Rhodium-Catalyzed Direct C-H Functionalizations of Sulfoximines and Copper-Catalyzed Enantioselective Synthesis of Dihydropyrazoles

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Chapter 1

Rhodium-Catalyzed Direct C-H
Functionalizations of Sulfoximines
Part 1 Introduction

1 Introduction of Transition Metal-Catalyzed Direct C-H Bonds Functionalizations

The carbon-hydrogen bonds (abbreviated as C-H bonds) are fundamental and most common chemical bonds in a variety of organic compounds. Owing to the high bond dissociation energy and the inertness of C-H bonds,[1] e.g., 105 kcal/mol for H-CH$_3$ and 110 kcal/mol for H-C$_6$H$_5$, transformations of inert C-H bonds into C-C bonds or C-X bonds (X= S, O, N, Cl, Br, etc.) by metal catalysis are still great challenges nowadays. In general, traditional approaches for the transformations of C-H bonds rely on prefunctionalized starting materials for both reactivity and selectivity or require costly chemical steps. Thus, the development of a cheap and alternative method is still desirable to address the above issues. Transition metal-catalyzed direct functionalization of inert C-H bonds has attracted great attention and gradually emerged as a powerful method in organic synthesis. Compared with conventional approaches, the methodologies are environmental friendly and atom-economical and have been frequently applied in the synthesis of natural products, biologically active molecules and organic materials.

In general, directing group-assisted transition metal-catalyzed C-H bond activation involves a five-membered cyclometalated key intermediate A (Scheme 1), which provides a favorable driving force in inducing reactivity at the desired location. Various directing groups have been utilized to activate C-H bonds by aid of transition metal catalysts, such as ruthenium, rhodium, palladium, iridium and other metal catalysts.
Scheme 1 General mechanism for directing group-assisted ortho-C-H activation

Among all the transition metal catalysts, rhodium complexes are sustainable metal catalysts in the field of C-H activations. Despite the general high cost of rhodium complexes, rhodium catalysis will still be highly desirable if reaction systems are inaccessible under palladium or ruthenium catalysis. Indeed, the past decades have witnessed a dramatic development in the field. Rhodium-catalyzed directing group-assisted C-H activations and successive functionalization protocols have been extensively investigated. Very recently, rhodium(III) complexes, such as $[\text{RhCp}^*\text{Cl}_2]_2$, $[\text{Cp}^*\text{Rh(MeCN)}_3][\text{BF}_4]_2$ and $[\text{Cp}^*\text{Rh(MeCN)}_3][\text{SbF}_6]_2$ have proved to be highly efficient catalysts in the field of direct C-H bonds functionalization. In this chapter, we will focus on rhodium-catalyzed C-H activations and subsequent functionalization reactions.

1.1 Rhodium-Catalyzed C-H Activations and Subsequent Annulation Reactions

Within the past decades, the oxidative activations of C-H/N-H or C-H/O-H bonds and subsequent annulation reactions with alkynes or alkenes have emerged as powerful methods for the synthesis of heterocyclic or carbocyclic compounds in metal-catalyzed organic synthesis. In general, these reactions proceed by chelation-assisted C-H bonds activations and oxidative additions of metal complexes to the ortho-C-H bonds, insertion of the alkynes or alkenes, reductive eliminations, and then annihilations. These protocols have been utilized extensively for the
preparation of a wide range of substituted heterocyclic compounds such as indoles, isocumarines, isoquinolines, carbazoles, benzothiazoles and pyridines. In this part we will focus on Rh(III)-catalyzed annulation reactions and the involved mechanisms.

Satoh and Miura firstly reported a synthesis of polyarylated naphthyl and anthrylazole derivatives by direct coupling of phenyl azoles with internal alkynes in the presence of a rhodium catalyst and a copper oxidant (Scheme 2). The reaction involved the multiple C-H bonds cleavages and C-C bonds formations in a one-pot manner.\[^{[2]}\]

**Scheme 2** Annulation of phenyl azoles with alkynes

![Scheme 2](image)

The authors proposed a mechanism initiated with the coordination between the N-atom and the Rh(III) species. Followed by a regioselective C-H activation, a rhodacycle A was formed. Successive direct insertion of an alkyne to the rhodium-carbon bond of the intermediate A afforded a seven-membered rhodacycle B. Then, a metallaindene C was formed by a second cyclometallation with the loss of an
HX. Subsequent insertion of a second alkyne into the Rh-C bond and successive reductive elimination gave the final product and a Rh(I) species, which was then oxidized to a Rh(III) species for the next cycle (Scheme 3).

**Scheme 3 Proposed mechanism**

Miura and coworkers also reported carboxylate group-assisted oxidative annulation reactions with internal alkynes. Benzoic acids reacted with internal alkynes in the presence of (Cp*RhCl)₂ and a stoichiometric amount of Cu(OAc)₂·H₂O, affording the corresponding isocoumarin derivatives in high yields (5a and 5b in Scheme 4).[^3] Interestingly, a catalytic amount of Cu(OAc)₂·H₂O with air or a stoichiometric amount of Cu(OAc)₂·H₂O showed the same effect. Only in some cases, minor decarboxylative products (naphthalenes) were obtained (6a and 6b in Scheme 4).[^3a]
Scheme 4 Decarboxylative annulation of benzoic acids and alkynes

Ketones are less coordinative to the rhodium complexes. However, Glorius and Cheng independently disclosed a successful oxidative annulation reaction between ketones and alkynes, which opened an easy access to substituted indenols (6a-d in Scheme 5) in various solvents such as PhCl and t-AmylOH. The catalytic reaction was highly regioselective with unsymmetrical alkynes.

Scheme 5 Annulation of ketones and alkynes
Heterocyclic compounds such as substituted indoles are of great importance in the pharmaceutical area for being core structures of many commercial drugs. Numerous attempts in recent years have been made for the development of improved methods for the synthesis of heterocyclic compounds. In the context, Fagnou and coworkers reported a first Rh(III)-catalyzed annulation reaction of acetanilides with alkynes for the synthesis of substituted N-acyl indoles.\(^5\) The authors observed that no reaction took place when the reaction was carried out in the absence of the silver salt \(\text{AgSbF}_6\).

Furthermore, Fagnou and coworkers developed a second generation rhodium(III)-catalyst \([\text{Cp}^*\text{Rh(MeCN)}_3\text{(SbF}_6)_2]\), which was highly suitable under milder conditions (Scheme 6).\(^6\) Both systems showed good regioselectivities when asymmetric alkynes were applied.

**Scheme 6** Comparison of two generations of rhodium complexes

In a similar manner, the same authors extended their reaction scope to conjugated enynes with N-aryl ureas, producing the desired substituted indoles in good yields under unprecedented mild conditions (Scheme 7).\(^7\) Interestingly, the methodology was also applicable for the synthesis of 2-alkenyl pyrroles (11c in Scheme 7) at room
temperature (condition B in Scheme).

**Scheme 7** Annulation reaction of conjugated enynes with N-aryl ureas

In 2010, Rakshit and Glorius reported an oxidative annulation reaction of enamines with alkynes for tetrasubstituted pyrroles 12 through an allylic C-H activation pathway via intermediate 14 (Scheme 8). However, the ester group was deduced to play a key role for the transformations (13a-c in Scheme 8). KIE experiment results showed a quick exchange of H/D at the α-position of the substrate. In some cases no desired products were obtained or they were formed in very low yields (13c in Scheme 8, 31% yield). However, when substrates with a CN group were applied in the failed cases, the desired products were isolated in good yields, e.g., 13d in 72% yield (Scheme 8). This indicated that the CN group changed the pathway of the C-H activation.
Isoquinolone derivatives are important heterocyclic compounds and such types of skeletons are found in a wide range of natural products that show various biological activities. However, only few methods are available in the literature for the synthesis of isoquinolones. In most of these reactions, compounds with a carbon-halogen moiety were utilized as starting materials to generate the reactive species. Thus, protocols by direct C-H activations provide a good access to isoquinolones. To this end, Rh(III)-catalyzed annulation reaction of N-aryl benzamides with alkynes represented a promising method for the synthesis of isoquinolones. Miura[9], Rovis[10] and Li[11], independently reported isoquinolones synthetic routes under different reaction conditions (Scheme 9).
Scheme 9 Access to isoquinolones by annulation reactions

Park and coworkers developed a Rh(III)-catalyzed intramolecular C-H activation and subsequent annulation reaction of alkyne-tethered hydroxamic acid esters. This protocol provided a great opportunity for the synthesis of substituted isoquinolones in good yields with excellent regioselectivity.\(^{[12]}\) The significance of this reaction was demonstrated by its application to the total synthesis of some useful natural products, such as seco-antofine (21a), (±)-septicine (21b), (±)-antofine (22a) and (±)-tylophoring (22b) (Scheme 10).

Starting from the alkyne-tethered hydroxamic acid esters 17a and 17b, the intramolecular oxidative annulation reaction occurred in very high yields, producing 18a and 18b in 94% and 97% yields, respectively. Followed by a standard intramolecular Mitsunobu reaction,\(^{[13]}\) indolizidine compounds 19a and 19b were formed. Then the TMS group was removed by TBAF, affording 20a and 20b in 82% and 86% yields, respectively. Under Moore’s conditions,\(^{[14]}\) 20a and 20b changed into seco-antofine (21a) and (±)-septicine (21b), in 72% and 81% yields. In the end, the
target molecules (±)-antofine (22a) and (±)-tylophorine (22b) were synthesized by an oxidative coupling reaction under the Liepa conditions[15] in moderate yields, 65% and 77%, respectively (Scheme 10).

**Scheme 10** Total synthesis of some useful natural products

Very recently Cramer and coworkers reported a rhodium(III)-catalyzed synthetic route towards benzosultams (24a-c in Scheme 11) from N-acyl sulfonamides with alkynes using CuOAc/O2 as external oxidant. Under standard conditions, both ortho- and meta-substituted sulfonamides reacted well with alkynes to give corresponding substituted sultams in good yields. The new method showed good compatibility to
some N-acyl heteroaryl sulfonamides, e.g., 24c was obtained in an excellent yield (99%). Unsymmetrical alkynes gave moderate to good regioselectivities, which was somewhat dependent upon the alkynes concentrations.[16]

Scheme 11 Synthesis of sultams by a rhodium-catalyzed annulation reaction

1.2 Rhodium-Catalyzed Addition Reactions

Transition metal-catalyzed addition of ortho-C-H bond to some unsaturated carbon-carbon or carbon-hetero bonds constitute one of the most efficient and economical methods in the field of organic synthesis. The transformation has a great potential for the synthesis of ortho-alkylated compounds from simple starting materials via five membered intermediates. Herein, the transformations have attracted great attention and been well documented. Notably, alkylation reactions with new carbon-carbon bonds constructed by direct C-H activations are of great importance and highly desirable. Generally, the regioselective ortho-oriented C-H activations can be achieved by the coordination between metal complexes and the specific atoms on the directing groups. In this regard, various directing groups have been exploited for the transformations, resulting in mono- or di-alkylated products. In this part, we will introduce some rhodium-mediated ortho-C-H activations and subsequent addition
With a catalytic amount of Cp*Rh(C$_2$H$_5$SiMe$_3$)$_2$, acetophenones reacted well with trimethylvinylsilanes, forming \textit{anti}-Markovnikov products in good selectivity under mild conditions (80 °C, Scheme 12). As proposed, the methodology gave good selectivity owing to the coordination between the rhodium complex and the oxygen atom of the ketone group.$^{[17]}$

**Scheme 12** Rhodium-catalyzed \textit{ortho}-alkylation of ketones and mechanism cycle

With 3-methyl pyridinyl group utilized as the directing group, 2-phenyl-3-methyl pyridines reacted well with olefins, affording \textit{ortho}-substituted products in good yields (Scheme 13).$^{[18]}$ In this case, the 3-methyl pyridinyl group was utilized to avoid the bis-alkylated byproducts. In addition, a ligand was required for restraint coordination between the rhodium complex and substrates.$^{[19]}$ Notably, the cone angle of the ligands affected the yields significantly, from 92% to 21% (Scheme 13).
In a similar manner, the same authors extended the conditions to pyridinyl alkenyl compounds with the assistance of a Rh(I) catalyst.\(^{[20]}\) For example, 2-isopropenyl pyridine (30) reacted smoothly with 1-hexene (26d), forming the β-alkylated products 31 and 32 as a mixture with a 2:1 E/Z isomeric ratio (Scheme 14).

Some other nitrogen atom-containing functional groups, such as aromatic ketimines or aldimines, can also be used as the directing groups for the rhodium-catalyzed addition reactions. Thus, Jun and coworkers developed a chelation-assisted Rh(I)-catalyzed ortho-alkylation reaction of aromatic ketimines with olefins (Scheme 15). As proposed, the catalytic cycle initiated with the oxidative addition of the ortho-C-H bond to the electron-rich \([\text{RhCl(PPh}_3\text{)_3}]\), followed by olefin coordination and hydride insertion. Then, the ortho-alkylated ketone was formed by
reductive elimination and successive hydrolysis (Scheme 54).[^21]

**Scheme 15** Imine-directed addition reaction towards *ortho*-alkylated ketones

![Scheme 15 Imine-directed addition reaction](image)

The reaction was then extended to aromatic ketimines with active alkenes, giving *ortho*-alkylated ketones in the same manner.[^22] Various functional groups on the alkenes were well tolerated in the system. For example, methyl acrylate (26f), N,N-dimethyl acrylamide (26g), phenyl vinyl sulfone (26h) and acrylonitrile (26i) reacted with ketimine 33b successfully, giving the desired products in acceptable to good yields (34c-f in Scheme 16).

**Scheme 16** Rhodium-catalyzed ketimine-directed addition for alkylated ketones

![Scheme 16 Rhodium-catalyzed ketimine-directed addition](image)

Very recently, Bergman and Ellman reported a rhodium-catalyzed alkylation reaction of α,β-unsaturated aldimines. The intermolecular reaction of α,β-unsaturated aldimines led to α,β-unsaturated aldehydes in excellent yields. For example, N-(2-methylallylidene)-butanamine (35) reacted with 1-hexene (26d) successfully, affording the desired products 36 and 37 in a combined 100% yield with an E:Z
isomeric ratio of 95:5 after hydrolysis (Scheme 17).\[^{23}\]

**Scheme 17** Rhodium-catalyzed alkylation of \(\alpha,\beta\)-unsaturated aldimines

\[
\begin{align*}
\text{Me} = \text{Bn} & \quad + \quad \text{n-Bu} \\
\text{35} & \quad \text{26d} \\
\text{Me} & \quad \text{36} \quad \text{37}
\end{align*}
\]

Yield: 100\% (36+37)
ratio: 95:5 (36/37)

In a similar way, aromatic aldimines with tethered alkenes \textit{meta} to the imine group (38a-c) underwent an intramolecular C-H addition reaction, affording the desired products in good yields (Scheme 18). The formation of linear or branched addition products depended on the alkene tether.\[^{24}\]

**Scheme 18** Rh-mediated intramolecular C-H addition reaction

Selected examples

39a: 71\% yield (38a)  
40a: 85\% yield (38b)  
39c: 64\% yield (38c)

Similarly, Ellman and Bergman reported an intramolecular addition reaction of
N-alkenyl benzimidazole 41 in the presence of \([\text{RhCl(coe)}_2]_2\) and \(\text{PCy}_3\), yielding the desired products 42 in moderate to good yields (Scheme 19). As proposed, the reaction proceeded via intermediates A, B and C. \(^1\text{H-NMR}\) spectra confirmed the existence of the intermediates. To get a better understanding of the mechanism, an isotopic labeling experiment was carried out, affording a \(d_2\)-product 44-\(d_2\) as shown in the Scheme 19.\(^{[25]}\)

**Scheme 19** Intramolecular addition reaction of N-alkenyl benzimidazoles

![Scheme 19](image)

A more challenging asymmetric synthesis of some ortho-chained products was disclosed by Murai and coworkers. For example, N-methyl-2-octa-1,5-dienyl-1H-imidazole (45) underwent the reaction smoothly, by aid of \([\text{RhCl}_2(\text{cyclooctene})]_2\) and a ferrocenylphosphine ligand (\(L^*\) in Scheme 20), giving the annulated product 46 in 75% yield with 82% ee. The N-methyl imidazole group was deduced to play a key role as the directing group with coordination to the rhodium complex. Interestingly, the pyridinyl group was also compatible as a new directing group. Finally, chiral
cyclo-aliphatic ketones 48 were produced by a ruthenium-mediated oxidative cleavage reaction (Scheme 20).[26]

**Scheme 20 Intramolecular asymmetric addition reaction**

Recently, Li and coworkers documented an efficient Rh(III)-catalyzed 2-phenyl pyridine-assisted C-H activation and subsequent conjugative addition reaction. Under the mild conditions, phenyl pyridines 49 reacted with 2-cyclohexenone (50), providing mono-alkylated products 51 in good to excellent yields (57% - 98%). Interestingly, 4-acetyl phenyl pyridine reacted with 2-cyclohexenone (50), affording the di-alkylated product 52 in a quantitative yield (Scheme 21).[27]
**Scheme 21** Rh(III)-catalyzed addition reaction of 2-phenyl pyridines and 2-cyclohexenone

\[ \text{R}^1 \text{R}^2 \text{N} \quad + \quad \text{O} \quad \text{Cp}^*\text{Rh(MeCN)}_3\text{SbF}_6 \quad \xrightarrow{\text{CH}_2\text{Cl}_2, 40 \, ^\circ\text{C}} \quad \text{R}^1 \text{R}^2 \text{N} \quad + \quad \text{O} \quad \text{51: 57%-98%} \]

\[ \text{52: 100% yield (48 h)} \]

\( \alpha,\beta \)-Unsaturated ketones such as chalcones were able to react with 2-aryl pyridines, presented by Huang and coworkers, affording conjugative addition products under mild conditions (60 °C, Scheme 22). As proposed, the reaction proceeded by the coordination of the chalcone and the rhodium complex, which produced arylrhodium complex A. Subsequent conjugative addition afforded rhodium enolate B or (oxa-\(\pi\)-allyl) rhodium species C, which provided the desired product after protonation by the aid of acetic acid (Scheme 22).\(^\text{[28]}\)
Scheme 22 Rh(III)-catalyzed addition reaction of aryl pyridines and chalcones

\[
\begin{align*}
\text{aryl pyridine} + \text{chalcone} &\xrightarrow{(\text{Cp}^*\text{RhCl}_2)_2/\text{AgSbF}_6} \text{product} \\
\text{53} &\xrightarrow{60 \degree C, 24 \text{ h}} \text{product}
\end{align*}
\]

- 54a: R\(^1\) = 4-MeC\(_6\)H\(_4\), R\(^2\) = Ph
- 54b: R\(^1\) = 4-FC\(_6\)H\(_4\), R\(^2\) = Ph
- 54c: R\(^1\) = Me, R\(^2\) = Ph

55a: 94% yield  
55b: 93% yield  
55c: 95% yield

2 General Introduction of Sulfoximines and Metal-catalyzed Synthesis of N-Substituted Sulfoximines

2.1 General Introduction of Sulfoximines

Sulfoximines, the stable monoaza analogues of sulfones, have a distorted tetrahedral structure with some distinguishing features: 1) IR spectra could provide evidence for the existence of the S=N and S=O double bonds in sulfoximines; 2) The nitrogen atom linked to the sulfur (R\(^1\) ≠ CH\(_2\)R\(^3\)) is nucleophilic; 3) The hydrogens of the alkyl group on the α-position of the sulfur atom are acidic, and the acidity is largely affected by the R\(^3\) group on the nitrogen atom. For example, the pKa is 32 when R\(^3\) = Me, while the pKa is 23 when R\(^3\) = Ts (Figure 1).
 Consequently, sulfoximine derivatives have attracted a great attention not only for biomedical and pharmaceutical chemistry, but also for applications as chiral ligands and building blocks for pseudopeptides. For example, (2S,5S)-methionine sulfoximine (compound 56 in Scheme 23) was recognized as the toxic factor for *canine hysteria* while buthionine sulfoximine (compound 57 in Scheme 23) has specific inhibitory effects on $\gamma$-glutamylcysteine synthetase. Various sulfoximines (e.g., 58, 59 in Scheme 23) have been proved to be applicable as chiral ligands in metal-catalyzed asymmetric Diels-Alder, hetero-Diels-Alder, allylic alkylation and Mukaiyama-type aldol reactions.$^{[29]}$

**Scheme 25** Some sulfoximine-cored compounds
N-Substituted sulfoximines are of great significance for various properties with different functional groups on the nitrogen atom. In this part, we will introduce some important approaches towards N-substituted sulfoximines by transition metal-catalyzed reactions.

2.2 Synthesis of N-Substituted Sulfoximines by Metal-Catalysis

Transition metal-catalyzed C-H or N-H activations and subsequent functionalization protocols of NH-sulfoximines are highly useful and interesting topics in organic synthesis. The construction of different C-C and C-N bonds on the NH-sulfoximines is extremely difficult by traditional organic synthesis. In this context, Bolm and Harmata have reported various valuable new C-C and C-N bonds formation methodologies from NH-sulfoximines with assistance of transition metal catalysts.

In 2000, Bolm and coworkers described a direct approach towards N-aryl sulfoximines by using a palladium-catalyzed cross-coupling reaction. In the presence of Pd(OAc)$_2$ and tol-BINAP, NH-sulfoximines reacted with halo arenes, affording N-aryl sulfoximines in acceptable to excellent yields (Scheme 24).[30] Interestingly, aryl bromides showed the best activity, giving the desired products in nearly quantitative yields. Lithium or silver salts were required when aryl iodides were applied as coupling partners.

As proposed by the authors, the catalytic cycle initiated with reduction of Pd(II) into Pd(0) species A (Scheme 24). Then oxidative addition of complex A into the aryl-bromide bond took place, forming C-Pd-Br species B. Followed by the coordination of the NH-sulfoximine to the palladium complex B, HBr was released in the presence of base, forming aryl-palladium-sulfoximide intermediate D, which was easily transformed into the product with a reductive elimination step (Scheme 24).
Scheme 24 Palladium-catalyzed N-arylation of NH-sulfoximines and proposed mechanism

In a similar manner, N-vinyl sulfoximines were obtained in excellent yields by a palladium-catalyzed intermolecular coupling reaction of NH-sulfoximines with vinyl bromides. Interestingly, vinyl triflate 65 also effectively coupled with NH-sulfoximines, giving the desired products in nearly quantitative yields (66a and 66b in Scheme 25).[31]
Scheme 25 Palladium-catalyzed N-vinylation of NH-sulfoximines

Based on the previous results of the palladium-catalyzed approaches for N-aryl or N-vinyl sulfoximines, Harmata disclosed a one-pot reaction for the synthesis of various 1,2-benzothiazines from NH-sulfoximines and o-halobenzaldehyde under Buchwald-Hartwig conditions (Scheme 26). The simple protocol gave rise to 1,2-benzothiazines in a one-pot manner.

Scheme 26 Synthesis of 1,2-benzothiazines under Buchwald-Hartwig conditions
To make a complement to the palladium-catalyzed methodologies, Cho and Bolm developed a high-yielding protocol for N-aryl sulfoximines with less expensive CuI as catalyst. The novel ligand-free protocol showed good compatibility with various substituted aryl iodides and substituted NH-sulfoximines (Scheme 27).[33]

**Scheme 27 Cu(I)-catalyzed N-arylation of NH-sulfoximines**

Organoboron reagents have attracted great attention due to the advantages of air and moisture stability, low toxicity, and availability. In addition, organoboronic acid possibly enhances electron density at the boron center in the presence of base and thus facilitates the transmetallation with a metal catalyst under mild conditions. In this context, several examples of metal-catalyzed coupling of organoboron reagents with aryl or alkyl-XH (X = O, S, and N) have been reported. Among those contributions, Bolm and coworkers developed a convenient method for the N-arylation sulfoximines. NH-Sulfoximines reacted with aryl boronic acids in the presence of a catalytic amount of the Cu(OAc)$_2$ (10 mmol%) in MeOH at room temperature, yielding the desired products in moderate to good yields (Scheme 30).[34]
Scheme 28 Copper(II)-mediated N-arylation of NH-sulfoximines with boronic acids

\[
\text{Ph-B(OH)₂} + \text{O-SMe} \xrightarrow{\text{Cu(OAc)₂, MeOH, r.t.}} \text{O-SMe-N-Ph} \]

68a-c: 
- 68a: \( R^1 = H \)
- 68b: \( R^1 = 2\text{-Me} \)
- 68c: \( R^1 = 4\text{-Me} \)

61a: 
- 62a: 93% yield
- 62d: 75% yield
- 62f: 92% yield

Diaryliodonium salts also can be utilized as the arylation reagents. To this end, an ultrasound-assisted approach towards N-aryl sulfoximines was described by Vaddula and Varma. The reaction proceeded in aqueous polyethylene glycol-400 with a catalytic amount of cuprous bromide at room temperature, affording the desired N-aryl sulfoximines in high yields (Scheme 29).\[^{[35]}\]

Scheme 29 Ultrasound-assisted N-arylation of NH-sulfoximines

The above methodologies towards N-aryl sulfoximines required prefunctionlized substrates or harsh reaction conditions. In this context, Bolm and Miura reported an attractive copper-catalyzed direct dehydrogenative C-N coupling of heteroarenes with NH-sulfoximines, affording N-heteroaryl sulfoximines in good yields. Notably, the enantiopure N-heteroaryl sulfoximines were easily obtained under the standard conditions (Scheme 30).\[^{[36]}\]
Scheme 30 Synthesis of N-arylated sulfoximines by hetero-dehydrogenative coupling reaction

Recently, Bolm and coworkers introduced a high-yielding dehydrogenative cross-coupling method for the synthesis of previously unknown N-alkynylated sulfoximines from NH-sulfoximines with terminal alkynes. This unprecedented protocol utilized a copper(II) salt as catalyst and oxygen as oxidant, involving a dual C-H/N-H activation procedure (Scheme 31).[37]

Scheme 31 Copper-catalyzed N-alknylation of NH-sulfoximines

Selected examples

73a: 78% yield 73b: 84% yield 73c: 60% yield
Later, the same authors developed a copper-catalyzed dehydrogenative cross coupling protocol towards N-acyl sulfoximines with low catalyst loadings (1 mol%). With easily commercial available aldehydes as coupling partners, the representative transformation was easily realized by dual C-H/N-H functionalization procedures with tert-butyl hydroperoxide (TBHP) as oxidant, affording the desired products in good to high yields (Scheme 32).[38]

**Scheme 32** Cu(I)-catalyzed N-acylation of NH-sulfoximines

Very recently, Parthasarathy and Bolm reported a Rh(III)-catalyzed alkenylation method from N-acyl and N-aroyl sulfoximines by a direct ortho-C-H bond activation procedure (Scheme 33). AgSbF₆ was deduced to play a key role in facilitating the reaction by removing the chloride from the [RhCp*Cl₂]₂ complex, generating a more active cationic rhodium species.[39]

**Scheme 33** Rh(III)-catalyzed alkenylation of sulfoximines
Part II Rhodium-catalyzed Annulation Reaction of Sulfoximines and Alkynes

1 Research Objective

Previously, N-H or C-H functionalization transformations of NH-sulfoximines have been extensively studied and documented. However, there are no reports on the synthesis of 1,2-benzothiazines from NH-sulfoximines by dual C-H/N-H activation procedures. 1,2-Benzothiazines have attracted significant attention due to their usefulness as scaffolds or as synthetic intermediates in pharmaceutical development. Approaches towards 1,2-benzothiazines by annulation reactions of either alkynes or alkenes with sulfonimidoyl chlorides, or by a domino sequence involving a Buchwald-Hartwig protocol followed by ring formation are well established.\[40\] In the context, Harmata and coworkers reported a new approach to 1,2-benzothiazines and benzoisothiazoles by Sonogashira coupling of S-2-bromophenyl-S-methyl NH-sulfoximines with terminal alkynes (Scheme 34, eq. A).\[41\] However, most of the documented methodologies required toxic halogenated starting materials or harsh reaction conditions, including a low temperature (-78 °C) and strong base (n-BuLi).

In this part we will describe a new approach towards 1,2-benzothiazines from NH-sulfoximines with alkynes by a Rh(III)-catalyzed C-H/N-H activations strategy. The C-H/N-H activations and subsequent annulations proceed in the presence of a rhodium catalyst (Scheme 34, eq. B).
Chapter 1

Scheme 34 Research Objective

2 Results and Discussions

2.1 Optimization of Annulation Reaction of Sulfoximines with Alkynes

2.1.1 Screening of Transition Metal Catalysts

To find suitable reaction conditions, sulfoximine 61a and diphenylacetylene (2a) were used as model starting materials. The effect of rhodium complexes and oxidants were also examined (see Table 1).

Rhodium complex \([\text{Cp}^*\text{Rh(MeCN)}_3][\text{BF}_4]\) was the most effective complex at forming 76a, in 89% yield (Table 1, entry 1). Other rhodium complexes such as \([\text{RhCp}^*\text{Cl}_2]_2\), \([\text{Rh(OAc)}_2]_2\), \([\text{RhCl(COD)}]_2\) and \(\text{Rh(PPh}_3)_3\text{Cl}\) were less reactive (Table 1, entries 2-3) or completely inactive (entries 4-5). Palladium(II) complexes, such as \(\text{PdCl}_2(\text{CH}_3\text{CN})_2\), \(\text{PdCl}_2(\text{PhCN})_2\), \(\text{PdCl}_2(\text{PPh}_3)_2\) and \(\text{Pd(OAc)}_2\) were ineffective for the reaction (entries 6-9). \(\text{Fe(OAc)}_2\) was a much more efficient additive (entry 1) than \(\text{Fe(acac)}_3\), \(\text{Fe(OTf)}_3\), or \(\text{Cu(OAc)}_2\) (entries 10-12). Other additives such as \(\text{PhI(OAc)}_2\)
and K$_2$S$_2$O$_8$ were totally inactive (entries 13, 14). Notably, no reaction took place when the reaction was carried out in the absence of the metal catalyst and additive (entry 15).

![Reaction Scheme](image)

**Table 1** Screening of transition metal catalysts

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Additive</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[Cp*Rh(MeCN)$_3$][BF$_4$]$_2$</td>
<td>Fe(OAc)$_2$</td>
<td>89</td>
</tr>
<tr>
<td>2</td>
<td>[Cp*Rh(MeCN)$_3$][BF$_4$]$_2$</td>
<td>Fe(OAc)$_2$</td>
<td>35</td>
</tr>
<tr>
<td>3</td>
<td>[Cp*Rh(MeCN)$_3$][BF$_4$]$_2$</td>
<td>Fe(OAc)$_2$</td>
<td>trace</td>
</tr>
<tr>
<td>4</td>
<td>[Cp*Rh(MeCN)$_3$][BF$_4$]$_2$</td>
<td>Fe(OAc)$_2$</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>[Cp*Rh(MeCN)$_3$][BF$_4$]$_2$</td>
<td>Fe(OAc)$_2$</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>[Cp*Rh(MeCN)$_3$][BF$_4$]$_2$</td>
<td>Fe(OAc)$_2$</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>[Cp*Rh(MeCN)$_3$][BF$_4$]$_2$</td>
<td>Fe(OAc)$_2$</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>[Cp*Rh(MeCN)$_3$][BF$_4$]$_2$</td>
<td>Fe(OAc)$_2$</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>[Cp*Rh(MeCN)$_3$][BF$_4$]$_2$</td>
<td>Fe(OAc)$_2$</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>[Cp*Rh(MeCN)$_3$][BF$_4$]$_2$</td>
<td>Fe(acac)$_3$</td>
<td>trace</td>
</tr>
<tr>
<td>11</td>
<td>[Cp*Rh(MeCN)$_3$][BF$_4$]$_2$</td>
<td>Fe(acac)$_3$</td>
<td>trace</td>
</tr>
<tr>
<td>12</td>
<td>[Cp*Rh(MeCN)$_3$][BF$_4$]$_2$</td>
<td>Fe(acac)$_3$</td>
<td>trace</td>
</tr>
<tr>
<td>13</td>
<td>[Cp*Rh(MeCN)$_3$][BF$_4$]$_2$</td>
<td>Fe(acac)$_3$</td>
<td>trace</td>
</tr>
<tr>
<td>14</td>
<td>[Cp*Rh(MeCN)$_3$][BF$_4$]$_2$</td>
<td>Fe(acac)$_3$</td>
<td>trace</td>
</tr>
<tr>
<td>15</td>
<td>[Cp*Rh(MeCN)$_3$][BF$_4$]$_2$</td>
<td>Fe(acac)$_3$</td>
<td>trace</td>
</tr>
</tbody>
</table>

Notes: [a] Unless otherwise mentioned, all reactions were carried out using sulfoximine 61a (0.30 mmol), alkyne 2a (0.36 mmol), catalyst (5.0 mol %), additive (20 mol %) and toluene (2.5 mL) under O$_2$ (1 atm) at 100 °C for 48 h.
2.1.2 Effect of Solvents

The effect of solvents was also important to the catalytic reaction (Table 2). Toluene was found to be the optimal solvent, affording 76a in 89% yield (entry 1). Other solvents such as tert-amyl alcohol, acetonitrile and DCE (1,2-dichloroethane) were less effective for the catalytic reaction giving 76a in 79%, 56% and 58% yields, respectively (entries 2-4). DMF (dimethylformamide) and DMSO (dimethyl sulfoxide) were totally ineffective (entries 5, 6).

Table 2 Screening of solvents

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Yield(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>toluene</td>
<td>89</td>
</tr>
<tr>
<td>2</td>
<td>tert-amyl alcohol</td>
<td>79</td>
</tr>
<tr>
<td>3</td>
<td>CH₃CN</td>
<td>56</td>
</tr>
<tr>
<td>4</td>
<td>DCE</td>
<td>58</td>
</tr>
<tr>
<td>5</td>
<td>DMF</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>DMSO</td>
<td>0</td>
</tr>
</tbody>
</table>

Note: [a] Conditions: sulfoximine 61a (0.30 mmol), alkyne 2a (0.36 mmol), [Cp°Rh(MeCN)₃][BF₄]₂ (5.0 mol %), Fe(OAc)₂ (20 mol %), O₂ (1 atm), solvent (2.5 mL), 100 °C, 48 h.
2.2 Substrate Scope

Table 3 Substrate scope

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>61</th>
<th>2</th>
<th>76</th>
<th>R¹</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>61a</td>
<td>2a</td>
<td>76a</td>
<td>R¹ = H</td>
<td>89</td>
</tr>
<tr>
<td>2</td>
<td>61b</td>
<td>2a</td>
<td>76b</td>
<td>R¹ = 3-Me</td>
<td>88ᵇ</td>
</tr>
<tr>
<td>3</td>
<td>61c</td>
<td>2a</td>
<td>76c</td>
<td>R¹ = 4-MeO</td>
<td>86</td>
</tr>
<tr>
<td>4</td>
<td>61d</td>
<td>2a</td>
<td>76d</td>
<td>R¹ = 4-NO₂</td>
<td>72</td>
</tr>
<tr>
<td>5</td>
<td>61e</td>
<td>2a</td>
<td>76e</td>
<td>R¹ = 4-Cl</td>
<td>79</td>
</tr>
<tr>
<td>6</td>
<td>61f</td>
<td>2a</td>
<td>76f</td>
<td>R¹ = 4-Br</td>
<td>81</td>
</tr>
<tr>
<td>7</td>
<td>61h</td>
<td>2a</td>
<td>76g</td>
<td></td>
<td>85</td>
</tr>
<tr>
<td>8</td>
<td>61a</td>
<td>2b</td>
<td>76h</td>
<td>R³, R⁴ = 4-MeOC₆H₄</td>
<td>93</td>
</tr>
<tr>
<td>9</td>
<td>61a</td>
<td>2c</td>
<td>76i</td>
<td>R³, R⁴ = 4-FC₆H₄</td>
<td>78</td>
</tr>
<tr>
<td>10</td>
<td>61a</td>
<td>2d</td>
<td>76j</td>
<td>R³, R⁴ = 4-ClC₆H₄</td>
<td>86</td>
</tr>
<tr>
<td>11</td>
<td>61a</td>
<td>2e</td>
<td>76k</td>
<td>R³, R⁴ = 2-Thienyl</td>
<td>87</td>
</tr>
<tr>
<td>12</td>
<td>61a</td>
<td>2f</td>
<td>76l</td>
<td>R³, R⁴ = Et</td>
<td>67</td>
</tr>
<tr>
<td>13</td>
<td>61a</td>
<td>2g</td>
<td>76m</td>
<td>R³, R⁴ = n-Pr</td>
<td>72</td>
</tr>
</tbody>
</table>
To evaluate the substrate scope of the reaction, several substituted NH-sulfoximines (61b-g) were reacted with diphenylacetylene (2a) under the optimized reaction conditions. In general, all transformations proceeded well, affording the corresponding 1,2-benzothiazines in yields ranging from 72-89% (Table 3, entries 1-7). The reaction of meta-substituted NH-sulfoximine 76b revealed a regioselective favor for a less hindered C-H activation pathway, leading to the two expected regioisomers (76b and 76b’) in a combined 88% yield with an isomeric ratio of 90:10 (entry 2). Reactions with para-substituted NH-sulfoximines 61c-f showed that the influence of electronic effects induced by methoxy, nitro, and halo groups were minor and both chloro and bromo substituents were well tolerated (Table 3, entries 3-6). If an S-phenyl group (as in 61h) was utilized instead of an S-methyl substituent (as in 61a-f), the yield of the resulting 1,2-benzothiazine (76g) remained essentially unaffected (85%, Table 3, entry 7). Pleasingly, other alkynes also reacted well (as determined by the reactions with 61a as the coupling partner). In the series of
symmetrically substituted diphenylacetylenes, the 4,4’-dimethoxy-, 4,4’-difluoro-, and 4,4’-dichloro derivatives were tested, and all gave the corresponding products (76h-j) in high yields (up to 93%, Table 3, entries 8-10). Starting from di(2-thienyl)acetylene (2e), 1,2-benzothiazine 76k was obtained in 87% yield (Table 3, entry 11). When aliphatic alkynes were applied, the yields were slightly lower as indicated by conversions of hex-3-yne (2f) and oct-4-yne (2g), providing 1,2-benzothiazines 76l and 76m in 67% and 72% yields, respectively (Table 3, entries 12 and 13).

Reactions of NH-sulfoximine 61a with unsymmetrically substituted alkynes were expected to lead to regioisomeric products. Depending on the substitution pattern, the regioselectivity was either high (up to >95:5) or nil (Table 3, entries 14-18). Thus, 1-phenyl-1-propyne (2h) and phenyl propiolate (2i) underwent the oxidative annulation reaction effectively, leading to the two regioisomeric products (76n/76n’ and 76o/76o’) in high yields with isomeric ratios of 85:15 and >95:5, respectively (Table 3, entries 14 and 15). The chemical identity of 76n was unequivocally established by X-ray single crystal structure analysis (Figure 4). In contrast, no regioselectivity was observed from unsymmetrical diarylacetylenes 2j, 2k, and 2l, which gave the corresponding regioisomeric pairs 76p/76p’, 76q/76q’, and 76r/76r’ in equal amounts (Table 3, entries 16-18). The yields were 90%, 80%, and 78% respectively.

![Figure 4 ORTEP diagram and X-ray data of 76n (CCDC No. 937990)](https://example.com/figure4.png)
2.3 Mechanistic Investigation

Based on the earlier work, a reasonable mechanism for the presented reaction can be deduced, as illustrated in Scheme 37. Most likely, the catalytic cycle initiated with an acetate transfer from Fe(OAc)$_2$ to [Cp*Rh(MeCN)$_3$][BF$_4$]$_2$. Then, the resulting rhodium species Cp*Rh(OAc)$_2$ reacted with the NH-sulfoximine 61a, affording five-membered rhodacycle II with a loss of acetic acid and subsequent ortho-C-H bond activation. Subsequently, coordinative insertion of alkyne 2a into the rhodium-carbon bond of intermediate II gave a seven-membered rhodacycle IV. Then, reductive elimination of rhodacycle IV afforded the 1,2-benzothiazine and a Rh(I) species, which was reoxidized by oxygen combined with the iron salt, regenerating the active Rh(III) species for the next catalytic cycle (Scheme 37).

**Scheme 37** Proposed mechanism for the annulation reaction
In order to support the proposed mechanism, we tried to isolate the key intermediate \( \text{II} \) (Scheme 37). Thus, heating of \( 61a \) in the presence of \([\text{Cp}^*\text{Rh}(\text{MeCN})_3][\text{BF}_4]_2\) (1 equivalent) in toluene at 100 °C for 16 h led to the five-membered rhodacycle \( \text{II} \) with one molecule of probably coordinated compound \( 61a \). This complex was characterized by \(^1\text{H}, \ ^{13}\text{C} \) NMR, IR and mass spectrum. However, several attempts to crystallize intermediate \( \text{II} \) from various co-solvents failed. Finally, we found that when intermediate \( \text{II} \) was treated with NaI in MeOH at room temperature for 30 min, a rhodium intermediate \( \text{II}' \) was formed that could be isolated (Scheme 38). The structure was elucidated by single crystal X-ray diffraction (Figure 5). The reaction of rhodacycle \( \text{II} \) (\( X = \text{BF}_4^- \)) with \( 2a \) and Fe(OAc)\(_2\) in toluene at 100 °C for 2 h afforded \( 76a \), whereas the reaction of rhodium intermediate \( \text{II}' \) (\( X = \text{I} \)) required 15 h to give \( 76a \) in 78% yield.

**Scheme 38** Intermediates isolation and test of activities
To get further mechanistic insight, an intramolecular kinetic isotopic effect (KIE) experiment was carried out (eq. 3). For this study, a deuterated sulfoximine (61a-$d_1$) was prepared and employed. An intramolecular competition experiment of 76a-$d_1$ with 2a showed a $k_H/k_D$ constant of 2.22 (Scheme 39). The KIE result indicated that a direct C-H bond cleavage was involved.

**Scheme 39** KIE research

\[
\begin{array}{ccc}
\text{61a-$d_1$} & \text{Fe(OAc)}_2/O_2 & \text{76a} \\
\text{2a} & \text{toluene, 100 °C} & \text{76a-$d_1$} \\
\end{array}
\]

\[K_H/K_D = 2.22\]

\[\text{76a+76a-$d_1$; 56% yield}\]

2.4 Oxidative Cleavages of 1,2-Benzothiazines

A selective oxidative transformations of 1,2-benzothiazines were demonstrated in Scheme 40. Thus, treatment of 76a with $m$-CPBA (meta-chloroperoxybenzoic acid) in DCM (dichloromethane) at 0 °C to r.t. for 8 h gave a clean conversion of
ortho-acyl-N-acyl sulfoximine 77a in 96% yield. In a similar fashion, 1,2-benzothiazines 76d and 76f were easily converted into 77b and 77c in high yields, without affecting any other functional groups.

Scheme 40 Clevages of 1,2-benzothiazines

3 Summary

In summary, we developed a rhodium-catalyzed process for the synthesis of 1,2-benzothiazines from NH-sulfoximines and alkynes. The combination of simple Fe(OAc)_2 (20 mol %) and O_2 (1 atm) allows the metal reoxidation, closing the catalytic cycle. Mechanistically, the transformation involves a dual C-H/N-H activation, which was substantiated by KIE studies and the isolation of a reactive rhodacycle intermediate. The method is high-yielding and suitable for the synthesis of libraries of functionalized 1,2-benzothiazines.
Chapter 1

4 Experimental Part

4.1 General Information

All reaction mixtures were analyzed by thin layer chromatography using aluminum foil backed silica TLC plates with a fluorescent indicator from Merck. UV-Active compounds were detected with a UV lamp ($\lambda = 254$ nm). For flash column chromatography, silica gel was used as stationary phase. $^1$H and $^{13}$C NMR spectrum were recorded either on a Varian V-NMRS 600, Varian V-NMRS 400 or Varian Mercury 300 in deuterated chloroform at 25 °C. Chemical shifts ($\delta$) were reported in ppm, and spin-spin coupling constants ($J$) were given in Hz, while multiplicities were abbreviated by br s (broad singlet), s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). High resolution mass spectra (HRMS) was recorded on a Finnigan MAT 95 spectrometer.

All solvents were dried according to known methods and distilled before use. Substituted NH-sulfoximines and alkynes were synthesized according to literature procedures. All other reagents were purchased from Sigma-Aldrich, Acros or Alfa Aesar and used without further purification.

4.2 General Procedure for the Synthesis of 1,2-Benzothioazines

A Schlenk tube (60 mL) equipped with a stirring bar was loaded with the NH-sulfoximine (0.5 mmol), alkyne (0.6 mmol), [Cp*Rh(MeCN)$_3$][BF$_4$]$_2$ (13.5 mg, 0.025 mmol, 5 mol %) and Fe(OAc)$_2$ (18 mg, 0.1 mmol, 20 mol %). Under an oxygen atmosphere (1 atm), dry toluene (3.0 mL) was added, and the reaction mixture was allowed to stir at 100 °C for 48 h. After cooling to room temperature, the mixture was filtered through a short celite pad and washed with dichloromethane ($3 \times 20$ mL). The filtrate was concentrated, and the product was purified by flash column chromatography using silica gel with a mixture of hexane and ethyl acetate as eluent.
4.3 Synthesis of Sulfoximine 60a-d₁

2-Bromothioanisole (2.03 g, 10 mmol) was dissolved in dry THF (20 mL). The solution was cooled to -78 °C, and n-BuLi (6.25 mL, 1.6 M, 10 mmol) was added dropwise. After stirring for 1 h at -78 °C, D₂O (4.0 mL) was added dropwise and stirring was continued while the Dewar flask was removed 10 min after the addition. The mixture was allowed to stir for an additional 4 h at room temperature. Then H₂O (20 mL) was added, the phases were separated, and the aqueous layer was extracted with DCM (3 × 20 mL). The combined organic layers were dried over anhydrous MgSO₄, filtered, concentrated, and the oily crude product was purified by distillation under reduced pressure (42-43 °C, 2 mm Hg) to give a colorless oil in 72% yield.

The subsequent two steps (oxidation of the sulfide to the sulfoxide and subsequent imination of the sulfoxide to the sulfoximine) were carried out according to the literature procedures.[42]

4.4 Intramolecular Kinetic Isotope Effect (KIE)

A Schlenk tube (60 mL) with a stirring bar was loaded with the sulfoximine 61a-d₁ (65.5 mg, 0.3 mmol), 2a (64.1 mg, 0.36 mmol), Cp*Rh(MeCN)₃(BF₄)₂ (8.0 mg, 5 mol %) and Fe(OAc)₂ (11 mg, 20 mol %). Under an oxygen atmosphere (1 atm), dry toluene (2.0 mL) was added, and the reaction mixture was allowed to stir at 100 °C for 48 h. After cooling to room temperature, the mixture was filtered through a short celite pad and washed with dichloromethane (3 × 20 mL). The filtrate was concentrated, and the product was purified by flash column chromatography using silica gel with a mixture of hexane and ethyl acetate as eluent to give a mixture of
products 76a and 76a-d_1 in 56% yield. The ratio of the two products was determined by ^1H NMR integration method to give intramolecular kinetic isotopic effect (KIE) constant as \( K_{\text{H}}/K_{\text{D}} = 2.22 \).

### 4.5 Synthesis of Rhodacycles II and II’

A Schlenk tube (25 mL) with a stirring bar was loaded with sulfoximine 61a (46.6 mg, 0.3 mmol) and \([\text{Cp}^*\text{Rh(MeCN)}_3][\text{BF}_4]_2\) (160.8 mg, 0.3 mmol). Under an argon atmosphere, dry toluene (5.0 mL) was added, and the reaction mixture was allowed to stir at 100 °C for 16 h, and then cooled to room temperature. The mixture was filtered through a short celite pad and washed with dichloromethane (3 × 10 mL) and MeOH (3 × 10 mL). The filtrate was concentrated by vacuum and the product was purified by preparative ALOX TLC (elute: EtOAc/hexane = 1:1) to afford the crude rhodium complex II as light yellow solid. The crude complex was characterized by ^1H, ^13C NMR, IR and mass spectrum. Then, crude II’ was treated with NaI in MeOH at room temperature for 30 min. After the remove of the solvent, the pure rhodium intermediate II’ was purified with a neutral Al_2O_3 column in 72% yield from the NH-sulfoximine. Single crystal of II’ was obtained from a MeOH solution, and the structure in the solid state was determined by X-ray diffraction.

### 4.6 Reactions of Rhodacycles II and II’ with Alkyne 2a

A Schlenk tube (25 mL) with a stirring bar was loaded with rhodium complex II (30 mg, 0.06 mmol), alkyne 2a (10.6 mg, 0.06 mmol) and Fe(OAc)_2 (2.4 mg, 0.01 mmol). Under an oxygen atmosphere (1 atm), dry toluene (1.0 mL) was added, and the reaction mixture was allowed to stir at 100 °C for 2 h. The mixture was filtered through a short celite pad and washed with dichloromethane (3 × 10 mL). The filtrate was concentrated, and the product was purified by flash column chromatography using silica gel with a mixture of hexane and ethyl acetate as eluent to afford 76a.
With an analogous experimental procedure, the rhodium complex II reacted with alkyne 2a, giving 76a in 78% yield for 15 h.

4.7 Oxidative Cleavages of 1,2-Benzothiazines

1,2-Benzothiazine 76a (66.3 mg, 0.2 mmol) was dissolved in dry DCM (2 mL). The solution was cooled to 0 °C, and m-CPBA (75% with water, 92.0 mg, 0.4 mmol) in dry DCM (2 mL) was added slowly at 0 °C. The resulting mixture was allowed to stir at the room temperature for 8 h. Then, the mixture was washed with a saturated solution of NaHCO₃, and the combined organic layers were washed with brine, dried over MgSO₄ and concentrated. The product was purified by silica gel column chromatography to give 76a in 96% yield. In a similar fashion, 1,2-benzothiazines 76d and 76f were converted into 77b and 77c in 82% and 90% yields, respectively.

5 Data and Characterization

1-Methyl-3,4-diphenyl benzothiazine 1-oxide (76a)

Following the general procedure, 1,2-benzothiazine 76a was obtained as pale yellow solid in 89% yield (147.5 mg). A gradient of n-hexane/EtOAc: 5/1 was applied as eluent for the flash column chromatography purification.

Melting point: 179-180 °C.

1H NMR (600 MHz, CDCl₃) δ = 7.81 (d, J = 7.9 Hz, 1H), 7.41- 7.37 (m, 2H), 7.22 – 7.15 (m, 5H), 7.09 – 7.06 (m, 5H), 3.64 (s, 3H) (ppm).

13C NMR (151 MHz, CDCl₃) δ = 146.0, 140.3, 137.7, 136.9, 132.4, 129.6, 128. 3, 127.3, 126.7, 126.1, 123.3, 118.6, 112.8, 45.2 (ppm).

MS (EI): m/z = 64.1 (39), 76.9 (100), 90.6 (26.7), 102.9 (99), 132.4 (63), 331.4 (M⁺,
2).
IR (KBr): $\nu = 3015, 2946, 2863, 1767, 1574, 1463, 1205, 967$ (cm$^{-1}$).
HRMS (ESI): 332.1098, calcd. for [M+H$^+$]: 332.1109.

1,7-Dimethyl-3,4-diphenyl benzothiazine 1-oxide and 1,5-dimethyl-3,4-diphenyl benzothiazine 1-oxide (76b and 76b$^\prime$)

Following the general procedure, 1,2-benzothiazines 76b and 76b$^\prime$ were obtained as pale yellow solid in a combined 88% yield (152.0 mg) with a isomeric ratio of 90:10, which was determined by $^1$H-NMR. A gradient of $n$-hexane/EtOAc: 5/1 was applied as eluent for the flash column chromatography purification.

Melting point: 186-190 °C.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 7.72 (d, $J = 7.2$ Hz, 0.3H, minor), 7.64 (s, 3H, major), 7.32 – 7.08 (m, 13H, major), 3.70 (s, 0.5H, minor), 3.66 (s, 3H, major), 2.54 (s, 0.5H, minor), 2.44 (s, 3H, major) (ppm).

$^{13}$C NMR (101 MHz, CDCl$_3$, major+minor) $\delta$ = 144.8, 140.3, 137.9, 136.4, 134.6, 133.8, 133.3, 132.4, 131.4, 130.7, 130.4, 129.6, 129.0, 128.9, 127.3, 127.1, 126.6, 126.1, 122.7, 118.6, 112.7, 46.3, 45.2, 21.4, 21.2 (ppm).

MS (EI): m/z = 104.2 (17), 181.8 (16), 224.4 (100), 226.5 (79), 344.1 (99), 345.7 (87), 347.6 (M$^+$, 6).
IR (KBr): $\nu = 3025, 2312, 2081, 1741, 1566, 1472, 1249, 974$ (cm$^{-1}$).

6-Methoxy-1-methyl-3,4-diphenyl benzothiazine 1-oxide (76c)

Following the general procedure, 1,2-benzothiazine 76c was obtained as pale yellow
solid in 86% yield (155.4 mg). A gradient of n-hexane/EtOAc: 5/1 was applied as eluent for the flash column chromatography purification.

Melting point: 196-197 °C.

$^1$H NMR (400 MHz, CDCl$_3$) δ = 7.79 (d, J = 8.8 Hz, 1H), 7.31 – 7.05 (m, 10H), 6.97 (d, J = 11.2 Hz, 1H), 6.57 (s, 1H), 3.65 (s, 3H), 3.61 (s, 3H) (ppm).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ = 162.4, 146.7, 140.4, 139.6, 137.8, 132.4, 129.5, 128.3, 127.3, 127.2, 126.7, 125.7, 114.6, 112.2, 111.7, 108.1, 55.3, 45.9 (ppm).

MS (EI): m/z = 106.3 (23), 181.8 (16), 224.4 (90), 226.5 (79), 344.1 (100), 345.7 (87), 362.1 (M$^+$, 15).

IR (KBr): ν = 3017, 2968, 2649, 2310, 2097, 1586, 1482, 1259, 972 (cm$^{-1}$)

HRMS (ESI) 362.1213, calcd. for [M+H$^+$]: 362.1215.

6-Nitro-1-methyl-3,4-diphenyl benzothiazine 1-oxide (76d)

Following the general procedure, 1,2-benzothiazine 76d was obtained as reddish solid in 72% yield (134.7 mg). A gradient of n-hexane/EtOAc: 2/1 was applied as eluent for the flash column chromatography purification.

Melting point: 125-127 °C

$^1$H NMR (400 MHz, CDCl3) δ = 8.17 (dd, J = 8.7, 2.2 Hz, 1H), 8.11 (d, J = 2.0 Hz, 1H), 8.01 (d, J = 8.7 Hz, 1H), 7.36 – 7.25 (m, 5H), 7.18 – 7.09 (m, 5H), 3.77 (s, 3H) (ppm).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ = 150.0, 148.7, 139.5, 138.3, 136.4, 132.3, 129.7, 129.0, 128.1, 127.7, 125.1, 121.8, 121.3, 119.9, 113.5, 45.0 (ppm).

MS (EI): m/z = 104.7 (21), 152.4 (17), 181.8 (16), 245.4 (100), 377.6 (M$^+$, 16).

IR (KBr): ν = 3016, 2933, 2336, 2110, 1889, 1739, 1559, 1446, 1254, 974 (cm$^{-1}$)

HRMS (ESI) 377.0962, calcd. for [M+H$^+$]: 377.0960.
6-Chloro-1-methyl-3,4-diphenyl benzothiazine 1-oxide (76e)

Following the general procedure, 1,2-benzothiazine 76e was obtained as bright yellow solid in 79% yield (144.5 mg). A gradient of n-hexane/EtOAc: 5/1 was applied as eluent for the flash column chromatography purification.

Melting point: 163-165 °C.

$^1$H NMR (600 MHz, CDCl$_3$): $\delta = 7.79$ (d, $J = 8.5$ Hz, 1H), 7.37 (d, $J = 8.5$ Hz, 1H), 7.26 (m, 5H), 7.17 (d, $J = 1.9$ Hz, 1H), 7.15 – 7.08 (m, 5H), 3.67 (s, 3H) (ppm).

$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta = 147.6$, 139.9, 138.9, 138.6, 137.0, 132.3, 129.5, 128.5, 127.5, 127.4, 127.0, 126.4, 125.4, 125.0, 116.5, 112.1, 45.4 (ppm).

MS (EI): $m/z = 63.3$ (27), 76.9 (100), 102.4 (76), 151.1 (14), 163.3 (15), 177.6 (13), 182.3 (12), 246.9 (3).

IR (KBr): $\nu = 3015$, 2923, 2323, 2071, 1891, 1739, 1559, 1446, 1254, 1094 (cm$^{-1}$).


6-Bromo-1-methyl-3,4-diphenyl benzothiazine 1-oxide (76f)

Following the general procedure, 1,2-benzothiazine 76f was obtained as bright yellow solid in 81% yield (166.2 mg). A gradient of n-hexane/EtOAc: 5/1 was applied as eluent for the flash column chromatography purification.

Melting point: 207-208 °C.

$^1$H NMR (600 MHz, CDCl$_3$): $\delta = 7.71$ (d, $J = 8.5$ Hz, 1H), 7.51 (d, $J = 17.5$, 8.8 Hz, 1H), 7.34 (t, $J = 8.9$ Hz, 1H), 7.30 – 7.22 (m, 5H), 7.18 – 7.03 (m, 5H), 3.66 (s, 3H) (ppm).

$^{13}$C NMR (151 MHz, CDCl$_3$) $\delta = 147.6$, 139.9, 138.6, 136.9, 132.3, 129.5, 129.2,
128.6, 128.5, 127.54, 127.52, 127.4, 127.1, 124.9, 116.9, 112.0, 45.3 (ppm).

MS (EI): \textit{m/z} = 51.7 (40), 76.9 (99), 103.5 (63), 105.2 (80), 120.6 (12), 138.3 (24), 150.1 (46), 161.5 (87), 163.0 (76), 177.3 (22), 181.6 (84), 183.3 (100), 188.0 (29), 208.9 (70), 211.8 (76), 409.6 (\textit{M}^+, 31).

IR (KBr): \textit{v} = 3008, 2922, 2315, 1739, 1571, 1461, 1199, 961 (cm$^{-1}$)


1,3,4-Triphenyl benzothiazine 1-oxide (76g)

Following the general procedure, 1,2-benzothiazine 76g was obtained as brownish thick oil in 85% yield (167.2 mg). A gradient of \textit{n}-hexane/EtOAc: 4/1 was applied as eluent for the flash column chromatography purification.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 8.11 (m, 2H), 7.68 – 7.57 (m, 3H), 7.41 – 7.19 (m, 11H), 7.15 – 7.06 (m, 3H) (ppm).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ = 146.2, 140.7, 140.0, 138.0, 136.9, 133.6, 132.6, 131.9, 129.85, 129.8, 129.1, 128.5, 127.4, 127.3, 126.9, 126.1, 125.8, 125.0, 119.6, 112.8 (ppm).

MS (EI): \textit{m/z} = 51.7 (21), 163.0 (32), 177.3 (22), 181.6 (84), 183.3 (100), 188.0 (29), 208.9 (70), 211.8 (76), 393.2 (\textit{M}^+, 6).

IR (KBr): \textit{v} = 3057, 2931, 1739, 1581, 1450, 1241, 1100, 911 (cm$^{-1}$)

1-Methyl-3,4-bis(4-methoxyphenyl) benzothiazine 1-oxide (76h)

Following the general procedure, 1,2-benzothiazine 76h was obtained as pale yellow solid in 93% yield (182.1 mg). A gradient of n-hexane/EtOAc: 4/1 was applied as eluent for the flash column chromatography.

Melting point: 105-107 °C.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 7.84 – 7.79 (d, $J$ = 20 Hz, 1H), 7.44 – 7.39 (m, 2H), 7.24 – 7.20 (m, 3H), 7.06-7.04 (d, $J$ = 8.0Hz, 2H), 6.85-6.83 (d, $J$ = 8.0 Hz, 2H), 6.67 – 6.65 (m, 2H), 3.80 (s, 3H), 3.72 (s, 3H), 3.65 (s, 3H) (ppm).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ = 158.6, 158.3, 145.5, 137.4, 133.4, 132.9, 132.2, 131.0, 130.1, 126.0, 125.8, 123.2, 118.6, 113.9, 112.8, 111.7, 55.2, 55.1, 45.5 (ppm).

MS (EI): $m/z$ = 63.3 (27), 76.9 (100), 102.4 (76), 151.1 (14), 163.3 (15), 177.6 (13), 182.3 (12), 246.9 (3), 391.6 (M$^+$, 12).

IR (KBr): $\nu$ = 3010, 2835, 2283, 2058, 1964, 1893, 1739, 1596, 1454, 1229 (cm$^{-1}$)


1-Methyl-3,4-bis(4-fluorophenyl) benzothiazine 1-oxide (76i)

Following the general procedure, 1,2-benzothiazine 76i was obtained as pale yellow thick oil in 82% yield (150.6 mg). A gradient of n-hexane/EtOAc: 4/1 was applied as eluent for the flash column chromatography.

$^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.87 = (d, $J$ = 7.9 Hz, 1H), 7.46 (m, 2H), 7.27 – 7.22
(m, 2H), 7.17 (d, $J = 8.8$ Hz, 1H), 7.09 (s, 2H), 6.99 (t, $J = 8.6$ Hz, 2H), 6.82 (t, $J = 8.7$ Hz, 2H), 3.68 (s, 3H) (ppm).

$^{13}$C NMR (151 MHz, CDCl$_3$) $\delta =$ 162.6 ($J_{C-F} = 17.6$ Hz), 161.0 ($J_{C-F} = 16.7$ Hz), 145.3, 136.7, 136.2 ($J_{C-F} = 3.3$ Hz), 133.9 ($J_{C-F} = 7.8$ Hz), 133.4 ($J_{C-F} = 3.5$ Hz), 132.5, 131.4 ($J_{C-F} = 8.1$ Hz), 126.4, 125.8, 123.4, 118.7, 115.5 ($J_{C-F} = 20.9$ Hz), 114.5, 114.4, 111.6, 45.1 (ppm).

$^{19}$F NMR (564 MHz, CDCl$_3$) $\delta = -114.2, -115.1$ (ppm).

MS (EI): $m/z =$ 64.1 (35), 131.2 (100), 102.4 (76), 151.1 (14), 163.3 (15), 368.2 ($M^+$, 12).

IR (KBr): $\nu =$ 3023, 2319, 2049, 1739, 1593, 1461, 1366, 1210, 1098, 965 (cm$^{-1}$).

HRMS (ESI): 368.0913, calcd. for [M+H$^+$]: 368.0921.

1-Methyl-3,4-bis(4-chlorophenyl) benzothiazine 1-oxide (76j)

Following the general procedure, 1,2-benzothiazine 76j was obtained as pale yellow solid in 86% yield (171.9 mg). A gradient of $n$-hexane/EtOAc: 4/1 was applied as eluent for the flash column chromatography.

Melting point: 185-187 $^\circ$C.

$^1$H NMR (600 MHz, CDCl$_3$) $\delta =$ 7.86 (d, $J = 7.9$ Hz, 1H), 7.47 (m, 2H), 7.27 (d, $J = 8.6$ Hz, 2H), 7.22 – 7.18 (m, 2H), 7.15 (d, $J = 8.2$ Hz, 1H), 7.12 (m, 2H), 7.06 (d, $J = 7.7$ Hz, 2H), 3.68 (s, 3H) (ppm).

$^{13}$C NMR (151 MHz, CDCl$_3$) $\delta =$ 145.0, 138.5, 136.4, 136.0, 133.7, 133.4, 133.0, 132.6, 131.0, 128.8, 127.8, 126.6, 125.8, 123.4, 118.8, 111.7, 45.1 (ppm).

MS (EI): $m/z =$ 64.1 (35), 131.2 (100), 102.4 (76), 151.1 (14), 163.3 (15), 400.0 ($M^+$, 7).
IR (KBr): $\nu = 3016, 2928, 2319, 2073, 1909, 1738, 1575, 1462, 1208, 1091, 968$ (cm$^{-1}$).

HRMS (ESI): 400.0327, calcd. for [M+H$^+$]: 400.0330.

1-Methyl-3,4-di(thiophen-2-yl) benzothiazine 1-oxide (76k)

Following the general procedure, 1,2-benzothiazine 76k was obtained as yellow thick oil in 87% yield (149.4 mg). A gradient of $n$-hexane/EtOAc: 5/1 was applied as eluent for the flash column chromatography.

$^1$H NMR (600 MHz, CDCl$_3$) $\delta = 7.80$ (d, $J = 9.0$ Hz, 1H), 7.54 (d, $J = 4.1$ Hz, 1H), 7.51 – 7.43 (m, 1H), 7.41 – 7.34 (m, 1H), 7.28 – 7.23 (m, 1H), 7.22 – 7.15 (m, 2H), 7.00 (d, $J = 3.4$ Hz, 1H), 6.95 (d, $J = 3.8$ Hz, 1H), 6.89 – 6.85 (m, 1H), 3.64 (s, 3H) (ppm).

$^{13}$C NMR (151 MHz, CDCl$_3$) $\delta = 143.3, 141.3, 138.6, 137.8, 132.7, 130.4, 129.1, 128.5, 128.0, 127.9, 126.9, 126.2, 126.1, 123.1, 119.1, 102.5, 45.2$ (ppm).

MS (EI): $m/z = 63.3$ (27), 76.9 (100), 102.4 (76), 151.1 (14), 163.3 (15), 177.6 (13), 182.3 (12), 246.9 (3).

IR (KBr): $\nu = 3072, 3011, 2924, 2327, 2100, 1738, 1567, 1460, 1306, 1219, 1078, 965$ (cm$^{-1}$)

HRMS (ESI): 344.0230, calcd. for [M+H$^+$]: 344.0238.

1-Methyl-3,4-diethyl benzothiazine 1-oxide (76l)

Following the general procedure, 1,2-benzothiazine 76l was obtained as brownish
thick oil in 67% yield (78.8 mg). A gradient of \( n \)-hexane/EtOAc: 5/1 was applied as eluent for the flash column chromatography.

\(^1\)H NMR (600 MHz, CDCl\(_3\)) \( \delta = 7.78 \) (d, \( J = 7.9 \) Hz, 1H), 7.63 – 7.55 (m, 2H), 7.39 (d, \( J = 6.6 \) Hz, 1H), 3.52 (s, 3H), 2.68 – 2.48 (m, 4H), 1.28 – 1.26 (t, \( J = 7.5 \) Hz, 3H), 1.19 – 1.17 (t, \( J = 7.5 \) Hz, 3H) (ppm).

\(^{13}\)C NMR (151 MHz, CDCl\(_3\)) \( \delta = 149.0, 136.2, 132.3, 124.9, 123.5, 123.2, 119.1, 108.5, 44.4, 28.8, 20.4, 14.6, 13.3 \) (ppm).

MS (EI): \( m/z = 64.1 \) (35), 148.2 (100), 178.6 (29), 235.2 (M\(^+\), 23).

IR (KBr): \( \nu = 3057, 2959, 2331, 1737, 1579, 1454, 1230, 1098, 1025, 972 \) (cm\(^{-1}\)).

HRMS (ESI): 236.1109, calcd. for [M+H\(^+\)]: 236.1109.

1-Methyl-3,4-dipropyl benzothiazine 1-oxide (76m)

\[ \text{O} \quad \text{Me} \quad \text{N} \]
\[ \text{Me} \ 
\text{n-Pr} \]

Following the general procedure, 1,2-benzothiazine 76m was obtained as brownish thick oil in 72% yield (94.8 mg). A gradient of \( n \)-hexane/EtOAc: 5/1 was applied as eluent for the flash column chromatography.

\(^1\)H NMR (600 MHz, CDCl\(_3\)) \( \delta = 7.74 \) (d, \( J = 7.9 \) Hz, 1H), 7.57 (t, \( J = 8.4 \) Hz, 1H), 7.52 (d, \( J = 8.3 \) Hz, 1H), 7.35 (t, \( J = 7.2 \) Hz, 1H), 3.48 (s, 3H), 2.57 – 2.38 (m, 4H), 1.72 (m, 2H), 1.53 (m, 2H), 1.00 (m, 6H) (ppm).

\(^{13}\)C NMR (151 MHz, CDCl\(_3\)) \( \delta = 147.9, 136.4, 132.3, 124.9, 123.5, 119.1, 107.9, 44.4, 37.5, 29.6, 23.2, 22.1, 14.4, 14.1 \) (ppm).

MS (EI): \( m/z = 123.1 \) (23), 163.2 (100), 192.6 (37), 263.2 (M\(^+\), 7).

IR (KBr): \( \nu = 3047, 2949, 2326, 1745, 1579, 1454, 1230, 1087, 1025, 972 \) (cm\(^{-1}\)).

1,4-Dimethyl-3-phenyl benzothiazine 1-oxide and 1,3-dimethyl-4-phenyl benzothiazine 1-oxide (76n and 76n’)

![Chemical structure of compounds 76n and 76n']

Following the general procedure, 1,2-benzothiazines 76n and 76n’ were obtained as pale yellow solid in a combined 82% yield (110.5 mg) with an isomeric ratio of 85:15, which was determined by 1H-NMR. A gradient of n-hexane/EtOAc: 5/1 was applied as eluent for the flash column chromatography.

Melting point: 156-158 °C.

1H NMR (600 MHz, CDCl3) δ = 7.83 (d, J = 7.5 Hz, 1H, major), 7.78 (d, J = 9.2 Hz, 0.2H, minor), 7.70 – 7.64 (m, 2H, major), 7.55 – 7.53 (m, 2H, major), 7.47 (m, 1H, major), 7.41 (t, J = 6.8 Hz, 2H, major), 7.34 (m, 1H, major), 7.21 (d, J = 7.1 Hz, 0.2H, minor), 6.89 (d, J = 9.0 Hz, 0.1H, minor), 3.61 (s, 3H, major), 3.60 (s, 0.5H, minor), 2.21 (s, 3H, major), 2.01 (s, 0.5H, minor) (ppm).

13C NMR (151 MHz, CDCl3, major+minor) δ = 145.4, 145.0, 140.4, 136.9, 132.4, 132.3, 129.7, 127.9, 127.0, 125.9, 125.5, 125.2, 124.3, 123.2, 123.0, 119.9, 104.4, 45.1, 44.1, 23.8, 15.5 (ppm).

MS (EI): m/z = 64.1 (35), 148.2 (100), 178.6 (29), 201.6 (13), 269.2 (M+, 27).

IR (KBr): ν = 3002, 2924, 2853, 1737, 1574, 1463, 1205 (cm⁻¹).

HRMS (ESI): 270.0964, calcd. for [M+H⁺]: 270.0953.

4-Methyl carboxylate-1-methyl-3-phenyl benzothiazine 1-oxide (76o)

![Chemical structure of compound 76o]

Following the general procedure, 1,2-benzothiazine 76o obtained as pale yellow solid in 82% yield (128.4 mg). A gradient of n-hexane/EtOAc: 5/1 was applied as eluent for
the flash column chromatography. The structure was confirmed by NOESY.

Melting point: 168-169 °C.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta = 7.96$ (d, $J = 8.4$ Hz, 1H), 7.77 (d, $J = 8.0$ Hz, 1H), 7.60 (t, $J = 7.2$ Hz, 1H), 7.52 (dd, $J = 7.7$, 1.8 Hz, 2H), 7.41 (t, $J = 8.1$ Hz, 1H), 7.37 – 7.24 (m, 3H), 3.52 (s, 3H), 3.39 (s, 3H) (ppm).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta =$ 169.4, 152.8, 140.2, 133.8, 133.3, 129.0, 128.2, 128.1, 126.7, 124.9, 123.4, 117.3, 105.4, 51.8, 45.0 (ppm).

MS (EI): $m/z$ = 58.1 (26), 131.2 (100), 178.6 (29), 201.6 (13), 269.2 (13).

IR (KBr): $\nu =$ 3011, 2637, 1737, 1564, 1464, 1358, 1278, 1203, 1128, 915 (cm$^{-1}$).


3-(4-Methoxyphenyl)-1-methyl-4-phenyl benzothiazine 1-oxide and 4-(4-methoxyphenyl)-1-methyl-3-phenyl benzothiazine 1-oxide ($76p$ and $76p'$)

Following the general procedure, 1,2-benzothiazines $84p$ and $84p'$ were obtained as pale yellow solid in a combined 90% yield (162.6 mg) with an isomeric ratio of 50:50, which was determined by $^1$H-NMR. A gradient of n-hexane/EtOAc: 5/1 was applied as eluent for the flash column chromatography.

Melting point: 104-106 °C.

$^1$H NMR (600 MHz, CDCl$_3$) $\delta =$ 7.85 (dd, $J = 3.5$, 1.3 Hz, 1H), 7.84 (dd, $J = 3.5$, 1.3 Hz, 1H), 7.46 – 7.38 (m, 4H), 7.31 – 7.27 (m, 4H), 7.25 – 7.21 (m, 4H), 7.21 – 7.03 (m, 8H), 6.82 (d, $J = 8.6$ Hz, 2H), 6.66 – 6.63 (m, 2H), 3.79 (s, 3H), 3.71 (s, 3H), 3.67 (d, $J = 2.0$ Hz, 6H) (ppm).

$^{13}$C NMR (151 MHz, CDCl$_3$) $\delta =$ 158.9, 158.5, 146.1, 145.6, 140.6, 138.2, 137.4, 137.2, 133.9, 133.5, 132.8, 132.6, 132.5, 131.2, 129.9, 129.7, 129.3, 128.6, 127.6, 127.3, 126.9, 126.6, 126.3, 125.2, 123.9, 118.9, 118.6, 114.0, 112.9, 112.4, 55.32,
55.29, 45.29, 45.24 (ppm).

MS (EI): \( m/z = 64.1 \) (35), 131.2 (100), 102.4 (76), 151.1 (14), 163.3 (15), 361.4 (M⁺, 7).

IR (KBr): \( \nu = 3014, 2927, 2837, 1740, 1594, 1505, 1458, 1241 \) (cm⁻¹).

HRMS (ESI): 362.1203, calcd. for [M+H⁺]: 362.1215.

1-Methyl-3-(4-nitrophenyl)-4-phenyl benzothiazine 1-oxide and 1-methyl-4-(4-nitrophenyl)-3-phenyl benzothiazine 1-oxide (76q and 76q’)

Following the general procedure, 1,2-benzothiazines 76q and 76q’ were obtained as brownish thick oil in a combined 80% yield (150.6 mg) with an isomeric ratio of 50:50, which was determined by \(^1\)H-NMR. A gradient of \( n \)-hexane/EtOAc: 3/1 was applied as eluent for the flash column chromatography.

\(^1\)H NMR (600 MHz, CDCl₃, mixture) \( \delta = 8.13 \) (d, \( J = 8.9 \) Hz, 2H), 7.96 (d, \( J = 9.0 \) Hz, 2H), 7.91 – 7.88 (m, 2H), 7.53 – 7.47 (m, 4H), 7.43 (d, \( J = 9.0 \) Hz, 2H), 7.33 – 7.28 (m, 5H), 7.23 – 7.19 (m, 3H), 7.16 – 7.10 (m, 6H), 3.71 (s, 3H), 3.71 (s, 3H) (ppm).

\(^{13}\)C NMR (151 MHz, CDCl₃, mixture) \( \delta = 147.3, 147.0, 146.53, 146.49, 145.6, 143.2, 139.6, 136.7, 133.4, 132.8, 132.6, 132.2, 130.5, 129.4, 127.9, 127.8, 127.5, 127.1, 126.6, 126.5, 125.2, 123.6, 123.5, 123.3, 122.6, 45.1, 45.0 \) (ppm).

MS (EI): \( m/z = 63.3 \) (27), 76.9 (32), 102.4 (100), 151.1 (14), 163.3 (15), 177.6 (13), 182.3 (12), 246.9 (3).

IR (KBr): \( \nu = 3024, 2928, 1737, 1584, 1464, 1333, 1213, 1101, 972 \) (cm⁻¹).

1-Methyl-3-(naphthalen-1-yl)-4-phenyl benzothiazine 1-oxide and 1-methyl-4-(naphthalen-1-yl)-3-phenyl benzothiazine 1-oxide (76r and 76r')

Following the general procedure, 1,2-benzothiazines 76r and 76r' were obtained as brownish thick oil in a combined 78% yield (148.8 mg) with an isomeric ratio of 50:50, which was determined by $^1$H-NMR. A gradient of n-hexane/EtOAc: 5/1 was applied as eluent for the flash column chromatography.

$^1$H NMR (600 MHz, CDCl$_3$, mixture) $\delta = 7.88$ (d, $J = 8.5$ Hz, 1H), 7.85 (s, 1H), 7.70 – 7.62 (m, 3H), 7.54 (d, $J = 8.5$ Hz, 1H), 7.49 – 7.32 (m, 7H), 7.29 – 7.16 (m, 7H), 7.07 – 7.03 (m, 1H), 3.73 (s, 3H), 3.72 (s, 1H) (ppm).

$^{13}$C NMR (151 MHz, CDCl$_3$, mixture) $\delta = 146.3, 145.7, 140.2, 137.7, 137.68, 136.9, 132.8, 132.5, 132.47, 132.4, 131.3, 130.6, 129.6, 129.4, 128.5, 128.4, 127.9, 127.6, 127.5, 127.46, 127.34, 127.32, 126.9, 126.6, 126.2, 126.16, 126.0, 125.9, 125.8, 125.7, 123.3, 118.7, 118.66, 113.1, 112.6, 45.2, 45.1 (ppm).

MS (EI): $m/z = 63.3$ (27), 76.9 (100), 102.4 (76), 151.1 (14), 163.3 (15), 177.6 (13), 182.3 (12), 246.9 (3), 352.1 (27), 382.1 (M$^+$, 17).

IR (KBr): $\nu = 3052, 2926, 1740, 1567, 1463, 1200, 982$ (cm$^{-1}$).


Sulfoximine 61a-d$_1$:

$^1$H NMR (600 MHz, CDCl$_3$) $\delta = 8.02$ (d, $J = 8.6$ Hz, 1H), 7.62 (t, $J = 7.4$ Hz, 1H), 7.56 (t, $J = 7.0$ Hz, 2H), 3.12 (s, 3H), 2.47 (s, NH) (ppm).

$^{13}$C NMR (151 MHz, CDCl$_3$) $\delta = 143.5, 133.3, 129.4, 129.3, 127.81, 127.59$ ($J_{C-D}$=25.6Hz), 46.3 (ppm).

1-Methyl-3,4-diphenyl benzothiazine 1-oxide (76a-d₁+76a)

Following the general procedure, 1,2-benzothiazines 76a-d₁ and 76a were obtained as pale yellow solid in 56% yield. A gradient of n-hexane/EtOAc: 5/1 was applied as eluent for the flash column chromatography.

\[^1^H\text{ NMR}\ (600\ MHz, CDCl}_3\) \(\delta = 7.87\ (d, J = 7.2\ Hz, 0.55H), 7.50 - 7.45\ (m, 1H), 7.45 - 7.40\ (m, 1H), 7.31 - 7.21\ (m, 5H), 7.18 - 7.08\ (m, 5H), 3.69\ (s, 3H)\) (ppm).

\[^{13}C\text{ NMR}\ (151\ MHz, CDCl}_3\) \(\delta = 146.1, 140.4, 137.8, 137.0, 132.6, 132.5, 129.7, 128.5, 127.5, 127.4, 126.9, 126.3, 126.2, 126.0, 123.3, 118.7, 112.8, 77.37, 77.16, 76.95, 45.2\) (ppm).

HRMS (ESI): 333.1164, calcd. for [M+H⁺]: 333.1172.

Crude Rhodacycle II:

\[^1^H\text{ NMR}\ (600\ MHz, CDCl}_3\) \(\delta = 8.02\ (d, J = 7.6\ Hz, 2H), 7.83\ (d, J = 7.7\ Hz, 1H), 7.60\ (m, 3H), 7.40\ (t, J = 7.3\ Hz, 2H), 7.15\ (t, J = 7.4\ Hz, 1H), 3.32\ (s, 3H), 3.14\ (s, 3H), 1.64\ (s, 15H)\) (ppm).

\[^{13}C\text{ NMR}\ (151\ MHz, CDCl}_3\) \(\delta = 167.63\ (J_{C-Rh} = 32.3\ Hz), 144.1, 138.5, 133.3, 129.5, 127.9, 126.1, 124.1, 95.19, 50.22, 9.3\) (ppm).

IR: \(v(B-F) = 1042\ (cm^{-1})\).

HRMS (ESI): 392.0542 (pos), 87.0036 (neg), calcd. for \([C_{17}H_{22}NOSRh+H⁺]\): 392.0544 (pos), \([BF_4]⁻\): 87.0035 (neg).
Rhodacycle II’:

Following the described procedure, rhodacycle II’ was obtained as reddish solid. A gradient of n-hexane/EtOAc: 1/1 was applied as eluent for the flash column chromatography (neutral Al₂O₃).

¹H NMR (600 MHz, CDCl₃) δ = 7.72 (d, J = 7.7 Hz, 1H), 7.36 (m, 2H), 7.11 (t, J = 8.0 Hz, 1H), 3.27 (s, 3H), 1.74 (s, 15H) (ppm).

¹³C NMR (151 MHz, CDCl₃) δ = 166.21 (d, J_C-Rh = 31.7 Hz), 143.2, 140.5, 133.0, 125.9, 124.0, 96.0, 48.2, 10.0 (ppm).

HRMS (ESI): 517.9552, calcd. for [C₁₇H₂₂NSOIRh]: 517.9522.

N-Benzoyl-2-benzoyl-S-phenyl sulfoximine (77a)

Following the described procedure, N-Benzoyl-2-benzoyl-S-phenyl sulfoximine 85a was obtained as white solid in 96% yield. EtOAc was applied as eluent for the flash column chromatography.

Melting point: 150-151 °C.

¹H NMR (600 MHz, CDCl₃) δ = 8.32 (d, J = 7.5 Hz, 1H), 7.78 – 7.70 (m, 4H), 7.55 (d, J = 8.3 Hz, 2H), 7.43 – 7.39 (m, 2H), 7.30 – 7.22 (m, 3H), 7.04 (t, J = 7.8 Hz, 2H), 3.70 (s, 3H) (ppm).

¹³C NMR (151 MHz, CDCl₃) δ = 195.6, 174.5, 139.3, 137.9, 135.7, 134.9, 134.1, 133.0, 131.6, 130.8, 130.5, 130.1, 129.1, 128.9, 128.6, 127.5, 46.0 (ppm).

MS (EI): m/z = 104.7 (16), 195.4 (35), 243.7 (100), 364.0 (M⁺, 2).

IR(KBr): ν = 3015, 2927, 2325, 1739, 1660, 1615, 1450, 1261, 984 (cm⁻¹).

N-Benzoyl-2-benzoyl-S-4-nitrophenyl sulfoximine (77b)

Following the described procedure, N-Benzoyl-2-benzoyl-S-4-nitrophenyl sulfoximine 85b was obtained as white solid in 82% yield. EtOAc was applied as eluent for the flash column chromatography. Melting point: 179-181 °C.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta = 8.55$ (d, $J = 3.4$ Hz, 2H), 8.23 (s, 1H), 7.71 (d, $J = 7.1$ Hz, 2H), 7.57 (d, $J = 7.1$ Hz, 2H), 7.39 (t, $J = 7.4$ Hz, 1H), 7.33 – 7.21 (m, 4H), 7.12 – 7.05 (m, 2H), 3.68 (s, 3H) (ppm).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta = 193.4$, 174.5, 150.0, 144.2, 141.1, 134.9, 134.5, 134.2, 132.3, 132.2, 130.8, 129.3, 128.9, 127.7, 125.2, 123.7, 46.1 (ppm).

MS (EI): $m/z = 409.1$ (M$^+$, 3).

IR(KBr): $\nu = 3015$, 2610, 2184, 1665, 1615, 1448, 1368, 1264, 1123, 979 (cm$^{-1}$).


N-Benzoyl-2-benzoyl-S-4-bromophenyl sulfoximine (77c)

Following the described procedure, N-Benzoyl-2-benzoyl-S-4-bromophenyl sulfoximine 85c was obtained as white solid in 82% yield. EtOAc was applied as eluent for the flash column chromatography. Melting point: 171-173 °C.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta = 8.16$ (d, $J = 8.5$ Hz, 1H), 7.87 (dd, $J = 8.5$, 2.0 Hz, 1H), 7.73 (d, $J = 7.1$ Hz, 2H), 7.55 (dd, $J = 6.4$, 5.1 Hz, 3H), 7.40 (t, $J = 7.4$ Hz, 1H), 7.31 – 7.22 (m, 3H), 7.05 (t, $J = 7.8$ Hz, 2H), 3.65 (s, 3H) (ppm).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta = 194.0$, 174.4, 140.8, 137.0, 135.1, 134.7, 134.4,
133.7, 131.8, 131.76, 131.67, 130.8, 129.2, 128.7, 128.4, 127.6, 46.3 (ppm).

MS (EI): $m/z = 105.1 (13), 195.4 (25), 243.7 (90), 443.1 (M^+, 3)$.

IR(KBr): $\nu = 3019, 2601, 2320, 1739, 1666, 1615, 1450, 1370, 1219, 1118, 984$ (cm$^{-1}$).

HRMS (ESI): 444.0075, calcd. for [M+H$^+$]: 444.0092.
Part III Rhodium-Catalyzed Sulfoximine-Directed \textit{ortho}-C-H Addition Reaction

1 Research Objective

Until now, several examples of metal-catalyzed directing group-assisted C-H additions to activated alkenes or inactivated alkenes have been reported. However, the \textit{ortho}-C-H addition to heterobicyclic alkenes has not yet been well documented. Bicyclic alkenes such as oxa- and azabenzonorbornadienes, can be readily activated by transition metal complexes. Thus Bolm’s group demonstrated an example of rhodium-catalyzed intermolecular hydroacylation reaction of salicylaldehydes with 1,4-epoxy-1,4-dihydro naphthalenes to give ketone products in moderate to good yields (Scheme 41, eq. A).\textsuperscript{43} In this chapter we will disclose an \textit{ortho}-alkylation reaction of NH-sulfoximines with heterobicyclic alkenes by a new Rh(III)-catalyzed C-H bond activation pathway (Scheme 41, eq. B).

\textbf{Scheme 41} Research objective

\begin{equation}
\begin{array}{cc}
\text{78} & \text{79a} \\
\text{K}_3\text{PO}_4, \text{DCE}, 80 \degree \text{C} & \text{80} \\
& \text{Eq. A}
\end{array}
\end{equation}

\begin{equation}
\begin{array}{cc}
\text{61a} & \text{79a} \\
\text{transition metal complex} & \text{81a} \\
\text{solvent, temp., time} & \text{Eq. B}
\end{array}
\end{equation}
2 Results and Discussions

The reaction of NH-sulfoximine 61a with oxa-bicyclic alkene 79a under annulation reaction conditions (Table 3, on page 33) gave the addition product 81a in only 62% yield. Interestingly, elevated reaction temperature (120 °C) increased the yield dramatically, affording the addition product in 89% yield (Scheme 42).

Scheme 42 Temperature influence on the reaction

[Diagram showing the reaction and yield at different temperatures]
3 Substrate Scope

Table 4 Substrate scope

![Reaction Scheme]

<table>
<thead>
<tr>
<th>Entry</th>
<th>61</th>
<th>79</th>
<th>81</th>
<th>R¹</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>61a</td>
<td>79a</td>
<td></td>
<td>81a: R¹ = H</td>
<td>89</td>
</tr>
<tr>
<td>2</td>
<td>61b</td>
<td>79a</td>
<td></td>
<td>81b: R¹ = 3-Me</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>61c</td>
<td>79a</td>
<td></td>
<td>81c: R¹ = 4-OMe</td>
<td>92</td>
</tr>
<tr>
<td>4</td>
<td>61d</td>
<td>79a</td>
<td></td>
<td>81d: R¹ = 4-NO₂</td>
<td>72</td>
</tr>
<tr>
<td>5</td>
<td>61e</td>
<td>79a</td>
<td></td>
<td>81e: R¹ = 4-Cl</td>
<td>79</td>
</tr>
<tr>
<td>6</td>
<td>61f</td>
<td>79a</td>
<td></td>
<td>81f: R¹ = 4-Br</td>
<td>79</td>
</tr>
<tr>
<td>7</td>
<td>61h</td>
<td>79a</td>
<td></td>
<td>81g: R¹ = 4-Me</td>
<td>88</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>81h</td>
<td></td>
<td>79</td>
</tr>
<tr>
<td>8</td>
<td>61i</td>
<td>79a</td>
<td></td>
<td>81i: R¹ = Et</td>
<td>88</td>
</tr>
<tr>
<td>9</td>
<td>61j</td>
<td>79a</td>
<td></td>
<td>81j: R¹ = i-Pr</td>
<td>78</td>
</tr>
</tbody>
</table>

61
Under standard reaction conditions, we examined the scope of the present reaction by using a variety of NH-sulfoximines (61a-f and 61h-k) with oxabicyclic alkenes (79a-d) (Table 4). Thus, the reaction of meta-methylphenyl NH-sulfoximine (61b) with 134a gave the regioselective product 136b in good yield (90%). Substrates with electron donating substituents such as 4-methoxyphenyl and 4-methylphenyl NH-sulfoximines (61h and 61c) underwent the C-H addition reaction with alkene 79a, affording the desired products 81c and 81g in 92% and 88% yields (entries 3 and 7). Halogen substituted NH-sulfoximines were compatible with the present reaction conditions. Interestingly, S-4-chlorophenyl-, and S-4-bromophenyl-S-methyl NH-sulfoximines 61e-f reacted well with alkene 79a to give the desired products 81e-f in 79% yield equally (entries 5-6). Notably, electron withdrawing substituent such as S-4-nitrophenyl-S-methyl NH-sulfoximine gave a moderate yield (72% for entry 4). The reaction of 2-naphthyl NH-sulfoximine (61h) with 79a, afforded 81h in 79% yield (entry 6). In this case, there were two possible C-H bond activation sites at
C1 and C3 positions of 61h. However, the activation occurred exclusively at C3 position, most likely due to the steric influence of the fused aromatic ring. The effect of other substituents on the yields were also investigated. Thus, S-phenyl-S-ethyl sulfoximine (61i) and S-phenyl-S-isopropyl sulfoximine (61j) reacted with 79a providing 81i and 81j in 88% and 78% yields, respectively (entries 9-10). The scope of the C-H activation/addition reaction was further extended to various bicyclic alkenes. Thus, bulky 1,4-oxa-1,4-dihydrotriphenylene (79b) reacted well with 61a to afford the corresponding addition product 81k in 78% yield (entry 11). In a similar manner, the reaction of electron donating 6,7-methylenedioxy alkene 79c reacted with 61a affording the ortho-alkylation product 81m in 80% yield (entry 13). Interestingly, 7-azabenzenorbornadine 79d reacted smoothly with 61a to give 81m in good yield (82% for entry 13). In addition the structure of 81m was further confirmed by single crystal X-ray diffraction (Figure 5).

**Figure 5** ORTEP Diagram and X-ray Data of of 81n (CCDC No. 945223)

4 Summary

In summary, we have developed a rhodium-catalyzed process for the synthesis of tetrahydro-epoxynaphthyl substituted sulfoximines from NH-sulfoximines and alkenes. The combination of simple Fe(OAc)₂ (20 mol %) and O₂ (1 atm) allows the
metal reoxidation to close the catalytic cycle. The method is high-yielding and suitable for the synthesis of various functionalized tetrahydro-epoxynaphthyl sulfoximines.

5 Experimental Part

A Schlenk tube (20 mL) equipped with a stirring bar was loaded with the NH-sulfoximine (0.5 mmol), oxabicyclic alkene (0.6 mmol), [Cp*Rh(MeCN)₃][BF₄]₂ (13.5 mg, 0.025 mmol, 5 mol %) and Fe(OAc)₂ (18 mg, 0.1 mmol, 20 mol %). Under an oxygen atmosphere (1 atm), dry toluene (3.0 mL) was added, and the reaction mixture was allowed to stir at 120 °C for 4 h. After cooling to room temperature, the mixture was filtered through a short celite pad and washed with dichloromethane (3 × 20 mL). The filtrate was concentrated, and the product was purified by flash column chromatography using silica gel with a mixture of hexane and ethyl acetate as eluent.

6 Data and Characterization

S-Phenyl-S-methyl-2-(1’,2’,3’,4’-tetrahydro-1’,4’-epoxynaphthyl) sulfoximine (81a)

Following the general procedure, product 81a was obtained as off-white foamy solid in 85% yield (127.2 mg). A gradient of n-hexane/EtOAc: 3/1 was applied as eluent for the flash column chromatography purification.

Melting point: 69-71 °C

¹H NMR (600 MHz, CDCl₃) δ = 8.11 (d, J = 6.6 Hz, 1H), 7.89 (d, J = 7.9 Hz, 1H), 7.60 (t, J = 7.6 Hz, 1H), 7.40 – 7.35 (m, 1H), 7.32 – 7.26 (m, 2H), 7.20 – 7.16 (m, 2H),
5.58 (d, \( J = 4.8 \) Hz, 1H), 5.20 (s, 1H), 4.02 (dd, \( J = 8.4, 4.5 \) Hz, 1H), 3.06 (s, 3H), 2.65(br, NH), 2.19 – 2.10 (m, 2H) (ppm).

\(^{13}\)C NMR (151 MHz, CDCl\(_3\)) \( \delta = 145.8, 145.6, 145.0, 141.7, 133.7, 129.5, 129.0, 127.04, 126.98, 126.8, 119.23, 119.20, 85.7, 79.2, 45.6, 41.2, 38.6 \) (ppm).

MS (EI): \( m/z = 63.1 \) (28), 78.2 (19), 89.1 (30), 118.1 (100), 165.1 (11), 299.1 (M\(^+\), 0.8).

IR (KBr): \( \nu = 3269, 3005, 1740, 1585, 1459, 1359, 1217, 1118, 1064, 984, 934 \) (cm\(^{-1}\)).

HRMS (ESI): 300.1058, calcd. for [M+H\(^+\)]: 300.1053.

S-5-Methylphenyl-S-methyl-2-(1’,2’,3’,4’-tetrahydro-1’,4’-epoxynaphthyl) sulfoximine (81b)

Following the general procedure, product 81b was obtained as off-white foamy solid in 90% yield (141.1 mg). A gradient of \( n\)-hexane/EtOAc: 3/1 was applied as eluent for the flash column chromatography purification.

Melting point: 156-158 °C

\(^1\)H NMR (600 MHz, CDCl\(_3\)) \( \delta = 7.92 \) (s, 1H), 7.77 (d, \( J = 8.0 \) Hz, 1H), 7.40 (d, \( J = 8.0 \) Hz, 1H), 7.31 – 7.23 (m, 2H), 7.20 – 7.14 (m, 2H), 5.56 (d, \( J = 4.6 \) Hz, 1H), 5.17 (s, 1H), 3.97 (dd, \( J = 8.3, 4.6 \) Hz, 1H), 3.04 (s, 3H), 2.57 (br, NH), 2.39 (s, 3H), 2.15 – 2.07 (m, 2H) (ppm).

\(^{13}\)C NMR (151 MHz, CDCl\(_3\)) \( \delta = 145.9, 145.7, 141.8, 141.4, 136.9, 134.5, 129.5, 129.4, 127.0, 126.95, 119.2, 119.19, 85.8, 79.2, 45.7, 40.9, 38.6, 20.9 \) (ppm).

MS (EI): \( m/z = 89.1 \) (17), 118.1 (100), 164.1(10), 180.2 (10), 202.2 (10), 234.2 (18), 250.3 (20), 296.2 (11), 314.3 (M\(^+\), 20).

IR (KBr): \( \nu = 3248, 3012, 2287, 2172, 1740, 1457, 1366, 1221, 1103, 1066, 996 \) (cm\(^{-1}\)).
HRMS (ESI): 314.1209, [M+H\(^+\)]: 314.1209.

S-4-Methoxyphenyl-S-methyl-2-(1’,2’,3’,4’-tetrahydro-1’,4’-epoxynaphthyl) sulfoximine (**81c**)

Following the general procedure, product **81c** was obtained as off-white foamy solid in 92% yield (151.5 mg). A gradient of *n*-hexane/EtOAc: 3/1 was applied as eluent for the flash column chromatography purification.

Melting point: 150-152 °C

\(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta = 8.06\) (d, \(J = 8.9\) Hz, 1H), 7.41 (s, 1H), 7.32 – 7.27 (m, 2H), 7.21 – 7.15 (m, 2H), 6.85 (d, \(J = 6.2\) Hz, 1H), 5.56 (s, 1H), 5.22 (s, 1H), 3.99 (dd, \(J = 8.1, 4.7\) Hz, 1H), 3.88 (s, 3H), 3.05 (s, 3H), 2.48 (br, NH), 2.16 – 2.10 (m, 2H) (ppm).

\(^{13}\)C NMR (151 MHz, CDCl\(_3\)) \(\delta =\) 163.7, 147.4, 145.9, 145.6, 133.6, 131.6, 127.1, 127.0, 119.3, 119.2, 115.2, 111.5, 85.7, 79.2, 55.7, 46.1, 41.4, 38.8 (ppm).

MS (EI): \(m/z = 89.1\) (11), 118.1 (100), 182.3 (14), 266.3 (43), 331.4 (M\(^+\), 1).

IR (KBr): \(\nu = 3306, 3003, 2284, 1739, 1565, 1461, 1365, 1290, 1219, 1113, 1067, 987, 938\) (cm\(^{-1}\)).


S-4-Nitrophenyl-S-methyl-2-(1’,2’,3’,4’-tetrahydro-1’,4’-epoxynaphthalene) sulfoximine (**81d**)
Following the general procedure, product 81d was obtained as pale yellow foamy solid in 72% yield (124.0 mg). A gradient of n-hexane/EtOAc: 3/1 was applied as eluent for the flash column chromatography purification.

Melting point: 164-166 °C

^1^H NMR (400 MHz, CDCl\(_3\)) \(\delta = 8.73\) (s, 1H), 8.34 (d, \(J = 8.7\) Hz, 1H), 8.20 (d, \(J = 6.4\) Hz, 1H), 7.35 – 7.30 (m, 2H), 7.24 – 7.19 (m, 2H), 5.68 (d, \(J = 4.3\) Hz, 1H), 5.24 (s, 1H), 4.08 (dd, \(J = 7.9, 4.8\) Hz, 1H), 3.12 (s, 3H), 2.23 – 2.15 (m, 2H) (ppm).

^13^C NMR (101 MHz, CDCl\(_3\)) \(\delta = 151.1, 147.8, 147.4, 145.8, 145.0, 130.7, 127.4, 127.3, 124.7, 121.6, 119.5, 85.6, 79.4, 45.6, 41.8, 39.0\) (ppm).

MS (EI): \(m/z = 89.2\) (15), 118.2 (90), 164.0 (3), 189.3 (8), 327.3 (2).

IR (KBr): \(\nu = 3314, 3017, 2945, 1739, 1521, 1457, 1347, 1218, 1118, 982, 928\) (cm\(^{-1}\)).

HRMS (ESI): 345.0893, calcd. for [M+H\(^+\)]: 345.0904.

S-4-chlorophenyl-S-methyl-2-(1',2',3',4'-tetrahydro-1',4'-epoxynaphthalene) sulfoximine (81e)

Following the general procedure, product 81e was obtained as off-white foamy solid in 79% yield (131.9 mg). A gradient of n-hexane/EtOAc: 3/1 was applied as eluent for the flash column chromatography purification.

Melting point: 88-90 °C

^1^H NMR (600 MHz, CDCl\(_3\)) \(\delta = 8.04\) (d, \(J = 8.6\) Hz, 1H), 7.88 (s, 1H), 7.35 (d, \(J = 8.6\) Hz, 1H), 7.31 – 7.27 (m, 2H), 7.21 – 7.15 (m, 2H), 5.58 (d, \(J = 3.8\) Hz, 1H), 5.20 (s, 1H), 3.98 (dd, \(J = 7.5, 5.4\) Hz, 1H), 3.04 (s, 3H), 2.66 (br, NH), 2.13 – 2.11 (m, 2H) (ppm).

^13^C NMR (151 MHz, CDCl\(_3\)) \(\delta = 147.0, 145.8, 145.3, 140.3, 140.2, 130.7, 129.6,\)
127.1, 127.0, 119.3, 119.2, 85.5, 79.2, 45.7, 41.3, 38.8 (ppm).

MS (EI): $m/z = 89.1$ (6.0), 118.1 (100), 189.1 (6), 334.2 (1).

IR (KBr): $\nu = 3453, 3270, 3008, 2931, 2283, 1739, 1566, 1457, 1388, 1218, 1057, 984, 938$ (cm$^{-1}$).


S-4-Bromophenyl-S-methyl-2-(1’,2’,3’,4’-tetrahydro-1’,4’-epoxynaphthalene) sulfoximine (81f)

Following the general procedure, product 81f was obtained as off-white foamy solid in 79% yield (149.4 mg). A gradient of $n$-hexane/EtOAc: 3/1 was applied as eluent for the flash column chromatography purification.

Melting point: 84-86 ºC

$^1$H NMR (600 MHz, CDCl$_3$) $\delta = 8.02$ (s, 1H), 7.96 (d, $J = 8.5$ Hz, 1H), 7.51 (d, $J = 6.5$ Hz, 1H), 7.31 – 7.26 (m, 2H), 7.20 – 7.15 (m, 2H), 5.58 (d, $J = 4.0$ Hz, 1H), 5.20 (s, 1H), 3.96 (dd, $J = 7.9$, 4.9 Hz, 1H), 3.03 (s, 3H), 2.82 (br, NH), 2.14 – 2.09 (m, 2H) (ppm).

$^{13}$C NMR (151 MHz, CDCl$_3$) $\delta = 206.6, 205.9, 147.1, 145.7, 145.3, 140.8, 132.5, 130.7, 130.1, 128.9, 127.1, 119.3, 119.2, 85.4, 79.2, 45.6, 41.3, 38.8$ (ppm).

MS (EI): $m/z = 89.1$ (6.5), 118.1 (100), 189.1 (11), 230.0 (9), 380.3 (M$^+$, 1.4).

IR (KBr): $\nu = 3269, 3005, 2929, 2178, 1739, 1552, 1457, 1383, 1219, 1124, 1056, 986, 937$ (cm$^{-1}$).

S-4-methylphenyl-S-methyl-2-(1’,2’,3’,4’-tetrahydro-1’,4’-epoxynaphthalene) sulfoximine (81g)

Following the general procedure, product 81g was obtained as off-white foamy solid in 88% yield (137.9 mg). A gradient of n-hexane/EtOAc: 4/1 was applied as eluent for the flash column chromatography purification.

Melting point: 72-74 °C

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta = 7.92 (d, J = 8.1 \text{ Hz}, 1\text{H}), 7.61 (s, 1\text{H}), 7.24 – 7.18 (m, 2\text{H}), 7.14 – 7.07 (m, 3\text{H}), 5.51 (d, J = 4.7 \text{ Hz}, 1\text{H}), 5.13 (s, 1\text{H}), 3.91 (dd, J = 8.3, 4.6 \text{ Hz}, 1\text{H}), 2.97 (s, 3\text{H}), 2.36 (s, 3\text{H}), 2.54 (br, NH), 2.12 – 2.00 (m, 2\text{H}) (ppm).

\(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta = 145.9, 145.7, 144.8, 144.6, 138.9, 130.0, 129.3, 127.5, 127.04, 126.96, 119.24, 119.20, 85.7, 79.2, 45.8, 41.1, 38.5, 21.7 (ppm).

MS (EI): \(m/z = 63.1 (17), 77.8 (30), 89.4 (75), 117.6 (100).\)

IR (KBr): \(\nu = 3275, 3005, 2934, 2249, 1740, 1597, 1457, 1366, 1280, 1215, 1057, 986 (\text{cm}^{-1}).\)

HRMS (ESI): 314.1207, calcd. for [M+H\(^+\)]: 314.1209.

S-2-Naphthyl-S-methyl-3-(1’,2’,3’,4’-tetrahydro-1’,4’-epoxynaphthalene) sulfoximine (81h)

Following the general procedure, product 81h was obtained as off-white foamy solid in 79% yield (138.0 mg). A gradient of n-hexane/EtOAc: 4/1 was applied as eluent for
the flash column chromatography purification.

Melting point: 179-181 °C

\(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta = 8.73\) (s, 1H), 8.31 (s, 1H), 7.94 (dd, \(J = 13.5, 8.2\) Hz, 2H), 7.66 – 7.61 (m, 1H), 7.59 – 7.54 (m, 1H), 7.37 – 7.30 (m, 2H), 7.24 – 7.19 (m, 2H), 5.67 (d, \(J = 4.9\) Hz, 1H), 5.30 (s, 1H), 4.06 (dd, \(J = 8.5, 4.3\) Hz, 1H), 3.15 (s, 3H), 2.61 (br, NH), 2.35 – 2.19 (m, 2H) (ppm).

\(^{13}\)C NMR (151 MHz, CDCl\(_3\)) \(\delta = 146.0, 145.8, 140.1, 135.7, 130.9, 130.8, 129.2, 129.1, 128.9, 127.8, 127.2, 127.1, 127.0, 119.5, 119.3, 86.2, 79.4, 45.7, 41.4, 39.2\) (ppm).

MS (EI): \(m/z = 89.2\) (10), 118.2 (100), 164.0 (9), 351.0 (1).

IR (KBr): \(\nu = 3280, 3005, 2945, 1739, 1521, 1462, 1345, 1216, 1109, 936\) (cm\(^{-1}\)).

HRMS (ESI): 350.1198, calcd. for [M+H\(^+\)]: 350.1209.

S-Phenyl-S-ethyl-2-(1',2',3',4'-tetrahydro-1',4'-epoxynaphthalene) sulfoximine (81i)

Following the general procedure, product 81i was obtained as off-white foamy solid in 88% yield (137.9 mg). A gradient of \(n\)-hexane/EtOAc: 4/1 was applied as eluent for the flash column chromatography purification.

Melting point: 149-151 °C

\(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta = 8.08\) (d, \(J = 9.3\) Hz, 1H), 7.91 (d, \(J = 9.0\) Hz, 1H), 7.60 (t, \(J = 7.6\) Hz, 1H), 7.39 (t, \(J = 7.6\) Hz, 1H), 7.33 – 7.26 (m, 2H), 7.23 – 7.15 (m, 2H), 5.58 (d, \(J = 4.8\) Hz, 1H), 5.19 (s, 1H), 4.06 (dd, \(J = 8.4, 4.5\) Hz, 1H), 3.20 – 3.06 (m, 2H), 2.61 (br, NH), 2.19 – 2.07 (m, 2H), 1.24 (t, \(J = 7.4\) Hz, 3H) (ppm).

\(^{13}\)C NMR (151 MHz, CDCl\(_3\)) \(\delta = 145.9, 145.7, 145.5, 139.7, 133.8, 130.4, 129.6, 127.1, 127.0, 126.8, 119.3, 85.8, 79.3, 51.5, 41.2, 38.8, 7.9\) (ppm).

MS (Cl): \(m/z = 324.1\).
IR (KBr): $\nu = (\text{cm}^{-1})$.
HRMS (ESI): 324.1207, calcd. for [M+H$^+$]: 314.1209.

S-Phenyl-S-isopropyl-2-(1’,2’,3’,4’-tetrahydro-1’,4’-epoxynaphthalene) sulfoximine (81j)

Following the general procedure, product 81j was obtained as off-white foamy solid in 78% yield (127.9 mg). A gradient of $n$-hexane/EtOAc: 4/1 was applied as eluent for the flash column chromatography purification.

Melting point: 117-119 °C

$^1$H NMR (600 MHz, CDCl$_3$) $\delta = 8.06$ (d, $J = 8.0$ Hz, 1H), 7.90 (d, $J = 7.3$ Hz, 1H), 7.58 (t, $J = 7.6$ Hz, 1H), 7.37 (t, $J = 8.1$ Hz, 1H), 7.28 (dd, $J = 8.9, 5.8$ Hz, 2H), 7.21 – 7.15 (m, 2H), 5.57 (d, $J = 4.8$ Hz, 1H), 5.16 (s, 1H), 4.13 (dd, $J = 8.5, 4.4$ Hz, 1H), 3.15 (dt, $J = 13.6, 6.8$ Hz, 1H), 2.58 (br, NH), 2.20 – 2.03 (m, 2H), 1.27 (dd, $J = 6.8, 3.9$ Hz, 6H) (ppm).

$^{13}$C NMR (151 MHz, CDCl$_3$) $\delta = 146.0, 145.8, 145.7, 138.6, 133.6, 131.0, 129.6, 127.0, 126.9, 126.5, 119.2, 118.18, 85.9, 79.2, 56.1, 41.1, 38.7, 16.2, 15.7$ (ppm).

MS (EI): $m/z = 87.6$ (27), 118.1 (100), 183.0 (17), 328.1 (M$^+$, 3).

IR (KBr): $\nu = 3226, 3005, 2956, 2170, 1739, 1449, 1366, 1217, 1072, 983$ (cm$^{-1}$).

HRMS (ESI): 328.1365, calcd. for [M+H$^+$]: 328.1366.
S-phenyl-S-methyl-2-(1’’,2’,3’,4’-tetrahydro-1’,4’-epoxytriphenylene)sulfoximine (81k)

Following the general procedure, product 81k was obtained as yellow foamy solid in 78% yield (155.8 mg). A gradient of n-hexane/EtOAc: 4/1 was applied as eluent for the flash column chromatography purification.

Melting point: 215-217 °C

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 8.77 (t, $J$ = 7.9 Hz, 2H), 8.14 (t, $J$ = 6.7 Hz, 2H), 7.95 (d, $J$ = 9.2 Hz, 2H), 7.78 – 7.57 (m, 5H), 7.44 (t, $J$ = 8.3 Hz, 1H), 6.19 (d, $J$ = 4.3 Hz, 1H), 5.88 (s, 1H), 4.06 (dd, $J$ = 8.1, 4.4 Hz, 1H), 2.97 (s, 3H), 2.31 – 2.18 (m, 2H) (ppm).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ = 145.3, 141.8, 141.5, 140.9, 134.0, 130.5, 130.4, 129.9, 129.0, 127.2, 127.1, 126.9, 126.6, 125.9, 125.6, 124.4, 124.2, 123.8, 123.7, 85.2, 78.7, 45.6, 41.6, 39.5 (ppm).

MS (EI): $m/z$ = 88.9 (25), 118.1 (100), 164.0 (35).

IR (KBr): $\nu$ = 3015, 2956, 2145, 1745, 1376, 1333, 1217, 1086, 989 (cm$^{-1}$).

HRMS (ESI): 400.153, [M+H$^+$]: 400.1366.

S-Phenyl-S-methyl-2-(1’’,2’,3’,4’-tetrahydro-6’,7’-dioxole-1’,4’-epoxynaphthalene) sulfoximine (81l)
Following the general procedure, product 81l was obtained as off-white foamy solid in 80% yield (137.4 mg). A gradient of n-hexane/EtOAc: 4/1 was applied as eluent for the flash column chromatography purification.

Melting point: 151-153 °C.

$^1$H NMR (600 MHz, CDCl$_3$) $\delta = 8.12$ (d, $J = 7.9$ Hz, 1H), 7.86 (d, $J = 7.8$ Hz, 1H), 7.60 (t, $J = 7.6$ Hz, 1H), 7.40 (t, $J = 7.6$ Hz, 1H), 6.81 (d, $J = 11.6$ Hz, 2H), 5.96 (d, $J = 19.2$ Hz, 2H), 5.50 (d, $J = 4.6$ Hz, 1H), 5.13 (s, 1H), 3.96 (dd, $J = 8.3$, 4.4 Hz, 1H), 3.10 (s, 3H), 2.68 (br, NH), 2.14 – 2.05 (m, 2H) (ppm).

$^{13}$C NMR (151 MHz, CDCl$_3$) $\delta = 146.8$, 146.7, 145.1, 139.6, 139.5, 133.9, 129.5, 129.1, 126.9, 101.7, 101.66, 101.4, 45.7, 41.6, 39.0 (ppm).

MS (EI): $m/z = 89.2$ (10), 118.2 (90), 164.0 (9).

IR (KBr): $\nu = 3256$, 2986, 2156, 1755, 1367, 1215, 1073, 986 (cm$^{-1}$).


S-Phenyl-S-methyl-2-(1’,2’,3’,4’-tetrahydro-9’-carboxylic acid methyl ester -1’,4’-imine- naphthalene) sulfoximine (81m)

Following the general procedure, product 81m was obtained as off-white foamy solid in 82% yield (146.1 mg). A gradient of n-hexane/EtOAc: 4/1 was applied as eluent for the flash column chromatography purification.

Melting point: 168-170 °C

$^1$H NMR (400 MHz, CDCl$_3$) $\delta = 8.15$ (d, $J = 8.0$ Hz, 1H), 7.85 (d, $J = 7.5$ Hz, 1H), 7.60 (t, $J = 7.6$ Hz, 1H), 7.41 (t, $J = 8.2$ Hz, 1H), 7.36 – 7.28 (m, 2H), 7.22 – 7.13 (m, 2H), 5.37 (s, 1H), 5.05 (s, 1H), 3.95 (dd, $J = 8.7$, 4.5 Hz, 1H), 3.57 (s, 3H), 3.07 (s, 3H), 2.46 (br, NH), 2.36 – 1.96 (m, 2H) (ppm).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta = 156.7$, 144.0, 133.8, 129.5, 129.0, 127.3, 127.16,
127.11, 120.3, 68.2, 61.5, 52.8, 45.8 (ppm).

MS (EI): \( m/z = 89.2 \) (10), 118.2 (100), 164.0 (9), 357.0 (M\(^+\), 1).

IR (KBr): \( \nu = 3242, 3003, 2170, 1739, 1449, 1366, 1217, 1072, 973 \text{ (cm}^{-1}) \).

HRMS (ESI): 357.1263, calcd. for [M+H\(^+\)]: 357.1267.
Chapter 2

Enantioselective Synthesis of Dihydropyrazoles by Formal [4+1] Cycloaddition of in Situ-Derived Azoalkenes and Sulfur Ylides

Author contributions: Wanrong Dong synthesized the sulfur ylides 125a-d, performed the experiments for substrate scope table 8, entries 1-4.
1 General Introduction

1.1 General Introduction of Dihydropyrazole Compounds

Dihydropyrazoles, a catalogue of five-membered aza-heterocyclic compounds, have attracted great attention not only in pharmaceutical applications but also in the natural products synthesis.\[^{44}\] In addition, the dihydropyrazoles have been used as key building blocks for a wide range of compounds with excellent bioactivities for anti-depression, anti-cancer and anti-inflammatory. Moreover, some moleculars have been identified as good anti-diabetic, anaesthetic, analgesic agents with potential selective activities such as Nitric Oxide Synthase (NOS) inhibitor and Cannabinoid CB1 receptor antagonist activities. For example, compound **82** was tested to be the most active agent against *Mycobacterium tuberculosis* (MTB), while the compound **83** showed good antimicrobial activity against *Escherichia coli* and *Aspergillus niger diseases* (Scheme 43).

**Scheme 43** Some biological active pyrazoline-cored compounds

![Scheme 43](image)

Previously, numerous examples have been reported for the synthesis of dihydropyrazole. Most of the reported protocols utilize asymmetric 1,3-dipolar cycloadDITION (1,3-DC) reactions for the preparations of the five-membered compounds, and this methodology dominate the field today. 1,3-Dipoles such as diazomethanes, azomethine imines and nitrile imines have been frequently utilized as
the coupling partners ever since the first example from Fischer and Knövenagel.[45] In this chapter, we will introduce some transition metal-catalyzed [3+2] cycloaddition reactions towards pyrazoles or pyrazolines.

1.1.1 Diazooalkanes as Substrates for Pyrazoles by [3+2] Cycloadditions

In 2000, the first examples of a 1,3-cycloaddition reactions between diazoalkanes with acrylamides were reported by Kanemasa and Kanai.[46] Diazomethanes were utilized in the Lewis acid-catalyzed transformation without fatal deactivation of the catalyst. For example, trimethylsilyl diazomethane (84) reacted with dipolarophiles 85a-c in the presence of a (R,R)-DBFOX/Ph metal complex (Scheme 44), giving the desired 2-pyrazolines in high yields (up to 93%) with excellent ee (up to 99%) (Scheme 44).

**Scheme 44 R,R-DBFOX/Ph-catalyzed [3+2] cycloaddition reaction**

Ever since the pioneering work, Lewis acid-catalyzed asymmetric [3+2] cycloaddition reactions between 1,3-dipoles such as diazoalkanes, azomethine imines or nitrile imines with unsaturated aldehydes, ketones or esters have been well documented.
In this context, Maruoka and coworkers disclosed examples of [3+2] cycloaddition reactions between diazoacetates and monodentate α-substituted acroleins. In the presence of chiral titanium/BINOLate complexes 90a-c,[47] the asymmetric cycloaddition reaction afforded an easy access to highly functionalized pyrazoline adducts in good yields. The importance of the pyrazolines was demonstrated by a short synthesis of manzacidin A (Scheme 66). The system gave remarkably good yields and good enantioselectivities, without tedious protection and deprotection steps (Scheme 45).

Scheme 45 Chiral titanium/BINOLate complexes-catalyzed [3+2] cycloaddition reaction

Similarly, Sibi and coworkers developed a [3+2] cycloaddition of diazoesters with α,β-unsaturated pyrazolidinone imides towards pyrazoline derivatives in good yields (up to 91%) with high ee (up to 99%).[48] The advantages for the new system lay in...
the elevated reaction temperature, and better rotamer geometry control. However, the restriction on the $\alpha$-substituted acroleins remained unsolved (Scheme 46).

**Scheme 46** BOX liganded-Mg-catalyzed [3+2] cycloaddition reaction

To surmount these shortcomings, chiral (S)-oxazaborolidinium ions (97a-c) were utilized as catalysts for the [3+2] cycloaddition reaction between unsaturated aldehydes with $\alpha$-substituted and $\alpha,\beta$-disubstituted acroleins.$^{[49]}$ The methodology gave the desired adducts in good yields with excellent ee (96a-c in Scheme 47). The author credited the good results to the coordination between the catalysts and aldehyde substrates.$^{[50]}$
1.1.2 Azomethine Imines as Substrates for Pyrazoles by [3+2] Cycloadditions

Previously, the use of azomethine imines in asymmetric cycloaddition reactions is limited, and the attention has been focused on the use of azomethine imines for the stereoselective synthesis of five-membered heterocyclic compounds such as 1,2,3-triazoles or β-lactams.

Shintani and Fu developed a new combination of Cu(I)/phosphaferroceneoxazoline for the [3+2] cycloaddition reaction between azomethine imines with terminal alkynes, affording enantioselective bi-heterocyclic pyrazolidinones in excellent yields with good ee under mild conditions (Scheme 48). Notably, aromatic, alkenyl and alkyl substituted azomethine imines reacted well in the system. Electron-poor terminal alkynes gave better results than electron-rich terminal alkynes.
Later, Sibi and coworkers described an exo-dominant, enantioselective 1,3-dipolar cycloaddition reaction of azomethine imines with α,β-unsaturated pyrazolidinone imides. In the presence of a catalytic amount of Cu(OTf)$_2$ and a chiral bis(oxazoline) ligand, 2-acryloyl-3-pyrazolidinones were formed in high yields with good ee.$^{[52]}$ In this case, the Cu(II) complex afforded better results than the Ni(II) complex due to metal geometric difference (Scheme 49).

**Scheme 49** Bis(oxazoline) liganded Cu(II)-catalyzed [3+2] cycloaddition

Later, Sibi and coworkers described an exo-dominant, enantioselective 1,3-dipolar cycloaddition reaction of azomethine imines with α,β-unsaturated pyrazolidinone imides. In the presence of a catalytic amount of Cu(OTf)$_2$ and a chiral bis(oxazoline) ligand, 2-acryloyl-3-pyrazolidinones were formed in high yields with good ee.$^{[52]}$ In this case, the Cu(II) complex afforded better results than the Ni(II) complex due to metal geometric difference (Scheme 49).

**Scheme 48** Cu(I)/phosphaferrocene-oxazoline-catalyzed cycloaddition reaction

Later, Sibi and coworkers described an exo-dominant, enantioselective 1,3-dipolar cycloaddition reaction of azomethine imines with α,β-unsaturated pyrazolidinone imides. In the presence of a catalytic amount of Cu(OTf)$_2$ and a chiral bis(oxazoline) ligand, 2-acryloyl-3-pyrazolidinones were formed in high yields with good ee.$^{[52]}$ In this case, the Cu(II) complex afforded better results than the Ni(II) complex due to metal geometric difference (Scheme 49).
Other successful examples of the [3+2] cycloaddition reaction between azomethine imines and substituted acroleins by aid of a titanium-BINOLate complex (90b in Scheme 45) were disclosed by Maruoka.\textsuperscript{[53]} Various substituted C,N-cyclic azomethine imines were well tolerated. α,β-Disubstituted unsaturated aldehydes showed high diastereomeric selectivities and enantioselectivities (Scheme 50). However, β-unsubstituted unsaturated aldehydes afforded almost equal amounts of the two diastereomers, probably owing to the steric factor.

Scheme 50 Titanium-BINOLate complex-mediated [3+2] cycloaddition reaction

1.1.3 Nitrile Imines as Substrates for Pyrazoles by [3+2] Cycloadditions

Nitrile imines are well known 1,3-dipoles for the [3+2] cycloadditions with olefins for the synthesis of biological 4, 5-dihydropyrazole compounds. Although the inter- and intramolecular cycloaddition reactions of nitrile imines with olefins have been well established, however, only diastereoselective reactions are known. In this context, Sibi firstly reported a highly regio- and enantioselective cycloaddition reaction of nitrile imines with olefins which was catalyzed by chiral Mg(II) complexes\textsuperscript{[54]}. Compared with some traditional Lewis acids such as Cu(OTf)\textsubscript{2}, Ni(ClO\textsubscript{4})\textsubscript{2} and Zn(NTf\textsubscript{2})\textsubscript{2}, Mg(NTf\textsubscript{2})\textsubscript{2} afforded better results probably owing to the adverse interactions between those Lewis acids and either the 1,3-dipoles or the amine bases (Scheme 51).
Kobayashi successfully reported chiral zirconium complex-catalyzed intra- and inter-molecular asymmetric [3+2] cycloaddition reactions of hydrazones with olefins, yielding optical active pyrazolidine and pyrazoline derivatives. Interestingly, addition of PrOH increased the yields and selectivities dramatically, giving the desired products with 96% ee in up to 99% yields under mild conditions. Notably, the chirality of the catalytic complex had a great influence on the cis/trans selectivities (Scheme 52).[55]

**Scheme 52** Zirconium complex-catalyzed asymmetric [3+2] cycloaddition reactions

**Intramolecular [3+2] cycloaddition**

\[
\text{NH(p-NO}_2\text{Bz)} \quad \text{NH(p-NO}_2\text{Bz)} \quad \text{NH(p-NO}_2\text{Bz)}
\]

\[
\text{Me}_3\text{Si} \quad \text{Me}_3\text{Si} \quad \text{Me}_3\text{Si}
\]

\[
\text{Me}_3\text{Si} \quad \text{Me}_3\text{Si} \quad \text{Me}_3\text{Si}
\]

\[
\text{Me}_3\text{Si} \quad \text{Me}_3\text{Si} \quad \text{Me}_3\text{Si}
\]

\[
\text{Me}_3\text{Si} \quad \text{Me}_3\text{Si} \quad \text{Me}_3\text{Si}
\]

\[
\text{Me}_3\text{Si} \quad \text{Me}_3\text{Si} \quad \text{Me}_3\text{Si}
\]

**Intermolecular [3+2] cycloaddition**

\[
\text{Ph} \quad \text{Ph} \quad \text{Ph} \quad \text{Ph} \quad \text{Ph} \quad \text{Ph}
\]

\[
\text{Me}_3\text{Si} \quad \text{Me}_3\text{Si} \quad \text{Me}_3\text{Si} \quad \text{Me}_3\text{Si} \quad \text{Me}_3\text{Si} \quad \text{Me}_3\text{Si}
\]

\[
\text{Me}_3\text{Si} \quad \text{Me}_3\text{Si} \quad \text{Me}_3\text{Si} \quad \text{Me}_3\text{Si} \quad \text{Me}_3\text{Si} \quad \text{Me}_3\text{Si}
\]

\[
\text{Me}_3\text{Si} \quad \text{Me}_3\text{Si} \quad \text{Me}_3\text{Si} \quad \text{Me}_3\text{Si} \quad \text{Me}_3\text{Si} \quad \text{Me}_3\text{Si}
\]

\[
\text{Me}_3\text{Si} \quad \text{Me}_3\text{Si} \quad \text{Me}_3\text{Si} \quad \text{Me}_3\text{Si} \quad \text{Me}_3\text{Si} \quad \text{Me}_3\text{Si}
\]

\[
\text{Me}_3\text{Si} \quad \text{Me}_3\text{Si} \quad \text{Me}_3\text{Si} \quad \text{Me}_3\text{Si} \quad \text{Me}_3\text{Si} \quad \text{Me}_3\text{Si}
\]

**Scheme 51** Mg/BOX-mediated cycloaddition of nitrile imines with olefins
1.1.4 Hydroxylamines and Hydrazines as Substrates for Pyrazoles by [3+2] Cycloadditions

The bisnucleophilic donors such as hydroxylamines and hydrazines also have been applied as the substrates for the [3+2] cycloaddition reactions, affording heterocyclic adducts of potential pharmaceutical interests. As a clear differentiation of nucleophilicity between the two donor atoms, N-monosubstituted hydroxylamines and hydrazines underwent the enantioselective reactions in good chemoselectivities. Thus, Sibi described a first example of the enantioselective and chemoselective cycloaddition reaction of monosubstituted hydrazines to α,β-unsaturated imides with a catalytic amount of a chiral Lewis acid.[56] Monosubstituted hydrazines other than parent hydrazines were utilized for the latter ones could give amidation products (Scheme 53).

**Scheme 53** Mg(II)-mediated cycloaddition of monosubstituted hydrazines with oxazolidinone crotonates

![Scheme 53](image)

Very recently, Müller and List reported an alternative access to dihydropyrazolines by asymmetric 6π electrocyclization of α,β-unsaturated hydrazones in high yields and enantioselectivities, which was mediated by phosphoric acids.[57] Under the existence of 3,3'-bis-(9-anthracenyl) substituted binol phosphate, α,β-unsaturated hydrazones cyclized smoothly at 30 °C in chlorobenzene in high yields (up to 99%) and enantioselectivities (up to 98:2 er). Interestingly, all kinds of halogen atoms, as well
as strongly electron-withdrawing substituents of the enones part and electron-donating substituents of the hydrazines part were well tolerated except for aliphatic group on the enones parts (Scheme 54).

**Scheme 54** 6π electrocycloaddition of α,β-unsaturated hydrazones

It is noteworthy that reports on the enantioselective synthesis of 4,5-dihydropyrazoles with a polar group on N1 position of hydrazones are rare. Brière and coworkers developed a powerful domino aza-Michael addition/cyclocondensation strategy for the enantioselective synthesis of 3,5-diaryl dihydropyrazoles.\(^{[58]}\) In the presence of a quaternary ammonium salt, K\(_3\)PO\(_4\) afforded higher ee than Cs\(_2\)CO\(_3\). A virtually enantiopure pyrazoline 121a was obtained after recrystallization. The only drawback of the new methodology was that only the N-Boc hydrazines underwent the cycloaddition reaction (Scheme 55).

**Scheme 55** Synthesis of N1-Boc 4,5-dihydropyrazolines

120a: Ar = Ph  
120b: Ar = 4-FC\(_6\)H\(_4\)  
121a: 77% yield, 92% ee (>99% ee after recrystallization)  
121b: 72% yield, 90% ee
These pioneering works stand out however, there are still some drawbacks that hinder the wide applications of these methods, such as unsatisfactory yields, poor chemo- and/or stereoselectivities, and limited substrate scope. Therefore, it is still highly desirable to develop a general strategy towards enantioenriched dihydropyrazole derivatives with functional diversity.

1.1.5 Introduction of the Formal [4+1] Cycloaddition Reactions

Initiated by Murai, the formal [4+1] cycloadditions of 1,3-conjugated systems, which act as four-atom assembling units, with two electrons, one-carbon synthons have proven as attractive strategies towards structurally diverse five-membered carbo- and heterocyclic compounds. As reported, the [4+1] cycloaddition of 1,3-dienes and carbon monoxide afforded an easy access to cyclopentenones. Thus, if replaced by a hetero-atom on the terminal carbon, five-membered heterocyclic compounds such as unsaturated γ-lactones or γ-lactams will be formed. Under the context, Murai reported first examples of [4+1] cycloadditions of structurally simple α,β-unsaturated imines with carbon monoxide, affording unsaturated γ-lactams in the presence of a catalytic amount of Ru$_3$(CO)$_{12}$. But high temperature and long reaction time were required for moderate to good yields (Scheme 56).[59]

**Scheme 56** Synthesis of cyclopentenones through the [4+1] cycloaddition

![Scheme 56](image)

122a: R = Ph
122b: R = Bu
123a: 51%
123b: 71%

After the pioneering exploration on the [4+1] cycloaddition reactions, numerous attempts were made for the synthesis of five-membered carbo- and heterocyclic compounds. For example, Chatani successively reported a [4+1] cycloaddition of
α,β-unsaturated carbonyl compounds with isocyanides affording γ-lactones derivatives, by aid of a catalytic amount of GaCl₃. Barluenga applied the cycloaddition reaction on the Fischer carbene complexes with unsaturated ketones giving 2,3-dihydrofurans adducts. However, the research on the topic remains unexploited.

1.1.6 Introduction of Sulfur Ylides

Sulfur ylides are identified as versatile and valuable 1,1’-dipolar synthons that react with a variety of electron-deficient conjugated alkenes affording multi-functionalized carbo-/heterocyclic motifs. Therefore, sulfur ylides have been applied towards all kinds three-membered compounds such as epoxides, aziridines, and cyclopropanes. Initiated by Xiao, stable sulfur ylides were applied in axial-to-central chirality transfer [4+1] cycloaddition strategies to react with ester-bearing unsaturated imines and nitroolefins, giving access to some pharmaceutically and biologically useful five-membered hetero-compounds (Scheme 57).
Scheme 57 [4+1] Cycloaddition strategies of sulfur ylides for five-membered compounds

2 Research Objective

For the current report, it is also noteworthy that azoalkenes, which can be readily formed by a two-electron oxidation procedure from halo-N-sulfonyl hydrazones, are highly susceptible to conjugate addition to give the corresponding functionalized hydrazones (Scheme 58, eq. A).[^64]

In the light of all of those findings, we wondered about the possibility of formal asymmetric [4+1] cycloaddition of in situ-generated azoalkenes with sulfur ylides
providing optically active dihydropyrazoles under chiral Lewis acid catalysis (Scheme 58, eq. B). In this scenario, several challenges had to be encountered: 1) the conditions for the generation of the reactive azoalkenes should not interfere with the following asymmetric cycloaddition; 2) the Lewis acids should preferentially coordinate with the azoalkenes over the sulfur ylides; 3) possible background reactions could be detrimental to the enantioselectivities. The methodological difficulties were mostly expressed by the lack of examples of catalytic asymmetric cycloadditions of sulfur ylides leading to five-membered carbo-/heterocyclic systems. Herein, we reported a successful introduction of such a strategy using a chiral copper complex for the catalytic asymmetric formal [4+1] cycloaddition, providing dihydropyrazoles with high enantioselectivities in good yields (Scheme 58, eq. B).

**Scheme 58** Research objective

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3 Results and Discussions

3.1 Screening on Metal Catalysts

With N-benzoyl hydrazine 124d and sulfur ylide 125a as substrates and (R)-tol-BINAP as ligand for the model reaction, the activities of different transition metal salts were tested (Table 5). In general, Cu salts provided better yields and ee ratios than Zn(OTf)$_2$, AgOTf and Mg(OTf)$_2$ (entries 1-3). Among all the Cu(I) and Cu(II) salts, Cu(OTf)$_2$ was the most active catalyst for the reaction, providing the highest yield (89%) and er (90:10) (entries 4-7). Surprisingly, when the reaction took place at -40 °C, the er ratio was lower, at 85:15 (entry 12).

**Table 5** Screening of metal catalysts$^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Metal</th>
<th>Temp. (°C)</th>
<th>t (h)</th>
<th>Yield (%)</th>
<th>er (%)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Zn(OTf)$_2$</td>
<td>r.t.</td>
<td>1</td>
<td>84</td>
<td>51:49</td>
</tr>
<tr>
<td>2</td>
<td>AgOTf</td>
<td>r.t.</td>
<td>1</td>
<td>71</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>Mg(OTf)$_2$</td>
<td>r.t.</td>
<td>16</td>
<td>73</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>CuCl</td>
<td>r.t.</td>
<td>1</td>
<td>83</td>
<td>75:25</td>
</tr>
<tr>
<td>5</td>
<td>CuBr$_2$</td>
<td>r.t.</td>
<td>2</td>
<td>84</td>
<td>73:27</td>
</tr>
<tr>
<td>6</td>
<td>CuI</td>
<td>r.t.</td>
<td>2</td>
<td>85</td>
<td>73:27</td>
</tr>
<tr>
<td>7</td>
<td>CuI</td>
<td>-20</td>
<td>16</td>
<td>84</td>
<td>89:11</td>
</tr>
<tr>
<td>8</td>
<td>Cu(OTf)$_2$</td>
<td>r.t.</td>
<td>2</td>
<td>80</td>
<td>77:23</td>
</tr>
</tbody>
</table>
Cu(OTf)$_2$ was proven to be the best catalyst for the [4+1] cycloaddition reaction. Thus, the optimization studies were started using N-Boc hydrazone 124a and sulfurylde 125a in the presence of the chiral complex, which was formed in situ from sulfoximine L1 and copper(II) triflate. To our delight, this combination showed good catalytic activity for the reaction, giving the product 126aa in 80% yield with an er ratio of 58:42 (Table 5, entry 1). The use of BINAP improved the er to 66:34 (entry 2). Another phosphine ligand L4 gave the best enantioselectivity. Some N-ligands or P,N-ligands were less active or ineffective (entries 4-11). The effects of changing R substituents at the hydrazone acyl group were examined. As a result, it slightly improved the enantioselectivities (entries 3-5). Notably, the er ratio of the product increased to 73:27 when benzoyl hydrazone 124d was employed (entry 14). By using this substrate, various ligands were investigated. Fortunately, use of (R)-tol-BINAP (L3) greatly improved the er ratio, up to 77:23 and 80% yield (entry 15). Finally, we found that 10 mol % of Cu(OTf)$_2$, 11 mol % of ligand L3, and 1.0 equiv. of Na$_2$CO$_3$ at -30 °C proved to be the most effective conditions. The product was obtained in 83% yield with an er ratio of 92:8 (Table 5, entry 16).
Table 6 Optimization on ligands

<table>
<thead>
<tr>
<th>Entry</th>
<th>124</th>
<th>Ligand</th>
<th>Temp (°C)</th>
<th>t (h)</th>
<th>Yield (%)</th>
<th>er&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>124a</td>
<td>L1</td>
<td>r.t.</td>
<td>2</td>
<td>80</td>
<td>58:42</td>
</tr>
<tr>
<td>2</td>
<td>124a</td>
<td>L2</td>
<td>r.t.</td>
<td>2</td>
<td>90</td>
<td>66:34</td>
</tr>
<tr>
<td>3</td>
<td>124a</td>
<td>L3</td>
<td>r.t.</td>
<td>8</td>
<td>80</td>
<td>56:44</td>
</tr>
<tr>
<td>4</td>
<td>124a</td>
<td>L4</td>
<td>r.t.</td>
<td>2</td>
<td>81</td>
<td>71:29</td>
</tr>
<tr>
<td>5</td>
<td>124a</td>
<td>L5</td>
<td>r.t.</td>
<td>2</td>
<td>83</td>
<td>57:43</td>
</tr>
<tr>
<td>6</td>
<td>124a</td>
<td>L6</td>
<td>r.t.</td>
<td>1</td>
<td>77</td>
<td>57:43</td>
</tr>
<tr>
<td>7</td>
<td>124a</td>
<td>L7</td>
<td>r.t.</td>
<td>1</td>
<td>86</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>124a</td>
<td>L8</td>
<td>r.t.</td>
<td>1</td>
<td>86</td>
<td>0</td>
</tr>
</tbody>
</table>
Table 6

<p>| | | | | | |</p>
<table>
<thead>
<tr>
<th></th>
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</tbody>
</table>

Notes: [a] Conditions: 124 (0.3 mmol, 1.0 eq.), 125a (0.45 mmol, 1.5 eq.), metal/ligand (10 mol %), Na₂CO₃ (0.5 eq.), THF (10 mL) under Ar. [b] Determined by HPLC using a chiral stationary phase. [c] Performed with 1.0 eq. of Na₂CO₃ and 11 mol % of the ligand.

3.3 Substrate Scope

Under the optimized conditions, several sulfur ylides were tested with N-benzoyle hydrazone 124d. The results were summarized in Table 6. Thus, electron-poor and electron-rich sulfur ylides underwent the [4+1] cycloaddition reaction effectively with 124d, affording corresponding cyclized products in high yields (85-95%, entries 2-6). The excellent er values were obtained (to 98:2) by recrystallization (entries 2 and 3). The best er ratio was 92:8 (entries 4 and 5). 4-Methoxy and 2-naphthyl sulfur ylides gave the adducts 126df and 126dg in good yields with good er ratios, respectively (entries 6 and 7). Except 124d, another N-benzoyle hydrazone 124e was also tested for the [4+1] cycloaddition reaction. The reaction the hydrazone 124e with phenyl sulfur ylide 125a, substantially afforded improved enantioselectivity (entry 8 vs entry 1, er ratios of 97:3 vs 91:9). Likewise, sulfur ylides having both electron-withdrawing and electron-donating groups at the para- and meta-positions of the phenyl ring reacted
well with **124e** to provide the corresponding dihydropyrazoles in good yields and better enantioselectivities (with er values ranging from 92:8 to 97:3) (entries 8-17). The scope of this method was further extended to ylides bearing heterocycles. For example, 2-furyl sulfur ylide **125k** and 2-thienyl sulfur ylide **125l** reacted with **124e** affording products **126ek** and **126el** with er values of 93:7 and 94:6, respectively (entries 18 and 19).

**Table 7** Substrate scope on sulfur ylides

<table>
<thead>
<tr>
<th>Entry</th>
<th>124</th>
<th>R²</th>
<th>Yield</th>
<th>erᵇ</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>126da</td>
<td>R² = H</td>
<td>89</td>
<td>91:9</td>
</tr>
<tr>
<td>2</td>
<td>126db</td>
<td>R² = 4-BrC₆H₄</td>
<td>89(80)</td>
<td>91:9 (92:8)ᶜ</td>
</tr>
<tr>
<td>3</td>
<td>126dc</td>
<td>R² = 4-ClC₆H₄</td>
<td>85(76)</td>
<td>90:10 (98:2)ᶜ</td>
</tr>
<tr>
<td>4</td>
<td>126dd</td>
<td>R² = 3-NO₂C₆H₄</td>
<td>92</td>
<td>92:8</td>
</tr>
<tr>
<td>5</td>
<td>126de</td>
<td>R² = 4-CNC₆H₄</td>
<td>87</td>
<td>92:8</td>
</tr>
<tr>
<td>6</td>
<td>126df</td>
<td>R² = 4-MeOC₆H₄</td>
<td>95</td>
<td>90:10</td>
</tr>
<tr>
<td>7</td>
<td>126dg</td>
<td>R² = 2-Naphthyl</td>
<td>81</td>
<td>90:10</td>
</tr>
<tr>
<td>No.</td>
<td>R&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Product</td>
<td>Yield</td>
<td>Ratio</td>
</tr>
<tr>
<td>-----</td>
<td>--------------</td>
<td>---------</td>
<td>-------</td>
<td>-------</td>
</tr>
<tr>
<td>8&lt;sup&gt;a&lt;/sup&gt;</td>
<td>R&lt;sup&gt;2&lt;/sup&gt; = H</td>
<td>126ea</td>
<td>84</td>
<td>97:3</td>
</tr>
<tr>
<td>9</td>
<td>R&lt;sup&gt;2&lt;/sup&gt; = 4-BrC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>126eb</td>
<td>84</td>
<td>97:3</td>
</tr>
<tr>
<td>10</td>
<td>R&lt;sup&gt;2&lt;/sup&gt; = 4-ClC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>126ec</td>
<td>93</td>
<td>96:4</td>
</tr>
<tr>
<td>11&lt;sup&gt;a&lt;/sup&gt;</td>
<td>R&lt;sup&gt;2&lt;/sup&gt; = 3-NO&lt;sub&gt;2&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>126ed</td>
<td>84</td>
<td>92:8</td>
</tr>
<tr>
<td>12</td>
<td>R&lt;sup&gt;2&lt;/sup&gt; = 4-CNC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>126ee</td>
<td>88</td>
<td>94:6</td>
</tr>
<tr>
<td>13</td>
<td>R&lt;sup&gt;2&lt;/sup&gt; = 4-MeOC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>126ef</td>
<td>95</td>
<td>92:8</td>
</tr>
<tr>
<td>14</td>
<td>R&lt;sup&gt;2&lt;/sup&gt; = 2-Naphthyl</td>
<td>126eg</td>
<td>92</td>
<td>95:5</td>
</tr>
<tr>
<td>15</td>
<td>R&lt;sup&gt;2&lt;/sup&gt; = 4-FC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>126eh</td>
<td>93</td>
<td>96:4</td>
</tr>
<tr>
<td>16&lt;sup&gt;d&lt;/sup&gt;</td>
<td>R&lt;sup&gt;2&lt;/sup&gt; = 3,4-Cl&lt;sub&gt;2&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;3&lt;/sub&gt;</td>
<td>126ei</td>
<td>94</td>
<td>92:8</td>
</tr>
<tr>
<td>17&lt;sup&gt;d&lt;/sup&gt;</td>
<td>R&lt;sup&gt;2&lt;/sup&gt; = 4-MeC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>126ej</td>
<td>92</td>
<td>95:5</td>
</tr>
<tr>
<td>18</td>
<td>R&lt;sup&gt;2&lt;/sup&gt; = 2-furyl</td>
<td>126ek</td>
<td>85</td>
<td>93:7</td>
</tr>
<tr>
<td>19</td>
<td>R&lt;sup&gt;2&lt;/sup&gt; = 2-thienyl</td>
<td>126el</td>
<td>88</td>
<td>94:6</td>
</tr>
</tbody>
</table>

Notes: [a] Conditions: 124d or 124e (0.3 mmol, 1.0 eq.), 125 (0.45 mmol, 1.5 eq.), Cu(OTf)<sub>2</sub> (10 mol %), (R)-tol-BINAP (11 mol %), Na<sub>2</sub>CO<sub>3</sub> (1.0 eq.), and THF (10 mL) under Ar at -20 °C. [b] Determined by HPLC using a chiral stationary phase. [c] Values in parentheses are the results after single recrystallizations. [d] With 2.0 eq. of the sulfur ylide. [e] Performed at -30 °C.

The relationship between the absolute configurations of the ligand and a product was unambiguously determined by X-ray single crystal structure analysis of product (S)-185db (Figure 6) stemming from a copper catalysis with (R)-tol-BINAP as ligand.
The scope of the present copper-catalyzed asymmetric formal [4+1] cycloaddition was further extended to other hydrazones with phenyl sulfur ylide 125a (Table 8). Under the standard reaction conditions, hydrazones 124f-124h bearing Cl, F, and Me in the para-position of aryl ring, reacted with phenyl sulfur ylide 125a, affording the corresponding products in 94-97% yields with er values of up to 91:9 (entries 1-3). In a similar pattern, methoxybenzoyl hydrazones 124i-124m reacted smoothly with 125a affording the corresponding products in up to 96% yields and er values of up to 94:6 (entries 4-8). In addition, aliphatic substituted hydrazones 124n-124s were employed, giving good to excellent yields and er ratios (entries 9-14). Interestingly, meta- or para-substituted hydrazones 124t-124v also reacted nicely with 125a, providing the products in high yields and with good enantioselectivities (entries 15-17).
Table 8 Substrate scope on hydrazones

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>(124)</th>
<th>(126)</th>
<th>Yield</th>
<th>(\text{cr}^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cl</td>
<td><img src="image1.png" alt="Image" /></td>
<td>(\text{R}^2 = 4\text{-ClC}_6\text{H}_4)</td>
<td>94</td>
<td>91:9</td>
</tr>
<tr>
<td>2</td>
<td>Cl</td>
<td><img src="image2.png" alt="Image" /></td>
<td>(\text{R}^2 = 4\text{-FC}_6\text{H}_4)</td>
<td>97</td>
<td>90:10</td>
</tr>
<tr>
<td>3</td>
<td>Br</td>
<td><img src="image3.png" alt="Image" /></td>
<td>(\text{R}^2 = 4\text{-MeC}_6\text{H}_4)</td>
<td>95</td>
<td>90:10</td>
</tr>
<tr>
<td>4</td>
<td>Cl</td>
<td><img src="image4.png" alt="Image" /></td>
<td>(\text{R}^2 = 2,4\text{-Cl}_2\text{C}_6\text{H}_3)</td>
<td>84</td>
<td>93:7</td>
</tr>
<tr>
<td>5</td>
<td>Cl</td>
<td><img src="image5.png" alt="Image" /></td>
<td>(\text{R}^2 = 4\text{-FC}_6\text{H}_4)</td>
<td>92</td>
<td>94:6</td>
</tr>
<tr>
<td>6</td>
<td>Br</td>
<td><img src="image6.png" alt="Image" /></td>
<td>(\text{R}^2 = 4\text{-BrC}_6\text{H}_4)</td>
<td>88</td>
<td>88:12</td>
</tr>
<tr>
<td>7</td>
<td>Cl</td>
<td><img src="image7.png" alt="Image" /></td>
<td>(\text{R}^2 = 4\text{-ClC}_6\text{H}_4)</td>
<td>96</td>
<td>88:12</td>
</tr>
<tr>
<td>8</td>
<td>Br</td>
<td><img src="image8.png" alt="Image" /></td>
<td>(\text{R}^2 = 4\text{-MeOC}_6\text{H}_4)</td>
<td>86</td>
<td>92:8</td>
</tr>
<tr>
<td>9</td>
<td>Cl</td>
<td><img src="image9.png" alt="Image" /></td>
<td>(\text{R}^2 = \text{Me})</td>
<td>90</td>
<td>77:23</td>
</tr>
<tr>
<td>10</td>
<td>Cl</td>
<td><img src="image10.png" alt="Image" /></td>
<td>(\text{R}^2 = \text{i-Bu})</td>
<td>93</td>
<td>79:21</td>
</tr>
<tr>
<td>11</td>
<td>Br</td>
<td><img src="image11.png" alt="Image" /></td>
<td>(\text{R}^2 = \text{i-Bu})</td>
<td>84</td>
<td>87:13</td>
</tr>
<tr>
<td></td>
<td></td>
<td>126qa $R^2 = \text{PhCH}_2\text{CH}_2$</td>
<td>93</td>
<td>87:13</td>
<td></td>
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<tr>
<td>12</td>
<td>Cl</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>13</td>
<td>Br</td>
<td>126ra $R^2 = \text{COOEt}$</td>
<td>93</td>
<td>93:7</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>Cl</td>
<td>126sa $R^2 = \text{PhCH}=\text{CH}$</td>
<td>91</td>
<td>71:29</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>Cl</td>
<td><img src="image1.png" alt="Image" /></td>
<td>83</td>
<td>92:8</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>Cl</td>
<td>126ua</td>
<td>88</td>
<td>91:9</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>Br</td>
<td>126va</td>
<td>97</td>
<td>90:10</td>
<td></td>
</tr>
</tbody>
</table>

Notes: [a] Conditions: 124 (0.3 mmol, 1.0 eq.), 125a (0.45 mmol, 1.5 eq.), Cu(OTf)$_2$ (10 mol %), (R)-tol-BINAP (11 mol %), Na$_2$CO$_3$ (1.0 eq.), and THF (10 mL) under Ar at -20 °C. [b] Determined by HPLC using a chiral stationary phase.

To demonstrate the synthetic potential of the method, the reaction of hydrazone 124e and sulfur ylide 125a was carried out on a gram scale (Scheme 59). To our delight, the catalyst loading could be reduced to 5 mol % of the copper salt combined with 6 mol % of ligand L3, and the corresponding product (126ea) was isolated in 92% yield with an er ratio of 96:4.
4 Summary

In summary, we developed a copper-catalyzed asymmetric formal [4+1] cycloaddition reaction of in situ-generated azoalkenes with sulfur ylides. It provided an efficient, enantioselective access to a variety of optically active dihydropyrazoles.

5 Experimental Part

The metal catalyst Cu(OTf)$_2$ (10 mol %) and (R)-tol-BINAP L3 (11 mol %) were stirred in 10.0 mL of THF at room temperature for 1 h in a 50 mL schlenk tube under Ar. Then, the mixture was placed at -20 °C cooling bath and stirred for 20 minutes. Hydrazone 124 (0.30 mmol) and Na$_2$CO$_3$ (0.30 mmol) were added and the reaction mixture was stirred for additional 20 minutes. Then, sulfur ylide 125 (0.45 mmol) was added quickly to the mixture. Upon the completion of the reaction (by TLC), the reaction was quenched by saturated NH$_4$Cl solution (5 mL) and then extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over MgSO$_4$. After removal of the solvent, the residue was purified directly by flash column chromatography on silica gel (pentane/ethyl acetate (3:1 to 1.5:1) as eluent) to give the corresponding cyclized product 126 as white solid.
6 Data and Characterization

(5S)-1-tert-Butyl carboxylic acid ester-3-phenyl-5-benzoyl-4,5-dihydro pyrazole (126aa)

Yield: 80%. Melting point: 123.2 - 124.1 °C.
The er was determined by HPLC (Chiralpak AD column, heptane/i-PrOH 7:3, flow rate 0.8 mL/min, λ = 254 nm, 20 °C). tR (minor) = 16.1 min; tR (major) = 25.5 min, er = 66:34.

1H NMR (400 MHz, CDCl3) δ = 7.91 (d, J = 7.6 Hz, 2H), 7.64 (s, 2H), 7.54 (t, J = 7.3 Hz, 1H), 7.43 (t, J = 7.6 Hz, 2H), 7.34 – 7.23 (m, 3H), 5.61 (s, 1H), 3.62 (t, J = 15.0 Hz, 1H), 3.15 (s, 1H), 1.36 (s, 9H) (ppm).

13C NMR (100 MHz, CDCl3) δ = 195.0, 151.5, 133.9, 133.8, 130.9, 130.0, 128.9, 128.5, 128.4, 126.6, 81.9, 62.1, 38.2, 28.0 (ppm).

MS (EI): m/z = 350 (M+).
IR (KBr): 2975, 1731, 1694, 1398, 1254, 1146, 756, 689 (cm⁻¹).

(5S)-1-Ethyl carboxylic acid ester-3-phenyl-5-benzoyl-4,5-dihydro pyrazole (126ba)

Yield: 85%. Melting point: 119.4-120.6 °C.
The er was determined by HPLC (Chiralpak AD column, heptane/i-PrOH 6:4, flow rate 0.8 mL/min, λ = 254 nm, 20 °C). tR (major) = 24.6 min; tR (minor) = 39.9 min, er = 55:45.
$^1$H NMR (300 MHz, CDCl$_3$) $\delta = 8.01$ (d, $J = 7.3$ Hz, 2H), 7.73–7.70 (m, 2H), 7.63 (t, $J = 7.4$ Hz, 1H), 7.51 (t, $J = 7.5$ Hz, 2H), 7.38–7.33 (m, 3H), 5.82 (d, $J = 6.8$ Hz, 1H), 4.29 (s, 2H), 3.72 (dd, $J = 17.4$, 12.9 Hz, 1H), 3.22 (dd, $J = 17.4$, 6.0 Hz, 1H), 1.33 (s, 3H) (ppm).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta = 194.3$, 152.3, 133.8, 130.7, 130.2, 128.9, 128.6, 128.5, 126.6, 62.5, 61.2, 37.6, 14.5 (ppm).

MS (EI): m/z = 322 (M$^+$).

IR (KBr): 2987, 1716, 1691, 1417, 1264, 1177, 1132, 1017, 758, 689 (cm$^{-1}$).

Anal. calcd for (C$_{19}$H$_{18}$N$_2$O$_3$): C, 70.79; H, 5.63; N, 8.69. Found: C, 70.80; H, 5.45; N, 8.67.

(5S)-1-Methyl carboxylic acid ester-3-phenyl-5-benzoyl-4,5-dihydro pyrazole (126ca)

Yield: 72%. Melting point: 136.5-138.0 °C.

The er was determined by HPLC (Chiralpak AD column, heptane/i-PrOH 6:4, flow rate 0.8 mL/min, $\lambda = 254$ nm, 20 °C). $t_R$ (major) = 25.5 min; $t_R$ (minor) = 37.7 min, er = 55:45.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta = 8.02$ (d, $J = 7.5$ Hz, 2H), 7.72 (dd, $J = 7.4$, 1.8 Hz, 2H), 7.64 (t, $J = 7.4$ Hz, 1H), 7.53 (t, $J = 7.7$ Hz, 2H), 7.40–7.36 (m, 3H), 5.84 (s, 1H), 3.89 (s, 3H), 3.74 (dd, $J = 17.3$, 13.0 Hz, 1H), 3.25 (dd, $J = 17.4$, 6.0 Hz, 1H) (ppm).

$^{13}$C NMR (150 MHz, CDCl$_3$) $\delta = 194.1$, 153.4, 152.6, 133.9, 133.7, 130.6, 130.3, 128.9, 128.7, 128.5, 126.6, 61.0, 53.6, 37.6 (ppm).

MS (EI): m/z = 308 (M$^+$).

IR (KBr): 2957, 1676, 1463, 1407, 1333, 1158, 869, 756, 694 (cm$^{-1}$).

Anal. calcd for (C$_{19}$H$_{18}$N$_2$O$_3$): C, 70.12; H, 5.23; N, 9.09. Found: C, 69.77; H, 5.14; N, 8.89.
(5S)-1,5-Dibenzoyl-3-phenyl-4,5-dihydro pyrazole (126da)

Yield: 83%. Melting point: 177.4-178.0 °C.

The er was determined by HPLC (Chiralpak OD column, heptane/i-PrOH 7:3, flow rate 0.8 mL/min, λ = 254 nm, 20 °C). t_R (minor) = 14.1 min; t_R (major) = 19.0 min, ee = 92:8.

^1^H NMR (400 MHz, CDCl_3) δ = 8.09 (d, J = 7.3 Hz, 4H), 7.69 – 7.62 (m, 3H), 7.55 – 7.44 (m, 5H), 7.42 – 7.36 (m, 3H), 6.17 (dd, J = 12.5, 6.3 Hz, 1H), 3.70 (dd, J = 17.4, 12.5 Hz, 1H), 3.25 (dd, J = 17.4, 6.3 Hz, 1H) (ppm).

^13^C NMR (150 MHz, CDCl_3) δ = 194.2, 166.0, 154.1, 134.2, 133.9, 133.5, 131.2, 130.8, 130.5, 130.1, 128.9, 128.8, 128.7, 127.7, 126.6, 60.9, 36.6 (ppm).

MS (EI): m/z = 354 (M^+).

IR (KBr): 3056, 1689, 1603, 1564, 1448, 1426, 1336, 761, 697 (cm^{-1}).

Anal. calcd for (C_{23}H_{18}N_2O_2): C, 77.95; H, 5.12; N, 7.90. Found: C, 77.90; H, 5.18; N, 7.79.

(5S)-1-Benzoyl-3-phenyl-5-(para-bromobenzoyl)-4,5-dihydro pyrazole (126db)

Yield: 89%. Melting point: 203.3-204.0 °C.

The er was determined by HPLC (Chiralpak OD column, heptane/i-PrOH 7:3, flow rate 0.8 mL/min, λ = 254 nm, 20 °C). t_R (minor) = 15.7 min; t_R (major) = 28.5 min, ee = 98:2.

^1^H NMR (400 MHz, CDCl_3) δ = 8.08 (dd, J = 8.3, 1.3 Hz, 2H), 7.96 (d, J = 8.6 Hz, 2H), 7.68 (d, J = 8.4 Hz, 4H), 7.54 – 7.37 (m, 6H), 6.10 (dd, J = 12.4, 6.4 Hz, 1H), 3.68 (dd, J = 17.4, 12.5 Hz, 1H), 3.24 (dd, J = 17.4, 6.4 Hz, 1H) (ppm).
\[ ^{13}C \text{ NMR (100 MHz, CDCl}_3 \] \delta = 193.8, 166.3, 153.9, 133.4, 133.4, 133.2, 132.2, 131.3, 130.8, 130.6, 130.3, 130.2, 129.2, 128.7, 127.7, 126.7, 60.7, 36.6 (ppm).

MS (EI): \textit{m/z} = 433 (M}^+1\). IR (KBr): 3054, 1688, 1604, 1562, 1423, 1334, 822, 703, 681 (cm\(^{-1}\)).

\[
\text{Anal. calcd for (C}_{23}\text{H}_{17}\text{BrN}_2\text{O}_2): C, 63.75; H, 3.95; N, 6.47. Found: C, 64.10; H, 4.17; N, 6.15.}
\]

\((5S)-1\text{-Benzoyl-3-phenyl-5-(para-chlorobenzoyl)-4,5-dihydro pyrazole (126dc)}\)

Yield: 85%. Melting point: 190.8-191.9 °C.

The er was determined by HPLC (Chiralpak OD column, heptane/i-PrOH 7:3, flow rate 0.8 mL/min, \(\lambda = 254 \text{ nm, } 20 \degree\text{C}\)). \(t_R\) (minor) = 13.4 min; \(t_R\) (major) = 24.8 min, ee = 98:2.

\[^1\text{H NMR (600 MHz, CDCl}_3 \] \delta = 8.07 (d, \(J = 7.4 \text{ Hz, } 2\text{H}\)), 8.03 (d, \(J = 8.4 \text{ Hz, } 2\text{H}\)), 7.67 (d, \(J = 6.9 \text{ Hz, } 2\text{H}\)), 7.57 - 7.31 (m, 8H), 6.10 (dd, \(J = 12.4, 6.4 \text{ Hz, } 1\text{H}\)), 3.67 (dd, \(J = 17.3, 12.5 \text{ Hz, } 1\text{H}\)), 3.23 (dd, \(J = 17.3, 6.4 \text{ Hz, } 1\text{H}\)) (ppm).

\[^{13}\text{C NMR (150 MHz, CDCl}_3 \] \delta = 193.6, 166.3, 153.9, 140.4, 133.2, 132.9, 131.3, 130.8, 130.5, 130.2, 129.2, 128.7, 127.7, 126.7, 60.7, 36.6 (ppm).

MS (EI): \textit{m/z} = 388 (M\(^+\)).

IR (KBr): 3054, 1689, 1606, 1563, 1424, 1335, 1224, 822, 682 (cm\(^{-1}\)).

\[
\text{Anal. calcd for (C}_{23}\text{H}_{17}\text{ClN}_2\text{O}_2): C, 71.04; H, 4.41; N, 7.20. Found: C, 71.06; H, 4.31; N, 7.05.}
\]
(5S)-1-Benzoyl-3-phenyl-5-(meta-nitrobenzoyl)-4,5-dihydro pyrazole (126dd)

Yield: 92%. Melting point: 203.5-204.5 °C.
The er was determined by HPLC (Chiralpak OD column, heptane/i-PrOH 6:4, flow rate 0.8 mL/min, λ = 254 nm, 20 °C). t<sub>R</sub> (minor) = 20.4 min; t<sub>R</sub> (major) = 34.5 min, er = 92:8.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ = 8.91 (t, J = 1.9 Hz, 1H), 8.48 – 8.46 (m, 1H), 8.45 – 8.42 (m, 1H), 8.07 (dd, J = 8.3, 1.4 Hz, 2H), 7.74 – 7.68 (m, 3H), 7.56 – 7.39 (m, 6H), 7.14 (dd, J = 12.3, 6.7 Hz, 1H), 3.74 (dd, J = 17.4, 12.3 Hz, 1H), 3.30 (dd, J = 17.4, 6.7 Hz, 1H) (ppm).

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ = 193.4, 166.2, 154.2, 148.5, 136.2, 134.3, 132.8, 131.5, 130.7, 130.6, 130.2, 128.8, 128.0, 127.8, 126.8, 123.5, 60.7, 36.5 (ppm).

MS (EI): m/z = 399 (M<sup>+</sup>).

IR (KBr): 3055, 1700, 1625, 1525, 1431, 1338, 1214, 769, 699 (cm<sup>-1</sup>).

Anal. calcd for (C<sub>23</sub>H<sub>17</sub>N<sub>3</sub>O<sub>4</sub>): C, 69.17; H, 4.29; N, 10.52. Found: C, 69.20; H, 4.31; N, 10.59.

(5S)-1-Benzoyl-3-phenyl-5-(para-nitrobenzoyl)-4,5-dihydro pyrazole (126de)

Yield: 87%. Melting point: 235.0-235.8 °C.
The er was determined by HPLC (Chiralpak OD column, heptane/i-PrOH 6:4, flow rate 0.8 mL/min, λ = 254 nm, 20 °C). t<sub>R</sub> (minor) = 19.9 min; t<sub>R</sub> (major) = 45.3 min, er = 92:8.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 8.18 (d, J = 8.5 Hz, 2H), 8.07 (dd, J = 8.4, 1.3 Hz, 2H), 7.83 (d, J = 8.6 Hz, 2H), 7.69 (dd, J = 7.8, 1.7 Hz, 2H), 7.53 – 7.39 (m, 6H), 6.09
(dd, \( J = 12.3, 6.7 \text{ Hz}, 1\text{H} \)), 3.69 (dd, \( J = 17.4, 12.4 \text{ Hz}, 1\text{H} \)), 3.27 (dd, \( J = 17.4, 6.7 \text{ Hz}, 1\text{H} \)) (ppm).

\(^{13}\text{C} \text{ NMR} \ (100 \text{ MHz, CDCl}_3) \ \delta = 194.3, 166.3, 154.1, 138.1, 132.9, 132.7, 131.5, 130.8, 130.6, 130.2, 129.1, 128.8, 127.8, 126.8, 117.8, 117.0, 60.8, 36.5 \ (\text{ppm}).

MS (EI): \( m/z = 379 \ (M^+) \).

IR (KBr): 3053, 1696, 1604, 1561, 1419, 1335, 823, 702 \ (\text{cm}^{-1}).

Anal. calcd for \((\text{C}_{24}\text{H}_{17}\text{N}_3\text{O}_2)\): C, 75.97; H, 4.52; N, 11.08. Found: C, 75.81; H, 4.44; N, 11.06.

\((55)\)-1-Benzoyl-3-phenyl-5-(meta-methoxybenzoyl)-4,5-dihydro pyrazole (126df)

Yield: 95%. Melting point: 154.9-155.8 °C.

The er was determined by HPLC (Chiralpak OD column, heptane/i-PrOH 7:3, flow rate 0.8 mL/min, \( \lambda = 254 \text{ nm}, 20 \text{ °C} \)). \( t_R \) (minor) = 17.8 min; \( t_R \) (major) = 23.2 min, er = 90:10.

\(^1\text{H} \text{ NMR} \ (300 \text{ MHz, CDCl}_3) \ \delta = 8.08 \ (\text{dd, } J = 8.1, 1.6 \text{ Hz}, 2\text{H}), 7.65 - 7.57 \ (\text{m, } 4\text{H}), 7.52 - 7.30 \ (\text{m, } 7\text{H}), 7.16 - 7.12 \ (\text{m, } 1\text{H}), 6.10 \ (\text{dd, } J = 12.6, 6.3 \text{ Hz}, 1\text{H}), 3.82 \ (\text{s, } 3\text{H}), 3.64 \ (\text{dd, } J = 17.5, 12.6 \text{ Hz}, 1\text{H}), 3.19 \ (\text{dd, } J = 17.5, 6.3 \text{ Hz}, 1\text{H}) \ (\text{ppm}).

\(^{13}\text{C} \text{ NMR} \ (75 \text{ MHz, CDCl}_3) \ \delta = 193.9, 166.1, 159.9, 153.8, 135.6, 133.4, 131.1, 130.8, 130.3, 130.1, 129.8, 128.6, 127.6, 126.6, 121.2, 120.4, 112.9, 61.0, 55.4, 36.6 \ (\text{ppm}).

MS (EI): \( m/z = 384 \ (M^+) \).

IR (KBr): 3066, 1691, 1619, 1450, 1425, 1331, 1259, 1030, 762, 689 \ (\text{cm}^{-1}).

Anal. calcd for \((\text{C}_{24}\text{H}_{20}\text{N}_2\text{O}_3)\): C, 74.98; H, 5.24; N, 7.29. Found: C, 73.90; H, 5.39; N, 7.29.
(5S)-1-Benzoyl-3-phenyl-5-(2-naphthalenylcarbonyl)-4,5-dihydro pyrazole (126dg)

Yield: 81%. Melting point: 178.5-179.5 °C.
The er was determined by HPLC (Chiralpak OD column, heptane/i-PrOH 7:3, flow rate 0.8 mL/min, λ = 254 nm, 20 °C). t<sub>R</sub> (major) = 26.8 min; t<sub>R</sub> (minor) = 43.8 min, er = 90:10.

1H NMR (400 MHz, CDCl<sub>3</sub>) δ = 8.60 (s, 1H), 8.11 – 8.06 (m, 3H), 7.95 (d, J = 8.0 Hz, 1H), 7.88 (d, J = 8.6 Hz, 1H), 7.84 (d, J = 8.1 Hz, 1H), 7.63 (dd, J = 7.8, 1.7 Hz, 2H), 7.61 – 7.30 (m, 8H), 6.30 (dd, J = 12.5, 6.3 Hz, 1H), 3.69 (dd, J = 17.5, 12.6 Hz, 1H), 3.24 (dd, J = 17.5, 6.3 Hz, 1H) (ppm).

13C NMR (100 MHz, CDCl<sub>3</sub>) δ = 194.3, 166.2, 154.0, 135.8, 133.5, 132.4, 131.7, 131.1, 130.8, 130.7, 130.4, 130.2, 129.6, 128.8, 128.8, 128.6, 127.7, 127.6, 126.9, 126.6, 124.1, 60.9, 36.7 (ppm).

MS (EI): m/z = 404 (M<sup>+</sup>).

IR (KBr): 3052, 1687, 1609, 1566, 1449, 1424, 1180, 756, 694 (cm<sup>-1</sup>).

Anal. calcd for (C<sub>27</sub>H<sub>20</sub>N<sub>2</sub>O<sub>2</sub>): C, 80.18; H, 4.98; N, 6.93. Found: C, 80.21; H, 4.92; N, 6.60.

(5S)-1-(ortho-Methoxybenzoyl)-3-phenyl-5-(meta-methoxybenzoyl)-4,5-dihydro pyrazole (126ea)

Yield: 84%. Melting point: 156.0-156.8 °C.
The er was determined by HPLC (Chiralpak OD column, heptane/i-PrOH 7:3, flow rate 0.8 mL/min, λ = 254 nm, 20 °C). t<sub>R</sub> (minor) = 16.9 min; t<sub>R</sub> (major) = 26.7 min, er
\( \delta = 97:3 \).

\( ^1H \) NMR (300 MHz, CDCl\(_3\)) \( \delta = 8.08 (t, J = 1.3 \text{ Hz}, 1\text{H}), 8.06 (t, J = 1.7 \text{ Hz}, 1\text{H}), 7.69 - 7.58 (m, 1\text{H}), 7.58 - 7.47 (m, 5\text{H}), 7.44 - 7.37 (m, 1\text{H}), 7.31 - 7.29 (m, 3\text{H}), 7.04 - 6.95 (m, 2\text{H}), 6.12 (dd, J = 12.6, 6.0 \text{ Hz}, 1\text{H}), 3.83 (s, 3\text{H}), 3.70 (dd, J = 17.5, 6.0 \text{ Hz}, 1\text{H}), 3.22 (dd, J = 17.5, 6.0 \text{ Hz}, 1\text{H})\) (ppm).

\( ^{13}C \) NMR (75 MHz, CDCl\(_3\)) \( \delta = 194.0, 166.2, 156.7, 153.2, 134.3, 133.7, 130.9, 130.9, 130.2, 129.4, 128.8, 128.5, 126.5, 125.0, 120.1, 111.2, 60.3, 55.8, 37.2 \) (ppm).

MS (EI): \( m/z = 384 \) (M\(^+\)).

IR (KBr): 2968, 1697, 1631, 1594, 1458, 1431, 1224, 758, 693 (cm\(^{-1}\)).

Anal. calcd for \( \text{C}_{24}\text{H}_{20}\text{N}_{2}\text{O}_{3} \): C, 74.98; H, 5.24; N, 7.29. Found: C, 75.38; H, 5.07; N, 7.12.

(5S)-1-(ortho-Methoxybenzoyl)-3-phenyl-5-(para-bromobenzoyl)-4,5-dihydro pyrazole (126eb)

Yield: 91%. Melting point: 113.8-114.5 °C.

The er was determined by HPLC (Chiralpak OD column, heptane/i-PrOH 7:3, flow rate 0.8 mL/min, \( \lambda = 254 \text{ nm}, 20 \text{ °C} \)). \( t_R \) (minor) = 19.3 min; \( t_R \) (major) = 50.5 min, er = 97:3.

\( ^1H \) NMR (600 MHz, CDCl\(_3\)) \( \delta = 7.94 (d, J = 8.3 \text{ Hz}, 2\text{H}), 7.63 (d, J = 8.3 \text{ Hz}, 2\text{H}), 7.54 (d, J = 7.4 \text{ Hz}, 2\text{H}), 7.49 (d, J = 7.3 \text{ Hz}, 1\text{H}), 7.41 (t, J = 7.8 \text{ Hz}, 1\text{H}), 7.33 (m, 3\text{H}), 7.01 (t, J = 7.4 \text{ Hz}, 1\text{H}), 6.97 (d, J = 8.3 \text{ Hz}, 1\text{H}), 6.05 (dd, J = 12.5, 6.1 \text{ Hz}, 1\text{H}), 3.82 (t, J = 7.8 \text{ Hz}, 1\text{H}), 3.69 (dd, J = 17.3, 12.7 \text{ Hz}, 1\text{H}), 3.22 (dd, J = 17.4, 6.0 \text{ Hz}, 1\text{H})\) (ppm).

\( ^{13}C \) NMR (150 MHz, CDCl\(_3\)) \( \delta = 193.6, 166.3, 156.8, 153.3, 133.2, 132.1, 131.0, 130.8, 130.3, 129.4, 129.1, 128.5, 126.6, 124.8, 120.1, 111.2, 60.2, 55.8, 37.2 \) (ppm).

MS (EI): \( m/z = 462 \) (M\(^+\)).

IR (KBr): 2836, 1696, 1638, 1583, 1425, 1336, 1005, 833, 753, 690 (cm\(^{-1}\)).
(5S)-1-(ortho-Methoxybenzoyl)-3-phenyl-5-(meta-chlorobenzoyl)-4,5-dihydro pyrazole (126ec)

Yield: 93%. Melting point: 119.0-120.0 °C.

The er was determined by HPLC (Chiralpak OD column, heptane/i-PrOH 6:4, flow rate 0.8 mL/min, λ = 254 nm, 20 °C). \( t_R \) (minor) = 13.0 min; \( t_R \) (major) = 32.3 min, er = 96:4.

\(^1\)H NMR (600 MHz, CDCl\(_3\)) \( \delta = 8.02 \) (d, \( J = 8.5 \) Hz, 2H), 7.55 (d, \( J = 7.2 \) Hz, 2H), 7.48 (t, \( J = 9.0 \) Hz, 3H), 7.43 – 7.40 (m, 1H), 7.36 (t, \( J = 7.2 \) Hz, 1H), 7.32 (t, \( J = 7.4 \) Hz, 2H), 7.02 (t, \( J = 7.4 \) Hz, 1H), 6.97 (d, \( J = 8.3 \) Hz, 1H), 6.06 (dd, \( J = 12.5, 6.1 \) Hz, 1H), 3.83 (s, 3H), 3.69 (dd, \( J = 17.3, 12.6 \) Hz, 1H), 3.23 (dd, \( J = 17.4, 6.2 \) Hz, 1H) (ppm).

\(^{13}\)C NMR (150 MHz, CDCl\(_3\)) \( \delta = 193.4, 166.3, 156.8, 153.3, 140.3, 132.8, 131.0, 130.9, 130.3, 129.5, 129.1, 128.6, 126.6, 124.8, 120.1, 111.2, 60.2, 55.9, 37.2 (ppm).

MS (EI): \( m/z = 418 \) (M\(^+\)).

IR (KBr): 2325, 1695, 1639, 1588, 1425, 1222, 1009, 835, 753, 690 cm\(^{-1}\).

Anal. Calcd for (C\(_{24}\)H\(_{19}\)BrN\(_2\)O\(_3\)): C, 62.22; H, 4.13; N, 6.05. Found: C, 62.00; H, 4.08; N, 5.89.

Anal. Calcd for (C\(_{24}\)H\(_{19}\)ClN\(_2\)O\(_3\)): C, 68.82; H, 4.57; N, 6.69. Found: C, 68.64; H, 4.57; N, 6.55.
(5S)-1-(ortho-Methoxybenzoyl)-3-phenyl-5-(meta-nitrobenzoyl)-4,5-dihydro pyrazole (126ed)

Yield: 84%. Melting point: 121.5-122.8 °C.

The er ratio was determined by HPLC (Chiralpak OD column, heptane/i-PrOH 1:1, flow rate 0.8 mL/min, λ = 254 nm, 20 °C). t_R (minor) = 21.6 min; t_R (major) = 53.8 min, er = 92:8.

^1^H NMR (300 MHz, CDCl_3) δ = 8.90 (s, 1H), 8.44 (t, J = 8.1 Hz, 2H), 7.72 (t, J = 8.0 Hz, 1H), 7.57 (dd, J = 7.7, 1.4 Hz, 2H), 7.48 – 7.29 (m, 5H), 7.00 (dd, J = 15.8, 8.0 Hz, 2H), 6.10 (dd, J = 12.4, 6.5 Hz, 1H), 3.83 (s, 3H), 3.80 – 3.67 (m, 1H), 3.30 (dd, J = 17.4, 6.4 Hz, 1H) (ppm).

^1^3^C NMR (75 MHz, CDCl_3) δ = 193.2, 166.3, 156.8, 153.5, 148.4, 136.1, 134.4, 131.3, 130.7, 130.5, 130.1, 129.4, 128.6, 127.8, 126.6, 124.4, 123.5, 120.1, 111.3, 60.1, 55.8, 37.1 (ppm).

MS (EI): m/z = 279.3 (78), 409.2 (100), 429.5 (6, M^+).

IR (KBr): 3081, 1702, 1637, 1530, 1462, 1427, 1343, 1249, 1222, 1018, 756, 711 (cm^{-1}).

Anal. calcd for (C_{24}H_{19}N_{3}O_5): C, 67.13; H, 4.46; N, 9.79. Found: C, 66.82; H, 4.44; N, 9.68.

(5S)-1-(ortho-Methoxybenzoyl)-3-phenyl-5-(para-nitrobenzoyl)-4,5-dihydro pyrazole (126ee)

Yield: 88%. Melting point: 121.0-122.5 °C.
The er ratio was determined by HPLC (Chiralpak OD column, heptane/i-PrOH 1:1, flow rate 0.8 mL/min, λ = 254 nm, 20 °C). t_R (minor) = 20.9 min; t_R (major) = 78.2 min, er = 94:6.

^1^H NMR (300 MHz, CDCl_3) δ = 8.16 (d, J = 8.3 Hz, 2H), 7.79 (d, J = 8.3 Hz, 2H), 7.56 (dd, J = 7.8, 1.4 Hz, 2H), 7.47 – 7.30 (m, 5H), 7.01 (dd, J = 15.8, 8.0 Hz, 2H), 6.04 (dd, J = 12.4, 6.5 Hz, 1H), 3.83 (s, 3H), 3.71 (dd, J = 17.4, 12.4 Hz, 1H), 3.26 (dd, J = 17.4, 6.5 Hz, 1H) (ppm).

^1^3^C NMR (75 MHz, CDCl_3) δ = 194.1, 166.3, 156.8, 153.5, 137.9, 132.6, 131.3, 130.7, 130.5, 129.4, 129.2, 128.6, 126.6, 124.4, 120.2, 117.8, 116.8, 111.3, 60.3, 55.8, 37.1 (ppm).

MS (EI): m/z = 278.6 (61), 409.2 (100, M^+).

IR (KBr): 2940, 1700, 1636, 1600, 1427, 1247, 1223, 1015, 840, 755, 691 (cm^{-1}).

Anal. calcd for (C_{25}H_{19}N_3O_3): C, 73.34; H, 4.68; N, 10.26. Found: C, 73.00; H, 4.89; N, 10.05.

(5S)-1-(ortho-Methoxybenzoyl)-3-phenyl-5-(meta-methoxybenzoyl)-4,5-dihydro pyrazole (126ef)

Yield: 95%. (liquid)

The er was determined by HPLC (Chiralpak OD column, heptane/i-PrOH 1:1, flow rate 0.7 mL/min, λ = 254 nm, 20 °C). t_R (minor) = 17.3 min; t_R (major) = 21.2 min, er = 92:8.

^1^H NMR (400 MHz, CDCl_3) δ = 7.66 – 7.63 (m, 1H), 7.60 (dd, J = 2.5, 1.6 Hz, 1H), 7.56 – 7.49 (m, 3H), 7.44 – 7.39 (m, 2H), 7.32 – 7.30 (m, 3H), 7.17 – 7.15 (m, 1H), 7.04 – 7.00 (m, 1H), 6.97 (d, J = 8.3 Hz, 1H), 6.10 (dd, J = 12.6, 6.0 Hz, 1H), 3.85 (s, 3H), 3.84 (s, 3H), 3.71 (dd, J = 17.5, 12.7 Hz, 1H), 3.24 (dd, J = 17.5, 6.0 Hz, 1H).

^1^3^C NMR (100 MHz, CDCl_3) δ = 193.8, 166.3, 160.0, 156.8, 153.2, 135.6, 131.0,
130.9, 130.2, 129.7, 129.5, 128.5, 126.5, 125.1, 121.3, 120.5, 120.1, 113.0, 111.2, 60.5, 55.9, 55.4, 37.3 (ppm).

MS (EI): m/z = 279.2 (45), 414.2 (100, M⁺).

IR (KBr): 2938, 1639, 1593, 1488, 1459, 1426, 1253, 1020, 755 (cm⁻¹).

Anal. calcd for (C₂₅H₂₂N₂O₄): C, 72.45; H, 5.35; N, 6.76. Found: C, 71.84; H, 5.41; N, 6.68.

(5S)-1-(ortho-Methoxybenzoyl)-3-phenyl-5-(2-naphthalenylcarbonyl)-4,5-dihydro pyrazole (126eg)

Yield: 92%. Melting point: 122.0-123.4 °C.

The er was determined by HPLC (Chiralpak OD column, heptane/i-PrOH 1:1, flow rate 0.7 mL/min, λ = 254 nm, 20 °C). tᵣ (major) = 27.7 min; tᵣ (minor) = 33.0 min, er = 95:5.

¹H NMR (600 MHz, CDCl₃) δ = 8.63 (s, 1H), 8.11 (d, J = 8.5 Hz, 1H), 7.98 (d, J = 8.1 Hz, 1H), 7.93 (d, J = 8.6 Hz, 1H), 7.88 (d, J = 8.1 Hz, 1H), 7.62 (t, J = 7.4 Hz, 1H), 7.58 – 7.54 (m, 4H), 7.43 – 7.40 (m, 1H), 7.36 – 7.30 (m, 3H), 7.03 (t, J = 7.4 Hz, 1H), 6.98 (d, J = 8.3 Hz, 1H), 6.31 (dd, J = 12.6, 5.9 Hz, 1H), 3.84 (s, 3H), 3.77 (dd, J = 17.4, 12.7 Hz, 1H), 3.30 (dd, J = 17.4, 5.9 Hz, 1H) (ppm).

¹³C NMR (150 MHz, CDCl₃) δ = 194.1, 166.3, 156.8, 153.3, 135.8, 132.4, 131.8, 131.1, 130.9, 130.8, 130.2, 129.7, 129.5, 128.8, 128.5, 127.8, 126.9, 126.6, 125.1, 124.3, 120.1, 111.3, 60.3, 55.9, 37.5 (ppm).

MS (EI): m/z = 269.9 (81), 278.2 (94), 434.3 (100, M⁺).

IR (KBr): 3057, 1687, 1637, 1597, 1462, 1427, 1248, 755, 692 (cm⁻¹).

(5S)-1-(ortho-Methoxybenzoyl)-3-phenyl-5-(para-fluorobenzoyl)-4,5-dihydropyrazole (126eh)

Yield: 93%. Melting point: 120.0-120.9 °C.

The er was determined by HPLC (Chiralpak OD column, heptane/i-PrOH 6:4, flow rate 0.8 mL/min, λ = 254 nm, 20 °C). t_R (minor) = 11.2 min; t_R (major) = 26.7 min, er = 96:4.

^1H NMR (600 MHz, CDCl_3) δ = 8.12 (dd, J = 8.6, 5.4 Hz, 2H), 7.55 (d, J = 7.1 Hz, 2H), 7.50 (dd, J = 7.4, 1.3 Hz, 1H), 7.43 - 7.40 (m, 1H), 7.36 - 7.30 (m, 3H), 7.17 (t, J = 8.5 Hz, 2H), 7.02 (t, J = 7.4 Hz, 1H), 6.97 (d, J = 8.3 Hz, 1H), 6.08 (dd, J = 12.6, 6.1 Hz, 1H), 3.83 (s, 3H), 3.70 (dd, J = 17.4, 12.6 Hz, 1H), 3.23 (dd, J = 17.4, 6.1 Hz, 1H) (ppm).

^13C NMR (150 MHz, CDCl_3) δ = 192.9, 166.9, 166.3, 165.2, 156.8, 153.3, 131.6, 131.5, 131.0, 130.9, 130.3, 129.4, 128.5, 126.5, 124.9, 120.1, 116.1, 115.9, 111.2, 60.1, 55.8, 37.2 (ppm).

MS (EI): m/z = 278.3 (95), 402.0 (100, M^+).

IR (KBr): 2933, 1696, 1637, 1595, 1423, 1225, 1155, 1017, 842, 754, 691 (cm^-1).

Anal. calcd for (C_{24}H_{19}FN_2O_3): C, 71.63; H, 4.76; N, 6.96. Found: C, 71.41; H, 4.77; N, 6.86.

(5S)-1-(ortho-Methoxybenzoyl)-3-phenyl-5-(3,4-dichlorobenzoyl)-4,5-dihydropyrazole (126ei)

Yield: 94%. Melting point: 163.0-164.1 °C.
The er was determined by HPLC (Chiralpak OD column, heptane/i-PrOH 6:4, flow rate 0.8 mL/min, $\lambda = 254$ nm, 20 °C). $t_R$ (minor) = 14.9 min; $t_R$ (major) = 41.2 min, er = 92:8.

$^1$H NMR (600 MHz, CDCl$_3$) $\delta$ = 8.16 (d, $J = 1.7$ Hz, 1H), 7.91 (dd, $J = 8.3$, 1.8 Hz, 1H), 7.58 – 7.54 (m, 3H), 7.48 (d, $J = 7.5$ Hz, 1H), 7.43 – 7.40 (m, 1H), 7.38 – 7.31 (m, 3H), 7.01 (t, $J = 7.4$ Hz, 1H), 6.97 (d, $J = 8.3$ Hz, 1H), 6.01 (dd, $J = 12.5$, 6.3 Hz, 1H), 3.82 (s, 3H), 3.69 (dd, $J = 17.3$, 12.5 Hz, 1H), 3.23 (dd, $J = 17.4$, 6.3 Hz, 1H).

$^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ = 192.8, 166.3, 156.8, 153.4, 138.4, 134.2, 133.5, 131.2, 130.9, 130.7, 130.4, 129.4, 128.6, 127.8, 126.6, 124.6, 120.1, 111.3, 60.1, 55.8, 37.1 (ppm).

MS (EI): m/z = 279.7 (100), 452.3 (18, M$^+$).

IR (KBr): 2935, 1700, 1636, 1425, 1335, 1211, 1024, 840, 753 (cm$^{-1}$).

Anal. calcd for (C$_{24}$H$_{18}$Cl$_2$N$_2$O$_3$): C, 63.59; H, 4.00; N, 6.18. Found: C, 63.34; H, 3.98; N, 6.02.

(5S)-1-(ortho-Methoxybenzoyl)-3-phenyl-5-(para-methylbenzoyl)-4,5-dihydro pyrazole (126ej)

Yield: 92%. Melting point: 109.8-110.8 °C.

The er was determined by HPLC (Chiralpak OD column, heptane/i-PrOH 1:1, flow rate 0.7 mL/min, $\lambda = 254$ nm, 20 °C). $t_R$ (minor) = 12.5 min; $t_R$ (major) = 22.0 min, er = 95:5.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ = 7.98 (d, $J = 8.2$ Hz, 2H), 7.53 (d, $J = 6.7$ Hz, 3H), 7.40 – 7.37 (m, 1H), 7.34 – 7.26 (m, 5H), 7.04 – 6.95 (m, 2H), 6.11 (dd, $J = 12.6$, 5.9 Hz, 1H), 3.83 (s, 3H), 3.69 (dd, $J = 17.4$, 12.6 Hz, 1H), 3.21 (dd, $J = 17.5$, 5.9 Hz, 1H), 2.42 (s, 3H) (ppm).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ = 193.5, 166.3, 156.7, 153.2, 144.7, 131.7, 131.0, 130.8,
(5S)-1-(ortho-Methoxybenzoyl)-3-phenyl-5-(2-furanylcarbonyl)-4,5-dihydro pyrazole (126ek)

Yield: 85%. Melting point: 122.8–123.7 °C.

The er was determined by HPLC (Chiralpak OD column, heptane/i-PrOH 1:1, flow rate 0.7 mL/min, λ = 254 nm, 20 °C). t_R (minor) = 14.5 min; t_R (major) = 26.6 min, er = 93:7.

^1^H NMR (600 MHz, CDCl_3) δ = 7.65 (s, 1H), 7.54 (d, J = 7.2 Hz, 2H), 7.48 (d, J = 7.5 Hz, 1H), 7.41 – 7.38 (m, 2H), 7.36 – 7.30 (m, 3H), 7.00 (t, J = 7.4 Hz, 1H), 6.96 (d, J = 8.4 Hz, 1H), 6.58 (t, J = 1.8 Hz, 1H), 5.91 (dd, J = 12.5, 6.2 Hz, 1H), 3.81 (s, 4H), 3.68 (dd, J = 17.5, 12.6 Hz, 1H), 3.28 (dd, J = 17.5, 6.3 Hz, 1H) (ppm).

^13^C NMR (150 MHz, CDCl_3) δ = 183.2, 166.3, 156.7, 153.5, 150.5, 147.2, 130.9, 130.2, 129.3, 128.5, 126.5, 125.0, 120.1, 119.1, 112.7, 111.2, 60.4, 55.8, 37.1 (ppm).

MS (EI): m/z = 279.1 (73), 374.3 (100, M^+).

IR (KBr): 2938, 1680, 1637, 1598, 1461, 1425, 1249, 1017, 756, 691 (cm^-1).

Anal. calcd for (C_{22}H_{18}N_{2}O_{4}): C, 70.58; H, 4.85; N, 7.48. Found: C, 70.35; H, 4.86; N, 7.38.
(5S)-1-(ortho-Methoxybenzoyl)-3-phenyl-5-(2-thienylcarbonyl)-4,5-dihydro pyrazole (126el)

Yield: 88%. Melting point: 118.7-119.5 °C.

The er was determined by HPLC (Chiralpak OD column, heptane/i-PrOH 1:1, flow rate 0.8 mL/min, λ = 254 nm, 20 °C). tR (minor) = 12.8 min; tR (major) = 22.6 min, er = 94:6.

1H NMR (600 MHz, CDCl3) δ = 7.93 (d, J = 3.3 Hz, 1H), 7.71 (d, J = 4.7 Hz, 1H), 7.55 (d, J = 7.1 Hz, 2H), 7.49 (d, J = 7.4 Hz, 1H), 7.42 – 7.39 (m, 1H), 7.36 – 7.30 (m, 3H), 7.16 (t, J = 4.8 Hz, 1H), 7.01 (t, J = 7.4 Hz, 1H), 6.97 (d, J = 8.3 Hz, 1H), 5.92 (dd, J = 12.5, 6.2 Hz, 1H), 3.82 (s, 3H), 3.71 (dd, J = 17.5, 12.5 Hz, 1H), 3.71 (dd, J = 17.5, 6.2 Hz, 1H) (ppm).

13C NMR (150 MHz, CDCl3) δ = 187.4, 166.4, 156.7, 153.5, 140.8, 134.9, 133.1, 131.0, 130.9, 130.2, 129.4, 128.5, 128.4, 126.6, 125.0, 120.1, 111.2, 61.3, 55.8, 37.6 (ppm).

MS (EI): m/z = 278.2 (69), 390.2 (100, M+).

IR (KBr): 2936, 1638, 1598, 1460, 1415, 1240, 1021, 756, 692 (cm⁻¹).


(5S)-1-Benzoyl-3-(para-chlorophenyl)-5-benzoyl-4,5-dihydro pyrazole (126fa)

Yield: 94%. Melting point: 208.5-209.6 °C.

The er was determined by HPLC (Chiralpak OD column, heptane/i-PrOH 7:3, flow
rate 0.8 mL/min, $\lambda = 254$ nm, 20 °C). $t_R$ (minor) = 20.5 min; $t_R$ (major) = 24.2 min, er = 91:9.

$^1$H NMR (600 MHz, CDCl$_3$) $\delta$ = 8.06 (dd, $J = 12.6, 7.5$ Hz, 4H), 7.64 – 7.62 (m, 1H), 7.58 (d, $J = 8.5$ Hz, 2H), 7.51 (dd, $J = 15.5, 7.6$ Hz, 3H), 7.45 (t, $J = 7.7$ Hz, 2H), 7.34 (d, $J = 8.5$ Hz, 2H), 6.17 (dd, $J = 12.6, 6.3$ Hz, 1H), 3.65 (dd, $J = 17.4, 12.6$ Hz, 1H), 3.20 (dd, $J = 17.4, 6.3$ Hz, 1H) (ppm).

$^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ = 194.2, 166.3, 152.8, 136.4, 134.3, 133.9, 133.3, 131.2, 130.1, 129.4, 129.0, 128.9, 128.8, 127.9, 127.7, 60.9, 36.5 (ppm).

MS (EI): m/z = 282.5 (100), 388.1 (30, $M^+$).

IR (KBr): 3053, 1693, 1607, 1429, 1332, 1227, 825, 700 (cm$^{-1}$).

Anal. calcd for (C$_{23}$H$_{17}$ClN$_2$O$_2$): C, 71.04; H, 4.41; N, 7.20. Found: C, 70.87; H, 4.00; N, 7.03.

(5S)-1-Benzoyl-3-(para-fluorophenyl)-5-benzoyl-4,5-dihydro pyrazole (126ga)

Yield: 97%. Melting point: 188.9-190.5 °C.

The er was determined by HPLC (Chiralpak OD column, heptane/i-PrOH 7:3, flow rate 0.8 mL/min, $\lambda = 254$ nm, 20 °C). $t_R$ (minor) = 16.3 min; $t_R$ (major) = 21.8 min, er = 90:10.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ = 8.09 – 8.04 (m, 4H), 7.67 – 7.60 (m, 3H), 7.54 – 7.41 (m, 5H), 7.06 (t, $J = 8.7$ Hz, 2H), 6.17 (dd, $J = 12.5, 6.2$ Hz, 1H), 3.66 (dd, $J = 17.5, 12.5$ Hz, 1H), 3.20 (dd, $J = 17.4, 6.2$ Hz, 1H) (ppm).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ = 194.2, 166.3, 165.6, 162.3, 152.8, 134.4, 133.9, 133.4, 131.2, 130.1, 128.9, 128.8, 128.7, 128.6, 127.7, 127.2, 116.0, 115.7, 60.9, 36.7 (ppm).

MS (EI): m/z = 265.9 (100), 372.1 (49, $M^+$).

IR (KBr): 3055, 1691, 1606, 1431, 1222, 1155, 837, 700 (cm$^{-1}$).
Anal. calcd for (C$_{23}$H$_{17}$FN$_2$O$_2$): C, 74.18; H, 4.60; N, 7.52. Found: C, 73.98; H, 4.59; N, 7.30.

(5S)-1-Benzoyl-3-(para-methylphenyl)-5-benzoyl-4,5-dihydro pyrazole (126ha)

Yield: 95%. Melting point: 169.0-170.1 °C.

The er was determined by HPLC (Chiralpak OD column, heptane/i-PrOH 1:1, flow rate 0.7 mL/min, λ = 254 nm, 20 °C). $t_R$ (minor) = 13.7 min; $t_R$ (major) = 15.8 min, er = 90:10.

$^1$H NMR (300 MHz, CDCl$_3$) δ = 8.09 – 8.06 (m, 4H), 7.64 – 7.41 (m, 8H), 7.17 (d, $J$ = 8.0 Hz, 2H), 6.13 (dd, $J$ = 12.5, 6.3 Hz, 1H), 3.66 (dd, $J$ = 17.5, 12.5 Hz, 1H), 3.21 (dd, $J$ = 17.5, 6.3 Hz, 1H), 2.36 (s, 3H) (ppm).

$^{13}$C NMR (75 MHz, CDCl$_3$) δ = 194.3, 166.1, 154.0, 140.8, 134.4, 133.8, 133.5, 131.1, 130.2, 129.4, 128.9, 128.8, 128.1, 127.6, 126.6, 60.9, 36.6, 21.5 (ppm).

MS (EI): m/z = 262.0 (100), 368.1 (47, M$^+$).

IR (KBr): 3055, 1690, 1606, 1448, 1334, 1226, 817, 701 (cm$^{-1}$).

Anal. calcd for (C$_{24}$H$_{20}$N$_2$O$_2$): C, 78.24; H, 5.47; N, 7.60. Found: C, 77.78; H, 5.38; N, 7.31.

(5S)-1-(ortho-Methoxybenzoyl)-3-(2,4-dichlorophenyl)-5-benzoyl-4,5-dihydro pyrazole (126ia)

Yield: 84%. Melting point: 102.6-103.9 °C.
The er was determined by HPLC (Chiralpak OD column, heptane/i-PrOH 1:1, flow rate 0.7 mL/min, λ = 254 nm, 20 °C). \( t_R \) (minor) = 12.0 min; \( t_R \) (major) = 20.2 min, er = 93:7.

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta = 8.07 \) (d, \( J = 7.3 \) Hz, 2H), 7.62 (t, \( J = 7.3 \) Hz, 1H), 7.53 – 7.48 (m, 4H), 7.42 – 7.36 (m, 1H), 7.34 (d, \( J = 1.8 \) Hz, 1H), 7.18 – 7.14 (m, 1H), 7.01 (t, \( J = 7.5 \) Hz, 1H), 6.95 (d, \( J = 8.4 \) Hz, 1H), 6.14 (dd, \( J = 12.7, 5.8 \) Hz, 1H), 3.94 (dd, \( J = 17.9, 12.7 \) Hz, 1H), 3.84 (s, 3H), 3.37 (dd, \( J = 18.0, 5.8 \) Hz, 1H) (ppm).

\(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \( \delta = 193.8, 166.5, 156.6, 151.6, 136.1, 134.1, 133.8, 133.3, 131.4, 131.1, 130.4, 129.4, 128.84, 128.82, 128.7, 127.2, 124.7, 120.1, 111.1, 60.6, 55.8, 39.9 (ppm).

MS (EI): m/z = 317.0 (100), 422.2 (21).

IR (KBr): 3069, 1694, 1646, 1420, 1224, 1015, 835, 754, 701 (cm\(^{-1}\)).

Anal. calcd for (C\(_{24}\)H\(_{18}\)Cl\(_2\)N\(_2\)O\(_3\)): C, 63.59; H, 4.00; N, 6.18. Found: C, 63.41; H, 4.04; N, 6.05.

(5S)-1-(ortho-Methoxybenzoyl)-3-(para-fluorophenyl)-5-benzoyl-4,5-dihydropyrazole (126ja)

Yield: 92%. Melting point: 170.6-171.9 °C.

The er was determined by HPLC (Chiralpak OD column, heptane/i-PrOH 1:1, flow rate 0.7 mL/min, λ = 254 nm, 20 °C). \( t_R \) (minor) = 13.1 min; \( t_R \) (major) = 19.3 min, er = 94:6.

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta = 8.07 \) (dd, \( J = 8.3, 1.2 \) Hz, 2H), 7.64 – 7.58 (m, 1H), 7.51 – 7.47 (m, 5H), 7.41 – 7.38 (m, 1H), 7.01 – 6.95 (m, 4H), 6.13 (dd, \( J = 12.6, 5.9 \) Hz, 1H), 3.82 (s, 3H), 3.68 (dd, \( J = 17.4, 12.6 \) Hz, 1H), 3.19 (dd, \( J = 17.4, 5.9 \) Hz, 1H) (ppm).
13C NMR (75 MHz, CDCl3) δ = 194.0, 166.2, 165.4, 162.1, 156.7, 152.2, 134.2, 133.8, 130.9, 129.4, 128.8, 128.6, 128.5, 127.3, 127.2, 125.0, 120.1, 115.8, 115.5, 111.2, 60.3, 55.8, 37.2 (ppm).

MS (EI): m/z = 297.0 (100), 402.2 (46, M').

IR (KBr): 2971, 1701, 1634, 1598, 1440, 1222, 840, 758, 699 (cm⁻¹).

Anal. calcd for (C24H19FN2O3): C, 71.63; H, 4.76; N, 6.96. Found: C, 71.24; H, 4.73; N, 6.85.

(5S)-1-(ortho-Methoxybenzoyl)-3-(para-bromophenyl)-5-benzoyl-4,5-dihydro pyrazole (126ka)

Yield: 88%. Melting point: 124.0-124.9 °C.

The er was determined by HPLC (Chiralpak OD column, heptane/i-PrOH 1:1, flow rate 0.7 mL/min, λ = 254 nm, 20 °C). tᵣ (minor) = 16.5 min; tᵣ (major) = 22.2 min, er = 88:12.

1H NMR (300 MHz, CDCl3) δ = 8.06 (dd, J = 8.4, 1.1 Hz, 2H), 7.64 – 7.58 (m, 1H), 7.52 – 7.47 (m, 3H), 7.44 – 7.36 (m, 5H), 7.04 – 6.96 (m, 2H), 6.13 (dd, J = 12.6, 6.0 Hz, 1H), 3.82 (s, 3H), 3.67 (dd, J = 17.5, 12.6 Hz, 1H), 3.18 (dd, J = 17.5, 6.0 Hz, 1H) (ppm).

13C NMR (75 MHz, CDCl3) δ = 193.9, 166.2, 156.7, 152.2, 134.2, 133.8, 131.7, 131.0, 129.9, 129.4, 128.8, 128.0, 124.9, 124.6, 120.1, 111.2, 60.3, 55.8, 37.0 (ppm).

MS (EI): m/z = 357.1 (100), 463.5 (42, M').

IR (KBr): 2836, 1694, 1640, 1594, 1428, 1247, 1224, 1005, 827, 755, 699 (cm⁻¹).

Yield: 96%. Melting point: 169.5-170.3 °C.

The er was determined by HPLC (Chiralpak OD column, heptane/i-PrOH 1:1, flow rate 0.7 mL/min, λ = 254 nm, 20 °C). \( t_R \) (minor) = 15.0 min; \( t_R \) (major) = 20.8 min, er = 88:12.

\(^1H\) NMR (300 MHz, CDCl\(_3\)) \( \delta \) = 8.06 (dd, \( J = 8.3, 1.2 \text{ Hz}, 2\text{H} \)), 7.64 – 7.58 (m, 1H), 7.52 – 7.38 (m, 6H), 7.27 – 7.24 (m, 2H), 7.04 – 6.96 (m, 2H), 6.13 (dd, \( J = 12.6, 6.0 \text{ Hz}, 1\text{H} \)), 3.82 (s, 3H), 3.67 (dd, \( J = 17.5, 12.6 \text{ Hz}, 1\text{H} \)), 3.18 (dd, \( J = 17.5, 6.0 \text{ Hz}, 1\text{H} \)) (ppm).

\(^13\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) = 193.9, 166.2, 156.7, 152.2, 136.1, 134.2, 133.8, 131.0, 129.5, 129.4, 128.8, 128.1, 127.8, 124.9, 120.1, 111.2, 60.3, 55.8, 37.1 (ppm).

MS (EI): m/z = 312.9 (100), 418.3 (80, M\(^+\)).

IR (KBr): 2960, 1699, 1635, 1595, 1434, 1401, 1246, 1224, 1008, 835, 758, 695 (cm\(^{-1}\)).

Anal. calcd for (C\(_{24}\)H\(_{19}\)ClN\(_2\)O\(_3\)): C, 68.82; H, 4.57; N, 6.69. Found: C, 68.94; H, 4.62; N, 6.55.

(5S)-1-(ortho-Methoxybenzoyl)-3-(para-methoxyphenyl)-5-benzoyl-4,5-dihydro pyrazole (126ma)
Yield: 86%. Melting point: 154.0-155.2 °C.
The er was determined by HPLC (Chiralpak OD column, heptane/i-PrOH 1:1, flow rate 0.7 mL/min, λ = 254 nm, 20 °C). t_R (minor) = 17.6 min; t_R (major) = 23.9 min, er = 92:8.

1H NMR (400 MHz, CDCl3) δ = 8.08 (dd, J = 8.3, 1.2 Hz, 2H), 7.65 – 7.60 (m, 1H), 7.54 – 7.48 (m, 5H), 7.42 – 7.38 (m, 1H), 7.04 – 6.99 (m, 1H), 6.97 (d, J = 8.4 Hz, 1H), 6.83 (d, J = 8.9 Hz, 2H), 6.11 (dd, J = 12.5, 6.0 Hz, 1H), 3.84 (s, 3H), 3.80 (s, 3H), 3.68 (dd, J = 17.3, 12.6 Hz, 1H), 3.68 (dd, J = 17.3, 6.0 Hz, 1H) (ppm).

13C NMR (75 MHz, CDCl3) δ = 194.2, 166.0, 161.2, 156.7, 153.1, 134.4, 133.6, 130.8, 129.5, 128.8, 128.2, 125.2, 123.6, 120.1, 113.9, 111.2, 60.3, 55.8, 55.3, 37.3 (ppm).

MS (EI): m/z = 309.3 (69), 414.3 (100, M+).

IR (KBr): 2837, 1636, 1600, 1430, 1249, 1019, 834, 755, 703 (cm⁻¹).

Anal. calcd for (C25H22N2O4): C, 72.45; H, 5.35; N, 6.76. Found: C, 72.03; H, 5.53; N, 6.60.

(5S)-1-(mata-Methoxybenzoyl)-3-methyl-5-benzoyl-4,5-dihydro pyrazole (126na)

Yield: 90%. Melting point: 144.2-145.1 °C.
The er was determined by HPLC (Chiralpak OD column, heptane/i-PrOH 1:1, flow rate 0.7 mL/min, λ = 254 nm, 20 °C). t_R (minor) = 10.8 min; t_R (major) = 15.3 min, er = 77:23.

1H NMR (300 MHz, CDCl3) δ = 8.04 (dd, J = 8.3, 1.1 Hz, 2H), 7.60 (t, J = 7.3 Hz, 1H), 7.49 (t, J = 7.6 Hz, 2H), 7.44 (dd, J = 7.5, 1.7 Hz, 1H), 7.40 – 7.34 (m, 1H), 7.01 – 6.93 (m, 2H), 5.97 (dd, J = 12.4, 5.9 Hz, 1H), 3.84 (s, 3H), 3.30 (dd, J = 18.0, 12.4 Hz, 1H), 2.80 (dd, J = 18.0, 5.9 Hz, 1H), 1.95 (s, 3H) (ppm).

13C NMR (75 MHz, CDCl3) δ = 194.4, 165.6, 156.3, 154.8, 134.3, 133.6, 130.7, 128.9, 127.2, 125.2, 123.6, 120.1, 113.9, 111.2, 60.3, 55.8, 55.3, 37.3 (ppm).
128.7, 128.7, 125.3, 120.1, 111.3, 59.7, 55.8, 41.1, 15.7 (ppm).

MS (EI): m/z = 322 (M⁺).

IR KBr: 2923, 1689, 1633, 1594, 1497, 1455, 1247, 1224, 1021, 834, 748, 709 (cm⁻¹).

Anal. calcd for (C₁₉H₁₈N₂O₃): C, 70.79; H, 5.63; N, 8.69. Found: C, 70.90; H, 5.78; N, 8.74.

(5S)-1-(meta-Methoxybenzoyl)-3-tert-butyl-5-benzoyl-4,5-dihydro pyrazole (126oa)

Yield: 93%. Melting point: 51-52 °C.

The er was determined by HPLC (Chiralpak OD column, hexane/i-PrOH 7:3, flow rate 1.0 mL/min, λ = 254 nm, 20 °C). tᵣ (minor) = 8.7 min; tᵣ (major) = 14.6 min, er = 79:21.

¹H NMR (400 MHz, CDCl₃) δ = 8.04 (d, J = 7.8 Hz, 2H), 7.60 (t, J = 7.2 Hz, 1H), 7.50 – 7.45 (m, 1H), 7.36 (t, J = 7.8 Hz, 1H), 6.97 (t, J = 7.4 Hz, 2H), 6.91 (d, J = 8.3 Hz, 1H), 5.95 (dd, J = 12.3, 5.8 Hz, 1H), 3.83 (s, 3H), 3.33 (dd, J = 17.6, 12.5 Hz, 1H), 2.84 (dd, J = 17.6, 5.8 Hz, 1H), 1.10 (s, 9H) (ppm).

¹³C NMR (100 MHz, CDCl₃) δ = 194.5, 165.9, 164.4, 156.6, 134.4, 133.5, 130.7, 129.5, 128.8, 128.7, 125.1, 119.9, 110.9, 60.1, 55.6, 36.5, 33.9, 27.9 (ppm).

MS (EI): m/z = 364 (M⁺).

IR (KBr): 2965, 1642, 1600, 1438, 1252, 1224, 841, 754, 705, 657 (cm⁻¹).


(5S)-1-(meta-Methoxybenzoyl)-3-iso-buyl-5-benzoyl-4,5-dihydro pyrazole (126pa)
Yield: 84%. Melting point: 85-86 °C.

The er was determined by HPLC (Chiralpak OD column, hexane/i-PrOH 7:3, flow rate 1.0 mL/min, λ = 254 nm, 20 °C). tR (minor) = 13.0 min; tR (major) = 17.5 min, er = 87:13.

1H NMR (400 MHz, CDCl3) δ = 8.03 (d, J = 7.8 Hz, 2H), 7.58 (t, J = 7.3 Hz, 1H), 7.49 – 7.43 (m, 3H), 7.36 (t, J = 7.9 Hz, 1H), 6.98 (t, J = 7.4 Hz, 1H), 6.92 (d, J = 8.3 Hz, 1H), 5.95 (dd, J = 12.3, 5.7 Hz, 1H), 3.81 (s, 3H), 3.27 (dd, J = 17.8, 12.5 Hz, 1H), 2.76 (dd, J = 17.9, 5.6 Hz, 1H), 2.14 (d, J = 7.2 Hz, 2H), 1.86 – 1.79 (m, 1H), 0.89 (d, J = 6.5 Hz, 6H) (ppm).

13C NMR (100 MHz, CDCl3) δ = 194.4, 165.7, 157.5, 156.3, 134.3, 133.5, 130.7, 129.0, 128.7, 128.6, 125.2, 120.0, 110.9, 59.4, 55.5, 38.6, 26.2, 22.2, 22.1 (ppm).

MS (EI): m/z = 364 (M+).

IR (KBr): 2957, 2927, 1694, 1641, 1495, 1461, 1251, 1221, 1020, 754, 695, 652 (cm⁻¹).


(5S)-1-(mata-Methoxybenzoyl)-3-phenylethyl-5-benzo-4,5-dihydro pyrazole (126qa)

Yield: 93%. Melting point: 46-47 °C.

The er was determined by HPLC (Chiralpak OD column, hexane/i-PrOH 7:3, flow rate 1.0 mL/min, λ = 254 nm, 20 °C). tR (minor) = 23.6 min; tR (major) = 37.7 min, er = 87:13.

1H NMR (400 MHz, CDCl3) δ = 8.00 (d, J = 7.6 Hz, 2H), 7.59 (t, J = 7.3 Hz, 1H), 7.48 (t, J = 7.5 Hz, 2H), 7.42 – 7.36 (m, 2H), 7.24 – 7.14 (m, 3H), 7.10 (d, J = 7.3 Hz, 2H), 7.00 (t, J = 7.4 Hz, 1H), 6.94 (d, J = 8.3 Hz, 1H), 5.93 (dd, J = 12.4, 5.8 Hz, 1H), 3.81 (s, 3H), 3.27 (dd, J = 17.8, 12.5 Hz, 1H), 2.76 (dd, J = 17.9, 5.6 Hz, 1H), 2.14 (d, J = 7.2 Hz, 2H), 1.86 – 1.79 (m, 1H), 0.89 (d, J = 6.5 Hz, 6H) (ppm).
3.82 (s, 3H), 3.21 (dd, J = 17.8, 12.5 Hz, 1H), 2.80 (t, J = 7.4 Hz, 2H), 2.72 (dd, J = 17.9, 5.7 Hz, 1H), 2.58 (t, J = 7.3 Hz, 2H) (ppm).

$^{13}$C NMR (100 MHz, CDCl$_3$) δ = 194.3, 165.8, 157.3, 156.4, 140.4, 134.3, 133.6, 130.8, 129.2, 128.8, 128.7, 128.4, 128.3, 126.2, 125.1, 120.1, 111.1, 59.6, 55.7, 39.90, 32.3, 31.6 (ppm).

MS (EI): m/z = 412 (M$^+$).

IR (KBr): 2930, 1643, 1599, 1466, 1446, 1250, 1222, 754, 701, 654 (cm$^{-1}$).

HRMS (EI): m/z calcd for C$_{26}$H$_{25}$N$_2$O$_3$: 413.1860 [M+H]$^+$; found: 413.1851.

(5S)-1-((mata-Methoxybenzoyl)-3-ethyl carbonyl ester-5-benzoyl-4,5-dihydro pyrazole (126ra)

![Chemical structure of (5S)-1-((mata-Methoxybenzoyl)-3-ethyl carbonyl ester-5-benzoyl-4,5-dihydro pyrazole]

Yield: 93%. Melting point: 56–57 °C.

The er was determined by HPLC (Chiralpak OD column, hexane/i-PrOH 7:3, flow rate 1.0 mL/min, λ = 254 nm, 20 °C). t$_R$ (minor) = 20.1 min; t$_R$ (major) = 37.1 min, er = 93:7.

$^1$H NMR (400 MHz, CDCl$_3$) δ = 8.03 (d, J = 7.8 Hz, 2H), 7.63 (t, J = 7.1 Hz, 1H), 7.53 – 7.48 (m, 3H), 7.41 (t, J = 7.9 Hz, 1H), 7.01 (t, J = 7.5 Hz, 1H), 6.97 (d, J = 8.4 Hz, 1H), 6.11 (dd, J = 12.9, 6.2 Hz, 1H), 4.24 (dd, J = 13.9, 6.8 Hz, 2H), 3.85 (s, 3H), 3.56 (dd, J = 18.4, 13.2 Hz, 1H), 3.12 (dd, J = 18.6, 6.1 Hz, 1H), 1.26 (t, J = 7.0 Hz, 3H) (ppm).

$^{13}$C NMR (100 MHz, CDCl$_3$) δ = 193.0, 167.2, 161.2, 156.9, 146.1, 134.0, 133.7, 131.6, 129.6, 128.9, 128.8, 123.7, 120.3, 111.6, 61.8, 61.0, 55.9, 36.8, 14.0 (ppm).

MS (EI): m/z = 380 (M$^+$).

IR KBr): 2980, 1700, 1663, 1598, 1464, 1447, 1318, 1251, 1102, 1019, 849, 757, 702, 654 (cm$^{-1}$).

HRMS (EI): m/z calcd for C$_{21}$H$_{21}$N$_2$O$_3$: 381.1445 [M+H]$^+$; found: 381.1433.
(5S)-1-(meta-Methoxybenzoyl)-3-E-phenylethenyl-5-benzoyl-4,5-dihydro pyrazole (126sa)

Yield: 92%. Melting point: 134-135 °C.

The er was determined by HPLC (Chiralpak OD column, hexane/i-PrOH 1:1, flow rate 1.0 mL/min, λ = 254 nm, 20 °C). tR (minor) = 23.1 min; tR (major) = 32.8 min, er = 71:29.

1H NMR (400 MHz, CDCl3) δ = 8.06 (d, J = 7.9 Hz, 2H), 7.61 (t, J = 7.3 Hz, 1H), 7.50 (t, J = 8.0 Hz, 3H), 7.41 – 7.34 (m, 3H), 7.29 – 7.25 (m, 3H), 7.02 (d, J = 7.5 Hz, 1H), 6.99 – 6.91 (m, 2H), 6.66 (d, J = 16.5 Hz, 1H), 6.06 (dd, J = 12.6, 5.9 Hz, 1H), 3.83 (s, 3H), 3.54 (dd, J = 17.1, 12.7 Hz, 1H), 3.08 (dd, J = 17.1, 5.8 Hz, 1H) (ppm).

13C NMR (100 MHz, CDCl3) δ = 193.8, 166.1, 156.4, 154.4, 137.0, 135.5, 134.1, 133.7, 131.0, 129.1, 128.9, 128.8, 128.8, 126.9, 124.9, 120.6, 120.2, 111.3, 60.1, 55.8, 36.0 (ppm).

MS (EI): m/z = 410 (M+).  
IR (KBr): 3057, 2935, 1697, 1645, 1598, 1463, 1432, 1340, 1249, 1224, 1020, 840, 752, 692, 652 (cm⁻¹).


(5S)-1-(meta-Methoxybenzoyl)-3-phenyl-5-benzoyl-4,5-dihydro pyrazole (126ta)

Yield: 88%. Melting point: 126.9-128.0 °C.
The er was determined by HPLC (Chiralpak OD column, heptane/i-PrOH 7:3, flow rate 0.8 mL/min, \(\lambda = 254 \text{ nm}, 20 \degree \text{C}\)). \(t_R\) (minor) = 19.0 min; \(t_R\) (major) = 25.7 min, er = 92:8.

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta = 8.07\) (d, \(J = 7.1\) Hz, 2H), 7.72 (d, \(J = 7.7\) Hz, 1H), 7.67 – 7.59 (m, 4H), 7.51 – 7.47 (m, 2H), 7.39 – 7.33 (m, 4H), 7.07 – 7.03 (m, 1H), 6.14 (dd, \(J = 12.5, 6.3\) Hz, 1H), 3.84 (s, 3H), 3.67 (dd, \(J = 17.5, 12.5\) Hz, 1H), 3.21 (dd, \(J = 17.5, 6.3\) Hz, 1H) (ppm).

\(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta = 194.3, 165.9, 158.9, 154.0, 134.6, 134.4, 133.8, 130.8, 130.4, 128.9, 128.8, 128.7, 128.6, 126.6, 122.7, 117.8, 114.7, 60.9, 55.3, 36.5\) (ppm).

MS (EI): \(m/z = 384\) (M\(^+\)).

IR (KBr): 2948, 1689, 1612, 1570, 1440, 1332, 1221, 768, 685 (cm\(^{-1}\)).

Anal. calcd for (C\(_{24}\)H\(_{20}\)N\(_2\)O\(_3\)): C, 74.98; H, 5.24; N, 7.29. Found: C, 74.85; H, 4.91; N, 7.15.

(55)-1-(\(\text{para-}\)Methoxybenzoyl)-3-phenyl-5-benzoyl-4,5-dihydro pyrazole (126ua)

Yield: 88%. Melting point: 173.8-174.7 °C.

The er was determined by HPLC (Chiralpak OD column, heptane/i-PrOH 7:3, flow rate 0.8 mL/min, \(\lambda = 254 \text{ nm}, 20 \degree \text{C}\)). \(t_R\) (minor) = 20.2 min; \(t_R\) (major) = 34.5 min, er = 91:9.

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta = 8.16\) (d, \(J = 9.1\) Hz, 2H), 8.07 (dd, \(J = 8.4, 1.3\) Hz, 2H), 7.69 – 7.59 (m, 3H), 7.52 – 7.48 (m, 2H), 7.39 – 7.37 (m, 3H), 6.94 (d, \(J = 9.1\) Hz, 2H), 6.14 (dd, \(J = 12.5, 6.5\) Hz, 1H), 3.85 (s, 3H), 3.64 (dd, \(J = 17.5, 12.5\) Hz, 1H), 3.19 (dd, \(J = 17.5, 6.5\) Hz, 1H) (ppm).

\(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta = 194.6, 165.4, 162.0, 153.6, 134.5, 133.7, 132.4, 131.0, 130.3, 128.8, 128.8, 128.6, 126.6, 125.5, 112.9, 61.0, 55.3, 36.4\) (ppm).
MS (EI): m/z = 384 (M⁺).

IR (KBr): 2842, 1685, 1599, 1422, 1334, 1256, 1229, 1021, 838, 754, 687 (cm⁻¹).

Anal. calcd for (C_{24}H_{20}N_{2}O_{3}): C, 74.98; H, 5.24; N, 7.29. Found: C, 74.92; H, 5.01; N, 7.09.

\((5S)-1-(\text{para-Methylbenzoyl})-3\text{-phenyl-5-benzoyl-4,5-dihydro pyrazole (126va)}\)

Yield: 97%. Melting point: 165.3-166.3 °C.

The er was determined by HPLC (Chiralpak OD column, heptane/i-PrOH 7:3, flow rate 0.8 mL/min, \(\lambda = 254\) nm, 20 °C). \(t_R\) (minor) = 14.9 min; \(t_R\) (major) = 20.6 min, er = 90:10.

\(^1\)H NMR (300 MHz, CDCl₃) \(\delta = 8.09\) (d, \(J = 7.1\) Hz, 2H), 8.02 (d, \(J = 8.1\) Hz, 2H), 7.70 – 7.66 (m, 2H), 7.62 (d, \(J = 6.9\) Hz, 1H), 7.53 (t, \(J = 7.8\) Hz, 2H), 7.42 – 7.38 (m, 3H), 7.30 – 7.21 (m, 3H), 6.16 (dd, \(J = 12.5\), 6.4 Hz, 1H), 3.68 (dd, \(J = 17.5\), 12.5 Hz, 1H), 3.24 (dd, \(J = 17.4\), 6.4 Hz, 1H), 2.42 (s, 3H) (ppm).

\(^{13}\)C NMR (75 MHz, CDCl₃) \(\delta = 194.5\), 166.2, 153.6, 141.6, 134.5, 133.8, 131.0, 130.5, 130.4, 130.3, 128.9, 128.8, 128.6, 128.4, 126.6, 60.9, 36.5, 21.5 (ppm).

MS (EI): m/z = 368 (M⁺).

IR (KBr): 2324, 1688, 1617, 1427, 1330, 1219, 778, 686 (cm⁻¹).

Anal. Calcd for (C_{24}H_{20}N_{2}O_{3}): C, 78.24; H, 5.47; N, 7.60. Found: C, 78.12; H, 5.18; N, 7.52.
Reference


# Appendix

## 1 List of Abbreviations

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<th>Abbreviation</th>
<th>Full Form</th>
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<td>Å</td>
<td>Angstrom</td>
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<tr>
<td>Ac</td>
<td>acetyl</td>
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<td>aq.</td>
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<td>Bn</td>
<td>benzyl</td>
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<td>broad (NMR signal)</td>
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<td>Hz</td>
<td>Hertz</td>
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Appendix

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<th>Abbreviation</th>
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<td>infrared spectroscopy</td>
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<td>$J$</td>
<td>coupling constant (in NMR spectroscopy)</td>
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<td>metal</td>
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<td>TMS</td>
<td>trimethylsilyl</td>
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2 Curriculum Vitae

Personal Information

Name: Wanrong Dong  
Gender: Male

Nationality: China  
Date of Birth: 1983.09.17

Email Address: wanrong.dong@oc.rwth-aachen.de

Education Background

1: 09.2002-06.2006  
Bachelor Student  
Organic Chemistry  
Hunan University  
China  
Supervisor: Prof. Dr. Delie An.
**Appendix**

**Thesis:** Synthesis of a Novel Helical Cyclophane Using Chiral Binaphthyl as Structural Templates

2: 09.2006-06.2008  **Master Degree**  Organic Chemistry  **Hunan University**  China  Supervisor: Prof. Dr. Delie An.

**Thesis:** The Design and Synthesis of Potential Liquid Crystal Compounds with Optically Active Double Helical Block Buildings

3: 10.2009-2014.05  **Doctoral Degree**  RWTH Aachen University, Aachen. Germany (With CSC Scholarship). Supervisor: Prof. Dr. Carsten Bolm.

**Topic:** Rhodium catalyzed Direct C-H Functionalizations on Sulfoximines

**Languages Skills**

Good at Reading and Writing, Passed the College English Test, Band four and Six, Got A in Band Four.

**Publication List**

1. Rhodium-Catalyzed Oxidative Annulation of Sulfoximines and Alkynes as an Approach to 1,2-Benzothiazines.
   

   

3. Hydroarylations of Heterobicyclic Alkenes through Rhodium-Catalyzed Directed C-H Functionalizations of Sulfoximines.
   

   


6. Selective Tandem Inter/intramolecular Eglington Coupling for Chiral Cyclophyne Synthesis