 (t, $J = 1.8$ Hz, 1H),

7.14 (dt, $J = 7.5, 1.5$ Hz, 1H), 6.95-6.87 (m, 2H), 3.31 (s, 2H), 2.38-2.32 (m, 2H), 1.70-1.59 (m, 8H), 1.42-1.38 (m, 1H).

^{13}C NMR (101 MHz; CDCl_3): δ 173.0, 148.3, 138.78, 138.60, 136.2, 134.25, 134.17, 129.46, 129.26, 127.9, 127.7, 127.3, 125.9, 121.49, 121.38, 116.4, 48.9, 44.2, 33.9, 25.7, 22.8

HRMS Calculated for $[\text{C}_{23}\text{H}_{24}\text{ClN}_2\text{OS}]^+$: 411.1292, Found: 411.1203.

21f: **N-(quinolin-8-yl)-1-((3-(trifluoromethyl)phenyl)thio)methyl)cyclohexanecarboxamide** was prepared following the general procedure **Condition B** and purified by flash chromatography (Hexane-EtOAc, v/v 20/1) as colorless oil; Isolated yield 70%;

^1H -NMR (400 MHz; CDCl_3): δ 10.38 (s, 1H), 8.81 (dd, $J = 4.2, 1.7$ Hz, 1H), 8.65 (dd, $J = 5.6, 3.4$ Hz, 1H), 8.14 (dd, $J = 8.3, 1.7$ Hz, 1H), 7.50-7.42 (m, 5H), 7.12 (dt, $J = 17.2, 8.3$ Hz, 2H), 3.34 (s, 2H), 2.37 (dd, $J = 15.4, 7.3$ Hz, 2H), 1.72-1.56 (m, 7H), 1.44-1.36 (m, 1H).

^{13}C NMR (101 MHz; CDCl_3): δ 172.9, 148.2, 138.7, 138.0, 136.2, 134.1, 132.5, 131.0-130.7 (q, $J = 32.1$ Hz), 128.8, 127.8, 127.3, 125.98 (q, $J = 5.8$ Hz), 123.6 (q, $J = 271.6$ Hz), 122.390 (q, $J = 5.8$ Hz), 121.50, 121.41, 116.3, 48.9, 44.1, 33.9, 25.7, 22.8

HRMS Calculated for $[\text{C}_{24}\text{H}_{27}\text{N}_2\text{OS}]^+$: 445.1556, Found: 455.1564.

21g: N-(quinolin-8-yl)-1-((m-tolylthio)methyl)cyclohexanecarboxamide was prepared following the general procedure **Condition B** and purified by flash chromatography (Hexane-EtOAc, v/v 20/1) as colorless oil; Isolated yield 37%;

¹H-NMR (400 MHz; CDCl₃): δ 10.38 (s, 1H), 8.82 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.70 (dd, *J* = 5.7, 3.3 Hz, 1H), 8.15 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.49-7.43 (m, 3H), 7.12-7.08 (m, 2H), 6.94 (t, *J* = 7.6 Hz, 1H), 6.77-6.75 (m, 1H), 3.30 (s, 2H), 2.36-2.32 (m, 3H), 2.07 (s, 3H), 1.73-1.58 (m, 7H), 1.39 (dd, *J* = 5.9, 4.2 Hz, 1H).

¹³C NMR (101 MHz; CDCl₃): δ 173.4, 148.2, 138.8, 138.3, 136.26, 136.17, 134.4, 130.6, 128.4, 127.8, 127.3, 127.0, 126.7, 121.4, 121.2, 116.4, 49.0, 44.6, 33.8, 25.8, 22.9, 21.0

HRMS Calculated for [C₂₄H₂₇N₂OS]⁺: 391.1837, Found: 391.1848.

22a: 2-methyl-6-(phenylthio)-N-(quinolin-8-yl)benzamide was prepared following the general procedure and purified by flash chromatography (Hexane-EtOAc, v/v 20/1) as colorless solid; Isolated yield 89%;

¹H-NMR (400 MHz; CDCl₃): δ 9.94 (s, 1H), 8.96 (dd, *J* = 7.4, 1.6 Hz, 1H), 8.68 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.15 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.61-7.53 (m, 2H), 7.41 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.34-7.31 (m, 2H), 7.25-7.12 (m, 6H), 2.47 (s, 3H).

¹³C NMR (101 MHz; CDCl₃): δ 166.94, 166.94, 148.13, 148.13, 140.11, 140.11, 138.46, 138.46, 136.22, 136.22, 136.13, 136.13, 135.68, 135.68, 134.28, 134.28, 133.00, 133.00, 131.31, 131.31, 130.41, 130.41, 129.65, 129.65, 129.55, 129.55, 129.06, 129.06, 127.92, 127.92, 127.39, 127.39, 127.05, 127.05, 121.93, 121.93, 121.54, 121.54, 116.87, 116.87, 19.59, 19.59.

HRMS Calculated for [C₂₃H₁₉N₂OS]⁺: 371.1213, Found: 371.1217.

22b: 2-(phenylthio)-N-(quinolin-8-yl)-6-(trifluoromethyl)benzamide was prepared following the general procedure and purified by flash chromatography (Hexane-EtOAc, v/v 20/1) as colorless solid; Isolated yield 85%;

¹H-NMR (400 MHz; CDCl₃): δ 10.07 (s, 1H), 8.96 (dd, *J* = 7.1, 1.8 Hz, 1H), 8.73 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.17 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.63-7.57 (m, 3H), 7.46-7.41 (m, 5H), 7.30-7.25 (m, 3H).

¹³C NMR (101 MHz; CDCl₃): δ 164.0, 148.2, 138.4, 137.6, 136.3, 134.8, 134.1, 133.5, 133.0, 129.8, 129.5, 128.32 (q, *J* = 31.2 Hz), 128.28, 128.0, 127.4, 124.6 (q, *J* = 4.7 Hz), 123.4 (q, *J* = 272.4 Hz), 122.3, 121.6, 117.1.

HRMS Calculated for [C₂₃H₁₆F₃N₂OS]⁺: 425.0930, Found: 425.0939

22c: 5-methyl-2-(phenylthio)-N-(quinolin-8-yl)benzamide was prepared following the general procedure and purified by flash chromatography (Hexane-EtOAc, v/v 20/1) as colorless oil; Isolated yield 78%;

¹H-NMR (400 MHz; CDCl₃): δ 10.51 (s, 1H), 8.91 (dd, *J* = 7.3, 1.6 Hz, 1H), 8.74 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.17 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.63-7.62 (m, 1H), 7.59-7.52 (m, 2H), 7.44 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.39-7.36 (m, 2H), 7.27-7.25 (m, 2H), 7.24-7.19 (m, 3H), 2.41 (s, 3H).

¹³C NMR (101 MHz; CDCl₃): δ 166.5, 148.2, 137.34, 137.16, 136.3, 135.4, 134.6, 132.4, 132.11, 132.00, 131.82, 129.27, 129.19, 127.9, 127.42, 127.35, 121.8, 121.6, 116.8, 21.0

HRMS Calculated for [C₂₃H₁₉N₂OS]⁺: 371.1213, Found: 371.1221.

22d: 2-(phenylthio)-N-(quinolin-8-yl)-5-(trifluoromethyl)benzamide was prepared following the general procedure and purified by flash chromatography (Hexane-EtOAc, v/v 20/1) as colorless oil; Isolated yield 65%;

¹H-NMR (400 MHz; CDCl₃): δ 10.55 (s, 1H), 8.93 (dd, *J* = 6.7, 2.3 Hz, 1H), 8.82 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.21 (dd, *J* = 8.3, 1.7 Hz, 1H), 8.00 (t, *J* = 0.7 Hz, 1H), 7.64-7.58 (m, 2H), 7.55-7.47 (m, 4H), 7.41-7.38 (m, 3H), 7.12 (d, *J* = 8.4 Hz, 1H).

¹³C NMR (101 MHz; CDCl₃): δ 165.0, 148.4, 143.9, 138.6, 136.4, 134.96, 134.76, 134.2, 132.0, 129.8, 129.27, 129.23, 128.0, 127.7 (q, *J* = 33.3 Hz), 127.40, 127.3 (q, *J* = 3.5 Hz), 125.0 (q, *J* = 3.5 Hz), 123.7 (q, *J* = 271.0 Hz), 122.3, 121.8, 117.0

HRMS Calculated for [C₂₃H₁₅F₃N₂OSNa]⁺: 447.0749, Found: 447.0749

22e: 3-chloro-2-(phenylthio)-N-(quinolin-8-yl)benzamide was prepared following the general procedure and purified by flash chromatography (Hexane-EtOAc, v/v 20/1) as colorless solid; Isolated yield 81%;

¹H-NMR (400 MHz; CDCl₃): δ 10.25 (s, 1H), 8.80 (dd, *J* = 6.4, 2.6 Hz, 1H), 8.62 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.14 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.64 (ddd, *J* = 13.6, 7.8, 1.4 Hz, 2H), 7.55-7.51 (m, 2H), 7.46 (d, *J* = 7.7 Hz, 1H), 7.43-7.39 (m, 2H), 7.17-7.10 (m, 4H), 7.07-7.03 (m, 1H).

¹³C NMR (101 MHz; CDCl₃): δ 165.8, 148.1, 144.5, 140.8, 138.4, 136.2, 135.7, 134.2, 131.9, 130.3, 129.9, 128.9, 128.7, 127.8, 127.3, 126.2, 122.0, 121.6, 116.8

HRMS Calculated for [C₂₂H₁₆ClN₂OS]⁺: 391.0666, Found: 391.0678.

22f: 3-fluoro-2-(phenylthio)-N-(quinolin-8-yl)benzamide was prepared following the general procedure and purified by flash chromatography (Hexane-EtOAc, v/v 20/1) as colorless solid; Isolated yield 80%;

¹H-NMR (400 MHz; CDCl₃): δ 10.42 (s, 1H), 8.63 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.14 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.62-7.58 (m, 1H), 7.56-7.46 (m, 3H), 7.41 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.27-7.22 (m, 3H), 7.17-7.13 (m, 2H), 7.11-7.07 (m, 1H).

¹³C NMR (101 MHz; CDCl₃): δ 165.2, 162.91 (d, *J* = 248.8 Hz), 148.2, 143.3, 138.5, 136.2, 135.5, 134.3, 130.92 (d, *J* = 9.0 Hz), 129.02 (d, *J* = 23.7 Hz), 127.9, 127.3, 126.5, 124.55 (d, *J* = 3.8 Hz), 122.1, 121.6, 119.50, 119.30, 117.91 (d, *J* = 23.9 Hz), 116.8

HRMS Calculated for [C₂₂H₁₆FN₂OS]⁺: 375.0962, Found: 375.0969.

22g: 2,4-dimethyl-6-(phenylthio)-N-(quinolin-8-yl)benzamide was prepared following the general procedure and purified by flash chromatography (Hexane-EtOAc, v/v 20/1) as colorless solid; Isolated yield 91%;

¹H-NMR (400 MHz; CDCl₃): δ 9.91 (s, 1H), 8.94 (dd, *J* = 7.4, 1.6 Hz, 1H), 8.66 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.15 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.60-7.52 (m, 2H), 7.41 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.32-7.30 (m, 2H), 7.21-7.15 (m, 2H), 7.15-7.11 (m, 1H), 7.07-7.03 (m, 2H), 2.43 (s, 3H), 2.29 (s, 3H).

¹³C NMR (101 MHz; CDCl₃): δ 167.2, 148.1, 139.7, 138.5, 137.9, 136.19, 136.11, 136.03, 134.4, 132.3, 131.2, 130.9, 130.7, 129.0, 127.9, 127.4, 126.8, 121.8, 121.5, 116.8, 21.1, 19.5

HRMS Calculated for [C₂₄H₂₁N₂OS]⁺: 385.1369, Found: 385.1376.

22h: 2-(phenylthio)-N-(quinolin-8-yl)-1-naphthamide was prepared following the general procedure and purified by flash chromatography (Hexane-EtOAc, v/v 20/1) as colorless solid; Isolated yield 90%;

¹H-NMR (400 MHz; CDCl₃): δ 10.21 (s, 1H), 9.11 (dd, *J* = 7.5, 1.4 Hz, 1H), 8.63 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.16 (dd, *J* = 8.3, 1.6 Hz, 1H), 8.06-8.04 (m, 1H), 7.86-7.81 (m, 2H), 7.66-7.56 (m, 3H), 7.53-7.49 (m, 2H), 7.42-7.38 (m, 4H), 7.27-7.18 (m, 4H).

¹³C NMR (101 MHz; CDCl₃): δ 166.5, 148.2, 138.5, 137.5, 136.2, 134.4, 132.4, 131.5, 130.78, 130.63, 130.0, 129.34, 129.15, 128.08, 127.97, 127.7, 127.44, 127.24, 126.8, 125.3, 122.1, 121.6, 117.0.

HRMS Calculated for [C₂₆H₁₉N₂OS]⁺: 407.1212, Found: 407.1190.

22i: 3-(phenylthio)-N-(quinolin-8-yl)thiophene-2-carboxamide was prepared following the general procedure and purified by flash chromatography (Hexane-EtOAc, v/v 20/1) as colorless oil; Isolated yield 72%;

¹H-NMR (400 MHz; CDCl₃): δ 11.71 (s, 1H), 8.89 (dd, *J* = 7.3, 1.7 Hz, 1H), 8.74 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.14 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.55-7.49 (m, 3H), 7.45-7.40 (m, 3H), 7.32-7.24 (m, 3H), 6.98 (d, *J* = 5.2 Hz, 1H).

¹³C NMR (101 MHz; CDCl₃): δ 159.8, 148.3, 139.0, 138.3, 136.1, 135.1, 134.9, 133.4, 131.8, 130.3, 129.44, 129.27, 128.0, 127.35, 127.33, 121.9, 121.5, 117.3

HRMS Calculated for [C₂₀H₁₅N₂OS₂]⁺: 363.0620, Found: 363.0627

22j: 2-(phenylthio)-N-(quinolin-8-yl)cyclohex-1-enecarboxamide was prepared following the general procedure and purified by flash chromatography (Hexane-EtOAc, v/v 20/1) as colorless oil; Isolated yield 82%;

¹H-NMR (400 MHz; CDCl₃): δ 10.24 (s, 1H), 8.87 (dd, *J* = 7.5, 1.5 Hz, 1H), 8.72 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.14 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.53-7.47 (m, 4H), 7.44-7.40 (m, 1H), 7.35-7.27 (m, 3H), 2.66 (tt, *J* = 6.1, 2.3 Hz, 2H), 2.21 (tt, *J* = 6.1, 2.3 Hz, 2H), 1.80-1.68 (m, 4H).

¹³C NMR (101 MHz; CDCl₃): δ 167.8, 148.0, 136.9, 136.6, 136.3, 134.6, 133.7, 132.7, 131.5, 129.4, 128.9, 127.9, 127.5, 121.49, 121.41, 116.6, 77.3, 77.0, 76.7, 31.3, 28.4, 23.3, 21.9

HRMS Calculated for [C₂₂H₂₁N₂OS]⁺: 361.1369, Found: 361.1371.

22k: 3-chloro-2,6-bis(phenylthio)-N-(quinolin-8-yl)benzamide was prepared following the general procedure with 4 equiv. PhSH, 7 equiv. LiOtBU, and 15 mol% NiCl₂(DME) and purified by flash chromatography (Hexane-EtOAc, v/v 20/1) as colorless oil; Isolated yield 77%;

¹H-NMR (400 MHz; CDCl₃): δ 9.97 (s, 1H), 8.98 (dd, *J* = 7.2, 1.7 Hz, 1H), 8.68 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.20 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.65-7.58 (m, 2H), 7.52-7.45 (m, 4H), 7.38-7.28 (m, 5H), 7.23-7.20 (m, 2H), 7.16-7.12 (m, 1H).

¹³C NMR (101 MHz; CDCl₃): δ 164.4, 148.0, 145.7, 139.3, 138.3, 136.1, 135.4, 134.7, 134.0, 133.6, 133.3, 132.8, 131.4, 130.4, 129.5, 128.92, 128.87, 128.2, 127.8, 127.4, 126.4, 122.1, 121.5, 117.0

HRMS Calculated for [C₂₈H₁₉ClN₂OS₂Na]⁺: 521.0520, Found: 521.0527.

22l: **2,6-bis(phenylthio)-N-(quinolin-8-yl)-3-(trifluoromethyl)benzamide** was prepared following the general procedure with 4 equiv. PhSH, 7 equiv. LiOtBU, and 15 mol% NiCl₂(DME) and purified by flash chromatography (Hexane-EtOAc, v/v 20/1) as colorless oil; Isolated yield 72%;

¹H-NMR (400 MHz; CDCl₃): δ 9.80 (s, 1H), 8.83 (dd, *J* = 6.8, 2.2 Hz, 1H), 8.62 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.12 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.64 (d, *J* = 8.6 Hz, 1H), 7.56-7.49 (m, 4H), 7.41-7.34 (m, 4H), 7.10 (dd, *J* = 8.5, 0.6 Hz, 1H), 7.06-7.03 (m, 2H), 7.00-6.95 (m, 2H).

¹³C NMR (101 MHz; CDCl₃): δ 163.8, 148.0, 144.3, 143.5, 138.3, 136.7, 136.1, 134.7, 134.0, 131.6 (q, *J* = 30.0 Hz), 131.2, 130.03 (q, *J* = 1.6 Hz), 129.9, 129.33, 129.16, 128.8, 128.5, 127.83 (q, *J* = 5.5 Hz), 127.77, 127.3, 126.1, 123.3 (q, *J* = 271.0 Hz), 122.1, 121.5, 116.9

HRMS Calculated for [C₂₉H₂₀F₃N₂OS₂]⁺: 533.0964, Found: 533.0969.

22m: **2,6-bis(phenylthio)-N-(quinolin-8-yl)benzamide** was prepared following the general procedure with 4 equiv. PhSH, 7 equiv. LiOtBU, and 15 mol% NiCl₂(DME) and purified by flash chromatography (Hexane-EtOAc, v/v 20/1) as colorless oil; Isolated yield 83%;

¹H-NMR (400 MHz; CDCl₃): δ 10.05 (s, 1H), 8.97 (dd, *J* = 7.4, 1.4 Hz, 1H), 8.69 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.15 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.60-7.53 (m, 2H), 7.43-7.40 (m, 5H), 7.27-7.12 (m, 9H).

¹³C NMR (101 MHz; CDCl₃): δ 165.2, 148.1, 138.5, 136.2, 135.7, 134.38, 134.23, 132.5, 130.16, 130.08, 129.3, 127.91, 127.75, 127.5, 122.0, 121.5, 117.0.

HRMS Calculated for $[C_{28}H_{21}N_2OS_2]^+$: 465.1098, Found: 465.1090.

22n: 2,6-bis(phenylthio)-N-(quinolin-8-yl)-4-(trifluoromethyl)benzamide was prepared following the general procedure with 4 equiv. PhSH, 7 equiv. LiOtBU, and 15 mol% NiCl₂(DME) and purified by flash chromatography (Hexane-EtOAc, v/v 20/1) as yellow solid; Isolated yield 81%;

¹H-NMR (400 MHz; CDCl₃): δ 10.12 (s, 1H), 8.96 (dd, *J* = 7.0, 2.0 Hz, 1H), 8.74 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.18 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.62-7.56 (m, 2H), 7.47-7.43 (m, 5H), 7.33-7.28 (m, 6H), 7.26-7.22 (m, 3H).

¹³C NMR (101 MHz; CDCl₃): δ 164.0, 148.6, 148.2, 138.5, 138.0, 136.6, 136.3, 136.2, 133.9, 133.3, 132.5, 131.1, 129.66, 129.51, 128.7, 128.02-127.98(q, *J* = 4.4 Hz), 127.9, 127.4, 125.1(q, *J* = 3.7 Hz), 123.1(q, *J* = 265.6 Hz), 122.4, 121.7, 121.60-121.23 (q, *J* = 37.3 Hz), 117.2

HRMS Calculated for $[C_{29}H_{20}F_3N_2OS_2]^+$: 533.0963, Found: 533.0977.

22o: 4-methoxy-2,6-bis(phenylthio)-N-(quinolin-8-yl)benzamide was prepared following the general procedure with 4 equiv. PhSH, 7 equiv. LiOtBU, and 15 mol% NiCl₂(DME) and purified by flash chromatography (Hexane-EtOAc, v/v 20/1) as yellow solid; Isolated yield 77%;

¹H-NMR (400 MHz; CDCl₃): δ 10.07 (s, 1H), 8.95 (dd, *J* = 7.4, 1.5 Hz, 1H), 8.69 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.14 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.59-7.51 (m, 2H), 7.45-7.39 (m, 5H), 7.29-7.20 (m, 6H), 6.60 (s, 2H), 3.59 (s, 3H).

^{13}C NMR (101 MHz; CDCl_3): δ 165.2, 160.1, 148.0, 138.5, 137.3, 136.2, 134.3, 133.9, 132.8, 132.3, 129.3, 127.93, 127.88, 127.4, 121.8, 121.5, 116.9, 115.1, 55.3

HRMS Calculated for $[\text{C}_{29}\text{H}_{23}\text{N}_2\text{O}_2\text{S}_2]^+$: 495.1196, Found: 495.1203.

23a: 2-methyl-N-(quinolin-8-yl)-6-(o-tolylthio)benzamide was prepared following the general procedure and purified by flash chromatography (Hexane-EtOAc, v/v 20/1) as yellow solid; Isolated yield 86%;

^1H -NMR (400 MHz; CDCl_3): δ 9.98 (s, 1H), 8.98 (dd, $J = 7.4, 1.6$ Hz, 1H), 8.70 (dd, $J = 4.2, 1.7$ Hz, 1H), 8.16 (dd, $J = 8.3, 1.6$ Hz, 1H), 7.62-7.54 (m, 2H), 7.43 (dd, $J = 8.3, 4.2$ Hz, 1H), 7.35-7.33 (m, 1H), 7.20-7.10 (m, 5H), 6.94 (dd, $J = 7.7, 0.6$ Hz, 1H), 2.47 (s, 3H), 2.29 (s, 3H).

^{13}C NMR (101 MHz; CDCl_3): δ 19.59, 20.60, 116.88, 121.55, 121.91, 126.73, 127.42, 127.91, 128.29, 128.72, 129.58, 130.48, 133.35, 133.63, 133.76, 134.36, 136.10, 136.24, 138.51, 138.83, 140.12, 148.14, 166.95, 20.6, 19.6

HRMS Calculated for $[\text{C}_{24}\text{H}_{21}\text{N}_2\text{OS}]^+$: 385.1369, Found: 385.1373.

23b: 2-((2-fluorophenyl)thio)-6-methyl-N-(quinolin-8-yl)benzamide was prepared following the general procedure and purified by flash chromatography (Hexane-EtOAc, v/v 20/1) as colorless oil; Isolated yield 84%;

¹H-NMR (400 MHz; CDCl₃): δ 9.98 (s, 1H), 8.96 (dd, *J* = 7.4, 1.6 Hz, 1H), 8.69 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.15 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.61-7.53 (m, 2H), 7.41 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.32-7.25 (m, 2H), 7.22-7.13 (m, 3H), 7.02-6.93 (m, 2H), 2.47 (s, 3H).

¹³C NMR (101 MHz; CDCl₃): δ 166.7, 161.15 (d, *J* = 246.3 Hz) 148.1, 140.2, 138.5, 136.2, 134.3, 133.74, 133.73, 131.5, 130.2, 129.84, 129.71, 129.33, 129.25, 127.9, 127.4, 124.635(d, *J* = 3.8 Hz), 122.0, 121.6, 116.9, 115.78(d, *J* = 22.0 Hz), 19.6

HRMS Calculated for [C₂₃H₁₈FN₂OS]⁺: 389.1118, Found: 389.1122.

23c: 2-methyl-N-(quinolin-8-yl)-6-((2-(trifluoromethyl)phenyl)thio)benzamide was prepared following the general procedure at 120 °C and purified by flash chromatography (Hexane-EtOAc, v/v 20/1) as colorless oil; Isolated yield 73%;

¹H-NMR (400 MHz; CDCl₃): δ 9.90 (s, 1H), 8.91 (dd, *J* = 7.1, 1.9 Hz, 1H), 8.66 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.15 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.59-7.51 (m, 3H), 7.43-7.34 (m, 3H), 7.32 (s, 3H), 7.21-7.18 (m, 1H), 2.49 (s, 3H).

¹³C NMR (101 MHz; CDCl₃): δ 166.6, 148.1, 141.8, 138.5, 136.5, 136.3, 134.1, 132.8, 132.5, 132.2, 131.0, 130.8, 130.0, 127.9, 127.4, 126.4 (q, *J* = 3.7 Hz), 126.21, 123.6(q, *J* = 273.6 Hz), 122.0, 121.5, 117.0, 19.6

HRMS Calculated for [C₂₄H₁₈F₃N₂OS]⁺: 439.1086, Found: 439.1093.

23d: 2-methyl-N-(quinolin-8-yl)-6-(m-tolylthio)benzamide was prepared following the general procedure and purified by flash chromatography (Hexane-EtOAc, v/v 20/1) as colorless oil; Isolated yield 88%;

¹H-NMR (400 MHz; CDCl₃): δ 9.91 (s, 1H), 8.97 (dd, *J* = 7.4, 1.5 Hz, 1H), 8.68 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.16 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.62-7.53 (m, 2H), 7.42 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.24-7.18 (m, 2H), 7.15-7.14 (m, 2H), 7.08 (dd, *J* = 9.9, 5.7 Hz, 1H), 6.94 (d, *J* = 7.2 Hz, 1H), 2.47 (s, 3H), 2.17 (s, 3H).

¹³C NMR (101 MHz; CDCl₃): δ 167.0, 148.1, 138.9, 138.5, 136.26, 136.08, 135.2, 134.3, 133.4, 132.2, 130.3, 129.58, 129.40, 128.9, 128.7, 128.0, 127.4, 121.9, 121.5, 116.9, 21.2, 19.6

HRMS Calculated for [C₂₄H₂₁N₂OS]⁺: 385.1369, Found: 385.1370.

23e: 2-((3-fluorophenyl)thio)-6-methyl-N-(quinolin-8-yl)benzamide was prepared following the general procedure and purified by flash chromatography (Hexane-EtOAc, v/v 20/1) as colorless oil; Isolated yield 84%;

¹H-NMR (400 MHz; CDCl₃): δ 9.87 (s, 1H), 8.93 (dd, *J* = 7.3, 1.6 Hz, 1H), 8.65 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.15 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.60-7.53 (m, 2H), 7.42 (t, *J* = 4.1 Hz, 1H), 7.31-7.28 (m, 3H), 7.12-7.08 (m, 1H), 7.01 (dt, *J* = 7.8, 1.3 Hz, 1H), 6.94 (dt, *J* = 9.3, 2.1 Hz, 1H), 6.76 (tdd, *J* = 8.3, 2.5, 0.9 Hz, 1H), 2.48 (s, 3H).

¹³C NMR (101 MHz; CDCl₃): δ 166.7, 162.87 (d, *J* = 246.8 Hz), 148.1, 141.4, 139.1, 138.4, 136.5, 136.2, 134.2, 132.0, 130.78, 130.66, 130.11 (d, *J* = 8.3 Hz), 129.88, 127.9, 127.37, 127.34, 125.465 (d, *J* = 3.0 Hz), 122.0, 121.6, 116.8, 116.6, 113.504 (d, *J* = 21.2 Hz), 19.6

HRMS Calculated for [C₂₃H₁₈FN₂OS]⁺: 389.1118, Found: 389.1112.

23f: 2-methyl-N-(quinolin-8-yl)-6-((3-(trifluoromethyl)phenyl)thio)benzamide was prepared following the general procedure at 120 °C and purified by flash chromatography (Hexane-EtOAc, v/v 20/1) as colorless oil; Isolated yield 75%;

¹H-NMR (400 MHz; CDCl₃): δ 9.80 (s, 1H), 8.90 (dd, *J* = 7.2, 1.8 Hz, 1H), 8.57 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.14 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.59-7.52 (m, 2H), 7.44-7.34 (m, 5H), 7.26-7.22 (m, 2H), 2.50 (s, 3H).

¹³C NMR (101 MHz; CDCl₃): δ 166.6, 148.1, 142.6, 142.3, 138.2, 136.9, 136.2, 134.0, 133.1, 131.4, 130.1, 129.2, 128.4, 127.87, 127.78, 127.34, 127.31, 126.6, 125.70 (q, *J* = 3.7 Hz), 124.0 (q, *J* = 270.2 Hz), 122.1, 116.8, 19.6

HRMS Calculated for [C₂₄H₁₈F₃N₂OS]⁺: 439.1086, Found: 439.1091.

23g: 2-((3-methoxyphenyl)thio)-6-methyl-N-(quinolin-8-yl)benzamide was prepared following the general procedure and purified by flash chromatography (Hexane-EtOAc, v/v 20/1) as colorless oil; Isolated yield 80%;

¹H-NMR (400 MHz; CDCl₃): δ 9.90 (s, 1H), 8.97 (dd, *J* = 7.4, 1.6 Hz, 1H), 8.66 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.15 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.61-7.53 (m, 2H), 7.41 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.28-7.26 (m, 2H), 7.21 (td, *J* = 4.4, 0.9 Hz, 1H), 7.10 (t, *J* = 8.0 Hz, 1H), 6.90 (ddd, *J* = 7.7, 1.7, 0.9 Hz, 1H), 6.84 (dd, *J* = 2.4, 1.7 Hz, 1H), 6.65 (ddd, *J* = 8.3, 2.5, 0.9 Hz, 1H), 3.63 (s, 3H), 2.47 (s, 3H).

^{13}C NMR (101 MHz; CDCl_3): δ 166.9, 159.9, 148.1, 140.4, 138.4, 137.0, 136.20, 136.18, 134.3, 132.5, 130.8, 129.81, 129.79, 129.65, 127.9, 127.4, 123.3, 121.9, 121.5, 116.8, 116.0, 113.1, 55.1, 19.6

HRMS Calculated for $[\text{C}_{24}\text{H}_{21}\text{N}_2\text{O}_2\text{S}]^+$: 401.1318, Found: 401.1320.

23h: 2-((3-chlorophenyl)thio)-6-methyl-N-(quinolin-8-yl)benzamide was prepared following the general procedure and purified by flash chromatography (Hexane-EtOAc, v/v 20/1) as colorless oil; Isolated yield 72%;

^1H -NMR (400 MHz; CDCl_3): δ 9.85 (s, 1H), 8.92 (dd, $J = 7.4, 1.6$ Hz, 1H), 8.65 (dd, $J = 4.2, 1.7$ Hz, 1H), 8.13 (dd, $J = 8.3, 1.7$ Hz, 1H), 7.59-7.51 (m, 2H), 7.40 (dd, $J = 8.3, 4.2$ Hz, 1H), 7.32-7.24 (m, 3H), 7.21 (q, $J = 1.2$ Hz, 1H), 7.13-7.09 (m, 1H), 7.06-7.01 (m, 2H), 2.52-2.42 (m, 3H).

^{13}C NMR (101 MHz; CDCl_3): δ 166.7, 148.1, 141.3, 138.6, 138.4, 136.5, 136.2, 134.7, 134.1, 131.9, 130.9, 130.6, 129.90, 129.88, 129.7, 128.2, 127.9, 127.4, 126.7, 122.0, 121.6, 116.8, 19.6

HRMS Calculated for $[\text{C}_{23}\text{H}_{18}\text{ClN}_2\text{OS}]^+$: 405.0823, Found: 405.0828.

23i: 2-methyl-N-(quinolin-8-yl)-6-(p-tolylthio)benzamide was prepared following the general procedure and purified by flash chromatography (Hexane-EtOAc, v/v 20/1) as colorless oil; Isolated yield 90%;

¹H-NMR (400 MHz; CDCl₃): δ 9.94 (s, 1H), 8.98 (dd, *J* = 7.4, 1.5 Hz, 1H), 8.70 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.15 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.61-7.53 (m, 2H), 7.42 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.29-7.19 (m, 3H), 7.15-7.11 (m, 2H), 7.02-7.00 (m, 2H), 2.46 (s, 3H), 2.24 (s, 3H).

¹³C NMR (101 MHz; CDCl₃): δ 167.0, 148.1, 139.2, 138.5, 137.5, 136.2, 135.9, 134.34, 134.32, 132.4, 131.4, 129.9, 129.5, 129.3, 129.0, 127.9, 127.4, 121.9, 121.5, 116.9, 21.0, 19.6

HRMS Calculated for [C₂₄H₂₁N₂OS]⁺: 385.1369, Found: 385.1373.

23j: 2-((4-bromophenyl)thio)-6-methyl-N-(quinolin-8-yl)benzamide was prepared following the general procedure and purified by flash chromatography (Hexane-EtOAc, v/v 20/1) as colorless oil; Isolated yield 83%;

¹H-NMR (400 MHz; CDCl₃): δ 8.94 (dd, *J* = 7.3, 1.7 Hz, 1H), 8.65 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.14 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.58-7.54 (m, 2H), 7.42 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.30-7.29 (m, 2H), 7.26-7.23 (m, 3H), 7.12-7.10 (m, 2H), 2.47 (s, 3H).

¹³C NMR (101 MHz; CDCl₃): δ 166.7, 148.2, 141.0, 138.3, 136.5, 136.2, 135.6, 134.1, 132.04, 131.92, 131.53, 131.45, 130.4, 129.8, 127.9, 127.3, 122.0, 121.6, 120.8, 116.7, 19.6

HRMS Calculated for [C₂₃H₁₈BrN₂OS]⁺: 449.0318, Found: 449.0322.

23k: 2-methyl-N-(quinolin-8-yl)-6-((4-(trifluoromethyl)phenyl)thio)benzamide was prepared following the general procedure at 120 °C and purified by flash chromatography (Hexane-EtOAc, v/v 20/1) as colorless oil; Isolated yield 65%;

¹H-NMR (400 MHz; CDCl₃): δ 9.86 (s, 1H), 8.92 (dd, *J* = 7.2, 1.7 Hz, 1H), 8.62 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.15 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.58-7.55 (m, 2H), 7.49 (s, 1H), 7.41 (dd, *J* = 8.3, 4.1 Hz, 2H), 7.28-7.26 (m, 5H), 2.49 (s, 3H).

¹³C NMR (101 MHz; CDCl₃): δ 166.6, 148.1, 141.4, 138.35, 138.24, 136.7, 136.3, 134.1, 133.16, 133.15, 131.9, 131.3 (q, *J* = 31.7 Hz), 130.8, 130.6, 130.0, 129.4, 127.9, 127.4, 126.4 (q, *J* = 3.9 Hz), 123.3 (q, *J* = 3.9 Hz), 122.9-121.8 (q, *J* = 113 Hz), 122.1, 121.6, 116.8, 19.6

HRMS Calculated for [C₂₄H₁₈F₃N₂OS]⁺: 439.1086, Found: 439.1093.

23l: 2-((4-methoxyphenyl)thio)-6-methyl-N-(quinolin-8-yl)benzamide was prepared following the general procedure and purified by flash chromatography (Hexane-EtOAc, v/v 20/1) as colorless oil; Isolated yield 85%;

¹H-NMR (400 MHz; CDCl₃): δ 9.97 (s, 1H), 9.01 (dd, *J* = 7.5, 1.5 Hz, 1H), 8.72 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.16 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.62-7.54 (m, 2H), 7.44-7.37 (m, 3H),

7.18 (t, $J = 7.7$ Hz, 1H), 7.10 (d, $J = 7.6$ Hz, 1H), 7.01 (t, $J = 8.5$ Hz, 1H), 6.78-6.76 (m, 2H), 3.72 (s, 3H), 2.45 (s, 3H).

^{13}C NMR (101 MHz; CDCl_3): δ 167.0, 159.7, 148.2, 138.5, 138.2, 136.2, 135.8, 135.2, 134.3, 129.4, 128.4, 128.0, 127.4, 126.6, 124.6, 121.9, 121.6, 116.9, 114.8, 114.3, 55.2, 19.5

HRMS Calculated for $[\text{C}_{24}\text{H}_{21}\text{N}_2\text{O}_2\text{S}]^+$: 401.1318, Found: 401.1323.

23m: 2-methyl-6-(phenylselanyl)-N-(quinolin-8-yl)benzamide was prepared following the general procedure with 1.5 equiv. diphenylselenium and purified by flash chromatography (Hexane-EtOAc, v/v 20/1) as colorless oil; Isolated yield 81%;

^1H -NMR (400 MHz; CDCl_3): δ 9.93 (s, 1H), 8.98 (dd, $J = 7.4, 1.5$ Hz, 1H), 8.69 (dd, $J = 4.2, 1.7$ Hz, 1H), 8.17 (dd, $J = 8.3, 1.6$ Hz, 1H), 7.63-7.54 (m, 2H), 7.50-7.48 (m, 2H), 7.43 (dd, $J = 8.3, 4.2$ Hz, 1H), 7.29 (t, $J = 4.5$ Hz, 1H), 7.20-7.17 (m, 5H), 2.49 (s, 3H).

^{13}C NMR (101 MHz; CDCl_3): δ 167.5, 148.2, 140.6, 138.5, 136.3, 135.9, 134.3, 133.9, 131.6, 130.9, 129.8, 129.58, 129.46, 129.2, 128.0, 127.56, 127.43, 122.0, 121.6, 116.9, 19.9

HRMS Calculated for $[\text{C}_{23}\text{H}_{19}\text{N}_2\text{OSe}]^+$: 419.0657, Found: 419.0655.

23n: 2-(ethylthio)-6-methyl-N-(quinolin-8-yl)benzamide was prepared following the general procedure with 1.5 equiv. disulfide and purified by flash chromatography (Hexane-EtOAc, v/v 20/1) as colorless oil; Isolated yield 70%;

¹H-NMR (400 MHz; CDCl₃): δ 9.95 (s, 1H), 9.01 (dd, *J* = 7.5, 1.5 Hz, 1H), 8.74 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.18 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.63-7.55 (m, 2H), 7.44 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.35-7.31 (m, 2H), 7.15 (dt, *J* = 7.3, 0.7 Hz, 1H), 2.94 (q, *J* = 7.4 Hz, 2H), 2.44 (s, 3H), 1.26 (t, *J* = 7.4 Hz, 4H).

¹³C NMR (101 MHz; CDCl₃): δ 167.4, 148.2, 140.0, 138.6, 136.3, 135.8, 134.5, 133.3, 129.3, 128.6, 128.3, 128.0, 127.5, 121.9, 121.6, 116.9, 29.1, 19.5, 14.3

HRMS Calculated for [C₁₉H₁₉N₂OS]⁺: 323.1213, Found: 323.1216.

23o: 2-methyl-6-(propylthio)-N-(quinolin-8-yl)benzamide was prepared following the general procedure with 1.5 equiv. disulfide and purified by flash chromatography (Hexane-EtOAc, v/v 20/1) as colorless oil; Isolated yield 72%;

¹H-NMR (400 MHz; CDCl₃): δ 9.94-9.94 (m, 1H), 9.01 (dd, *J* = 7.5, 1.5 Hz, 1H), 8.74 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.18 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.64-7.55 (m, 2H), 7.44 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.35-7.29 (m, 2H), 7.14 (ddd, *J* = 7.4, 1.3, 0.7 Hz, 1H), 2.88 (t, *J* = 7.3 Hz, 2H), 2.43 (s, 3H), 1.66-1.57 (m, 2H), 0.93 (t, *J* = 7.3 Hz, 3H).

¹³C NMR (101 MHz; CDCl₃): δ 162.0, 148.2, 140.0, 139.5, 136.3, 135.8, 134.5, 133.6, 129.3, 128.51, 128.41, 128.0, 127.5, 121.9, 121.6, 116.9, 37.2, 22.6, 19.5, 13.4

HRMS Calculated for [C₂₀H₂₁N₂OS]⁺: 337.1369, Found: 323.1371.

23p: 2-(butylthio)-6-methyl-N-(quinolin-8-yl)benzamide was prepared following the general procedure with 1.5 equiv. disulfide and purified by flash chromatography (Hexane-EtOAc, v/v 20/1) as colorless oil; Isolated yield 73%;

¹H-NMR (400 MHz; CDCl₃): δ 9.95 (s, 1H), 9.01 (dd, *J* = 7.5, 1.4 Hz, 1H), 8.73 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.17 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.63-7.54 (m, 2H), 7.43 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.30 (dt, *J* = 14.8, 7.4 Hz, 2H), 7.14 (dd, *J* = 7.4, 0.5 Hz, 1H), 2.91 (t, *J* = 7.5 Hz, 2H), 2.43 (s, 3H), 1.61-1.53 (m, 2H), 1.37 (dt, *J* = 15.0, 7.4 Hz, 2H), 0.83 (t, *J* = 7.4 Hz, 3H).

¹³C NMR (101 MHz; CDCl₃): δ 167.4, 148.2, 139.9, 138.5, 136.3, 135.7, 134.5, 133.8, 129.3, 128.4, 128.2, 128.0, 127.5, 121.9, 121.6, 116.8, 34.8, 31.2, 21.9, 19.5, 13.6

HRMS Calculated for [C₂₀H₂₁N₂OS]⁺: 351.1526, Found: 351.1530.

Figure 2. ORTEP Drawing of the X-ray Crystal Structure **22a** ($\text{C}_{23}\text{H}_{18}\text{N}_2\text{OS}$)
CCDC Number: 1052404

Figure 3. ORTEP Drawing of the X-ray Crystal Structure **22e** ($\text{C}_{22}\text{H}_{15}\text{N}_2\text{ClSO}$)
CCDC Number: 1052405

Part VI

^1H NMR, ^{13}C NMR

Part I

**1,2,3-Triazoles as versatile directing group for selective sp^2 and sp^3 C–H
activation: cyclization vs substitution**

¹H 600MHz NMR 2a

¹H 600MHz NMR 3a

^{13}C 150MHz NMR 3a

¹H 600MHz NMR 4a'

¹³C 150MHz NMR 4a'

¹H 600MHz NMR 4a

¹³C 150MHz NMR 4a

¹H 600MHz NMR 4b'

¹H 600MHz NMR 4b

¹³C 150MHz NMR 4b

¹H 600MHz NMR 4c'

^{13}C 150MHz NMR 4c'

¹H 600MHz NMR 4c

¹³C 150MHz NMR 4c

¹H 600MHz NMR 4d'

^{13}C 150MHz NMR 4d'

¹H 600MHz NMR 4d

^{13}C 150MHz NMR 4d

¹H 600MHz NMR 4e'

¹³C 150MHz NMR 4e'

¹H 600MHz NMR 4e

¹³C 150MHz NMR 4e

¹H 600MHz NMR 4f'

^{13}C 150MHz NMR 4f'

¹H 600MHz NMR 4f

^{13}C 150MHz NMR 4f

¹H 600MHz NMR 4g'

^{13}C 150MHz NMR 4g'

160.128
157.632

144.041

133.956
130.752
129.412
129.216
128.386
128.077
127.477
125.143
120.839

110.400

55.454
54.623

40.029

30.337

¹H 600MHz NMR 4g

^{13}C 150MHz NMR 4g

¹H 600MHz NMR 4h'

^{13}C 150MHz NMR 4h'

¹H 600MHz NMR 4h

¹³C 150MHz NMR 4h

¹H 600MHz NMR 4i'

¹H 600MHz NMR 4i

^{13}C 150MHz NMR 4i

¹H 600MHz NMR 4j'

¹³C 150MHz NMR 4j'

¹H 600MHz NMR 4j

¹³C 150MHz NMR 4j

¹H 600MHz NMR 4k'

^{13}C 150MHz NMR 4k'

¹H 600MHz NMR 4k

¹³C 150MHz NMR 4k

¹H 600MHz NMR 4l'

¹H 600MHz NMR 4I

¹³C 150MHz NMR 4I

¹H 600MHz NMR 4m'

^{13}C 150MHz NMR 4m'

¹H 600MHz NMR 4m

^{13}C 150MHz NMR 4m

¹H 600MHz NMR 4n'

¹³C 150MHz NMR 4n'

¹H 600MHz NMR 4n

^{13}C 150MHz NMR 4n

¹H 600MHz NMR 40°

^{13}C 150MHz NMR 4o'

¹H 600MHz NMR 4o

¹H 600MHz NMR 4oa

^{13}C 150MHz NMR 4oa

¹H 600MHz NMR 4p'

¹³C 150MHz NMR 4p'

¹H 600MHz NMR 4pa

¹H 600MHz NMR 4pb

¹H 600MHz NMR 5a

¹³C 150MHz NMR 5a

¹H 600MHz NMR 6a

^{13}C 150MHz NMR 6a

¹H 600MHz NMR 7o

^{13}C 150MHz NMR 7o

¹H 600MHz NMR 7a'

^{13}C 150MHz NMR 7a'

¹H 600MHz NMR 7aa

^{13}C 150MHz NMR 7aa

¹H 600MHz NMR 7ab

¹³C 150MHz NMR 7ab

¹H 600MHz NMR 7b'

¹³C 150MHz NMR 7b'

¹H 600MHz NMR 7b

^{13}C 150MHz NMR 7b

¹H 600MHz NMR 7c'

^{13}C 150MHz NMR 7c'

¹H 600MHz NMR 7c

¹³C 150MHz NMR 7c

¹H 600MHz NMR 7d'

^{13}C 150MHz NMR 7d'

¹H 600MHz NMR 7d

^{13}C 150MHz NMR 7d

¹H 600MHz NMR 7e'

^{13}C 150MHz NMR 7e'

¹H 600MHz NMR 7e

¹³C 150MHz NMR 7e

¹H 600MHz NMR 7f'

^{13}C 150MHz NMR 7f'

¹H 600MHz NMR 7f

¹³C 150MHz NMR 7f

¹H 600MHz NMR 7g'

¹³C 150MHz NMR 7g'

¹H 600MHz NMR 7g

^{13}C 150MHz NMR 7g

¹H 600MHz NMR 7h'

^{13}C 150MHz NMR 7h'

¹H 600MHz NMR 7h

¹³C 150MHz NMR 7h

¹H 600MHz NMR 7i'

¹³C 150MHz NMR 7i'

¹H 600MHz NMR 7i

¹³C 150MHz NMR 7i

¹H 600MHz NMR 7j'

¹³C 150MHz NMR 7j'

¹H 600MHz NMR 7j

¹³C 150MHz NMR 7j

¹H 600MHz NMR 7n

¹³C 150MHz NMR 7n

¹H 600MHz NMR 7k'

¹³C 150MHz NMR 7k'

¹H 600MHz NMR 7k

^{13}C 150MHz NMR 7k

¹H 600MHz NMR 7m

¹³C 600MHz NMR 7m

¹H 600MHz NMR 7I'

¹³C 150MHz NMR 71'

¹H 600MHz NMR 7I

¹H 600MHz NMR 7p'

¹H 600MHz NMR 7pa

^{13}C 150MHz NMR 7pa

¹H 600MHz NMR 7pb

¹³C 150MHz NMR 7pb

¹H 600MHz NMR 7q'

^{13}C 150MHz NMR 7q'

¹H 600MHz NMR 7qa

^{13}C 150MHz NMR 7qa

¹H 600MHz NMR 7qb

^{13}C 150MHz NMR 7qb

¹H 600MHz NMR 7r'

^{13}C 150MHz NMR 7r'

¹H 600MHz NMR 7r

¹³C 150MHz NMR 7r

¹H 600MHz NMR 7s'

¹³C 600MHz NMR 7s'

¹H 600MHz NMR 7s

^{13}C 600MHz NMR 7s

¹H 600MHz NMR PyTAA

^{13}C 150MHz NMR PyTAA

Part II

**Palladium-Catalyzed Aerobic Oxidative C–H Olefination with
Removable 1,2,3-Triazole Directing Group**

Part III

Nickel-catalyzed directed sulfenylation of sp^2 and sp^3 C–H bonds

165.264
165.235
164.149
161.661

148.172
143.318
138.389
136.313
135.515
134.276
130.960
130.871
129.140
128.903
127.871
127.303
126.519
124.555
124.517
122.051
121.396
119.501
118.093
117.984
116.821