Cobalt-catalyzed alkenylation and alkylation of heteroarenes

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**NANYANG
TECHNOLOGICAL
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**COBALT-CATALYZED ALKENYLATION AND
ALKYLATION OF HETEROARENES**

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SCHOOL OF PHYSICAL AND MATHEMATICAL SCIENCES

2013

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SCHOOL OF PHYSICAL AND MATHEMATICAL SCIENCES

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Abstract

Heteroarene moieties are present in a variety of biologically active natural products, pharmaceuticals and electroactive materials. Hence, the development of efficient synthetic methods for functionalized heteroarenes has been an important issue for synthetic chemists. In this context, C–C bond forming reactions via activation of heteroaromatic C–H bonds are particularly attractive. This thesis describes the development of alkenylation and alkylation reactions of heteroarenes catalyzed by cobalt complexes.

Following a brief overview of major developments in this area (Chapter 1), Chapter 2 describes alkenylation of an azole C(2)–H bond with an internal alkyne using a cobalt-diphosphine catalyst. The reaction features mild conditions and high chem-, regio-, and stereoselectivities. C2-alkenylation has also been achieved for indole bearing an *N*-pyrimidyl directing group and internal alkynes with the aid of a cobalt-pyridylphosphine catalyst (Chapter 3). The reaction proceeds at room temperature to afford C2-alkenylated indoles in high yield with excellent stereoselectivity, showing broad scope with respect to indoles and alkynes. *N*-pyrimidylindole also participates in C2-alkylation with vinylsilane in the presence of a cobalt-bathophenanthroline catalyst under mild conditions (Chapter 4). Finally, Chapter 5 describes intramolecular C2-alkylation of an alkene-tethered indole through directed C–H activation, which is uniquely promoted by a cobalt-NHC catalyst. The reaction affords dihydropyrroloindole or tetrahydropyridoindole derivatives, many of which have not been accessed by other synthetic methods.

List of Abbreviations

δ	chemical shift (ppm)
$^{\circ}\text{C}$	degree centigrade
Ac	Acetyl
<i>t</i> -amy	<i>tert</i> -pentyl
aq	aqueous
Ar	aryl (substituted aromatic ring)
bathocup	bathocuproine
br	broad
<i>n</i> Bu	<i>n</i> -butyl
<i>t</i> Bu	<i>tert</i> -butyl
Bz	benzyl
cod	1,5-cyclooctadiene
coe	cyclooctene
Cy	cyclohexyl
Cyp	cyclopentyl
d	doublet
DMA	<i>N,N</i> -dimethylacetamide
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethyl sulfoxide
DPEphos	(oxydi-2,1-phenylene)bis(diphenylphosphine)
dppb	1,4-Bis(diphenylphosphino)butane
equiv	equivalent
ESI	electrospray ionization
Et	ethyl

h	hour
H	hydrogen
HRMS	High Resolution Mass Spectrometry
Hz	hertz
IMes	1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene
IPr	1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene
<i>J</i>	coupling constants
LA	Lewis acid
m	multiplet
M	concentration (mol/L)
M ⁺	parent ion peak (mass spectrum)
Me	methyl
mg	milligram
MHz	megahertz
min	minute(s)
mL	milliliter
mmol	millimole
mol%	mole percent
m.p.	melting point
NHC	<i>N</i> -heterocyclic carbene
NMR	nuclear magnetic resonance
Ph	phenyl
Phen	1,10-phenanthroline
Piv	pivalic
PMP	<i>p</i> -methoxyphenyl
ppm	parts per million

<i>i</i> Pr	<i>iso</i> -propyl
pyphos	2-(2-(diphenylphosphino)ethyl)pyridine
q	quartet
rt	room temperature
s	singlet
sat	saturated
t	triplet
THF	tetrahydrofuran
<i>p</i> -TsOH	<i>p</i> -toluenesulfonic acid
Xantphos	4,5-bis(diphenylphosphino)-9,9-dimethylxanthene

Chapter 1 Introduction

1.1 Transition Metal-Catalyzed Alkenylation and Alkylation of Heteroarenes

Heteroaromatic moieties are found in numerous natural products, pharmaceuticals and organic materials.¹ Therefore, the development of efficient and selective synthetic methods for densely functionalized heteroarenes has attracted much attention in synthetic chemistry. Over the past decades, transition-metal-catalyzed C–H bond activation has gone through rapid development as one of the most attractive approaches to C–C and C–heteroatom bond formation on simple, unfunctionalized starting materials.² As a part of this area, methods to directly elaborate heteroarenes through C–H bond activation have been extensively developed, and some of them have been practiced in the synthesis of natural products and other functional molecules.³ Herein, we focus on transition metal-catalyzed direct alkenylation and alkylation reactions of heteroarenes, and briefly outline their developments.

1.1.1 Alkenylation Reactions of Heteroarenes

In 1973, Fujiwara and Moritani first reported the alkenylation reaction of aromatic heterocycles using a stoichiometric amount of palladium(II) acetate (Scheme 1.1).⁴ The five-membered heteroarenes including furan, thiophene, selenophene and *N*-methylpyrrole were investigated. These heterocycles, except *N*-methylpyrrole, readily reacted with styrene to afford 2,5-dialkenylated derivatives as the major products.

Scheme 1.1 Pd-mediated alkenylation of heteroarenes

The apparent drawback of the above reaction is the requirement for a stoichiometric palladium(II) salt. Thus, over the past three decades, significant efforts have been devoted to the development of dehydrogenative Heck-type reactions of heteroarenes (as well as arenes) using a palladium catalyst and a stoichiometric oxidant.⁵ Generally, dehydrogenative Heck reaction is considered to involve: (1) electrophilic palladation of the heteroarene, (2) insertion of the alkene into the heteroaryl-Pd bond, (3) β -hydride elimination to give the alkenylated heteroarene and palladium(0), and (4) reoxidation of palladium(0) to palladium(II) by the stoichiometric oxidant. Notable breakthroughs that have been made along with this mechanistic scenario include Stoltz's intramolecular oxidative cyclization of alkene-tethered indoles (Scheme 1.2a),⁶ Gaunt's regiocontrollable alkenylation of indoles (Scheme 1.2b)⁷ and pyrroles,⁸ and Yu's C3-alkenylation of pyridines (Scheme 1.2c).⁹

Scheme 1.2 Pd-catalyzed dehydrogenative Heck-type reactions of heteroarenes

Besides the dehydrogenative Heck-type reaction, there are two major alternative methods for direct alkenylation of heteroarenes. One is a cross-coupling reaction between heteroarenes and alkenyl halides or pseudohalides.¹⁰ Such transformations have been achieved using palladium or copper catalysts, the scope including azoles (Scheme 1.3a)^b and *N*-iminopyridinium ylides (Scheme 1.3b).^f

Scheme 1.3 Transition metal-catalyzed alkenylation of heteroarenes with alkenyl halides

Another method involves insertion of an alkyne into a heteroaromatic C–H bond (i.e., hydroheteroarylation).¹¹ This type of reaction is attractive not only it is intrinsically atom-economical but also it allows facile access to trisubstituted olefin products, thus complementing the limitation of the dehydrogenative Heck reaction and the cross-coupling reaction with alkenyl halides. A variety of transition metals such as rhodium,^{a,b} nickel,ⁱ palladium,^{f,g,h} and ruthenium^{c,d} have been reported to promote such hydroheteroarylation reactions. The mechanism largely depends on the nature of the metal catalyst, and may involve oxidative addition of the heteroaromatic C–H bond, electrophilic/deprotonative metalation of the heteroaromatic C–H bond, or electrophilic activation of alkyne followed by a Friedel–Crafts type process.

Among various hydroheteroarylation reaction of alkynes, those catalyzed by nickel(0) complexes are particularly notable for the broad scope and the well-defined oxidative addition mechanism.ⁱ In 2006, Nakao and Hiyama reported on the addition reaction of indole bearing electron-withdrawing group at the C3 position with alkyne catalyzed by a Ni(0) complex.^{12, 13} Several other heteroarenes including benzimidazole, caffeine, purine, benzoxazole, benzofuran, benzothiophene and thiazole have also been employed in this reaction to afford the corresponding C2-alkenylated products in high yields (Scheme 1.4). High levels of regioselectivity were achieved for unsymmetric alkynes, where the C–C bond formation took place at less hindered acetylenic carbon atom.

Scheme 1.4 Ni-catalyzed hydroheteroarylation of alkynes

With successful reaction of five-membered heteroarenes, they sought to expand the reaction scope by turning attention to more challenging six-membered ring heteroarenes. The substrate scope was first extended to pyridine *N*-oxide.¹⁴ Then alkenylation of simple pyridine was achieved with a nickel/Lewis acid combined catalytic system (Scheme 1.5).¹⁵

Scheme 1.5 Ni-catalyzed alkenylation of pyridine and pyridine-oxide derivatives

1.1.2 Alkylation Reactions of Heteroarenes

Alkyl-substituted heteroarenes are ubiquitous structures in molecules relevant to pharmaceutical or material science. While Friedel–Crafts reaction,¹⁶ radical alkylation reaction,¹⁷ and cross-coupling reaction have served as conventional methods to access alkylated heteroarenes, recent years have witnessed the emergence of transition-metal-catalyzed C–H activation as a viable entry to direct heteroaromatic alkylation.

The hydroheteroarylation reaction of olefins is one of representative methods for the synthesis of alkylated heteroarenes via C–H activation. This transformation has been developed rapidly since the seminal work on *ortho*-alkylation of aryl ketones with terminal alkenes reported by Murai in 1993.¹⁸ Among others, the group of Bergman and Ellman has

developed highly efficient rhodium catalytic systems¹⁹ for the hydroheteroarylation reaction of olefins.

The first example of azole alkylation reaction via C–H activation was reported by Bergman and Ellman in their cyclization of imidazole derivatives (Scheme 1.6a).²⁰ An imidazole bearing *N*-tethered olefin undergoes cyclization in the presence of Wilkinson's catalyst to produce five- or six-membered ring products in good yields. Substrates bearing di- or trisubstituted olefin moieties required higher catalyst loading and temperature. They found that the catalyst for intramolecular alkylation is also applicable to an intermolecular synthesis of 2-alkyl azoles (Scheme 1.6b).²¹

Scheme 1.6 Rh-catalyzed alkylation of azole derivatives

Bergman and Ellman also developed rhodium-catalyzed chelation-assisted C–H alkylation reactions of arenes and heteroarenes, including enantioselective variants.²² The utility of such reactions was demonstrated by the synthesis of a PKC inhibitor through enantioselective cyclization of an *N*-allylindole bearing an aldimine directing group (Scheme 1.7).²³ The key intermediate was obtained from the enantioselective cyclization of *N*-allyl indole. Treatment of the indole substrate with a catalyst consisting of $[\text{RhCl}(\text{coe})_2]_2$ and a

chiral phosphoramidite ligand was followed by imine hydrolysis to afford the product in moderate yield with good enantioselectivity.

Scheme 1.7 Rh-catalyzed enantioselective intramolecular alkylation

Besides the above rhodium(I)-catalyzed reactions, nickel(0)-NHC catalysis has also emerged in the area of C–H alkylation of heteroarenes via hydroheteroarylation of alkenes.²⁴ Thus, Nakao and Hiyama developed a Ni(0)-IMes catalyst for the branched-selective alkylation of azoles, benzofuran, indoles bearing electron-withdrawing groups at the C3 position with vinylarenes (Scheme 1.8a),^a and Ni(0)-IPr/Lewis acid systems for the C4-alkylation of pyridine (Scheme 1.8b)^b and C6-alkylation of pyridones.^c

Scheme 1.8 Ni-catalyzed hydroheteroarylation of alkenes

Another strategy for C–H alkylation of heteroarenes that has emerged recently is a cross-coupling between heteroarenes and alkyl halides. Representative examples include palladium-catalyzed C2-alkylation of indoles and C2-alkylation of pyridine *N*-oxides²⁵ and nickel- or copper-catalyzed C2-alkylation of azoles.²⁶ These catalytic systems allow alkylation using primary alkyl halides, while the use of secondary alkyl halides remains challenging.

1.1.3 Summary

Transition metal-catalyzed direct alkenylation and alkylation of heteroarenes are efficient methods for the synthesis of functionalized heteroaromatic compounds. For alkenylation reaction, palladium-catalyzed dehydrogenative Heck reaction is suitable for the synthesis of disubstituted alkenes, while trisubstituted alkene products may be accessed by the alkyne hydroheteroarylation approach. As to alkylation reaction, the hydroheteroarylation of alkenes is attractive in terms of atom economy, while the reaction is typically limited to terminal alkenes (except for intramolecular reaction) and requires high temperature. In addition, the catalyst sometimes causes undesirable isomerization of alkenes. The alternative cross-coupling approach has a potential to complement the limitation of the hydroheteroarylation approach, while the use of alkyl halides containing β -hydrogen atoms, secondary alkyl halides in particular, is not yet an easy task.

In addition to the above background, it should also be mentioned that many of catalytic systems for heteroaromatic C–H bond functionalization are based on expensive

noble transition metals and often require harsh reaction conditions. Hence, the development of new catalytic system allowing efficient and regioselective functionalization of aromatic heterocycles under mild reaction conditions continues to be an attractive subject.

1.2 Cobalt-Catalyzed/Mediated C–H Bond Activation

In the mid of 1950s, Murahashi reported on an ortho-carbonylation reaction of Schiff base and azobenzene with carbon monoxide in the presence of $\text{Co}_2(\text{CO})_8$,²⁷ affording carbonylated heterocyclic products (Scheme 1.9). To our knowledge, this represents the first example of chelation-assisted C–H bond functionalization catalyzed by a transition metal complex.

Scheme 1.9 Cobalt-catalyzed ortho-carbonylation reaction

Regardless of this seminal discovery, cobalt later received scarce attention in the area of C–H bond functionalization during the period when noble transition metal complexes emerged as viable catalysts. However, a few notable studies on catalytic and stoichiometric organocobalt chemistry have drawn our attention and urged us to consider the potential of low-valent cobalt complexes as possible catalysts for C–H bond functionalization.

First, in the early 1990s, Klein et al. reported that a cobalt complex $\text{MeCo}(\text{PMe}_3)_4$ undergoes a cyclometalation reaction of azobenzene under very mild conditions, which presumably involves chelation-assisted oxidative addition of the ortho C–H bond followed by reductive elimination of methane.²⁸ Later, the same complex was found to undergo cyclometalation of a variety of aromatic substrates bearing heteroatom (N, O, S, P) directing groups (Scheme 1.10).²⁹ The mild conditions and the broad scope of this cyclometalation reaction hold promise for development of catalytic reactions involving cobalt-mediated chelation-assisted C–H activation.

Scheme 1.10 Cyclometalation reactions with $\text{MeCo(PMe}_3)_4$ complex

Second, Brookhart developed a hydroacylation reaction of vinylsilane with an aldehyde catalyzed by a $\text{Cp}^*\text{Co(I)}$ -bisolefin complex, which was proposed to go through oxidative addition of the aldehydic C–H bond (Scheme 1.11).³⁰ The cobalt complex was also found to promote H/D exchange between the coordinated olefin and C_6D_6 , which suggested that the ability of cobalt is not limited to the chelation-assisted C–H activation.

Scheme 1.11 Co-catalyzed hydroacylation of vinylsilane with aromatic aldehyde

Before this thesis research, no particular example of cobalt-mediated heteroaromatic C–H activation, either stoichiometric or catalytic, has been reported. Nevertheless, on the

basis of the above cyclometalation reactions with $\text{MeCo}(\text{PMe}_3)_4$ complex and hydroacylation reaction developed by Klein and Brookhart, respectively, we envisioned that a low-valent cobalt complex is capable of activating a heteroaromatic C–H bond with or without chelation assistance, and thus promoting catalytic transformations involving such an elementary process.

With the above conjecture, we formulated a possible catalytic cycle for cobalt-catalyzed hydroheteroarylation of an unsaturated C–C bond (Scheme 1.12). The catalytic cycle involves (1) oxidative addition of the heteroaryl C–H bond to the cobalt center, (2) insertion of the C–C unsaturated bond into the Co–H bond, and (3) reductive elimination of the resulting diorganocobalt species to afford the product and regenerate cobalt catalyst.

Scheme 1.12 Proposed catalytic cycle for hydroheteroarylation

1.3 Summary of Thesis Research

In recognition of the importance of functionalized heteroarenes as well as the potential reactivity of cobalt complexes, in this thesis research, we have explored direct alkenylation and alkylation reactions of heteroaromatic compounds using cobalt catalysts. As a result, we have successfully developed the following catalytic systems:

(1) Cobalt-catalyzed addition of azoles to alkynes. The combination of a cobalt(II) salt, a diphosphine ligand, and a Grignard reagent serves as an effective ternary catalytic system for the alkenylation of an azole C(2)-H bond with an unactivated internal alkyne. The reaction features mild conditions and high chem-, regio-, and stereoselectivities.

(2) C2-alkenylation of indoles with alkynes via cobalt-catalyzed C-H bond activation. A cobalt-pyridylphosphine catalyst promotes the addition of *N*-pyrimidylindole to an internal alkyne at room temperature to afford C2-alkenylated indoles in high yield with excellent stereoselectivity, showing broad scope with respect to indoles and alkynes. The removable nature of the pyrimidyl group allows facile diversification of the alkenylation products.

(3) Cobalt-catalyzed C2-alkylation of indole with vinylsilane. A cobalt-bathocuproine catalyst promotes the addition reaction of *N*-pyrimidylindole to vinylsilane under mild conditions to afford a C2-alkylation product. The alkylation reaction is also achieved with some other alkenes albeit in modest yield.

(4) Cobalt-catalyzed intramolecular olefin hydroheteroarylation. A cobalt-NHC catalyst system allows the intramolecular olefin hydroheteroarylation reaction on an indole platform under mild conditions, affording dihydropyrroloindole or tetrahydropyridoindole derivatives, many of which have not been accessed by other synthetic methods.

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Chapter 2 Cobalt-Catalyzed C2-Alkenylation of Azoles with Alkynes

2.1 Introduction

Azoles are among the most prevalent heterocyclic scaffolds in biologically active compounds and pharmaceuticals. For example, oxazole and thiazole core skeletons exist in the bioactive compounds Disorazole C₁¹ and Archazolid A², which exhibit high potency of antiproliferative activity against various cancer cell lines (Figure 2.1). Consequently, the development of effective methods for the rapid synthesis of densely functionalized azoles is of considerable importance in organic synthesis.

Figure 2.1 Biologically active compounds containing azole moiety

C–H bond functionalization of azoles represents a particularly attractive route to increase the complexity of the core structure. Over the past several years, increasing interest in C–H activation as a practical synthetic strategy³ have driven the development of a number of methods for direct C–C bond formation on the 2-position of azoles, such as arylation,⁴ alkenylation,^{5,6} alkylation,^{7,8} and alkynylation⁹ reactions. Among these

transformations, addition reactions of azoles to alkynes are attractive because they do not produce any byproducts.

In recent years, Nakao and Hiyama have extensively developed nickel-catalyzed hydroheteroarylation reactions of internal alkynes.^{a-e} For example, alkenylation of a series of azole derivatives has been achieved under mild conditions using a nickel(0)-phosphine catalyst (Scheme 2.1a). The reaction was proposed to involve oxidative addition of the azole C2–H bond to nickel(0), insertion of the alkyne into the Ni–H bond, and reductive elimination. In Addition, Miura et al. reported a similar nickel-catalyzed C–H alkenylation reaction of 1,3,4-oxadiazoles with alkynes including a terminal alkyne such as triisopropylsilylacetylene (Scheme 2.1b).^f In this particular reaction, a rhodium(I) catalyst showed a much narrower scope than the nickel(0) catalyst, allowing alkenylation with only triisopropylsilylacetylene, while many other heteroaromatic C–H functionalization reactions have been achieved with rhodium(I) catalysts.^{a,c,e,f}

Scheme 2.1 Ni-catalyzed alkenylation of azoles

In contrast to the versatility of rhodium catalysts in heteroaromatic C–H functionalization, cobalt, the lighter and more abundant homologue of rhodium, has rarely

been employed for such transformations.^{10, 11} However, examples of catalytic and stoichiometric aromatic C–H bond activation with low-valent cobalt complexes,¹² although sporadic, prompted us to look into a possibility of heteroaromatic C–H functionalization using a cobalt catalyst. In this chapter, we report that a cobalt complex serves as an efficient catalyst for C2-alkenylation of azoles with internal alkynes *via* C–H bond activation.

2.2 Results and Discussion

2.2.1 Cobalt-Catalyzed Addition Reaction of Benzoxazoles to Alkynes

Our investigation began with the addition reaction of benzoxazole **1a** to 4-octyne **2a**. After screening of catalysts generated from cobalt salts, ligands and reducing agents, we found that the combination of CoBr_2 (10 mol%), bis[(2-diphenylphosphino)phenyl]ether (DPEphos, 10 mol%), and $\text{Me}_3\text{SiCH}_2\text{MgCl}$ (100 mol%) serves as an efficient catalyst system to provide the alkenylated product **3aa** (*E/Z* > 99/1) in 75% yield at 20 °C (Table 2.1, entry 1). Addition of pyridine (40 mol%) as an additive further improved the product yield to 86% (entry 2). The amount of $\text{Me}_3\text{SiCH}_2\text{MgCl}$ could be reduced to 50 mol% without decrease in the catalytic activity (entry 3), while the reaction became very sluggish with 30-40 mol% of $\text{Me}_3\text{SiCH}_2\text{MgCl}$ and stopped with further decrease. A preformed cobalt-phosphine complex $\text{CoCl}_2(\text{DPEphos})$ gave rise to a similarly active catalyst (entry 4). Although low-valent cobalt complexes are well-known to catalyze cyclotrimerization of alkynes,¹³ no such product was observed in these experiments.

Table 2.1 Cobalt-Catalyzed Addition Reaction of Benzoxazole to 4-Octyne^a

Chemical structures of the ligands:

- DPEphos**: 1,2-bis(diphenylphosphino)ethane derivative, specifically 1,2-bis(diphenylphosphino)ethane.
- dppe**: 1,2-bis(diphenylphosphino)ethane derivative, specifically 1,2-bis(diphenylphosphino)ethane.
- dppp**: 1,3-bis(diphenylphosphino)propane derivative, specifically 1,3-bis(diphenylphosphino)propane.
- Xantphos**: 1,3-bis(diphenylphosphino)benzene derivative, specifically 1,3-bis(diphenylphosphino)benzene.

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metal precatalyst, CoBr_2 was superior to other common cobalt salts (e.g., CoCl_2 , CoI_2 , $\text{Co}(\text{acac})_3$), and other metal salts (e.g., Fe, Ni, Ru, Rh, Pd) did not promote the reaction at all under otherwise identical conditions.¹⁵

The present reaction was applicable to a variety of (benz)oxazole derivatives as illustrated in Figure 2.2. Benzoxazoles bearing 5-chloro and 5-methyl substituents underwent addition reaction to 4-octyne **2a** as smoothly as the parent benzoxazole **1a** to afford the products **3ba** and **3ca** in ca. 80% yield. 5-Aryl oxazole derivatives also participated in the reaction, and afforded the corresponding alkenylated products **3da**–**3ma** in moderate to excellent yields. The substrates bearing electron-withdrawing groups such as 4-trifluoromethyl and 2-fluoro groups gave the products **3ea** and **3ga**, respectively, in ca. 90% yields. On the other hand, a 4-methoxy substituent made the reaction sluggish, affording the product **3fa** in 55% yield. The yield could not be improved either by extending the reaction time or increasing the reaction temperature. Chloro and bromo substituents made the reaction even more sluggish. Thus, although the C–Cl and C–Br bonds remained intact, the products **3ha** and **3ia** were obtained in only modest yields. Cyano and amide functional groups are tolerable, as demonstrated by the formation of the addition products **3ka** and **3la** in 99% and 35% yields, respectively. A thienyl-substituted oxazole showed a modest reactivity, presumably due to undesirable coordination of the sulfur atom to the cobalt catalyst (see **3ma**). An oxadiazole derivative also underwent addition reaction to 4-octyne **2a** at room temperature, and afforded the product **3na** in 82% yield. On the other hand, other azole heterocycles such as (benz)imidazoles did not participate in the reaction even at elevated reaction temperatures.

Figure 2.2 Scope of oxazoles. Unless otherwise noted, the reaction was performed under the conditions described in Table 2.1, entry 3, and E/Z ratio of the product was $>99/1$. ^a100 mol% of $\text{Me}_3\text{SiCH}_2\text{MgCl}$ was used.

Next, we explored the reaction of (benz)oxazole derivatives with a variety of alkynes (Figure 2.3). Symmetrical aliphatic alkynes participated in the reaction smoothly, and afforded the alkenylation products in good to excellent yields with high stereoselectivity ($E/Z > 99/1$). Benzyl ethers and $\text{C}(\text{sp}^3)\text{--Cl}$ bonds were well tolerated (**3ac** and **3kd**). Interestingly, desilylation of one of the Me_3Si groups took place during the reaction of 1,4-bis(trimethylsilyl)but-2-yne, affording the product **3ae** in moderate yield. An elevated temperature of 80 °C was necessary for the reaction of an

unsymmetrical aliphatic alkyne. While 2-hexyne reacted with a moderate regioselectivity of 2:1 (see **3kf**), 4-methyl-2-pent-2-yne and 2,2-dimethyloct-3-yne underwent C–C bond formation exclusively at the less hindered position (see **3gg** and **3kh**). Arylalkynes also afforded the addition products **3ki** and **3kj** in good yields, while terminal alkynes failed to participate in the reaction presumably due to incompatibility of the acidic acetylenic proton and the reaction conditions including the Grignard reagent.

Figure 2.3 Scope of alkynes. Unless otherwise noted, the reaction was performed under the conditions described in Table 2.1, entry 3, and the *E/Z* ratio of the product was >99/1. ^aThe reaction was performed at 80 °C. ^b1,4-Bis(trimethylsilyl)but-2-yne was used as the alkyne. ^c**3kf** is the major regioisomer (regioselectivity was 2:1).

In order to gain insight into the reaction mechanism, we performed several mechanistic experiments. First, quenching the reaction of **1a** and **2a** with D₂O did not cause deuteration of either the product or the recovered starting material¹⁶ which rules out

stoichiometric formation of alkenylmetal and 2-oxazolylmetal intermediates.¹⁷ Consistent with this observation, the reaction of deuterated benzoxazole **1a-d** with **2a** afforded the corresponding deuterated adduct **3aa-d** in 43% yield (Scheme 2.2a). Notably, the reaction was apparently slower than that of parent benzoxazole (see Table 2.1, entry 1). In addition, the reaction of a 1:1 mixture of **1a-d** and the oxazole **1k** with **2a** afforded **3aa-d** and **3ka** in 80% and 98% yields, respectively, without H/D crossover (Scheme 2.2b). These results clearly show that the aryl group and the hydrogen (deuterium) atom in the product molecule come from the same reactant molecule. Finally, a competitive reaction of **1a** and **1a-d** with **2a**, which was quenched at an early stage of the reaction, afforded a mixture of **3aa** and **3aa-d** in 28% yield with a ratio of 74:26 (Scheme 2.2c). Thus, a kinetic isotope effect of ca. 2.8 is indicated for the C–H bond cleavage step.

Scheme 2.2 Mechanistic Experiments

The results of the deuterium-labeling experiments suggest that the present reaction does not go through either deprotonation^{18,19} or electrophilic metalation of the C2 position of the oxazole substrate.²⁰ We consider that the present reaction is mechanistically similar to the nickel-catalyzed hydroheteroarylation (*vide supra*), involving oxidative addition of the oxazolyl C–H bond to the cobalt center^{21,22} and insertion of the alkyne to the Co–H bond in a *syn*-fashion, followed by reductive elimination of the resulting alkenyl(oxazolyl)cobalt intermediate (Scheme 2.3). The proposed mechanism allows rationalization of the origin of the regioselectivity observed for the products such as **3gg** and **3kh**. Thus, the cobalt center would prefer to avoid steric hindrance during the alkyne

insertion step. The identity of the catalytically active cobalt species remains elusive at this stage. The necessity of a larger amount of the Grignard reagent than required for the reduction of Co(II) to Co(0) (20 mol%) and the significant influence of the Grignard reagent on the catalytic activity (see Table 2.1) suggest possible involvement of an organocobalt(0)ate species as the reactive species.²³ Note that, other mechanistic possibilities such as those involving a radical process may not be fully ruled out.²⁴

Scheme 2.3 Possible Catalytic Cycle

2.2.2 Cobalt-Catalyzed Alkenylation of Thiazoles with Alkynes

The Co-DPEphos catalyst, regardless of its success in alkenylation of (benz)oxazoles, poorly promoted the reaction of 4,5-dimethylthiazole **1o** and 4-octyne **2a** (Table 2.2, entry 1). After screening of ligands, we identified Xantphos as the most effective ligand, which allowed the reaction to proceed smoothly in THF at 60 °C to afford the addition product **3oa** in 75% yield with exclusively *syn* selectivity (entry 2). Note that Xantphos was a rather poor ligand for the reaction of (benz)oxazole derivatives with alkynes (Table 2.1, entry 8). The use of other bidentate phosphine ligands such as dppe, dppp, dppb, and dppf resulted in lower yields (entries 3-6). Other Grignard reagents such as methylmagnesium chloride and neopentylmagnesium bromide were less effective (entries 7 and 8). The reaction did not occur at all when the amount of Me₃SiCH₂MgCl was reduced to 30 mol%. The yield of the product was further improved to 90% when toluene was used as the solvent instead of THF (entry 9).

Table 2.2 Cobalt-Catalyzed Addition Reaction of 4,5-dimethylthiazole to 4-Octyne^a

entry	ligand	RMgX (50 mol%)	yield (%) ^b
1	DPEphos	Me ₃ SiCH ₂ MgCl	2
2	Xantphos	Me ₃ SiCH ₂ MgCl	75
3	dppe	Me ₃ SiCH ₂ MgCl	12
4	dppp	Me ₃ SiCH ₂ MgCl	64
5	dppb	Me ₃ SiCH ₂ MgCl	34
6	dppf	Me ₃ SiCH ₂ MgCl	29
7	Xantphos	MeMgCl	51
8	Xantphos	<i>t</i> BuCH ₂ MgBr	58
9	Xantphos	Me ₃ SiCH ₂ MgCl	90 ^c

^a Reaction was carried out on a 0.3 mmol scale at 0.2 M concentration. ^b GC yield. ^c Toluene was used as the solvent. Isolated yield.

The optimized reaction conditions allowed C2-alkenylation reaction of various thiazole derivatives with 4-octyne in good yields with high *syn* stereoselectivity (Figure 2.4). 4-Methylthiazole underwent addition reaction smoothly and afforded the corresponding alkenylation product **3pa** in 85% yield. On the other hand, the reaction became sluggish when unsubstituted thiazole was used (see **3qa**). A related thiazole substrate bearing a benzyloxy group participated in the reaction and gave the alkenylation product **3ra** in good yield. 5-Arylthiazole derivatives, which were synthesized by direct C5-arylation of thiazole with corresponding aryl bromides or iodides,²⁵ also afforded the corresponding alkenylation products **3sa-3xa** in moderate to good yields with high stereoselectivity. The aryl group on the thiazole ring could be either electron-rich (**3ta**, **3ua**) or electron-deficient (**3va**, **3wa**). The cobalt-Xantphos catalyst system tolerated a

cyano group, as did the cobalt-DPEphos catalyst in the alkenylation reaction of oxazole derivatives. Benzothiazole also underwent the addition reaction to **2a** to give the product **3ya** in good yield.

Figure 2.4 Scope of thiazoles. Unless otherwise noted, the reaction was performed under the conditions described in Table 2.2, entry 9, and the E/Z ratio was $>99:1$. ^aDetermined by GC using *n*-tridecane as internal standard.

Next, the scope of alkynes was examined (Figure 2.5). 5-Decyne afforded the addition product **3ob** in good yield with excellent stereoselectivity. Unsymmetric dialkyl alkynes such as hex-2-yne and 4-methylpent-2-yne underwent C–C bond formation preferentially at the less-hindered positions, while the regioselectivity (2:1) was modest for the former. The reaction of arylalkynes required heating at 80 °C, affording the products **3xi** and **3xj** in moderate yields. For 1-phenylprop-1-yne, C–C bond formation

took place exclusively at the position proximal to the methyl group. The regioselectivity trend observed for unsymmetric alkynes (**3xf**, **3og**, **3xi**) was the same as the reaction of oxazole derivatives catalyzed by Co-DPEphos. Terminal alkynes failed to participate in the reaction.

Figure 2.5 Scope of alkynes. Unless otherwise noted, the reaction was performed under the conditions described in Table 2, entry 9, and the *E/Z* ratio was > 99:1. ^a**3xf** is the major regioisomer (regioselectivity was 2:1). ^bThe reaction was performed at 80 °C.

Because of the different scopes of the Co-DPEphos and Co-Xantphos systems, we became interested in the chemoselectivity of each system. First, competition experiments were performed using benzoxazole **1a** and benzothiazole **1y** (Scheme 2.4a). The reaction of an equimolar mixture of **1y** and **1a** with 4-octyne **2a** in the presence of the Co-DPEphos catalyst resulted in exclusive formation of a benzoxazole adduct **3aa** expectedly. On the other hand, it was unexpected that the Co-Xantphos catalyst did not promote the alkenylation reaction of benzothiazole, but provided a small amount of **3aa**. Apparently, benzoxazole seems to have inhibited the reaction of benzothiazole, while the reason for the inhibition is not clear at this stage.

Scheme 2.4 Competition of benzothiazole and benzoxazole in cobaltcatalyzed reaction with oct-4-yne. Co-DPEphos: CoBr₂ (10 mol%), DPEphos (10 mol%), Me₃SiCH₂MgCl (50 mol%), pyridine (80 mol%), THF; Co-Xantphos: CoBr₂ (10 mol%), Xantphos (10 mol%), Me₃SiCH₂MgCl (50 mol%), toluene.

Next, a substrate **4** bearing both oxazole and thiazole moieties was subjected to the Co-DPEphos and Co-Xantphos catalytic systems (Scheme 2.4b). Although the reaction became very sluggish with both catalytic systems, a difference in the chemoselectivity was observed. While the oxazole moiety was exclusively alkenylated with the Co-DPEphos system, the Co-Xantphos system gave a mixture of **5** and **6** through activation of the oxazolyl and thiazolyl C–H bonds, respectively. The reason for the chemoselectivity difference is not clear at this moment, while we speculate that the

Co-DPEphos and Co-Xantphos-catalyzed alkenylation reactions essentially share the same catalytic cycle consisting of (1) oxidative addition of the C2–H bond to the cobalt center, (2) insertion of the alkyne into the Co–H bond, and (3) reductive elimination of the resulting diorganocobalt species.

2.3 Conclusion

We have developed ternary catalytic systems consisting of CoBr_2 , diphosphine ligands, and $\text{Me}_3\text{SiCH}_2\text{MgCl}$ for the activation of an azole C(2)–H bond followed by insertion of an unactivated internal alkyne, which affords the corresponding alkenylated product in moderate to good yield with high chemo-, regio-, and stereoselectivity. The different reactivity of the Co-DPEphos and Co-Xantphos catalyst system toward oxazole and thiazole is intriguing, and it deserves further synthetic and mechanistic investigations. The present catalyst systems make a useful addition to the rapidly expanding repertoire of methods for direct functionalization of azole heterocycles.

2.4 Experimental Section

Materials and Methods

General. All reactions dealing with air- or moisture-sensitive compound were performed by standard Schlenk techniques in oven-dried reaction vessels under nitrogen atmosphere. Analytical thin-layer chromatography (TLC) was performed on Merck 60 F254 silica gel plates. Flash chromatography was performed as described by Still et al., using 40–63 μm silica gel (Si 60, Merck). ^1H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on Bruker AV-400 (400 MHz) or JEOL ECX-400 (400 MHz) NMR spectrometers. ^1H and ^{13}C NMR spectra are reported in parts per million (ppm) downfield from an internal standard, tetramethylsilane (0 ppm) and CHCl_3 (77.0 ppm), respectively. Gas chromatographic (GC) analysis was performed on a Shimadzu GC-2010 system equipped with an FID detector and a capillary column, DB-5 (Agilent J&W, 0.25 mm i.d. x 30 m, 0.25 μm film thickness). High-resolution mass spectra (HRMS) were obtained with a Q-ToF Premier LC HR mass spectrometer. Melting points were uncorrected and were recorded on a Buchi B-54 melting point apparatus.

Materials. Unless otherwise noted, reagents were purchased from Aldrich, Alfa Aesar, and other commercial suppliers and were used as received. THF was distilled over Na/benzophenone. Toluene was distilled over calcium hydride. Grignard reagents except MeMgCl (purchased from Aldrich) were prepared from the corresponding halides and magnesium turnings in anhydrous THF and titrated before use. Anhydrous CoBr_2 (99%) was purchased from Alfa Aesar. $\text{CoCl}_2(\text{DPEphos})$ was prepared according to the literature procedure.

Preparation of Substrates for Cobalt-Catalyzed Reaction

A General Procedure for the Preparation of Substituted Oxazoles:²⁶ In a 100 mL round bottom flask were added arylidene diacetate (10 mmol, prepared from the corresponding aldehyde and Ac₂O in the presence of a catalytic amount of *p*-TsOH), 1-(isocyanomethylsulfonyl)-4-methylbenzene (TosMIC, 2.09 g, 10.4 mmol), K₂CO₃ (4.40 g, 31.6 mmol) and MeOH (30 mL). The reaction mixture was stirred at 55 °C for 2 h. After cooling to room temperature, the precipitate was filtered and washed with CH₂Cl₂ (20 mL). The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel chromatography (hexane/EtOAc = 15/1 to 10/1) to give the oxazole product.

Spectral data for the following oxazole derivatives showed good agreement with the literature data: 5-phenyloxazole (**1d**),²⁷ 5-(4-(trifluoromethyl)phenyl)oxazole (**1e**),²⁸ 5-(4-methoxyphenyl)oxazole (**1f**), 5-(4-chlorophenyl)oxazole (**1h**),²⁹ 5-(1-naphthyl)oxazole (**1j**), 2-(oxazol-5-yl)benzonitrile (**1k**),³⁰ 5-(thiophen-2-yl)oxazole (**1m**).³¹

5-(2-Fluorophenyl)oxazole (1g**):** 74% yield; A white solid; m.p. 44.2-44.3 °C; ¹H NMR (400 MHz, CDCl₃): δ 7.95 (s, 1 H), 7.79-7.75 (m, 1 H), 7.51 (d, *J* = 3.7 Hz, 1 H), 7.35-7.14 (m, 3 H); ¹³C NMR (100 MHz, CDCl₃): δ 158.8 (d, ¹*J*_{C-F} = 252 Hz), 150.2, 145.9, 129.7 (d, ³*J*_{C-F} = 8.6 Hz), 126.1 (d, ⁴*J*_{C-F} = 2.9 Hz), 125.7 (d, ³*J*_{C-F} = 12.5 Hz),

124.5 (d, $^4J_{\text{C-F}} = 2.9$ Hz), 116.2 (d, $^2J_{\text{C-F}} = 19$ Hz), 116.0 (d, $^2J_{\text{C-F}} = 21$ Hz); HRMS (ESI)

Calcd for $\text{C}_9\text{H}_7\text{NOF}$ $[\text{M} + \text{H}]^+$ 164.0512, found 164.0515.

5-(4-Bromophenyl)oxazole (1i): 86% yield; A white solid; m.p. 78.1-78.4 °C; ^1H NMR (400 MHz, CDCl_3): δ 7.92 (s, 1 H), 7.58-7.51 (m, 4 H), 7.37 (s, 1 H); ^{13}C NMR (100 MHz, CDCl_3): δ 150.53, 150.48, 132.0, 126.6, 125.7, 122.5, 121.9; HRMS (ESI) Calcd for $\text{C}_9\text{H}_7\text{NOBr}$ $[\text{M} + \text{H}]^+$ 223.9711, found 223.9706.

***N,N*-dimethyl-2-(oxazol-5-yl)benzamide (1l):** 80% yield; A white solid; m.p. 85.3-85.6 °C; ^1H NMR (400 MHz, CDCl_3): δ 7.93 (s, 1 H), 7.74 (d, $J = 7.8$ Hz, 1 H), 7.47-7.39 (m, 2 H), 7.32 (d, $J = 7.5$ Hz, 1 H), 7.27 (s, 1 H), 3.14 (s, 3 H), 2.72 (s, 3 H); ^{13}C NMR (100 MHz, CDCl_3): δ 170.5, 150.8, 149.3, 134.0, 129.2, 129.0, 126.9, 126.4, 124.1, 123.8, 38.3, 34.8; HRMS (ESI) Calcd for $\text{C}_{12}\text{H}_{13}\text{N}_2\text{O}_2$ $[\text{M} + \text{H}]^+$ 217.0977, found 217.0978.

A General Procedure for the Preparation of Substituted Thiazoles: Aryl iodide (5 mmol), thiazole (6 mmol), KOAc (0.59 g, 6 mmol) and $\text{Pd}(\text{OAc})_2$ (11.2 mg, 0.05 mmol) were dissolved in *N,N*-dimethylacetamide (15 mL), stirred at 130 °C for 18 h, and then

quenched with H₂O (10 mL). The resulting mixture was extracted with EtOAc (3 × 10 mL). The combined organic layer was dried over Na₂SO₄ and concentrated under reduced pressure. Purification of the crude product by silica gel chromatography (eluent: hexane/EtOAc = 10/1) afforded the thiazole product.

Spectral data for the following oxazole derivatives showed good agreement with the literature data: 5-[2-(benzyloxy)ethyl]-4-methylthiazole (**1r**),³² 5-phenylthiazole (**1s**),³³ 5-(4-tolyl)thiazole (**1t**), 5-(4-methoxyphenyl)thiazole (**1u**), and 4-(4-methylthiazol-5-yl)benzonitrile (**1x**).

5-[2-(Trifluoromethyl)phenyl]thiazole (1w**):** 70% yield; A colorless oil; *R_f* 0.13 (hexane/EtOAc, 10/1); ¹H NMR (400 MHz, CDCl₃): δ 8.88 (s, 1 H), 7.88 (s, 1 H), 7.80–7.78 (m, 1 H), 7.61–7.51 (m, 2 H), 7.48–7.46 (m, 1 H); ¹³C NMR (100 MHz, CDCl₃): δ 153.6, 142.9 (q, ⁴*J*_{C-F} = 2.0 Hz), 134.0, 133.4, 131.6, 129.6 (q, ²*J*_{C-F} = 30.0 Hz), 129.5, 128.9, 126.5 (q, ³*J*_{C-F} = 5.3 Hz), 123.6 (q, ¹*J*_{C-F} = 272 Hz); HRMS (ESI): calcd for C₁₀H₇NSF₃ [*M* + *H*]⁺ 230.0251, found 230.0248.

5-(2-Fluorophenyl)thiazole (1v**):** 75% yield; A yellow oil; *R_f* 0.52 (hexane/EtOAc, 3/1); ¹H NMR (400 MHz, CDCl₃): δ 8.84 (s, 1 H), 8.25 (s, 1 H), 7.63–7.59 (m, 1 H),

7.35–7.30 (m, 1 H), 7.22–7.16 (m, 2 H); ^{13}C NMR (100 MHz, CDCl_3): δ 158.7 (d, $^1J_{\text{C-F}} = 249$ Hz), 152.8 (d, $^4J_{\text{C-F}} = 4.0$ Hz), 141.4 (d, $^3J_{\text{C-F}} = 7.0$ Hz), 131.8 (d, $^3J_{\text{C-F}} = 5.0$ Hz), 129.5 (d, $^3J_{\text{C-F}} = 9.0$ Hz), 129.0 (d, $^4J_{\text{C-F}} = 3.0$ Hz), 124.5 (d, $^4J_{\text{C-F}} = 4.0$ Hz), 118.9 (d, $^2J_{\text{C-F}} = 14.0$ Hz), 116.2 (d, $^2J_{\text{C-F}} = 12.0$ Hz); HRMS (ESI): calcd for $\text{C}_9\text{H}_7\text{NSF}$ [$\text{M} + \text{H}$] $^+$ 180.0283; found: 180.0286.

Preparation of Alkynes.

1,8-Bis(benzyloxy)oct-4-yne (2c): To a THF solution of oct-4-yne-1,8-diol (0.70 g, 5 mmol, prepared according to the literature procedure³⁴) in THF (20 mL) was added NaH (0.60 mg, 15 mmol) portionwise at 0 °C. After stirring for 10 min, benzyl bromide (1.3 mL, 11 mmol) was added. The resulting mixture was refluxed for 2 h. Water (10 mL) was added to the reaction mixture at 0 °C. The resulting mixture was extracted with ether (10 mL $\times$ 3) and the combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the crude product by silica gel chromatography (eluent: hexane/EtOAc = 25/1) afforded the title compound as a colorless oil (1.02 g, 63%). *R_f* 0.52 (hexane/EtOAc = 5/1); ^1H NMR (400 MHz, CDCl_3): δ 7.34–7.33 (m, 8 H), 7.29–7.26 (m, 2 H), 4.50 (s, 4 H), 3.54 (t, $J = 6.3$ Hz, 4 H), 2.26 (t, $J = 6.9$ Hz, 4 H), 1.79–1.75 (m, 4 H); ^{13}C NMR (100 MHz, CDCl_3): δ 138.6, 128.3, 127.6, 127.5, 79.8, 72.9, 69.0, 29.2, 15.6; HRMS (ESI) Calcd for $\text{C}_{22}\text{H}_{27}\text{O}_2$ [$\text{M} + \text{H}$] $^+$ 323.2011, found 323.2010.

1,8-Dichlorooct-4-yne (2d): To a THF solution of oct-4-yne-1,8-diol (0.28 g, 2 mmol), pyridine (0.4 mL, 4.8 mmol) and LiCl (34 mg, 0.8 mmol) in DMF (10 mL) was added MsCl (0.4 mL, 4.8 mmol) dropwise at 0 °C. The resulting mixture was stirred for 12 h at room temperature. Water (5 mL) was added to the reaction mixture. The resulting mixture was extracted with ether (8 mL $\times$ 3) and the combined organic layer was dried over Na₂SO₄ and concentrated under reduced pressure. Purification of the crude product by silica gel chromatography (eluent: hexane/EtOAc = 25/1) afforded the title compound as a colorless oil (0.20 g, 56%). ¹H NMR (400 MHz, CDCl₃): δ 3.64 (t, J = 8.0 Hz, 4 H), 2.34 (t, J = 8.1 Hz, 4 H), 1.95-1.91 (m, 4 H); ¹³C NMR (100 MHz, CDCl₃): δ 79.2, 43.7, 31.6, 16.1.

1,4-Bis(trimethylsilyl)but-2-yne (**2e**)³⁵ and 2,2-dimethyloct-3-yne (**2h**)³⁶ were prepared according to the literature procedures.

Cobalt-Catalyzed Addition of Oxazole Derivatives to Alkynes

A Typical Procedure: (E)-2-(Oct-4-en-4-yl)benzo[d]oxazole (3aa). In a Schlenk tube were placed CoBr₂ (6.6 mg, 0.03 mmol), DPEphos (16.2 mg, 0.03 mmol), and pyridine (9.7 μ L, 0.12 mmol), which were then dissolved in THF (0.7 mL). To the solution was added Me₃SiCH₂MgCl (0.84 M in THF, 0.18 mL, 0.15 mmol) at 0 °C. After stirring for 30 min at this temperature, a THF solution (0.6 mL) of benzoxazole (**1a**, 35.7 mg, 0.3 mmol) and 4-octyne (**2a**, 53 μ L, 0.36 mmol) was added. The reaction mixture was stirred at 20 °C for 12 h, and then quenched by the addition of 1 M HCl (1.5 mL). The resulting mixture was extracted with ethyl acetate (5 mL $\times$ 3) and the combined organic layer was

dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the crude product by silica gel chromatography (eluent: hexane/EtOAc = 25/1) afforded the title compound as a colorless oil (56.4 mg, 82%).

R_f 0.60 (hexane/EtOAc = 10/1); ^1H NMR (400 MHz, CDCl_3): δ 7.71-7.69 (m, 1 H), 7.48-7.46 (m, 1 H), 7.30-7.26 (m, 2 H), 6.87 (t, J = 7.6 Hz, 1 H), 2.63 (t, J = 7.6 Hz, 2 H), 2.33-2.28 (m, 2 H), 1.65-1.51 (m, 4 H), 1.00 (t, J = 7.4 Hz, 3 H), 0.99 (t, J = 7.3 Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3): δ 164.7, 150.3, 142.1, 138.8, 128.5, 124.6, 124.0, 119.7, 110.1, 30.6, 29.4, 22.43, 22.39, 13.96 (two peaks are overlapped). The stereochemistry of the olefin moiety was assigned by a NOESY experiment.

(*E*)-5-Chloro-2-(4-octen-4-yl)benzoxazole (3ba): Obtained as a 12:1 mixture with its (*Z*)-isomer; 85% yield; A yellow oil; *R_f* 0.67 (hexane/EtOAc = 10/1); ^1H NMR (400 MHz, CDCl_3): δ 7.66 (d, J = 1.8 Hz, 1H), 7.38-7.36 (m, 1 H), 7.25-7.24 (m, 1 H), 6.88 (t, J = 7.3 Hz, 1 H), 2.60 (t, J = 7.3 Hz, 2 H), 2.31-2.29 (m, 2 H), 1.65-1.51 (m, 4 H), 1.00 (t, J = 7.4 Hz, 3 H), 0.99 (t, J = 7.4 Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3): δ 166.0, 148.9, 143.3, 139.7, 129.4, 128.2, 124.7, 119.6, 110.7, 30.7, 29.3, 22.38, 22.32, 13.93 (two peaks are overlapped); HRMS (ESI) Calcd for $\text{C}_{15}\text{H}_{19}\text{NOCl}$ [$\text{M} + \text{H}$] $^+$ 264.1155, found 264.1157.

(E)-5-Methyl-2-(4-octen-4-yl)benzoxazole (3ca): Obtained as a 25:1 mixture with its (Z)-isomer; 77% yield; A colorless oil; *R_f* 0.60 (hexane/EtOAc = 10/1); ¹H NMR (400 MHz, CDCl₃): δ 7.48 (s, 1 H), 7.34-7.32 (m, 1 H), 7.09-7.06 (m, 1 H), 6.84 (t, *J* = 7.8 Hz, 1 H), 2.61 (t, *J* = 7.8 Hz, 2 H), 2.44 (s, 3 H), 2.32-2.26 (m, 2 H), 1.63-1.52 (m, 4 H), 0.99 (t, *J* = 7.3 Hz, 3 H), 0.98 (t, *J* = 7.3 Hz, 3 H); ¹³C NMR (100 MHz, CDCl₃): δ 165.0, 148.8, 142.5, 138.6, 133.9, 128.8, 125.8, 119.9, 109.6, 30.8, 29.6, 22.64, 22.61, 21.65, 14.16 (two peaks are overlapped); HRMS (ESI) Calcd for C₁₆H₂₂NO [M + H]⁺ 244.1701, found 244.1703.

(E)-2-(4-Octen-4-yl)-5-phenyloxazole (3da): The reaction was performed by using 0.3 mmol (100 mol%) of Me₃SiCH₂MgCl; 66% yield; A yellow oil; *R_f* 0.35 (hexane/EtOAc = 10/1); ¹H NMR (400 MHz, CDCl₃): δ 7.64 (d, *J* = 8.2 Hz, 2 H), 7.42-7.38 (m, 2 H), 7.32-7.27 (m, 2 H), 6.64 (t, *J* = 7.6 Hz, 1 H), 2.55 (t, *J* = 7.6 Hz, 2 H), 2.29-2.23 (m, 2 H), 1.62-1.51 (m, 4 H), 0.99 (t, *J* = 7.4 Hz, 3 H), 0.98 (t, *J* = 7.3 Hz, 3 H); ¹³C NMR (100 MHz, CDCl₃): δ 162.9, 150.2, 134.9, 128.8, 128.25, 128.23, 128.0, 124.0, 122.8, 30.4, 29.4, 22.53, 22.47, 14.02, 13.96; HRMS (ESI) Calcd for C₁₇H₂₂NO [M + H]⁺ 256.1701, found 256.1706.

(E)-5-(4-Trifluoromethylphenyl)-2-(4-octen-4-yl)oxazole (3ea): The reaction was performed by using 0.3 mmol (100 mol%) of $\text{Me}_3\text{SiCH}_2\text{MgCl}$; 92% yield; A white solid; m.p. 67.5–68.0 °C; *R_f* 0.34 (hexane/EtOAc = 10/1); ^1H NMR (400 MHz, CDCl_3): δ 7.74–7.64 (m, 4 H), 7.42 (s, 1 H), 6.68 (t, J = 7.6 Hz, 1 H), 2.56 (t, J = 7.6 Hz, 2H), 2.30–2.45 (m, 2 H), 1.62–1.52 (m, 4 H), 1.01 (t, J = 7.3 Hz, 3 H), 0.99 (t, J = 7.3 Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3): δ 163.8, 148.8, 135.9, 131.5, 129.7 (q, $^2J_{\text{C-F}}$ = 32.5 Hz), 128.1, 125.9 (q, $^3J_{\text{C-F}}$ = 3.7 Hz), 124.7, 124.01, 124.00 (q, $^1J_{\text{C-F}}$ = 270 Hz), 30.5, 29.4, 22.51, 22.49, 14.02, 13.97; HRMS (ESI) Calcd for $\text{C}_{18}\text{H}_{21}\text{NOF}_3$ $[\text{M} + \text{H}]^+$ 324.1575, found 324.1575.

(E)-5-(4-Methoxyphenyl)-2-(4-octen-4-yl)oxazole (3fa): The reaction was performed by using 0.3 mmol (100 mol%) of $\text{Me}_3\text{SiCH}_2\text{MgCl}$; 55% yield; A colorless oil; *R_f* 0.28 (hexane/EtOAc = 10/1); ^1H NMR (400 MHz, CDCl_3): δ 7.57 (d, J = 8.7 Hz, 2 H), 7.19 (s, 1 H), 6.93 (d, J = 8.7 Hz, 2 H), 6.60 (t, J = 7.6 Hz, 1 H), 3.83 (s, 3 H), 2.54 (t, J = 7.5 Hz, 2 H), 2.26–2.24 (m, 2 H), 1.57–1.52 (m, 4 H), 0.99 (t, J = 7.3 Hz, 3 H), 0.98 (t, J = 7.4 Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3): δ 162.3, 159.5, 150.2, 134.3, 128.3, 125.5, 121.3, 121.2, 114.3, 55.3, 30.4, 29.4, 22.55, 22.48, 14.03, 13.95; HRMS (ESI) Calcd for $\text{C}_{18}\text{H}_{24}\text{NO}_2$ $[\text{M} + \text{H}]^+$ 286.1807, found 286.1807.

(E)-5-(2-Fluorophenyl)-2-(4-octen-4-yl)oxazole (3ga): The reaction was performed by using 0.3 mmol (100 mol%) of $\text{Me}_3\text{SiCH}_2\text{MgCl}$; 90% yield; A colorless oil; R_f 0.46 (hexane/EtOAc = 10/1); ^1H NMR (400 MHz, CDCl_3): δ 7.77-7.73 (m, 1 H), 7.46 (d, J = 3.9 Hz, 1 H), 7.28-7.10 (m, 3 H), 6.66 (t, J = 7.6 Hz, 1 H), 2.56 (t, J = 7.6 Hz, 2 H), 2.29-2.24 (m, 2 H), 1.62-1.49 (m, 4 H), 1.00 (t, J = 7.3 Hz, 3 H), 0.99 (t, J = 7.3 Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3): δ 162.6, 158.7 (d, $^1J_{\text{C-F}}$ = 250 Hz), 144.5 (d, $^3J_{\text{C-F}}$ = 3 Hz), 135.3, 128.9 (d, $^3J_{\text{C-F}}$ = 8.1 Hz), 128.1, 127.2 (d, $^3J_{\text{C-F}}$ = 12.7 Hz), 125.8 (d, $^4J_{\text{C-F}}$ = 3.1 Hz), 124.4 (d, $^4J_{\text{C-F}}$ = 3.4 Hz), 116.7 (d, $^2J_{\text{C-F}}$ = 13.0 Hz), 115.8 (d, $^2J_{\text{C-F}}$ = 20.8 Hz), 30.39, 29.35, 22.47, 22.44, 13.99, 13.93; HRMS (ESI) Calcd for $\text{C}_{17}\text{H}_{21}\text{NOF}$ $[\text{M} + \text{H}]^+$ 274.1607, found 274.1604.

(E)-5-(4-Chlorophenyl)-2-(4-octen-4-yl)oxazole (3ha): The reaction was performed by using 0.3 mmol (100 mol%) of $\text{Me}_3\text{SiCH}_2\text{MgCl}$; 34% yield; A yellow oil; R_f 0.36 (hexane/EtOAc = 10/1); ^1H NMR (400 MHz, CDCl_3): δ 7.57 (d, J = 8.5 Hz, 2 H), 7.37 (d, J = 8.5 Hz, 2 H), 7.31 (s, 1H), 6.63 (t, J = 7.6 Hz, 1 H), 2.54 (t, J = 7.5 Hz, 2 H), 2.29-2.23 (m, 2 H), 1.61-1.51 (m, 4 H), 0.99 (t, J = 7.3 Hz, 3 H), 0.98 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3): δ 163.1, 149.2, 135.3, 133.8, 129.1, 128.2, 126.8, 125.2, 123.3, 30.4, 29.4, 22.52, 22.48, 14.03, 13.99; HRMS (ESI) Calcd for $\text{C}_{17}\text{H}_{21}\text{NOCl}$

$[M + H]^+$ 290.1312, found 290.1314.

(E)-5-(4-Bromophenyl)-2-(4-octen-4-yl)oxazole (3ia): The reaction was performed by using 0.3 mmol (100 mol%) of $\text{Me}_3\text{SiCH}_2\text{MgCl}$; 22% yield; A yellow oil; R_f 0.24 (hexane/EtOAc = 10/1); ^1H NMR (400 MHz, CDCl_3): δ 7.54-7.49 (m, 4 H), 7.32 (s, 1 H), 6.63 (t, $J = 7.6$ Hz, 1 H), 2.54 (t, $J = 7.5$ Hz, 2 H), 2.29-2.23 (m, 2 H), 1.60-1.51 (m, 4 H), 0.99 (t, $J = 7.2$ Hz, 3 H), 0.98 (t, $J = 7.2$ Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3): δ 163.2, 149.2, 135.3, 132.0, 128.2, 127.2, 125.5, 123.4, 121.9, 30.4, 29.3, 22.52, 22.48, 14.03, 13.99; HRMS (ESI) Calcd for $\text{C}_{17}\text{H}_{21}\text{NOBr}$ $[M + H]^+$ 334.0807, found 334.0809.

(E)-5-(Naphthalen-1-yl)-2-(4-octen-4-yl)oxazole (3ja): Obtained as a 15:1 mixture with its (Z)-isomer; 65% yield; A colorless oil; R_f 0.37 (hexane/EtOAc = 10/1); ^1H NMR (400 MHz, CDCl_3): δ 8.32 (d, $J = 8.2$ Hz, 1 H), 7.90-7.84 (m, 2 H), 7.76 (d, $J = 7.2$ Hz, 1 H), 7.59-7.49 (m, 3 H), 7.42 (s, 1 H), 6.69 (t, $J = 7.6$ Hz, 1 H), 2.60 (t, $J = 7.6$ Hz, 2 H), 2.31-2.25 (m, 2 H), 1.82-1.49 (m, 4H), 1.02 (t, $J = 7.4$ Hz, 3 H), 0.99 (t, $J = 7.4$ Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3): δ 163.3, 149.4, 135.1, 133.9, 130.1, 129.2, 128.7, 128.3, 127.0, 126.25, 126.17 (two peaks are overlapped), 125.7, 125.3, 125.0, 30.47, 29.52, 22.62, 22.59, 14.15, 14.03; HRMS (ESI) Calcd for $\text{C}_{21}\text{H}_{24}\text{NO}$ $[M + H]^+$ 306.1858,

found 306.1857.

(E)-5-(2-Cyanophenyl)-2-(4-octen-4-yl)oxazole (3ka): 99% yield; A white solid; m.p. 56.5-57.2 °C; *R_f* 0.20 (hexane/EtOAc = 10/1); ¹H NMR (400 MHz, CDCl₃): δ 7.83 (s, 1H), 7.79 (d, *J* = 8.0 Hz, 1 H), 7.69 (d, *J* = 7.8 Hz, 1 H), 7.62 (t, *J* = 7.8 Hz, 1 H), 7.35 (t, *J* = 7.6 Hz, 1 H), 6.73 (t, *J* = 7.6 Hz, 1 H), 2.55 (t, *J* = 7.6 Hz, 2 H), 2.26 (m, 2 H), 1.62-1.48 (m, 4 H), 0.98 (t, *J* = 7.4 Hz, 3 H), 0.97 (t, *J* = 7.4 Hz, 3 H); ¹³C NMR (100 MHz, CDCl₃): δ 163.8, 146.4, 136.7, 134.1, 133.0, 130.8, 127.9, 127.7, 127.4, 125.7, 118.4, 107.1, 30.4, 29.2, 22.40 (two peaks are overlapped), 13.94, 13.89; HRMS (ESI) Calcd for C₁₈H₂₁N₂O [M + H]⁺ 281.1654, found 281.1658.

(E)-N,N-Dimethyl-2-(2-(4-octen-4-yl)oxazol-5-yl)benzamide (3la): 35% yield; A colorless oil; *R_f* 0.17 (CH₂Cl₂/EtOH = 40/1); ¹H NMR (400 MHz, CDCl₃): δ 7.75 (d, *J* = 7.9 Hz, 1 H), 7.49-7.45 (m, 1 H), 7.41-7.38 (m, 1 H), 7.34-7.28 (m, 2 H), 6.65 (t, *J* = 7.6 Hz, 1 H), 3.16 (s, 3 H), 2.77 (s, 3 H), 2.57 (t, *J* = 7.7 Hz, 2 H), 2.32-2.26 (m, 2 H), 1.63-1.54 (m, 4H), 1.03 (t, *J* = 7.2 Hz, 3 H), 1.01 (t, *J* = 7.2 Hz, 3 H); ¹³C NMR (100 MHz, CDCl₃): δ 170.6, 163.2, 148.0, 135.4, 133.5, 129.0, 128.4, 128.1, 127.00, 125.9, 125.1, 124.6, 38.2, 34.8, 30.4, 29.3, 22.51, 22.44, 14.00, 13.96; HRMS (ESI) Calcd for

$C_{20}H_{27}N_2O_2$ $[M + H]^+$ 327.2073, found 327.2071.

(E)-2-(Oct-4-en-4-yl)-5-(thiophen-2-yl)oxazole (3ma): 25% yield; A yellow oil; R_f 0.30 (hexane/EtOAc = 10/1); 1H NMR (400 MHz, $CDCl_3$): δ 7.31-7.30 (m, 2 H), 7.19 (s, 1 H), 7.09-7.07 (m, 1 H), 6.62 (t, $J = 7.6$ Hz, 1 H), 2.55 (t, $J = 7.6$ Hz, 2 H), 2.29-2.24 (m, 2 H), 1.63-1.52 (m, 4 H), 1.00 (t, $J = 7.3$ Hz, 3 H), 0.99 (t, $J = 7.2$ Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.5, 145.7, 135.1, 130.3, 128.0, 127.7, 125.2, 123.9, 122.6, 30.4, 29.4, 22.52, 22.47, 14.03, 13.98; HRMS (ESI) Calcd for $C_{15}H_{20}NOS$ $[M + H]^+$ 262.1266, found 262.1268.

(E)-5-Phenyl-2-(4-octen-4-yl)-1,3,4-oxadiazole (3na): 82% yield; A colorless oil; R_f 0.20 (hexane/EtOAc = 10/1); 1H NMR (400 MHz, $CDCl_3$): δ 8.07-8.05 (m, 2 H), 7.50-7.46 (m, 2 H), 6.65 (t, $J = 7.6$ Hz, 1 H), 2.60 (t, $J = 7.6$ Hz, 2 H), 2.28 (m, 2 H), 1.64-1.49 (m, 4 H), 0.99 (t, $J = 6.9$ Hz, 3 H), 0.98 (t, $J = 7.1$ Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.8, 163.8, 137.7, 131.4, 128.9, 126.8, 125.5, 124.2, 30.3, 29.3, 22.31, 22.23, 13.90, 13.89.

(E)-2-(Dec-5-en-5-yl)benzo[d]oxazole (3ab): 97% yield; A yellow oil; R_f 0.62

(hexane/EtOAc = 10/1); ^1H NMR (400 MHz, CDCl_3): δ 7.71-7.69 (m, 1 H), 7.47-7.45 (m, 1 H), 7.29-7.25 (m, 2 H), 6.85 (t, $J = 7.6$ Hz, 1 H), 2.64 (t, $J = 7.6$ Hz, 2 H), 2.34-2.27 (m, 2 H), 1.60-1.37 (m, 8 H), 0.95 (t, $J = 7.3$ Hz, 3 H), 0.94 (t, $J = 7.2$ Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3): δ 164.7, 150.3, 142.1, 138.7, 128.6, 124.5, 124.00, 119.7, 110.1, 31.5, 31.3, 28.3, 27.3, 22.65, 22.47, 13.99, 13.91; HRMS (ESI) Calcd for $\text{C}_{17}\text{H}_{24}\text{NO}$ $[\text{M} + \text{H}]^+$ 258.1858, found 258.1861.

(E)-2-(1,8-Benzyloxy-4-octen-4-yl)-benzoxazole (3ac): 58% yield; A colorless oil; R_f 0.14 (hexane/EtOAc = 10/1); ^1H NMR (400 MHz, CDCl_3): δ 7.70-7.69 (m, 1 H), 7.46-7.44 (m, 1 H), 7.33-7.22 (m, 12 H), 6.89 (t, $J = 7.6$ Hz, 1 H), 4.49 (s, 4 H), 3.52 (q, $J = 5.8$ Hz, 4 H), 2.76 (t, $J = 7.6$ Hz, 2 H), 2.47-2.42 (m, 2 H), 1.95-1.91 (m, 2 H), 1.86-1.80 (m, 2 H); ^{13}C NMR (100 MHz, CDCl_3): δ 164.3, 150.3, 142.0, 138.5, 138.4 (two peaks are overlapped), 128.30, 128.26 (two peaks are overlapped), 127.58, 127.56, 127.49, 127.40, 124.7, 124.1, 119.7, 110.1, 72.9, 72.8, 69.56, 69.50, 29.15, 29.02, 25.2, 24.0; HRMS (ESI) Calcd for $\text{C}_{29}\text{H}_{32}\text{NO}_3$ $[\text{M} + \text{H}]^+$ 442.2382, found 442.2381. The stereochemistry of the olefin moiety was assigned by a NOESY experiment.

(E)-5-(2-Cyanophenyl)-2-(1,8-chloro-4-octen-4-yl)oxazole (3kd): The reaction was performed at 80 °C; 81% yield; A colorless oil; R_f 0.30 (hexane/EtOAc = 3/1); ^1H NMR

(400 MHz, CDCl_3): δ 7.81 (s, 1H), 7.79-7.71 (m, 2 H), 7.64 (t, $J = 7.8$ Hz, 1 H), 7.38 (t, $J = 7.6$ Hz, 1 H), 6.74 (t, $J = 7.6$ Hz, 1H), 3.62-3.58 (m, 4 H), 2.79-2.75 (m, 2 H), 2.53-2.48 (m, 2 H), 2.08-1.97 (m, 4 H); ^{13}C NMR (100 MHz, CDCl_3): δ 162.8, 146.8, 135.3, 134.2, 133.0, 130.5, 128.0, 127.6, 127.3, 125.9, 118.3, 107.2, 44.5, 44.2, 31.77, 31.75, 25.51, 24.57; HRMS (ESI) Calcd for $\text{C}_{18}\text{H}_{19}\text{N}_2\text{OCl}_2$ $[\text{M} + \text{H}]^+$ 349.0874, found 349.0876. The stereochemistry of the olefin moiety was assigned by a NOESY experiment.

(Z)-2-(1-(Trimethylsilyl)but-2-en-2-yl)benzo[d]oxazole (3ae): 20% yield; A colorless oil; R_f 0.51 (hexane/EtOAc = 10/1); ^1H NMR (400 MHz, CDCl_3): δ 7.70-7.67 (m, 1 H), 7.48-7.44 (m, 1 H), 7.30-7.26 (m, 2 H), 6.84 (q, $J = 7.1$ Hz, 1 H), 2.17 (s, 2 H), 1.87 (d, $J = 7.2$ Hz, 3 H), 0.02 (s, 9 H); ^{13}C NMR (100 MHz, CDCl_3): δ 165.2, 150.4, 142.0, 129.2, 127.1, 124.5, 124.0, 119.7, 110.1, 17.7, 14.9, -1.0; HRMS (ESI) Calcd for $\text{C}_{13}\text{H}_{17}\text{NOSi}$ $[\text{M} - \text{CH}_3 + \text{H}]^+$ 232.1158, found 232.1157.

(E)-2-(2-(Hex-2-en-2-yl)oxazol-5-yl)benzonitrile (3kf): Obtained as a 2:1 mixture with its minor regioisomer, (E)-2-(2-(hex-2-en-3-yl)oxazol-5-yl)benzonitrile (**3kf'**); 82% yield; A colorless oil; R_f 0.50 (hexane/EtOAc = 3/1); ^1H NMR (400 MHz, CDCl_3): δ 7.85-7.79

(m, 2 H, **3kf** and **3kf'**), 7.72 (d, $J = 7.8$ Hz, 1 H, **3kf** and **3kf'**), 7.66-7.62 (m, 1 H, **3kf** and **3kf'**), 7.39-7.35 (m, 1 H, **3kf** and **3kf'**), 6.84 (q, $J = 7.2$ Hz, 1H, **3kf'**), 6.76 (t, $J = 7.5$ Hz, 1 H, **3kf**), 2.58 (t, $J = 7.6$ Hz, 2H, **3kf'**), 2.30-2.25 (m, 2 H, **3kf**), 2.12 (s, 3 H, **3kf**), 1.91 (d, $J = 7.2$ Hz, 3H, **3kf'**), 1.63-1.50 (m, 2 H, **3kf** and **3kf'**), 0.99 (t, $J = 7.4$ Hz, 3 H, **3kf** and **3kf'**); ^{13}C NMR (100 MHz, CDCl_3): δ 164.1, 163.7, 146.4, 146.3, 136.3, 134.1, 132.9, 131.0, 130.75, 130.73, 128.7, 127.73, 127.69, 127.34, 127.32, 125.75, 125.69, 123.1, 118.3, 30.5, 28.8, 22.13, 22.06, 14.06, 13.85, 13.80, 12.8; HRMS (ESI) Calcd for $\text{C}_{16}\text{H}_{17}\text{N}_2\text{O}$ $[\text{M} + \text{H}]^+$ 253.1341, found 253.1337.

(E)-5-(2-Fluorophenyl)-2-(4-methyl-2-penten-2-yl)oxazole (3gg): The reaction was performed at 80 °C; 61% yield; A colorless oil; R_f 0.48 (hexane/EtOAc = 10/1); ^1H NMR (400 MHz, CDCl_3): δ 7.78 (t, $J = 7.5$ Hz, 1 H), 7.46 (d, $J = 4.0$ Hz, 1 H), 7.27-7.11 (m, 3 H), 6.49 (d, $J = 9.6$ Hz, 1 H), 2.80-2.74 (m, 1 H), 2.13 (s, 3 H), 1.10 (d, $J = 6.7$ Hz, 6 H); ^{13}C NMR (100 MHz, CDCl_3): δ 163.0, 158.7 (d, $^1J_{\text{C-F}} = 250$ Hz), 144.7 (d, $^3J_{\text{C-F}} = 3$ Hz), 141.9, 129.0 (d, $^3J_{\text{C-F}} = 8.2$ Hz), 127.2 (d, $^3J_{\text{C-F}} = 12.9$ Hz), 125.9 (d, $^4J_{\text{C-F}} = 3.1$ Hz), 124.4 (d, $^4J_{\text{C-F}} = 3.3$ Hz), 121.3, 116.6 (d, $^2J_{\text{C-F}} = 13.0$ Hz), 115.8 (d, $^2J_{\text{C-F}} = 20.7$ Hz), 27.7, 22.4, 12.8; HRMS (ESI) Calcd for $\text{C}_{15}\text{H}_{17}\text{NOF}$ $[\text{M} + \text{H}]^+$ 246.1294, found 246.1298.

The stereochemistry of the olefin moiety was assigned by a NOESY experiment.

(E)-5-(2-Cyanophenyl)-2-((2E)-2,2-dimethyl-3-octen-4-yl)oxazole (3kh): The reaction was performed at 80 °C; 29% yield; A colorless oil; *R_f* 0.62 (hexane/EtOAc = 3/1); ¹H NMR (400 MHz, CDCl₃): δ 7.85 (s, 1H), 7.82-7.71 (m, 2 H), 7.66-7.62 (m, 1 H), 7.39-7.35 (m, 1 H), 6.75 (s, 1 H), 2.70-2.66 (m, 2 H), 1.61-1.53 (m, 2 H), 1.50-1.41 (m, 2 H), 1.27 (s, 9 H), 0.96 (t, *J* = 7.3 Hz, 3 H); ¹³C NMR (100 MHz, CDCl₃): δ 164.8, 146.4, 145.6, 134.2, 133.0, 130.9, 127.7, 127.6, 127.5, 125.8, 118.4, 107.2, 33.6, 32.2, 30.9, 27.8, 23.2, 14.0; HRMS (ESI) Calcd for C₂₀H₂₅N₂O [*M* + *H*]⁺ 309.1967, found 309.1971. The stereochemistry of the olefin moiety was assigned by a NOESY experiment.

(E)-5-(2-Cyanophenyl)-2-((1E)-1-phenyl-1-propen-2-yl)oxazole (3ki): The reaction was performed at 80 °C; 78% yield; A colorless oil; *R_f* 0.24 (hexane/EtOAc = 3/1); ¹H NMR (400 MHz, CDCl₃): δ 7.92 (s, 1 H), 7.87-7.85 (m, 1 H), 7.74-7.64 (m, 3 H), 7.48-7.26 (m, 6 H), 2.41 (s, 3 H); ¹³C NMR (100 MHz, CDCl₃): δ 164.3, 147.0, 136.1, 134.2, 133.3, 133.0, 130.6, 129.5, 128.3, 128.0, 127.9, 127.7, 125.9, 123.8, 118.3, 107.2, 14.52; HRMS (ESI) Calcd for C₁₉H₁₅N₂O [*M* + *H*]⁺ 287.1184, found 287.1186.

(E)-5-(2-Cyanophenyl)-2-(1,2-diphenylvinyl)oxazole (3kj): The reaction was performed at 80 °C; 67% yield; A yellow solid; m.p. 122.5-123.1 °C; *R_f* 0.25 (hexane/EtOAc = 3/1); ¹H NMR (400 MHz, CDCl₃): δ 7.92 (s, 1H), 7.85 (s, 1H), 7.79-7.72 (m, 2 H), 7.63 (t, *J* = 7.8 Hz, 1 H), 7.45-7.37 (m, 6 H), 7.24-7.10 (m, 5 H); ¹³C NMR (100 MHz, CDCl₃): δ 163.7, 147.2, 135.4, 135.1, 134.4, 134.2, 133.0, 131.3, 130.5, 130.2, 129.8, 128.9, 128.4, 128.3, 128.2, 128.1, 126.5, 126.0, 118.3, 107.3; HRMS (ESI) Calcd for C₂₄H₁₇N₂O [M + H]⁺ 349.1341, found 349.1336.

Deuterium-Labeling Experiments

(Z)-2-(5-Deuteriooct-4-en-4-yl)benzo[d]oxazole (3aa-d): The reaction was performed by using 2-deuteriobenzoxazole (**1a-d**, 0.3 mmol, 97% D), **2a** (0.36 mmol), CoBr₂ (0.03 mmol), DPEphos (0.03 mmol), and Me₃SiCH₂MgCl (0.3 mmol); 43% yield; ¹H NMR (400 MHz, CDCl₃): δ 7.71-7.69 (m, 1 H), 7.48-7.45 (m, 1 H), 7.30-7.26 (m, 2 H), 2.65-2.61 (m, 2 H), 2.32-2.28 (m, 2 H), 1.66-1.51 (m, 4 H), 1.00 (t, *J* = 7.4 Hz, 3 H), 0.99 (t, *J* = 7.3 Hz, 3 H); HRMS (ESI) Calcd for C₁₅H₁₉DNO [M + H]⁺ 231.1608, found 231.1608. The ¹H NMR analysis indicated > 95% deuterium incorporation into the olefinic position.

Crossover Experiment: A mixture of **1a-d** (0.15 mmol), **1k** (0.15 mmol), and **2a** (0.36 mmol) was subjected to the standard reaction conditions. Purification of the crude mixture by silica gel chromatography (eluent: hexane/EtOAc = 25/1) afforded **3aa-d** (27.5 mg,

80%) and **3ka** (41.2 mg, 98%). ^1H NMR analysis of each product indicated that no H/D crossover took place during the reaction.

Competition Experiment: An equimolar mixture of **1a** (0.15 mmol), **1a-d** (0.15 mmol) and **2a** (0.36 mmol) was subjected to the standard conditions for shorter reaction time (15 min) to give a mixture of **3aa** and **3aa-d** (19.3 mg, 28% yield). The ratio of **3aa** and **3aa-d** was determined by ^1H NMR analysis to be ca. 2.8.

Cobalt-Catalyzed Addition of Thiazole Derivatives to Alkynes

A Typical Procedure: (*E*)-4,5-dimethyl-2-(oct-4-en-4-yl)thiazole (3oa**).** In a Schlenk tube were placed CoBr_2 (6.6 mg, 0.03 mmol), Xantphos (17.9 mg, 0.03 mmol), and toluene (1.3 mL). To the solution was added $\text{Me}_3\text{SiCH}_2\text{MgCl}$ (0.89 M in THF, 0.17 mL, 0.15 mmol) at 0 °C. After stirring for 30 min at this temperature, 4,5-dimethylthiazole (34 mg, 0.3 mmol) and 4-octyne (53 μL , 0.36 mmol) were added sequentially. The reaction

mixture was stirred at 60 °C for 12 h, and then quenched with sat. aq NH₄Cl solution (1.5 mL) at r.t.. The resulting mixture was extracted with ethyl acetate (5 mL × 3) and the combined organic layer was dried over MgSO₄ and concentrated under reduced pressure. Purification of the crude product by silica gel chromatography (eluent: hexane/EtOAc = 100/1) afforded the title compound as a yellow oil (60 mg, 90%).

*R*_f 0.51 (hexane/EtOAc = 10/1); ¹H NMR (400 MHz, CDCl₃): δ 6.26 (t, *J* = 7.4 Hz, 1 H), 2.50 (t, *J* = 7.5 Hz, 2 H), 2.30 (s, 3 H), 2.29 (s, 3 H), 2.20-2.15 (m, 2 H), 1.54-1.45 (m, 4 H), 0.95 (t, *J* = 7.4 Hz, 3 H), 0.93 (t, *J* = 7.5 Hz, 3 H); ¹³C NMR (100 MHz, CDCl₃): δ 166.5, 148.1, 134.5, 131.9, 124.5, 31.3, 30.5, 22.6, 22.3, 14.8, 14.01, 13.96, 11.3; HRMS (ESI) Calcd for C₁₃H₂₂NS [M + H]⁺ 224.1473, found 224.1472.

(*E*)-4-Methyl-2-(oct-4-en-4-yl)thiazole (3pa): 85% yield; A yellow oil; *R*_f 0.50 (hexane/EtOAc = 10/1); ¹H NMR (400 MHz, CDCl₃): δ 6.69 (s, 1 H), 6.38 (t, *J* = 7.5 Hz, 1 H), 2.55 (t, *J* = 7.6 Hz, 2 H), 2.42 (s, 3 H), 2.23–2.17 (m, 2 H), 1.56–1.47 (m, 4 H), 0.96 (t, *J* = 7.4 Hz, 3 H), 0.94 (t, *J* = 7.5 Hz, 3 H); ¹³C NMR (100 MHz, CDCl₃): δ 170.7, 152.8, 134.5, 132.9, 111.7, 31.5, 30.5, 22.5, 22.3, 17.4, 14.02, 13.99; HRMS (ESI) calcd for C₁₂H₂₀NS [M + H]⁺ 210.1316, found 210.1317.

(E)-5-[2-(Benzyloxy)ethyl]-4-methyl-2-(oct-4-en-4-yl)thiazole (3ra): 81% yield; A yellow oil; R_f 0.46 (hexane/EtOAc = 10/1); ^1H NMR (400 MHz, CDCl_3): δ 7.35–7.24 (m, 5 H), 6.31 (t, J = 7.4 Hz, 1 H), 4.53 (s, 2 H), 3.63 (t, J = 6.8 Hz, 2 H), 2.99 (t, J = 6.8 Hz, 2 H), 2.54–2.50 (m, 2 H), 2.32 (s, 3 H), 2.21–2.16 (m, 2 H), 1.56–1.44 (m, 4 H), 0.95 (t, J = 7.3 Hz, 3 H), 0.94 (t, J = 7.3 Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3): δ 167.4, 148.5, 138.0, 134.5, 132.1, 128.3, 127.58, 127.57, 126.3, 73.0, 70.3, 31.3, 30.5, 27.2, 22.6, 22.3, 15.1, 14.0, 13.9; HRMS (ESI) calcd for $\text{C}_{21}\text{H}_{30}\text{NOS}$ $[\text{M} + \text{H}]^+$ 344.2048, found 344.2052.

(E)-2-(Oct-4-en-4-yl)-5-phenylthiazole (3sa): 71% yield; A colorless oil; R_f 0.45 (hexane/EtOAc = 10/1); ^1H NMR (400 MHz, CDCl_3): δ 7.88 (s, 1 H), 7.56–7.54 (m, 2 H), 7.40–7.36 (m, 2 H), 7.32–7.29 (m, 1 H), 6.41 (t, J = 7.4 Hz, 1 H), 2.60 (t, J = 7.7 Hz, 2 H), 2.27–2.22 (m, 2 H), 1.61–1.49 (m, 4 H), 0.99 (t, J = 7.4 Hz, 3 H), 0.98 (t, J = 7.3 Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3): δ 170.5, 138.2, 137.4, 134.9, 133.8, 131.7, 129.0, 127.9, 126.5, 31.1, 30.6, 22.6, 22.3, 14.1, 14.0; HRMS (ESI) calcd for $\text{C}_{17}\text{H}_{22}\text{NS}$ $[\text{M} + \text{H}]^+$ 272.1473, found 272.1476.

(E)-2-(Oct-4-en-4-yl)-5-(4-tolyl)thiazole (3ta): 67% yield; A yellow solid; m.p. 42–43 °C; *R_f* 0.62 (hexane/EtOAc = 10/1); ¹H NMR (400 MHz, CDCl₃): δ 7.84 (s, 1 H), 7.47–7.42 (m, 2 H), 7.22–7.17 (m, 2 H), 6.39 (t, *J* = 7.4 Hz, 1 H), 2.61–2.57 (m, 2 H), 2.36 (s, 3 H), 2.27–2.21 (m, 2 H), 1.63–1.49 (m, 4 H), 0.98 (t, *J* = 7.3 Hz, 3 H), 0.97 (t, *J* = 7.3 Hz, 3 H); ¹³C NMR (100 MHz, CDCl₃): δ 170.0, 137.9, 137.8, 137.5, 135.0, 133.6, 129.6, 128.8, 126.4, 31.1, 30.6, 22.6, 22.3, 21.2, 14.1, 14.0; HRMS (ESI) calcd for C₁₈H₂₄NS [M + H]⁺ 286.1629, found 286.1634.

(E)-5-(4-Methoxyphenyl)-2-(oct-4-en-4-yl)thiazole (3ua): 65% yield; A white solid; m.p. 44–45 °C; *R_f* 0.28 (hexane/EtOAc = 10/1); ¹H NMR (400 MHz, CDCl₃): δ 7.77 (s, 1 H), 7.51–7.45 (m, 2 H), 6.93–6.89 (m, 2 H), 6.37 (t, *J* = 7.4 Hz, 1 H), 3.82 (s, 3 H), 2.59 (t, *J* = 7.6 Hz, 2 H), 2.27–2.21 (m, 2 H), 1.60–1.47 (m, 4 H), 0.98 (t, *J* = 7.3 Hz, 3 H), 0.97 (t, *J* = 7.4 Hz, 3 H); ¹³C NMR (100 MHz, CDCl₃): δ 169.6, 159.5, 137.27, 137.22, 135.0, 133.4, 127.8, 124.3, 114.4, 55.3, 31.1, 30.6, 22.6, 22.3, 14.1, 13.9; HRMS (ESI) calcd for C₁₈H₂₄NOS [M + H]⁺ 302.1579, found 302.1578.

(E)-5-(2-Fluorophenyl)-2-(oct-4-en-4-yl)thiazole (3va): 85% yield; A yellow oil; *R_f* 0.51 (hexane/EtOAc = 10/1); ¹H NMR (400 MHz, CDCl₃): δ 8.05 (s, 1 H), 7.59–7.55 (m,

1 H), 7.30–7.24 (m, 1 H), 7.19–7.12 (m, 2 H), 6.44 (t, $J = 7.4$ Hz, 1 H), 2.61 (t, $J = 7.6$ Hz, 2 H), 2.28–2.22 (m, 2 H), 1.64–1.50 (m, 4 H), 0.99 (t, $J = 7.4$ Hz, 3 H), 0.98 (t, $J = 7.4$ Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3): δ 171.2 (d, $^5J_{\text{C-F}} = 3.0$ Hz), 158.9 (d, $^1J_{\text{C-F}} = 248$ Hz), 141.2 (d, $^4J_{\text{C-F}} = 8.0$ Hz), 134.8, 134.1, 130.2 (d, $^3J_{\text{C-F}} = 5.0$ Hz), 129.2 (d, $^3J_{\text{C-F}} = 11.0$ Hz), 129.0 (d, $^3J_{\text{C-F}} = 4.0$ Hz), 124.5 (d, $^4J_{\text{C-F}} = 4.0$ Hz), 119.7 (d, $^2J_{\text{C-F}} = 13.0$ Hz), 116.2 (d, $^2J_{\text{C-F}} = 22.0$ Hz), 31.1, 30.6, 22.5, 22.3, 14.1, 14.0; HRMS (ESI) calcd for $\text{C}_{17}\text{H}_{21}\text{NFS}$ $[\text{M} + \text{H}]^+$ 290.1379, found 290.1384.

(E)-2-(Oct-4-en-4-yl)-5-[2-(trifluoromethyl)phenyl]thiazole (3wa): 74 % yield; A yellow oil; R_f 0.42 (hexane/EtOAc = 10/1); ^1H NMR (400 MHz, CDCl_3): δ 7.78–7.76 (m, 1 H), 7.66 (s, 1 H), 7.58–7.55 (m, 1 H), 7.51–7.47 (m, 2 H), 6.43 (t, $J = 7.4$ Hz, 1 H), 2.60 (t, $J = 7.8$ Hz, 2 H), 2.28–2.22 (m, 2 H), 1.65–1.48 (m, 4 H), 0.99 (t, $J = 7.4$ Hz, 6 H); ^{13}C NMR (100 MHz, CDCl_3): δ 172.2, 142.1, 134.7, 134.1, 133.3, 132.2, 131.5, 130.2, 129.4 (q, $^2J_{\text{C-F}} = 30.0$ Hz), 128.5, 126.5 (q, $^3J_{\text{C-F}} = 5.3$ Hz), 123.8 (q, $^1J_{\text{C-F}} = 272$ Hz), 31.3, 30.6, 22.5, 22.2, 14.1, 14.0; HRMS (ESI) calcd for $\text{C}_{18}\text{H}_{21}\text{NF}_3\text{S}$ $[\text{M} + \text{H}]^+$ 340.1347, found 340.1349.

(E)-4-[4-Methyl-2-(oct-4-en-4-yl)thiazol-5-yl]benzonitrile (3xa): 81% yield; A white

solid; m.p. 86–87 °C; *R_f* 0.43 (hexane/EtOAc = 10/1); ¹H NMR (400 MHz, CDCl₃): δ 7.69–7.67 (m, 2 H), 7.55–7.53 (m, 2 H), 6.44 (t, *J* = 7.5 Hz, 1 H), 2.56 (t, *J* = 7.6 Hz, 2 H), 2.51 (s, 3 H), 2.26–2.21 (m, 2 H), 1.62–1.49 (m, 4 H), 0.98 (t, *J* = 7.4 Hz, 3 H), 0.97 (t, *J* = 7.3 Hz, 3 H); ¹³C NMR (100 MHz, CDCl₃): δ 169.5, 149.4, 137.4, 134.4, 134.1, 132.3, 129.3, 128.4, 118.6, 110.7, 31.2, 30.6, 22.5, 22.3, 16.7, 14.0, 13.9; HRMS (ESI) calcd for C₁₉H₂₃N₂S [M + H]⁺ 311.1582, found 311.1578.

(*E*)-2-(Oct-4-en-4-yl)benzo[*d*]thiazole (3ya): 74% yield; A yellow oil; *R_f* 0.50 (hexane/EtOAc = 10/1); ¹H NMR (400 MHz, CDCl₃, major isomer): δ 7.96 (d, *J* = 8.0 Hz, 1 H), 7.81–7.79 (m, 1 H), 7.46–7.25 (m, 2 H), 6.52 (t, *J* = 7.4 Hz, 1 H), 2.68 (t, *J* = 7.6 Hz, 2 H), 2.31–2.26 (m, 2 H), 1.65–1.47 (m, 4 H), 0.99 (t, *J* = 7.3 Hz, 3 H), 0.98 (t, *J* = 7.4 Hz, 3 H); ¹³C NMR (100 MHz, CDCl₃, major isomer): δ 171.1, 153.9, 137.2, 135.7, 134.3, 125.8, 124.7, 122.8, 121.2, 31.1, 30.8, 22.46, 22.31, 14.02, 13.97; HRMS (ESI) Calcd for C₁₅H₂₀NS [M + H]⁺ 246.1316, found 246.1315.

(*E*)-2-(Dec-5-en-5-yl)-4,5-dimethylthiazole (3ob): 94% yield; A yellow oil; *R_f* 0.64 (hexane/EtOAc = 10/1); ¹H NMR (400 MHz, CDCl₃): δ 6.25 (t, *J* = 7.5 Hz, 1 H), 2.53–2.50 (m, 2 H), 2.31 (s, 3 H), 2.30 (s, 3 H), 2.22–2.17 (m, 2 H), 1.47–1.32 (m, 8 H), 0.91 (t, *J* = 7.2 Hz, 3 H), 0.90 (t, *J* = 7.2 Hz, 3 H); ¹³C NMR (100 MHz, CDCl₃): δ 166.5, 148.1, 134.6, 131.8, 124.5, 31.5, 31.4, 29.2, 28.1, 22.7, 22.5, 14.8, 13.97, 13.96, 11.3;

HRMS (ESI) calcd for $C_{15}H_{26}NS$ $[M + H]^+$ 252.1786, found 252.1792.

3xf **3xf'**

(E)-4-[2-(Hex-2-en-2-yl)-4-methylthiazol-5-yl]benzonitrile (3xf): Obtained as a 2:1 mixture with its minor regioisomer, **(E)-4-[2-(hex-2-en-3-yl)-4-methylthiazol-5-yl]benzonitrile (3xf')**; 71% yield; A yellow solid; m.p. 60–61 °C; *R_f* 0.36 (hexane/EtOAc = 10/1); 1H NMR (400 MHz, $CDCl_3$): δ 7.69 (d, J = 8.4 Hz, 2 H, **3xf** and **3xf'**), 7.54 (d, J = 8.4 Hz, 2 H, **3xf** and **3xf'**), 6.54 (q, J = 7.1 Hz, 1 H, **3xf'**), 6.48 (t, J = 7.4 Hz, 1 H, **3xf**), 2.59–2.55 (m, 2 H, **3xf'**), 2.51 (s, 3 H, **3xf** and **3xf'**), 2.27–2.21 (m, 2 H, **3xf**), 2.13 (s, 3 H, **3xf**), 1.86 (d, J = 7.2 Hz, 3 H, **3xf'**), 1.60–1.49 (m, 2 H, **3xf** and **3xf'**), 0.97 (t, J = 7.3 Hz, 3 H, **3xf** and **3xf'**); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.0, 169.4, 149.38, 149.34, 137.4, 137.3, 135.2, 133.8, 132.3, 129.7, 129.3, 129.25, 129.24, 128.42, 128.39, 128.34, 118.58, 118.56, 110.7, 110.6, 30.8, 30.7, 22.2, 22.0, 16.67, 16.64, 14.7, 14.2, 13.92, 13.85; HRMS (ESI) calcd for $C_{17}H_{19}N_2S$ $[M + H]^+$ 283.1269, found 283.1266.

(E)-4,5-Dimethyl-2-(4-methylpent-2-en-2-yl)thiazole (3og): 68% yield; A colorless oil; *R_f* 0.47 (hexane/EtOAc = 10/1); 1H NMR (400 MHz, $CDCl_3$): δ 6.12 (d, J = 9.3 Hz, 1 H), 2.74–2.65 (m, 1 H), 2.31 (s, 3 H), 2.30 (s, 3 H), 2.08 (s, 3 H), 1.05 (d, J = 6.7 Hz, 6

H); ^{13}C NMR (100 MHz, CDCl_3): δ 167.11, 148.09, 138.59, 127.78, 124.62, 27.81, 22.53, 14.82, 14.72, 11.35; HRMS (ESI) calcd for $\text{C}_{11}\text{H}_{18}\text{NS}$ $[\text{M} + \text{H}]^+$ 196.1160, found 196.1165.

(E)-4-[4-Methyl-2-(1-phenylprop-1-en-2-yl)thiazol-5-yl]benzonitrile (3xi): 42% yield; A yellow solid; m.p. 136–138 °C; R_f 0.11 (hexane/EtOAc = 10/1); ^1H NMR (400 MHz, CDCl_3): δ 7.72–7.70 (m, 2 H), 7.59–7.57 (m, 2 H), 7.50 (s, 1 H), 7.45–7.38 (m, 4 H), 7.32–7.30 (m, 1 H), 2.56 (s, 3 H), 2.42 (s, 3 H); ^{13}C NMR (100 MHz, CDCl_3): δ 169.9, 149.9, 137.2, 136.5, 132.5, 131.2, 130.8, 129.5, 129.4, 128.4, 127.6, 118.6, 111.0, 16.7, 16.5; HRMS (ESI) calcd for $\text{C}_{20}\text{H}_{17}\text{N}_2\text{S}$ $[\text{M} + \text{H}]^+$ 317.1112, found 317.1114.

(E)-4-[2-(1,2-Diphenylvinyl)-4-methylthiazol-5-yl]benzonitrile (3xj): 36% yield; A yellow solid; m.p. 174–175 °C; R_f 0.10 (hexane/EtOAc = 10/1); ^1H NMR (400 MHz, CDCl_3): δ 7.85 (s, 1 H), 7.66–7.64 (m, 2 H), 7.51–7.49 (m, 2 H), 7.46–7.45 (m, 3 H), 7.39–7.37 (m, 2 H), 7.16–7.14 (m, 3 H), 7.08–7.06 (m, 2 H), 2.59 (s, 3 H); ^{13}C NMR (100 MHz, CDCl_3): δ 170.0, 150.5, 138.3, 137.3, 135.5, 134.0, 132.4, 131.3, 130.2, 130.1, 130.0, 129.3, 129.2, 128.7, 128.2, 128.0, 118.5, 111.0, 16.8; HRMS (ESI) calcd for $\text{C}_{25}\text{H}_{19}\text{N}_2\text{S}$ $[\text{M} + \text{H}]^+$ 379.1269, found 379.1272.

5-[4-(Thiazol-5-yl)phenyl]oxazole (4): 74% yield; A white solid; m.p. 152–153 °C; *R_f* 0.18 (hexane/EtOAc = 3/1); ¹H NMR (400 MHz, CDCl₃): δ 8.79 (s, 1 H), 8.14 (s, 1 H), 7.95 (s, 1 H), 7.72–7.69 (m, 2 H), 7.66–7.64 (m, 2 H), 7.41 (s, 1 H); ¹³C NMR (100 MHz, CDCl₃): δ 152.4, 150.9, 150.7, 139.4, 131.3, 127.7, 127.4, 125.0 (2 peaks are overlapped), 122.1; HRMS (ESI) calcd for C₁₂H₉N₂OS [M + H]⁺ 229.0436, found 229.0437.

(E)-2-(Oct-4-en-4-yl)-5-[4-(thiazol-5-yl)phenyl]oxazole (5): 20% yield; A yellow solid; m.p. 183–184 °C; *R_f* 0.20 (hexane/EtOAc = 3/1); ¹H NMR (400 MHz, CDCl₃): δ 8.78 (s, 1 H), 8.13 (s, 1 H), 7.70–7.61 (m, 4 H), 7.37 (s, 1 H), 6.67 (t, *J* = 7.6 Hz, 1 H), 2.56 (t, *J* = 7.6 Hz, 2 H), 2.54–2.25 (m, 2 H), 1.62–1.52 (m, 4 H), 1.01 (t, *J* = 7.2 Hz, 3 H), 0.99 (t, *J* = 7.2 Hz, 3 H); ¹³C NMR (100 MHz, CDCl₃): δ 163.2, 152.2, 149.5, 145.1, 139.2, 135.4, 130.6, 128.22, 128.18, 127.3, 124.6, 123.6, 30.4, 29.4, 22.54, 22.50, 14.1, 14.0; HRMS (ESI) calcd for C₂₀H₂₃N₂OS [M + H]⁺ 339.1531, found 339.1531.

(E)-5-[4-[2-(Oct-4-en-4-yl)thiazol-5-yl]phenyl]oxazole (6): 7% yield; A yellow solid;

m.p. 189–190 °C; *R*_f 0.22 (hexane/EtOAc = 3/1); ¹H NMR (400 MHz, CDCl₃): δ 7.94 (s, 1 H), 7.93 (s, 1 H), 7.70–7.60 (m, 4 H), 7.39 (s, 1 H), 6.43 (t, *J* = 6.8 Hz, 1 H), 2.60 (t, *J* = 7.6 Hz, 2 H), 2.29–2.23 (m, 2 H), 1.59–1.50 (m, 4 H), 0.99 (t, *J* = 7.2 Hz, 3 H), 0.98 (t, *J* = 7.2 Hz, 3 H); ¹³C NMR (100 MHz, CDCl₃): δ 163.28, 163.25, 152.2, 149.5, 141.4, 139.2, 135.4, 130.7, 128.2, 127.3, 124.6, 123.6, 30.5, 29.4, 22.54, 22.50, 14.1, 14.0; HRMS (ESI) calcd for C₂₀H₂₃N₂OS [M + H]⁺ 339.1531, found 339.1537.

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Chapter 3 Cobalt-Catalyzed C2-Alkenylation of Indoles with Alkynes

3.1 Introduction

The indole ring ubiquitously appears in biologically active natural and unnatural products.¹ Consequently, the development of synthetic methods for functionalized indoles has attracted considerable attention from synthetic chemists.² Recently, the transition metal-catalyzed direct C–H bond functionalization³ has emerged as a powerful strategy for the introduction of aryl and alkenyl groups to the indole ring. However, compared with arylation,^{4,5} catalysts that allow alkenylation of indoles at the C2-position are still limited despite the potential utility of such products.^{6,7} In most cases, the disubstituted and trisubstituted olefin products have been achieved by oxidative Heck reaction (Scheme 3.1a)⁸ and hydroarylation of internal alkynes (Scheme 3.1b),⁹ respectively.

Scheme 3.1 Transition metal-catalyzed C2-alkenylation of indole

There remain significant limitations that warrant further catalyst development, particularly for the hydroarylation reaction of alkynes. For example, the nickel catalysis of Nakao, Hiyama et al. requires an electron-withdrawing substituent at the C3-position

of indole (Scheme 3.2a),^{a,b} while the rhodium catalysis of Schipper and Fagnou does not allow the use of dialkylacetylenes (Scheme 3.2b).^c

Scheme 3.2 C2-alkenylation of indoles with alkynes

In this chapter, we report on an efficient C2-alkenylation of indole derivatives bearing an easily removable *N*-pyrimidyl group¹⁰ under room-temperature conditions with a versatile Co-Pyphos catalyst (Scheme 3.2c). The C2-alkenylated indole derivatives serve as useful platforms for further transformations, such as cycloaddition, Friedel–Crafts condensation, and direct C–H functionalization reactions.

3.2 Results and Discussion

With the recent development of cobalt catalysis¹¹ for aromatic and heteroaromatic C–H bond functionalization by our group^{12,13} and others,¹⁴ we started our study with the reaction of *N*-pyrimidylindole **1a** (0.3 mmol) and 4-octyne **2a** (1.5 equiv) in the presence of CoBr₂ (10 mol%), ligand (10–20 mol%), and neopentylmagnesium bromide (60 mol%) in THF at 20 °C for 12 h (Table 3.1). To our dismay, most of the phosphine, *N*-heterocyclic carbene, and nitrogen-based ligands that we employed previously for the cobalt catalysis poorly promoted the reaction (entries 1–6), except the use of tris(3-chlorophenyl)phosphine gave the desired alkenylation product **3aa** in 55% yield. However, the mass balance of the reaction was rather poor (>90% conversion of **1a**) because of formation of unidentified by-products (entry 7). As we reported for the alkenylation of aromatic imines,^f the use of pyridine (80 mol%) as a coligand accelerated the reaction and improved the yield of **3aa** (66% with 2 h reaction), while the mass balance remained unsatisfactory (entry 8). This acceleration effect eventually led us to the finding of a phosphine-pyridine bidentate ligand, 2-(diphenylphosphinoethyl) pyridine (pyphos),¹⁵ which allowed very clean conversion of the starting material within 2 h to afford **3aa** in 97% yield with exclusive (>50:1) *E* stereochemistry (entry 9). The amount of the Grignard reagent had a critical influence on the catalytic activity, as the product yield dropped significantly along with reduction of the amount of *t*BuCH₂MgBr (50 mol%, 20%; 40 mol%, 4%; 30 mol%, 1% for 12 h reaction). 1,3-Bis(diphenylphosphino)propane (dppp), a bidentate phosphine that has a bite angle similar to that of pyphos, was far less effective (entry 10). The reaction on a 5 mmol scale

using 1.2 equiv of 4-octyne **2a** and 5 mol% of the catalyst also afforded **3aa** in an excellent yield of 93% (entry 11).

Table 3.1 Screening of reaction conditions ^a

entry	ligand (mol%)	yield (%) ^b
1	PMePh ₂ (20 mol%)	3
2	PCy ₃ (20 mol%)	8
3	IMes·HCl (10 mol%)	5
4	DPEphos (10 mol%)	4
5	Xantphos (10 mol%)	13
6	1,10-phenanthroline (10 mol%)	1
7	P(3-ClC ₆ H ₄) ₃ (20 mol%)	55, 24 ^c
8	P(3-ClC ₆ H ₄) ₃ (20 mol%) + pyridine (80 mol%)	66 ^c
9	pyphos (10 mol%)	97 ^c , 96 ^d
10	dppp (10 mol%)	2
11 ^e	pyphos (5 mol%)	93 ^d

^a Reaction was carried out on a 0.3 mmol scale. ^b Determined by GC using *n*-tridecane as an internal standard. ^c Yield obtained at reaction time of 2 h. ^d Isolated yield.

^e Performed on a 5 mmol scale using 1.2 equiv of **2a** and 5 mol% of catalyst. Cy= cyclohexyl.

With the effective catalytic system in hand, we next investigated the scope of the alkenylation reaction. First, we explored the addition reaction of **1a** to a variety of alkynes

(Table 3.2). Various alkynes including dialkyl alkynes (entries 1-4), aryl alkyl alkynes (entries 5-10), diphenylacetylene (entries 11), and silyl-substituted alkynes (entries 12-15) were well tolerated in the present reaction, affording the corresponding alkenylation products in good to excellent yields with exclusive *E* stereochemistry. As was the case with 4-octyne, the addition reaction of **1a** to diphenylacetylene was also easily scaled up to 5 mmol scale without any problem (entry 11). High regioselectivity (8:1 to > 50:1) was achieved for unsymmetrical alkynes such as 4-methylpent-2-yne, 2,2-dimethyloct-3-yne, 1-aryl-1-propynes, and silyl-substituted alkynes (entries 3-7 and 12-15), where the C-C bond formation occurred at the less hindered acetylenic carbon atom. However, the sensitivity of the catalyst toward steric effect became clear when the methyl group of 1-phenyl-1-propyne was replaced by an ethyl or a cyclopropyl group (entries 8 and 9). Thus, these alkynes exhibited only moderate regioselectivity (ca. 1.5:1). The regioselectivity was slightly improved to 2.5:1 when a bulky aryl group was introduced (entry 10). It should be noted that the regioselectivity for 1-aryl-2-trimethylsilylacetylene (entries 14 and 15) was opposite to that observed for the rhodium(III)-catalyzed reaction of *N*-carbamoyl indole.^{c,16}

Table 3.2 Addition of indole **1a** to various alkynes^a

entry	R ¹	R ²	3	yield (%) ^b	r.r. ^c
1	<i>n</i> Pr	<i>n</i> Pr	3aa	96 (93)	-
2	CH ₂ SiMe ₃	CH ₂ SiMe ₃	3ab	88	-
3	<i>i</i> Pr	Me	3ac	88	8:1
4	<i>t</i> Bu	<i>n</i> Bu	3ad	57	>50:1
5	Ph	Me	3ae	91	12:1
6	4-MeOC ₆ H ₄	Me	3af	89	19:1
7	4-ClC ₆ H ₄	Me	3ag	40	13:1
8	Ph	Et	3ah	92	1.6:1
9	Ph	<i>o</i> -C ₃ H ₅	3ai	93	1.4:1
10	2,6-Me ₂ C ₆ H ₃	Et	3aj	88	2.5:1
11	Ph	Ph	3ak	96 (92)	-
12	SiMe ₃	Me	3al	81	>50:1
13	SiMe ₃	<i>n</i> Bu	3am	91	>50:1
14	SiMe ₃	Ph	3an	79	>50:1
15	SiMe ₃	4-CNC ₆ H ₄	3ao	62	>50:1 ^d

^a Reaction was performed on a 0.3 mmol scale. ^b Yield of isolated product. In parentheses the yield of isolated product is shown for a 5 mmol scale reaction using 1.2 equiv of the alkyne and 5 mol% of the catalyst. ^c Regioisomeric ratio determined by ¹H NMR spectroscopy. ^d *E/Z* ratio was 4:1.

Next, the reaction of various indole derivatives with 4-octyne **2a** was explored (Scheme 3.3). *N*-pyrimidyl indoles substituted at the 3-7-positions all participated in the reaction smoothly to give the corresponding alkenylated products in good to excellent yields. The reaction tolerated both electron-withdrawing and -donating substituents, such as fluoro (**3ba** and **3ga**), chloro (**3ca** and **3ha**), methoxy (**3da** and **3la**), cyano (**3ea** and **3ia**), tertiary amide (**3fa**), and alkyl (**3ja** and **3ka**) groups. Alkyl substituents at the 3- and 7-positions did not cause any steric inhibition, as demonstrated by formation of the alkenylated products **3ja** and **3ka** in 92% and 81% yields, respectively. *N*-pyrimidyl benzimidazole also underwent the alkenylation reaction with an increased loading of the

Grignard reagent (100 mol%) to afford the product **3ma** in 82% yield.

Scheme 3.3 Addition of various indoles to **2a**. Reaction was performed on a 0.3 mmol scale, and yields of isolated products are shown. ^a NR_2 = morpholino. Reaction time was 40 h. ^bReaction was performed using 100 mol% of $t\text{BuCH}_2\text{MgBr}$.

The pyrimidyl group on the alkenylation product could be easily removed by treatment with NaOEt in dimethylsulfoxide (DMSO) at 100 °C, with the stereochemistry

of the olefin moiety unchanged. Thus, the adducts of 4-octyne and diphenylacetylene **3aa** and **3ak** were successfully converted to their free indole derivatives **4aa** and **4ak** in 87% and 93% yields, respectively (Scheme 3.4a), which served as useful starting materials for further synthetic transformations. First, **4aa** and **4ak** underwent Diels–Alder reaction with *N*-phenylmaleimide in the presence of a catalytic amount of $\text{BF}_3 \cdot \text{OEt}_2$, followed by oxidation using DDQ to afford pyrrolocarbazole derivatives **5aa** and **5ak** in 85% and 81% yields, respectively (Scheme 3.4b). Next, condensation of **4aa** with *p*-anisaldehyde in the presence of TfOH (30 mol%) afforded 1,4-dihydrocyclopenta[*b*]indole derivative **6aa** in 61% yield (Scheme 3.4c). This reaction would have taken place through Friedel–Crafts reaction at the C3-position, followed by Brønsted acid activation of the resulting diarylmethanol, and intramolecular nucleophilic attack of the alkenyl moiety. Finally, oxidative Heck olefination of the C3-position of **4aa** and **4ak** was performed using the method developed by Gaunt and co-workers^a to afford dialkenylated indoles **7aa** and **7ak** in 61% and 70% yields, respectively (Scheme 3.4d).

Scheme 3.4 Transformation of 2-alkenylated indoles. ^a A mixture of stereoisomers with respect to the oct-4-en-4-yl group (ratio = 7:1). ^b A mixture of stereoisomers with respect to the 1,2-diphenylethenyl group (ratio = 2:1). DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, TfOH = trifluoromethanesulfonic acid.

3.3 Conclusion

We have developed a highly efficient Co–pyphos catalyst for the stereoselective C2-alkenylation reaction of *N*-pyrimidylindoles with alkynes under mild conditions. Convenient removal of the pyrimidyl directing group allows a variety of follow-up transformations on NH-free, C2-alkenylated indoles. With such attractive features, the reaction has significantly expanded the scope of indole C2-alkenylation, and may serve as a complementary method to the reported methods, such as the rhodium(III) catalyzed C2-alkenylation of *N*-carbamoyl indole with alkynes.^c The high performance of the pyphos ligand may have relevance to the acceleration effect of pyridine on the cobalt-phosphine-catalyzed *ortho*-alkenylation of aromatic ketimines,^f although mechanistic origin of the acceleration effect is not clear at this stage.

3.4 Experimental Section

Preparation of Starting Materials

A Typical Procedure: 1-(pyrimidin-2-yl)-1*H*-indoles (1a). NaH (60% dispersion in mineral oil, 440 mg, 11.0 mmol) was added in portions at 0 °C to a stirred solution of indole (1.17 g, 10.0 mmol) in DMF (25 mL). After stirring for 30 min at 0 °C, 2-chloropyrimidine (1.37 g, 12.0 mmol) was added and the mixture was stirred at 130 °C for 24 h. Then, the reaction mixture was cooled to ambient temperature, poured into H₂O (300 mL) and extracted with EtOAc (4 × 75 mL). The combined organic phase was dried over Na₂SO₄. After filtration and evaporation of the solvents under reduced pressure, the crude product was purified by column chromatography on silica gel (eluent: hexane/EtOAc = 10/1) to yield the product (1.76 g, 90%) as a white solid.

M.p. 87-88 °C (lit. 85-86 °C); *R*_f 0.41 (hexane/EtOAc = 5/1); ¹H NMR (400 MHz, CDCl₃): δ 8.81 (dd, *J* = 8.4, 0.8 Hz, 1 H), 8.70 (d, *J* = 4.8 Hz, 2 H), 8.27 (d, *J* = 3.7 Hz, 1 H), 7.62 (d, *J* = 7.7 Hz, 1 H), 7.34 (td, *J* = 8.0, 1.2 Hz, 1 H), 7.26-7.22 (m, 1 H), 7.04 (t, *J* = 4.8 Hz, 1 H), 6.70 (d, *J* = 3.7 Hz, 1 H); ¹³C NMR (100 MHz, CDCl₃): δ 158.1, 157.8, 135.4, 131.3, 125.8, 123.6, 122.1, 120.8, 116.2, 116.1, 106.9; HRMS (ESI) Calcd for C₁₂H₁₀N₃ [M + H]⁺ 196.0875, found 196.0870. The ¹H and ¹³C NMR spectra showed good agreement with the literature data.

5-Fluoro-1-(pyrimidin-2-yl)-1H-indole (1b): 95% yield; A white solid; m.p. 121-122 °C; *R_f* 0.41 (hexane/EtOAc = 5/1); ¹H NMR (400 MHz, CDCl₃): δ 8.77-8.73 (dd, *J* = 9.2, 4.8 Hz, 1 H), 8.66 (d, *J* = 4.8 Hz, 2 H), 8.30 (d, *J* = 3.6 Hz, 1 H), 7.25 (dd, *J* = 9.0, 2.2 Hz, 1 H), 7.08-7.01 (m, 2 H), 6.64 (d, *J* = 3.6 Hz, 1 H); ¹³C NMR (100 MHz, CDCl₃): δ 158.8 (d, ¹*J* = 264 Hz), 158.1, 157.8, 132.0 (d, ³*J* = 10.0 Hz), 131.8, 127.3, 117.2 (d, ³*J* = 8.8 Hz), 116.3, 111.3 (d, ²*J* = 24.7 Hz), 106.5 (d, ⁴*J* = 3.9 Hz), 106.0 (d, ²*J* = 23.2 Hz); HRMS (ESI) Calcd for C₁₂H₉N₃F [M + H]⁺ 214.0781, found 214.0777.

5-Chloro-1-(pyrimidin-2-yl)-1H-indole (1c): 87% yield; A white solid; m.p. 124-125 °C; *R_f* 0.32 (hexane/EtOAc = 5/1); ¹H NMR (400 MHz, CDCl₃): δ 8.71 (d, *J* = 8.9 Hz, 1 H), 8.65 (d, *J* = 4.8 Hz, 2 H), 8.27 (d, *J* = 3.6 Hz, 1 H), 7.56 (d, *J* = 1.8 Hz, 1 H), 7.26 (d, *J* = 8.9 Hz, 1 H), 7.02 (t, *J* = 4.8 Hz, 1 H), 6.61 (d, *J* = 3.5 Hz, 1 H); ¹³C NMR (100 MHz, CDCl₃): δ 158.1, 157.4, 133.6, 132.4, 127.6, 127.0, 123.7, 120.2, 117.3, 116.4, 106.1; HRMS (ESI) Calcd for C₁₂H₉N₃Cl [M + H]⁺ 230.0485, found 230.0484.

5-Methoxy-1-(pyrimidin-2-yl)-1H-indole (1d): 69% yield; A white solid; m.p. 114-115 °C; *R_f* 0.38 (hexane/EtOAc = 5/1); ¹H NMR (400 MHz, CDCl₃): δ 8.70 (d, *J* = 9.1 Hz, 1 H), 8.66 (d, *J* = 4.8 Hz, 2 H), 8.25 (d, *J* = 3.6 Hz, 1 H), 7.10 (d, *J* = 2.4 Hz, 1 H), 7.01-6.96 (m, 2 H), 6.64 (d, *J* = 3.6 Hz, 1 H), 3.89 (s, 3 H); ¹³C NMR (100 MHz, CDCl₃): δ 158.0, 157.6, 155.5, 132.1, 130.3, 126.3, 117.0, 115.9, 112.6, 106.7, 103.1, 55.7; HRMS (ESI) Calcd for C₁₃H₁₂N₃O [M + H]⁺ 226.0980, found 226.0983. The ¹H and ¹³C NMR spectra showed good agreement with the literature data.

1-(Pyrimidin-2-yl)-1H-indole-5-carbonitrile (1e): 62% yield; A white solid; m.p. 213-214 °C; *R_f* 0.24 (hexane/EtOAc = 5/1); ¹H NMR (400 MHz, CDCl₃): δ 8.90 (d, *J* = 8.7 Hz, 1 H), 8.74 (d, *J* = 4.8 Hz, 2 H), 8.39 (d, *J* = 3.7 Hz, 1 H), 7.94 (d, *J* = 1.2 Hz, 1 H), 7.56 (d, *J* = 8.7 Hz, 1 H), 7.15 (t, *J* = 4.8 Hz, 1 H), 6.74 (d, *J* = 3.7 Hz, 1 H); ¹³C NMR (100 MHz, CDCl₃): δ 158.3, 157.2, 137.0, 131.1, 128.0, 126.6, 125.7, 120.2, 117.2, 117.1, 106.6, 105.2; HRMS (ESI) Calcd for C₁₃H₉N₄ [M + H]⁺ 221.0827, found 221.0831.

Morpholino(1-(pyrimidin-2-yl)-1H-indol-5-yl)methanone (1f): 81% yield; A white solid; m.p. 152-153 °C; *R_f* 0.15 (hexane/EtOAc = 1/1); ¹H NMR (400 MHz, CDCl₃): δ

8.84 (d, $J = 8.6$ Hz, 1 H), 8.72 (d, $J = 4.8$ Hz, 2 H), 8.34 (d, $J = 3.7$ Hz, 1 H), 7.71 (d, $J = 1.2$ Hz, 1 H), 7.39 (d, $J = 8.6$ Hz, 1 H), 7.10 (t, $J = 5.0$ Hz, 1 H), 6.73 (d, $J = 3.6$ Hz, 1 H), 3.72 (brs, 8 H); ^{13}C NMR (100 MHz, CDCl_3): δ 171.3, 158.2, 157.5, 135.9, 131.0, 128.9, 127.0, 122.7, 120.2, 116.6, 116.2, 107.0, 67.0; HRMS (ESI) Calcd for $\text{C}_{17}\text{H}_{17}\text{N}_4\text{O}_2$ [$\text{M} + \text{H}$] $^+$ 309.1352, found 309.1357.

6-Fluoro-1-(pyrimidin-2-yl)-1H-indole (1g): 82% yield; A white solid; m.p. 133-134 °C; R_f 0.26 (hexane/EtOAc = 10/1); ^1H NMR (400 MHz, CDCl_3): δ 8.69 (d, $J = 4.8$ Hz, 2 H), 8.58 (dd, $J = 11.0, 2.2$ Hz, 1 H), 8.25 (d, $J = 3.7$ Hz, 1 H), 7.52 (dd, $J = 8.4, 5.6$ Hz, 1 H), 7.05 (t, $J = 8.8$ Hz, 1 H), 7.01 (td, $J = 9.0, 2.4$ Hz, 1 H), 6.67 (d, $J = 3.6$ Hz, 1 H); ^{13}C NMR (100 MHz, CDCl_3): δ 160.5 (d, $^1J = 236$ Hz), 158.1, 157.5, 135.3 (d, $^3J = 13.2$ Hz), 127.5, 126.1 (d, $^4J = 3.8$ Hz), 121.1 (d, $^3J = 10.0$ Hz), 116.3, 110.3 (d, $^2J = 24.4$ Hz), 106.6, 103.5 (d, $^2J = 29.0$ Hz); HRMS (ESI) Calcd for $\text{C}_{12}\text{H}_9\text{N}_3\text{F}$ [$\text{M} + \text{H}$] $^+$ 214.0781, found 214.0776.

6-Chloro-1-(pyrimidin-2-yl)-1H-indole (1h): 96% yield; A white solid; m.p. 127-128 °C; R_f 0.49 (hexane/EtOAc = 5/1); ^1H NMR (400 MHz, CDCl_3): δ 8.87 (s, 1 H), 8.70 (d, $J = 4.8$ Hz, 2 H), 8.26 (d, $J = 3.7$ Hz, 1 H), 7.51 (d, $J = 8.4$ Hz, 1 H), 7.21 (dd, $J =$

8.4, 2.0 Hz, 1 H), 7.07 (t, $J = 4.8$ Hz, 1 H), 6.66 (dd, $J = 3.7, 0.8$ Hz, 1 H); ^{13}C NMR (100 MHz, CDCl_3): δ 158.2, 157.4, 135.6, 129.7, 129.4, 126.4, 122.6, 121.4, 116.48, 116.43, 106.6; HRMS (ESI) Calcd for $\text{C}_{12}\text{H}_9\text{N}_3\text{Cl}$ $[\text{M} + \text{H}]^+$ 230.0485, found 230.0486.

1-(Pyrimidin-2-yl)-1H-indole-4-carbonitrile (1i): 54% yield; A white solid; m.p. 159-160 °C; R_f 0.25 (hexane/EtOAc = 5/1); ^1H NMR (400 MHz, CDCl_3): δ 9.03 (d, $J = 8.5$ Hz, 1 H), 8.72 (d, $J = 4.8$ Hz, 2 H), 8.42 (d, $J = 3.7$ Hz, 1 H), 7.54 (dd, $J = 7.5, 0.6$ Hz, 1 H), 7.35 (t, $J = 8.0$ Hz, 1 H), 7.13 (t, $J = 4.8$ Hz, 1 H), 6.89 (d, $J = 3.6$ Hz, 1 H); ^{13}C NMR (100 MHz, CDCl_3): δ 158.2, 157.2, 135.0, 132.8, 128.4, 126.7, 123.3, 121.0, 118.3, 117.1, 104.9, 103.3; HRMS (ESI) Calcd for $\text{C}_{13}\text{H}_9\text{N}_4$ $[\text{M} + \text{H}]^+$ 221.0827, found 221.0822.

3-Methyl-1-(pyrimidin-2-yl)-1H-indole (1j): 76% yield; A white solid; m.p. 80-81 °C; R_f 0.33 (hexane/EtOAc = 10/1); ^1H NMR (400 MHz, CDCl_3): δ 8.77 (dd, $J = 8.3, 0.6$ Hz, 1 H), 8.65 (d, $J = 4.8$ Hz, 2 H), 8.03 (s, 1 H), 7.55 (d, $J = 7.7$ Hz, 1 H), 7.34 (dd, $J = 8.2, 7.4$ Hz, 1 H), 7.24 (t, $J = 7.6$ Hz, 1 H), 6.96 (t, $J = 4.8$ Hz, 1 H), 2.35 (s, 3 H); ^{13}C NMR (100 MHz, CDCl_3): δ 158.0, 157.7, 135.6, 132.1, 123.7, 122.9, 121.7, 118.8, 116.2, 116.1,

115.5, 9.8; HRMS (ESI) Calcd for $C_{13}H_{12}N_3$ $[M + H]^+$ 210.1031, found 210.1034.

The 1H and ^{13}C NMR spectra showed good agreement with the literature data.

7-Ethyl-1-(pyrimidin-2-yl)-1H-indole (1k): 73% yield; A colorless oil; R_f 0.34 (hexane/EtOAc = 5/1); 1H NMR (400 MHz, $CDCl_3$): δ 8.75 (d, $J = 4.8$ Hz, 2 H), 7.77 (d, $J = 3.6$ Hz, 1 H), 7.49 (dd, $J = 6.8, 2.4$ Hz, 1 H), 7.22-7.18 (m, 2 H), 7.14 (t, $J = 4.8$ Hz, 1 H), 6.71 (d, $J = 3.6$ Hz, 1 H), 2.88 (q, $J = 7.5$ Hz, 2 H), 1.04 (t, $J = 7.5$ Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.3, 158.2, 133.8, 132.0, 130.4, 130.0, 124.6, 122.4, 118.8, 117.3, 107.0, 27.7, 13.8; HRMS (ESI) Calcd for $C_{14}H_{14}N_3$ $[M + H]^+$ 224.1188, found 224.1186. The 1H and ^{13}C NMR spectra showed good agreement with the literature data.

7-Methoxy-1-(pyrimidin-2-yl)-1H-indole (1l): 62% yield; A colorless oil; R_f 0.11 (hexane/EtOAc = 5/1); 1H NMR (400 MHz, $CDCl_3$): δ 8.75 (d, $J = 4.8$ Hz, 2 H), 7.69 (d, $J = 3.4$ Hz, 1 H), 7.26 (dd, $J = 7.6, 0.8$ Hz, 1 H), 7.18-7.14 (m, 2 H), 6.82 (d, $J = 7.8$ Hz, 1 H), 6.68 (d, $J = 3.4$ Hz, 1 H), 3.84 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.0, 157.9, 148.0, 133.1, 129.5, 125.1, 122.6, 117.5, 113.8, 106.4, 106.2, 55.8; HRMS (ESI) Calcd for $C_{13}H_{12}N_3O$ $[M + H]^+$ 226.0980, found 226.0978.

1-(Pyrimidin-2-yl)-1H-benzo[d]imidazole (1m): 73% yield; A white solid; m.p. 149-150 °C; *R_f* 0.22 (hexane/EtOAc = 1/1); ¹H NMR (400 MHz, CDCl₃): δ 9.07 (s, 1 H), 8.73 (d, *J* = 4.8 Hz, 2 H), 8.58 (d, *J* = 7.5 Hz, 1 H), 7.83 (dd, *J* = 7.4, 1.2 Hz, 1 H), 7.43-7.34 (m, 2 H), 7.17 (t, *J* = 5.0 Hz, 1 H); ¹³C NMR (100 MHz, CDCl₃): δ 158.5, 156.3, 145.0, 141.8, 131.8, 124.6, 123.7, 120.3, 118.0, 115.6; HRMS (ESI) Calcd for C₁₁H₉N₄ [M + H]⁺ 197.0827, found 197.0823. The ¹H and ¹³C spectra showed good agreement with the literature data.¹⁷

Cobalt-Catalyzed Addition of *N*-Pyrimidylindoles to Alkynes

A Typical Procedure: (*E*)-2-(Oct-4-en-4-yl)-1-(pyrimidin-2-yl)-1H-indole (3aa). In a Schlenk tube were placed 1-(pyrimidin-2-yl)-1H-indole (58.6 mg, 0.30 mmol), CoBr₂ (6.6 mg, 0.030 mmol), 2-[2-(diphenylphosphino)ethyl]pyridine (8.7 mg, 0.030 mmol), which were then dissolved in THF (1.3 mL). To the solution was added neopentylmagnesium bromide (0.67 M in THF, 0.27 mL, 0.18 mmol) at 0 °C. After stirring for 30 min at this temperature, 4-octyne (66 μL, 0.45 mmol) was added. The reaction mixture was stirred at 20 °C for 12 h, and then quenched with saturated aqueous solution of NH₄Cl (1.5 mL). The resulting mixture was extracted with ethyl acetate (15 mL × 3), and the combined organic layer was dried over Na₂SO₄ and concentrated under reduced pressure. Purification of the crude product by silica gel chromatography (eluent: hexane/EtOAc = 25/1) afforded the title compound as a colorless oil (88.0 mg, 96%). The

5 mmol-scale reaction was performed according to a similar procedure using a 50 mL 2-necked flask to afford the same product in 93% yield.

R_f 0.50 (hexane/EtOAc = 5/1); ^1H NMR (400 MHz, CDCl_3): δ 8.72 (d, J = 4.8 Hz, 2 H), 8.12 (dd, J = 8.0, 0.8 Hz, 1 H), 7.55 (dd, J = 6.8, 1.2 Hz, 1 H), 7.24-7.15 (m, 2 H), 7.07 (t, J = 4.8 Hz, 1 H), 6.54 (s, 1 H), 5.59 (t, J = 7.4 Hz, 1 H), 2.16-2.10 (m, 4 H), 1.42-1.32 (m, 4 H), 0.92 (t, J = 7.3 Hz, 3 H), 0.81 (t, J = 7.4 Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3): δ 158.3, 158.1, 143.4, 137.3, 133.9, 131.0, 129.2, 122.8, 121.7, 120.1, 117.2, 112.9, 106.9, 33.0, 30.2, 22.7, 21.8, 14.0, 13.7; HRMS (ESI) Calcd for $\text{C}_{20}\text{H}_{24}\text{N}_3$ $[\text{M} + \text{H}]^+$ 306.1970, found 306.1971. The *E*-stereochemistry was assumed from the *E*-stereochemistry of **3ka** and **3ma**, which was supported by NOESY measurements (see below). NOESY measurement of **3aa** itself did not allow determination of its stereochemistry because the signals of the allylic protons were overlapped.

(Z)-2-(1,4-Bis(trimethylsilyl)but-2-en-2-yl)-1-(pyrimidin-2-yl)-1H-indole (3ab): 88% yield; A colorless oil; R_f 0.42 (hexane/EtOAc = 10/1); ^1H NMR (400 MHz, CDCl_3): δ 8.80 (d, J = 4.8 Hz, 2 H), 8.17 (dd, J = 7.6, 1.2 Hz, 1 H), 7.60 (dd, J = 6.4, 1.6 Hz, 1 H), 7.29-7.21 (m, 2 H), 7.15 (t, J = 4.8 Hz, 1 H), 6.57 (s, 1 H), 5.75 (t, J = 8.6 Hz, 1 H), 1.58

(d, $J = 8.6$ Hz, 2 H), 1.54 (s, 2 H), 0.14 (s, 9 H), 0.10 (s, 9 H); ^{13}C NMR (100 MHz, CDCl_3): δ 158.4, 158.1, 145.2, 137.5, 129.2, 128.7, 124.0, 122.7, 121.7, 120.0, 117.2, 112.8, 106.6, 21.7, 19.8, -1.1, -1.5; HRMS (ESI) Calcd for $\text{C}_{22}\text{H}_{32}\text{N}_3\text{Si}_2$ $[\text{M} + \text{H}]^+$ 394.2135, found 394.2135.

(*E*)-2-(4-Methylpent-2-en-2-yl)-1-(pyrimidin-2-yl)-1*H*-indole (3ac): Obtained as a 8:1 mixture with its regioisomer (*E*)-2-(4-methylpent-2-en-3-yl)-1-(pyrimidin-2-yl)-1*H*-indole; 88% yield; A colorless oil; R_f 0.23 (hexane/EtOAc = 10/1); ^1H NMR (400 MHz, CDCl_3): 8.73 (d, $J = 4.8$ Hz, 2 H), 8.08 (dd, $J = 8.0, 0.8$ Hz, 1 H), 7.55 (dd, $J = 6.4, 1.2$ Hz, 1 H), 7.23-7.15 (m, 2 H), 7.07 (t, $J = 4.8$ Hz, 1 H), 6.57 (s, 1 H), 5.31 (d, $J = 9.3$ Hz, 1 H), 2.66-2.57 (m, 1 H), 1.86 (s, 3 H), 0.93 (d, $J = 6.6$ Hz, 6 H); ^{13}C NMR (100 MHz, CDCl_3): δ 158.4, 158.1, 144.2, 138.1, 137.4, 129.2, 126.1, 122.9, 121.8, 120.2, 117.2, 112.7, 106.0, 27.5, 22.4, 16.9; HRMS (ESI) Calcd for $\text{C}_{18}\text{H}_{20}\text{N}_3$ $[\text{M} + \text{H}]^+$ 278.1657, found 278.1662.

(*E*)-2-(2,2-Dimethyloct-3-en-4-yl)-1-(pyrimidin-2-yl)-1*H*-indole (3ad): 57% yield; A colorless oil; R_f 0.46 (hexane/EtOAc = 10/1); ^1H NMR (400 MHz, CDCl_3): δ 8.75 (d, $J = 4.8$ Hz, 2 H), 8.09 (d, $J = 8.0$ Hz, 1 H), 7.55 (dd, $J = 7.1, 1.8$ Hz, 1 H), 7.24-7.16 (m, 2 H),

7.11 (t, $J = 4.8$ Hz, 1 H), 6.52 (s, 1 H), 5.47 (s, 1 H), 2.31 (t, $J = 7.9$ Hz, 2 H), 1.41-1.33 (m, 2 H), 1.29-1.20 (m, 2 H), 1.11 (s, 9 H), 0.81 (t, $J = 7.3$ Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3): δ 158.4, 158.0, 144.2, 140.9, 137.1, 133.5, 129.2, 122.8, 121.7, 120.1, 117.2, 112.9, 106.4, 32.8, 31.5, 31.1, 31.0, 23.1, 13.9; HRMS (ESI) Calcd for $\text{C}_{22}\text{H}_{28}\text{N}_3$ [$\text{M} + \text{H}$] $^+$ 334.2283, found 334.2284.

(E)-2-(1-Phenylprop-1-en-2-yl)-1-(pyrimidin-2-yl)-1H-indole (3ae): Obtained as a 12:1 mixture with its regioisomer (*E*)-2-(1-phenylprop-1-enyl)-1-(pyrimidin-2-yl)-1H-indole; 91% yield; A yellow oil; R_f 0.22 (hexane/EtOAc = 10/1); ^1H NMR (400 MHz, CDCl_3): δ 8.72 (d, $J = 4.8$ Hz, 2 H), 8.22 (d, $J = 8.4$ Hz, 1 H), 7.59 (dd, $J = 7.2$, 1.0 Hz, 1 H), 7.34-7.33 (m, 4 H), 7.28-7.18 (m, 3 H), 7.07-7.03 (m, 1 H), 6.73 (s, 1 H), 6.66 (s, 1 H), 2.10 (d, $J = 1.3$ Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3): δ 158.4, 158.3, 144.6, 137.92, 137.87, 131.4, 129.3, 129.2, 129.1, 128.3, 126.7, 123.6, 122.2, 120.6, 117.4, 113.3, 107.3, 19.3; HRMS (ESI) Calcd for $\text{C}_{21}\text{H}_{18}\text{N}_3$ [$\text{M} + \text{H}$] $^+$ 312.1501, found 312.1506.

(E)-2-(1-(4-Methoxyphenyl)prop-1-en-2-yl)-1-(pyrimidin-2-yl)-1H-indole (3af): Obtained as a 19:1 mixture with its regioisomer (*E*)-2-(1-(4-methoxyphenyl)prop-1-enyl)-1-(pyrimidin-2-yl)-1H-indole; 89% yield; A

yellow oil; R_f 0.08 (hexane/EtOAc = 10/1); ^1H NMR (400 MHz, CDCl_3): δ 8.73 (d, J = 4.8 Hz, 2 H), 8.20 (d, J = 8.4 Hz, 1 H), 7.59 (d, J = 8.0 Hz, 1 H), 7.30-7.18 (m, 4 H), 7.06 (t, J = 4.8 Hz, 1 H), 6.89-6.87 (m, 2 H), 6.71 (s, 1 H), 6.62 (s, 1 H), 3.79 (s, 3 H), 2.07 (s, 3 H); ^{13}C NMR (100 MHz, CDCl_3): δ 158.3, 158.2, 158.1, 144.7, 137.7, 130.5, 130.2, 129.4, 129.2, 128.6, 123.3, 122.0, 120.3, 117.2, 113.6, 113.1, 106.9, 55.2, 19.1; HRMS (ESI) Calcd for $\text{C}_{22}\text{H}_{20}\text{N}_3\text{O}$ $[\text{M} + \text{H}]^+$ 342.1606, found 342.1611.

(E)-2-(1-(4-Chlorophenyl)prop-1-en-2-yl)-1-(pyrimidin-2-yl)-1H-indole (3ag):

Obtained as a 13:1 mixture with its regioisomer (E)-2-(1-(4-chlorophenyl)prop-1-enyl)-1-(pyrimidin-2-yl)-1H-indole; 40% yield; A yellow oil; R_f 0.22 (hexane/EtOAc = 10/1); ^1H NMR (400 MHz, CDCl_3): 8.71 (d, J = 4.8 Hz, 2 H), 8.16 (d, J = 7.8 Hz, 1 H), 7.53 (d, J = 7.3 Hz, 1 H), 7.24-7.15 (m, 6 H), 7.07 (t, J = 4.8 Hz, 1 H), 6.66 (s, 1 H), 6.54 (s, 1 H), 2.00 (s, 3 H); ^{13}C NMR (100 MHz, CDCl_3): 158.3, 158.2, 144.1, 137.8, 136.3, 132.2, 132.1, 130.3, 129.2, 128.3, 127.8, 123.6, 122.2, 120.5, 117.3, 113.3, 107.5, 19.2; HRMS (ESI) Calcd for $\text{C}_{21}\text{H}_{17}\text{N}_3\text{Cl}$ $[\text{M} + \text{H}]^+$ 346.1111, found 346.1107.

(E)-2-(1-Phenylbut-1-en-2-yl)-1-(pyrimidin-2-yl)-1H-indole (3ah): 57% yield; A

colorless oil; R_f 0.27 (hexane/EtOAc = 10/1); ^1H NMR (400 MHz, CDCl_3): δ 8.73 (d, J = 4.8 Hz, 2 H), 8.22 (d, J = 8.3 Hz, 1 H), 7.60 (d, J = 8.2 Hz, 1 H), 7.34-7.29 (m, 4 H), 7.27-7.21 (m, 3 H), 7.06 (t, J = 4.8 Hz, 1 H), 6.72 (s, 1 H), 6.57 (s, 1 H), 2.49 (q, J = 7.4 Hz, 2 H), 1.04 (t, J = 7.5 Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3): δ 158.3, 158.1, 142.6, 138.0, 137.7, 137.6, 129.2, 128.9, 128.7, 128.2, 126.5, 123.3, 122.0, 120.4, 117.3, 113.3, 107.8, 24.8, 13.2; HRMS (ESI) Calcd for $\text{C}_{22}\text{H}_{20}\text{N}_3$ $[\text{M} + \text{H}]^+$ 326.1657, found 326.1656.

(E)-2-(1-Phenylbut-1-enyl)-1-(pyrimidin-2-yl)-1H-indole (3ah'): 35% yield; A colorless oil; R_f 0.25 (hexane/EtOAc = 10/1); ^1H NMR (400 MHz, CDCl_3): δ 8.55 (d, J = 4.8 Hz, 2 H), 8.03 (dd, J = 8.4, 0.8 Hz, 1 H), 7.63-7.61 (m, 1 H), 7.24-7.19 (m, 2 H), 7.12-7.07 (m, 4 H), 7.05-7.02 (m, 1 H), 6.90 (t, J = 4.8 Hz, 1 H), 6.77 (s, 1 H), 6.14 (t, J = 7.4 Hz, 1 H), 2.38-2.31 (m, 2 H), 1.06 (t, J = 7.4 Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3): δ 157.8, 157.5, 142.6, 138.6, 137.3, 134.0, 133.8, 129.7, 128.9, 127.3, 126.6, 123.3, 121.8, 120.3, 116.9, 112.8, 108.8, 22.7, 14.5; HRMS (ESI) Calcd for $\text{C}_{22}\text{H}_{20}\text{N}_3$ $[\text{M} + \text{H}]^+$ 326.1657, found 326.1653.

3ai

3ai'

(E)-2-(1-Cyclopropyl-2-phenylvinyl)-1-(pyrimidin-2-yl)-1H-indole (3ai): Obtained as

a 1.4:1 mixture with its regioisomer

(*E*)-2-(2-cyclopropyl-1-phenylvinyl)-1-(pyrimidin-2-yl)-1*H*-indole (**3ai'**); 93% yield; A colorless oil; *R_f* 0.16 (hexane/EtOAc = 10/1); ¹H NMR (400 MHz, CDCl₃): 8.61 (d, *J* = 4.8 Hz, 2 H, **3ai**), 8.39 (d, *J* = 4.8 Hz, 2 H, **3ai'**), 8.17 (d, *J* = 8.0 Hz, 1 H, **3ai**), 7.90 (d, *J* = 8.0 Hz, 1 H, **3ai'**), 7.58-7.56 (m, 2 H, **3ai**), 7.51-7.47 (m, 2 H, **3ai'**), 7.26 (t, *J* = 7.5 Hz, 2 H, **3ai**), 7.19-7.17 (m, 1 H, **3ai**), 7.16-7.09 (m, 3 H, **3ai** and **3ai'**), 6.98 (t, *J* = 7.2 Hz, 2 H, **3ai'**), 6.93 (t, *J* = 4.8 Hz, 1 H, **3ai**), 6.91-6.89 (m, 1 H, **3ai'**), 6.76 (s, 1 H, **3ai**), 6.71 (t, *J* = 4.8 Hz, 1 H, **3ai'**), 6.65 (s, 1 H, **3ai'**), 6.50 (s, 1 H, **3ai**), 5.46 (d, *J* = 10.2 Hz, 1 H, **3ai'**), 1.71-1.62 (m, 1 H, **3ai** and **3ai'**), 0.73-0.70 (m, 2 H, **3ai'**), 0.50-0.45 (m, 2 H, **3ai** and **3ai'**), 0.31-0.27 (m, 2 H, **3ai**); ¹³C NMR (100 MHz, CDCl₃): δ 158.1, 157.9, 157.7, 157.4, 142.3, 141.8, 138.8, 137.7, 137.3, 136.94, 136.88, 136.1, 132.7, 130.7, 129.7, 129.4, 128.9, 128.8, 128.0, 127.3, 126.6, 126.4, 123.3, 123.1, 121.9, 121.7, 120.22, 120.19, 117.0, 116.8, 113.5, 112.7, 108.4, 108.1, 14.8, 12.0, 8.4, 8.3; HRMS (ESI) Calcd for C₂₃H₂₀N₃ [M + H]⁺ 338.1657, found 338.1658.

(*E*)-2-(1-(2,6-dimethylphenyl)but-1-en-2-yl)-1-(pyrimidin-2-yl)-1*H*-indole (**3aj**): 63% yield; A colorless oil; *R_f* 0.30 (hexane/EtOAc = 10/1); ¹H NMR (400 MHz, CDCl₃): 8.74 (d, *J* = 4.8 Hz, 2 H), 8.31 (d, *J* = 8.3 Hz, 1 H), 7.62-7.60 (m, 1 H), 7.29-7.20 (m, 2 H), 7.11-7.07 (m, 4 H), 6.76 (s, 1 H), 6.60 (s, 1 H), 2.35 (s, 6 H), 1.94 (q, *J* = 7.5 Hz, 2 H),

0.71 (t, $J = 7.6$ Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3): 158.24, 158.15, 142.0, 138.8, 137.5, 136.7, 136.5, 129.3, 127.6, 127.1, 126.6, 123.3, 122.1, 120.3, 117.2, 113.6, 108.5, 24.7, 20.2, 12.4; HRMS (ESI) Calcd for $\text{C}_{24}\text{H}_{24}\text{N}_3$ $[\text{M} + \text{H}]^+$ 354.1970, found 354.1973.

(*E*)-2-(1-(2,6-dimethylphenyl)but-1-enyl)-1-(pyrimidin-2-yl)-1*H*-indole (3aj'): 25% yield; A colorless oil; R_f 0.26 (hexane/EtOAc = 10/1); ^1H NMR (400 MHz, CDCl_3): 8.83 (d, $J = 4.8$ Hz, 2 H), 7.74 (d, $J = 7.6$ Hz, 1 H), 7.44 (d, $J = 7.4$ Hz, 1 H), 7.24-7.11 (m, 4 H), 7.09-7.06 (m, 2 H), 6.15 (s, 1 H), 5.21 (t, $J = 7.4$ Hz, 1 H), 2.29 (s, 6 H), 1.76-1.69 (m, 2 H), 0.72 (t, $J = 7.5$ Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3): 159.3, 158.5, 140.4, 139.3, 137.9, 137.3, 134.0, 129.6, 129.0, 127.2, 127.0, 123.2, 121.6, 120.5, 118.2, 111.5, 107.5, 22.7, 20.1, 13.3; HRMS (ESI) Calcd for $\text{C}_{24}\text{H}_{24}\text{N}_3$ $[\text{M} + \text{H}]^+$ 354.1970, found 354.1971.

(*E*)-2-(1,2-Diphenylvinyl)-1-(pyrimidin-2-yl)-1*H*-indole (3ak): 96% yield; A yellow solid; m.p. 152-153 °C; R_f 0.24 (hexane/EtOAc = 5/1); ^1H NMR (400 MHz, CDCl_3): δ 8.50 (d, $J = 4.8$ Hz, 2 H), 8.04 (dd, $J = 8.2, 1.0$ Hz, 1 H), 7.63 (dd, $J = 6.8, 1.2$ Hz, 1 H), 7.26-7.21 (m, 2 H), 7.13-7.10 (m, 7 H), 7.04-6.99 (m, 4 H), 6.86-6.83 (m, 2 H); ^{13}C NMR (100 MHz, CDCl_3): δ 157.9, 157.5, 142.7, 138.4, 137.8, 137.0, 135.3, 130.3, 129.6, 128.77, 128.76, 127.9, 127.6, 127.1, 126.8, 123.7, 121.9, 120.6, 117.0, 112.8, 110.0;

HRMS (ESI) Calcd for $C_{26}H_{20}N_3$ $[M + H]^+$ 374.1657, found 374.1653.

(E)-1-(Pyrimidin-2-yl)-2-(1-(trimethylsilyl)prop-1-en-2-yl)-1H-indole (3al): 81% yield;

A yellow oil; R_f 0.43 (hexane/EtOAc = 10/1); 1H NMR (400 MHz, $CDCl_3$): δ 8.74 (d, J = 4.8 Hz, 2 H), 8.10 (d, J = 7.6 Hz, 1 H), 7.55 (dd, J = 7.4, 0.8 Hz, 1 H), 7.24-7.15 (m, 2 H), 7.11 (t, J = 4.8 Hz, 1 H), 6.63 (s, 1 H), 5.54 (s, 1 H), 2.02 (s, 3 H), 0.11 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.4, 158.1, 145.3, 145.1, 137.7, 129.8, 129.1, 123.4, 122.0, 120.6, 117.3, 112.9, 106.6, 21.9, -0.3; HRMS (ESI) Calcd for $C_{18}H_{22}N_3Si$ $[M + H]^+$ 308.1583, found 308.1583.

(E)-1-(Pyrimidin-2-yl)-2-(1-(trimethylsilyl)hex-1-en-2-yl)-1H-indole (3am): 91% yield;

A colorless oil; R_f 0.34 (hexane/EtOAc = 10/1); 1H NMR (400 MHz, $CDCl_3$): δ 8.74 (d, J = 4.8 Hz, 2 H), 8.12 (d, J = 8.2 Hz, 1 H), 7.57 (d, J = 7.9 Hz, 1 H), 7.24-7.19 (m, 2 H), 7.11 (t, J = 4.8 Hz, 1 H), 6.62 (s, 1 H), 5.50 (s, 1 H), 2.31 (t, J = 8.0 Hz, 2 H), 1.42-1.36 (m, 2 H), 1.29-1.23 (m, 2 H), 0.81 (t, J = 7.3 Hz, 3 H), 0.12 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.3, 158.0, 151.0, 143.9, 137.5, 129.8, 129.1, 123.2, 121.9, 120.4, 117.3, 112.9, 106.9, 36.1, 31.7, 22.9, 13.9, 0.1; HRMS (ESI) Calcd for $C_{21}H_{28}N_3Si$ $[M + H]^+$ 350.2053, found 350.2052.

(*E*)-2-(1-Phenyl-2-(trimethylsilyl)vinyl)-1-(pyrimidin-2-yl)-1*H*-indole (3an): 79% yield; A yellow solid; m.p. 123-124 °C; *R*_f 0.18 (hexane/EtOAc = 10/1); ¹H NMR (400 MHz, CDCl₃): δ 8.54 (d, *J* = 4.8 Hz, 2 H), 7.94 (d, *J* = 8.3 Hz, 1 H), 7.54 (d, *J* = 7.8 Hz, 1 H), 7.19-7.14 (m, 4 H), 7.08-7.06 (m, 3 H), 6.89 (t, *J* = 4.8 Hz, 1 H), 6.66 (s, 1 H), 6.00 (s, 1 H), -0.15 (s, 9 H); ¹³C NMR (100 MHz, CDCl₃): δ 157.9, 157.8, 149.9, 143.6, 141.5, 137.8, 132.3, 129.4, 128.7, 127.4, 127.2, 123.7, 121.9, 120.7, 117.1, 112.6, 109.8, 0.17; HRMS (ESI) Calcd for C₂₃H₂₄N₃Si [M + H]⁺ 370.1740, found 370.1741. Recrystallization from hexane/ethyl acetate (8:1) afforded a single crystal suitable for X-ray diffraction analysis, which confirmed the regio- and stereochemistry of the compound (see below).¹⁸

Figure 3.1 Structure of **3an**

(*E*)-4-(1-(1-(pyrimidin-2-yl)-1*H*-indol-2-yl)-2-(trimethylsilyl)vinyl)benzonitrile (3ao):

Obtained as a 4:1 mixture with its stereoisomer (*Z*)-4-(1-(1-(pyrimidin-2-yl)-1*H*-indol-2-yl)-2-(trimethylsilyl)vinyl)benzonitrile; 62% yield; A yellow oil; *R*_f 0.08 (hexane/EtOAc = 10/1); ¹H NMR (400 MHz, CDCl₃): 8.59 (d, *J* = 4.8 Hz, 2 H), 8.05 (d, *J* = 7.5 Hz, 1 H), 7.62-7.57 (m, 1 H), 7.44-7.37 (m, 2 H), 7.33-7.18 (m, 4 H), 6.99 (t, *J* = 4.8 Hz, 1 H), 6.69 (s, 1 H), 6.16 (s, 1 H), -0.10 (s, 9 H); ¹³C NMR (100 MHz, CDCl₃): 158.0 (two peaks are overlapped), 157.8, 157.6, 148.2, 146.5, 144.6, 144.29, 144.26, 142.2, 141.2, 137.8, 136.5, 134.7, 131.7, 131.2, 130.0, 129.7, 129.2, 128.6, 124.2, 122.9, 122.3, 122.2, 120.8, 120.0, 118.9, 118.8, 117.3, 116.8, 114.6, 113.0, 111.0, 110.7, 110.5, 105.8, 0.5, 0.2; HRMS (ESI) Calcd for C₂₄H₂₃N₄Si [M + H]⁺ 395.1692, found 395.1690.

(*E*)-5-Fluoro-2-(oct-4-en-4-yl)-1-(pyrimidin-2-yl)-1*H*-indole (3ba): 87% yield; A colorless oil; *R*_f 0.24 (hexane/EtOAc = 10/1); ¹H NMR (400 MHz, CDCl₃): δ 8.74 (d, *J* = 4.8 Hz, 2 H), 8.12 (dd, *J* = 9.0, 4.6 Hz, 1 H), 7.22 (dd, *J* = 9.2, 2.4 Hz, 1 H), 7.12 (t, *J* = 4.8 Hz, 1 H), 6.96 (td, *J* = 9.2, 2.8 Hz, 1 H), 6.51 (s, 1 H), 5.61 (t, *J* = 7.4 Hz, 1 H), 2.18-2.13 (m, 4 H), 1.45-1.34 (m, 4 H), 0.94 (t, *J* = 7.4 Hz, 3 H), 0.84 (t, *J* = 7.3 Hz, 3 H); ¹³C NMR (100 MHz, CDCl₃): δ 158.9 (d, ¹*J*_{C-F} = 235 Hz), 158.12, 158.08, 145.1, 133.8, 133.7, 131.4, 129.9 (d, ³*J*_{C-F} = 10 Hz), 117.30, 114.0 (d, ³*J*_{C-F} = 9 Hz), 110.5 (d, ²*J*_{C-F} = 25 Hz), 106.7 (d, ⁴*J*_{C-F} = 4 Hz), 105.1 (d, ²*J*_{C-F} = 23 Hz), 33.0, 30.2, 22.6, 21.8, 14.0, 13.7; HRMS (ESI) Calcd for C₂₀H₂₃N₃F [M + H]⁺ 324.1876, found 324.1877.

(E)-5-Chloro-2-(oct-4-en-4-yl)-1-(pyrimidin-2-yl)-1H-indole (3ca): 85% yield; A yellow oil; R_f 0.32 (hexane/EtOAc = 10/1); ^1H NMR (400 MHz, CDCl_3): δ 8.75 (d, J = 4.8 Hz, 2 H), 8.08 (d, J = 8.8 Hz, 1 H), 7.52 (d, J = 2.0 Hz, 1 H), 7.18 (dd, J = 8.8, 2.0 Hz, 1 H), 7.13 (t, J = 4.8 Hz, 1 H), 6.49 (s, 1 H), 5.61 (t, J = 7.4 Hz, 1 H), 2.18-2.12 (m, 4 H), 1.44-1.32 (m, 4 H), 0.94 (t, J = 7.3 Hz, 3 H), 0.83 (t, J = 7.3 Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3): δ 158.1, 158.0, 144.8, 135.6, 133.6, 131.6, 130.4, 127.2, 122.8, 119.5, 117.5, 114.2, 106.2, 33.0, 30.2, 22.6, 21.8, 14.0, 13.7; HRMS (ESI) Calcd for $\text{C}_{20}\text{H}_{23}\text{N}_3\text{Cl}$ $[\text{M} + \text{H}]^+$ 340.1581, found 340.1581.

(E)-5-Methoxy-2-(oct-4-en-4-yl)-1-(pyrimidin-2-yl)-1H-indole (3da): 89% yield; A colorless oil; R_f 0.32 (hexane/EtOAc = 10/1); ^1H NMR (400 MHz, CDCl_3): δ 8.72 (d, J = 4.8 Hz, 2 H), 8.13 (d, J = 9.0 Hz, 1 H), 7.08-7.05 (m, 2 H), 6.88 (dd, J = 9.2, 2.4 Hz, 1 H), 6.49 (s, 1 H), 5.62 (t, J = 7.4 Hz, 1 H), 3.87 (s, 3 H), 2.19-2.14 (m, 4 H), 1.46-1.34 (m, 4 H), 0.95 (t, J = 7.4 Hz, 3 H), 0.84 (t, J = 7.3 Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3): δ 158.2, 157.9, 155.4, 144.1, 134.2, 132.3, 130.7, 130.0, 116.8, 114.2, 111.9, 107.0, 102.4, 55.6, 33.1, 30.2, 22.7, 21.8, 14.0, 13.7; HRMS (ESI) Calcd for $\text{C}_{21}\text{H}_{26}\text{N}_3\text{O}$ $[\text{M} + \text{H}]^+$ 336.2076, found 336.2078.

(E)-2-(Oct-4-en-4-yl)-1-(pyrimidin-2-yl)-1H-indole-5-carbonitrile (3ea): 75% yield; A colorless oil; *R_f* 0.28 (hexane/EtOAc = 5/1); ¹H NMR (400 MHz, CDCl₃): δ 8.79 (d, *J* = 4.8 Hz, 2 H), 8.11 (d, *J* = 8.6 Hz, 1 H), 7.87 (s, 1 H), 7.43 (dd, *J* = 8.8, 1.6 Hz, 1 H), 7.23 (t, *J* = 4.8 Hz, 1 H), 6.57 (s, 1 H), 5.57 (t, *J* = 7.4 Hz, 1 H), 2.15-2.10 (m, 4 H), 1.41-1.31 (m, 4 H), 0.90 (t, *J* = 7.4 Hz, 3 H), 0.82 (t, *J* = 7.3 Hz, 3 H); ¹³C NMR (100 MHz, CDCl₃): δ 158.4, 157.6, 145.7, 138.9, 132.9, 132.7, 129.0, 125.8, 125.0, 120.4, 118.3, 113.6, 106.0, 104.7, 32.8, 30.2, 22.5, 21.7, 13.9, 13.7; HRMS (ESI) Calcd for C₂₁H₂₃N₄ [M + H]⁺ 331.1923, found 331.1922.

(E)-Morpholino(2-(oct-4-en-4-yl)-1-(pyrimidin-2-yl)-1H-indol-5-yl)methanone (3fa): 83% yield; A yellow oil; *R_f* 0.12 (hexane/EtOAc = 1/1); ¹H NMR (400 MHz, CDCl₃): δ 8.76 (d, *J* = 4.8 Hz, 2 H), 8.10 (d, *J* = 8.6 Hz, 1 H), 7.63 (d, *J* = 1.2 Hz, 1 H), 7.26 (dd, *J* = 8.4, 1.6 Hz, 1 H), 7.17 (t, *J* = 4.8 Hz, 1 H), 6.55 (s, 1 H), 5.59 (t, *J* = 7.4 Hz, 1 H), 3.69 (brs, 8 H), 2.13-2.09 (m, 4 H), 1.42-1.31 (m, 4 H), 0.91 (t, *J* = 7.3 Hz, 3 H), 0.80 (t, *J* = 7.3 Hz, 3 H); ¹³C NMR (100 MHz, CDCl₃): δ 171.5, 158.2, 158.0, 144.6, 137.8, 133.5, 131.7, 128.9, 128.5, 122.0, 119.6, 117.7, 112.8, 106.8, 66.9, 32.9, 30.2, 22.6, 21.7, 13.9, 13.7; HRMS (ESI) Calcd for C₂₅H₃₁N₄O₂ [M + H]⁺ 419.2447, found 419.2443.

(E)-6-Fluoro-2-(oct-4-en-4-yl)-1-(pyrimidin-2-yl)-1H-indole (3ga): 92% yield; A colorless oil; R_f 0.50 (hexane/EtOAc = 10/1); ^1H NMR (400 MHz, CDCl_3): δ 8.75 (d, J = 4.8 Hz, 2 H), 7.95 (dd, J = 10.8, 2.0 Hz, 1 H), 7.47 (dd, J = 8.4, 5.6 Hz, 1 H), 7.12 (t, J = 4.8 Hz, 1 H), 6.97 (td, J = 9.0, 2.4 Hz, 1 H), 6.53 (s, 1 H), 5.60 (t, J = 7.4 Hz, 1 H), 2.18-2.13 (m, 4 H), 1.45-1.34 (m, 4 H), 0.95 (t, J = 7.3 Hz, 3 H), 0.84 (t, J = 7.3 Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3): δ 160.3 (d, $^1J_{\text{C-F}}$ = 236 Hz), 158.1 (two peaks are overlapped), 143.8 (d, $^4J_{\text{C-F}}$ = 4 Hz), 137.4 (d, $^3J_{\text{C-F}}$ = 13 Hz), 133.8, 131.0, 125.6, 120.5 (d, $^3J_{\text{C-F}}$ = 9 Hz), 117.3, 109.9 (d, $^2J_{\text{C-F}}$ = 24 Hz), 106.6, 100.4 (d, $^2J_{\text{C-F}}$ = 28 Hz), 33.0, 30.1, 22.7, 21.8, 14.0, 13.7; HRMS (ESI) Calcd for $\text{C}_{20}\text{H}_{23}\text{N}_3\text{F}$ $[\text{M} + \text{H}]^+$ 324.1876, found 324.1876.

(E)-6-Chloro-2-(oct-4-en-4-yl)-1-(pyrimidin-2-yl)-1H-indole (3ha): 89% yield; A colorless oil; R_f 0.33 (hexane/EtOAc = 10/1); ^1H NMR (400 MHz, CDCl_3): δ 8.76 (d, J = 4.8 Hz, 2 H), 8.20 (s, 1 H), 7.46 (d, J = 8.3 Hz, 1 H), 7.17 (dd, J = 8.4, 2.0 Hz, 1 H), 7.14 (t, J = 4.8 Hz, 1 H), 6.52 (s, 1 H), 5.60 (t, J = 7.4 Hz, 1 H), 2.18-2.12 (m, 4 H), 1.44-1.32 (m, 4 H), 0.94 (t, J = 7.3 Hz, 3 H), 0.83 (t, J = 7.3 Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3): δ 158.2, 158.0, 144.1, 137.6, 133.6, 131.4, 128.6, 127.7, 122.3, 120.8, 117.5, 113.3, 106.6, 33.0, 30.2, 22.6, 21.8, 14.0, 13.7; HRMS (ESI) Calcd for $\text{C}_{20}\text{H}_{23}\text{N}_3\text{Cl}$ $[\text{M} + \text{H}]^+$ 340.1581,

found 340.1582.

(E)-2-(Oct-4-en-4-yl)-1-(pyrimidin-2-yl)-1H-indole-4-carbonitrile (3ia): 70% yield; A colorless oil; *R_f* 0.30 (hexane/EtOAc = 5/1); ¹H NMR (400 MHz, CDCl₃): δ 8.79 (d, *J* = 4.8 Hz, 2 H), 8.28 (d, *J* = 8.4 Hz, 1 H), 7.50 (dd, *J* = 7.6, 0.8 Hz, 1 H), 7.25-7.21 (m, 2 H), 6.75 (s, 1 H), 5.61 (t, *J* = 7.4 Hz, 1 H), 2.17-2.11 (m, 4 H), 1.42-1.33 (m, 4 H), 0.91 (t, *J* = 7.3 Hz, 3 H), 0.83 (t, *J* = 7.3 Hz, 3 H); ¹³C NMR (100 MHz, CDCl₃): δ 158.4, 157.7, 146.3, 136.9, 133.1, 132.9, 131.0, 126.4, 122.4, 118.6, 118.2, 117.6, 104.7, 102.3, 32.9, 30.2, 22.5, 21.8, 13.9, 13.7; HRMS (ESI) Calcd for C₂₁H₂₃N₄ [M + H]⁺ 331.1923, found 331.1918.

(E)-3-Methyl-2-(oct-4-en-4-yl)-1-(pyrimidin-2-yl)-1H-indole (3ja): 92% yield; A colorless oil; *R_f* 0.43 (hexane/EtOAc = 10/1); ¹H NMR (400 MHz, CDCl₃): δ 8.66 (d, *J* = 4.8 Hz, 2 H), 8.28 (dd, *J* = 7.4, 1.0 Hz, 1 H), 7.53 (dd, *J* = 6.8, 1.6 Hz, 1 H), 7.27-7.19 (m, 2 H), 6.99 (t, *J* = 4.8 Hz, 1 H), 5.63 (t, *J* = 7.4 Hz, 1 H), 2.30 (s, 3 H), 2.24 (q, *J* = 7.3 Hz, 2 H), 2.00 (t, *J* = 7.6 Hz, 2 H), 1.55-1.50 (m, 2 H), 1.23-1.17 (m, 2 H), 1.01 (t, *J* = 7.3 Hz, 3 H), 0.74 (t, *J* = 7.3 Hz, 3 H); ¹³C NMR (100 MHz, CDCl₃): δ 158.2, 157.8, 138.9, 136.1,

133.1, 132.4, 130.7, 123.1, 121.4, 118.5, 116.4, 114.2, 113.5, 33.9, 30.2, 22.9, 21.6, 14.1, 13.8, 9.7; HRMS (ESI) Calcd for $C_{21}H_{26}N_3$ $[M + H]^+$ 320.2127, found 320.2122.

(E)-7-Ethyl-2-(oct-4-en-4-yl)-1-(pyrimidin-2-yl)-1H-indole (3ka): 81% yield; A colorless oil; R_f 0.29 (hexane/EtOAc = 10/1); 1H NMR (400 MHz, $CDCl_3$): δ 8.77 (d, J = 4.8 Hz, 2 H), 7.44 (dd, J = 7.6, 0.8 Hz, 1 H), 7.24 (t, J = 5.0 Hz, 1 H), 7.09 (t, J = 7.4 Hz, 1 H), 6.97 (d, J = 7.2 Hz, 1 H), 6.51 (s, 1 H), 5.47 (t, J = 7.4 Hz, 1 H), 2.27 (q, J = 7.5 Hz, 2 H), 2.12 (t, J = 7.3 Hz, 2 H), 1.96 (q, J = 7.3 Hz, 2 H), 1.39-1.34 (m, 2 H), 1.21-1.16 (m, 2 H), 0.90 (t, J = 7.5 Hz, 3 H), 0.81 (t, J = 7.3 Hz, 3 H), 0.77 (t, J = 7.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.8, 158.0, 144.7, 136.6, 133.4, 132.0, 129.6, 127.9, 122.9, 121.2, 119.5, 118.2, 104.2, 32.9, 30.1, 25.2, 22.6, 21.6, 14.2, 13.9, 13.7; HRMS (ESI) Calcd for $C_{22}H_{28}N_3$ $[M + H]^+$ 334.2283, found 334.2282.

(E)-7-Methoxy-2-(oct-4-en-4-yl)-1-(pyrimidin-2-yl)-1H-indole (3la): 36% yield; A colorless oil; R_f 0.21 (hexane/EtOAc = 5/1); 1H NMR (400 MHz, $CDCl_3$): δ 8.78 (d, J = 4.8 Hz, 2 H), 7.26 (t, J = 4.8 Hz, 1 H), 7.19 (d, J = 7.5 Hz, 1 H), 7.03 (t, J = 7.8 Hz, 1 H), 6.60 (d, J = 7.7 Hz, 1 H), 6.48 (s, 1 H), 5.48 (t, J = 7.4 Hz, 1 H), 3.58 (s, 3 H), 2.14 (t, J = 7.3 Hz, 2 H), 2.01-1.95 (m, 2 H), 1.41-1.35 (m, 2 H), 1.21-1.16 (m, 2 H), 0.81 (t, J = 7.3

Hz, 3 H), 0.77 (t, $J = 7.4$ Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3): δ 160.3, 157.6, 146.8, 144.0, 133.3, 131.6, 130.5, 127.8, 121.2, 119.2, 113.2, 104.1, 103.5, 55.6, 32.9, 30.2, 22.6, 21.7, 13.9, 13.7; HRMS (ESI) Calcd for $\text{C}_{21}\text{H}_{26}\text{N}_3\text{O}$ $[\text{M} + \text{H}]^+$ 336.2076, found 336.2073.

(*E*)-2-(Oct-4-en-4-yl)-1-(pyrimidin-2-yl)-1*H*-benzo[*d*]imidazole (3ma): 82% yield; A yellow oil; R_f 0.23 (hexane/EtOAc = 5/1); ^1H NMR (400 MHz, CDCl_3): δ 8.73 (d, $J = 4.8$ Hz, 2 H), 7.85 (dd, $J = 6.4, 2.0$ Hz, 1 H), 7.72 (dd, $J = 6.0, 2.0$ Hz, 1 H), 7.24-7.16 (m, 3 H), 5.60 (t, $J = 7.4$ Hz, 1 H), 2.36 (t, $J = 7.5$ Hz, 2 H), 2.07 (q, $J = 7.3$ Hz, 2 H), 1.45-1.39 (m, 2 H), 1.30-1.24 (m, 2 H), 0.82 (t, $J = 7.3$ Hz, 3 H), 0.79 (t, $J = 7.4$ Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3): δ 158.6, 157.3, 155.8, 142.9, 135.9, 134.5, 132.3, 123.6, 123.4, 119.7, 118.8, 112.6, 32.4, 30.3, 22.3, 21.9, 14.1, 13.8; HRMS (ESI) Calcd for $\text{C}_{19}\text{H}_{23}\text{N}_4$ $[\text{M} + \text{H}]^+$ 307.1923, found 307.1918.

Transformations of Alkenylated Indoles

Removal of the Pyrimidyl Group

(*E*)-2-(Oct-4-en-4-yl)-1*H*-indole (4aa): A mixture of (*E*)-2-(oct-4-en-4-yl)-1-(pyrimidin-2-yl)-1*H*-indole (**3aa**) (916 mg, 3 mmol) and freshly

prepared sodium ethoxide (408 mg, 6 mmol) in DMSO (5 mL) was stirred at 100 °C under nitrogen atmosphere for 20 h. After cooling to ambient temperature, the reaction mixture was diluted with EtOAc (40 mL) and washed with H₂O (2 × 20 mL). The aqueous phase was extracted with EtOAc (2 × 20 mL), and the combined organic phase was dried over Na₂SO₄. After filtration and evaporation of the solvents under reduced pressure, the crude product was purified by column chromatography on silica gel (hexane/EtOAc = 50/1) to yield **4aa** (593 mg, 87%) as a yellow solid.

m.p. 46-47 °C; *R_f* 0.51 (hexane/EtOAc = 10/1); ¹H NMR (400 MHz, CDCl₃): δ 7.94 (s, 1 H), 7.53 (d, *J* = 7.8 Hz, 1 H), 7.20 (dd, *J* = 8.0, 0.8 Hz, 1 H), 7.13-7.02 (m, 2 H), 6.42 (s, 1 H), 5.72 (t, *J* = 7.3 Hz, 1 H), 2.43 (t, *J* = 7.6 Hz, 2 H), 2.19 (q, *J* = 7.3 Hz, 2 H), 1.55-1.44 (m, 4 H), 0.96 (t, *J* = 7.4 Hz, 3 H), 0.94 (t, *J* = 7.4 Hz, 3 H); ¹³C NMR (100 MHz, CDCl₃): δ 139.6, 136.2, 131.7, 129.0, 126.3, 121.8, 120.2, 119.7, 110.3, 99.6, 31.0, 30.2, 23.0, 22.7, 14.1, 13.9; HRMS (ESI) Calcd for C₁₆H₂₂N [M + H]⁺ 228.1752, found 228.1753.

(*E*)-2-(1,2-Diphenylvinyl)-1*H*-indole (4ak): 93% yield; A yellow solid; m.p. 139-140 °C; *R_f* 0.38 (hexane/EtOAc = 10/1); ¹H NMR (400 MHz, CDCl₃): δ 7.94 (s, 1 H), 7.51 (d, *J* = 7.9 Hz, 1 H), 7.38-7.36 (m, 3 H), 7.32-7.29 (m, 2 H), 7.24-7.22 (m, 1 H), 7.16-7.04 (m, 5 H), 7.00-6.97 (m, 3 H), 6.39 (s, 1 H); ¹³C NMR (100 MHz, CDCl₃): δ 140.1, 138.2, 136.6, 136.4, 133.8, 130.1, 129.4, 128.9, 128.7, 128.1, 128.0, 126.9, 125.7, 122.6, 120.6, 120.1, 110.7, 102.9; HRMS (ESI) Calcd for C₂₂H₁₈N [M + H]⁺ 296.1439, found 296.1436.

Preparation of Pyrrolocarbazole Derivatives via Diels–Alder Reaction/Oxidation

(Scheme 2a)

2-Phenyl-4,5-dipropylpyrrolo[3,4-*c*]carbazole-1,3(2*H*,6*H*)-dione (5aa): A mixture of (*E*)-2-(oct-4-en-4-yl)-1*H*-indole (**4aa**) (45.5 mg, 0.2 mmol), *N*-phenylmaleimide (41.6 mg, 0.24 mmol) and $\text{BF}_3 \cdot \text{OEt}_2$ (5.0 μL , 0.04 mmol) in CH_2Cl_2 (1 mL) was stirred at room temperature for 4 h. The reaction was quenched with H_2O , and extracted with CH_2Cl_2 (2×15 mL), the combined organic phase was dried over Na_2SO_4 . After filtration and concentration, the crude product was dissolved in toluene (1.5 mL). To this was added DDQ (90 mg, 0.4 mmol), and the resulting mixture was stirred at 110 °C for 12 h. After cooling to ambient temperature, the reaction mixture was quenched with H_2O and extracted with EtOAc (2×10 mL), and the combined organic phase was dried over Na_2SO_4 . After filtration and evaporation of the solvents *in vacuo*, the crude product was purified by column chromatography on silica gel (hexane/EtOAc = 10/1) to yield **5aa** (67.2 mg, 85%) as a yellow solid.

m.p. 78–79 °C; *R*_f 0.30 (hexane/EtOAc = 10/1); ^1H NMR (400 MHz, CDCl_3): δ 9.03 (d, *J* = 7.9 Hz, 1 H), 8.55 (s, 1 H), 7.53–7.44 (m, 6 H), 7.38–7.24 (m, 2 H), 3.29–3.25 (m, 2 H), 2.96–2.92 (m, 2 H), 1.74–1.67 (m, 4 H), 1.10 (t, *J* = 7.2 Hz, 3 H), 1.09 (t, *J* = 7.3 Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3): δ 169.2, 168.2, 143.3, 140.9, 138.3, 132.2, 128.9, 128.8, 128.0, 127.6, 126.9, 125.9, 124.5, 121.6, 121.0, 120.8, 118.2, 110.6, 29.8, 29.7, 25.0, 23.2, 14.6, 14.5; HRMS (ESI) Calcd for $\text{C}_{26}\text{H}_{25}\text{N}_2\text{O}_2$ [*M* + *H*]⁺ 397.1916, found

397.1920.

2,4,5-Triphenylpyrrolo[3,4-*c*]carbazole-1,3(2*H*,6*H*)-dione (5ak): 81% yield; A yellow solid; m.p. 232-233 °C; *R*_f 0.25 (hexane/EtOAc = 10/1); ¹H NMR (400 MHz, CDCl₃): δ 9.15 (d, *J* = 8.0 Hz, 1 H), 8.33 (s, 1 H), 7.55-7.44 (m, 5 H), 7.42-7.33 (m, 6 H), 7.26-7.21 (m, 7 H); ¹³C NMR (100 MHz, CDCl₃): δ 167.9, 167.8, 142.9, 141.2, 136.4, 135.5, 135.2, 134.2, 132.1, 130.5, 130.2, 129.6, 128.9, 128.8, 128.6, 128.1, 127.6, 127.43, 127.41, 126.8, 126.4, 125.6, 121.5, 120.9, 119.4, 110.8; HRMS (ESI) Calcd for C₃₂H₂₁N₂O₂ [M + H]⁺ 465.1603, found 465.1604.

Friedel–Crafts Condensation of 4aa with *p*-Anisaldehyde (Scheme 2b)

1-(4-Methoxyphenyl)-2,3-dipropyl-1,4-dihydrocyclopenta[*b*]indole (6aa): A mixture of (*E*)-2-(oct-4-en-4-yl)-1*H*-indole (**4aa**) (45.5 mg, 0.2 mmol), *p*-anisaldehyde (24.3 μL, 0.2 mmol) and TfOH (5.3 μL, 0.06 mmol) in toluene (1 mL) was stirred at 60 °C for 2 h. After cooling to ambient temperature, the reaction mixture was quenched with H₂O and extracted with EtOAc (2 × 10 mL), and the combined organic phase was dried over Na₂SO₄. After filtration and concentration, the crude product was purified by column chromatography on silica gel (hexane/EtOAc = 25/1) to yield **6aa** (42.1 mg, 61%) as a

yellow oil.

*R*_f 0.29 (hexane/EtOAc = 10/1); ¹H NMR (400 MHz, CDCl₃): δ 8.02 (s, 1 H), 7.36 (d, *J* = 7.4 Hz, 1 H), 7.22 (d, *J* = 7.4 Hz, 1 H), 7.02-6.98 (m, 4 H), 6.80-6.78 (m, 2 H), 4.36 (s, 1 H), 3.78 (s, 3 H), 2.53 (t, *J* = 7.5 Hz, 2 H), 2.38-2.30 (m, 1 H), 2.10-2.03 (m, 1 H), 1.74-1.66 (m, 2 H), 1.59-1.51 (m, 1 H), 1.42-1.38 (m, 1 H), 1.02 (t, *J* = 7.4 Hz, 3 H), 0.90 (t, *J* = 7.4 Hz, 3 H); ¹³C NMR (100 MHz, CDCl₃): δ 158.1, 151.5, 147.6, 139.4, 132.2, 129.9, 129.0, 124.2, 123.2, 119.9, 119.6, 117.3, 113.9, 111.7, 55.2, 50.3, 29.1, 27.7, 24.1, 22.6, 14.1 (two peaks are overlapped); HRMS (ESI) Calcd for C₂₄H₂₈NO [M + H]⁺ 346.2171, found 346.2166.

Oxidative Heck Olefination of C3 Position (Scheme 2c)^a

(*E*)-Butyl 3-(2-((*E*)-oct-4-en-4-yl)-1*H*-indol-3-yl)acrylate (7aa): A mixture of *n*-butyl acrylate (57.3 μL, 0.4 mmol), *t*-butylbenzoyl peroxide (34 μL, 0.18 mmol) and palladium acetate (4.5 mg, 0.02 mmol) were added to a solution of **4aa** (45.5 mg, 0.2 mmol) in dioxane/DMSO (9:1, 1.5 mL), and the reaction mixture was stirred at 70 °C for 18 h. After cooling to room temperature, the reaction mixture was transferred directly on to a silica gel column and purified by column chromatography (hexane/EtOAc = 15/1) to afford a 7:1 mixture of **7aa** with its stereoisomer (*E*)-butyl 3-(2-((*Z*)-oct-4-en-4-yl)-1*H*-indol-3-yl)acrylate (43.1 mg, 61%) as a yellow oil.

R_f 0.25 (hexane/EtOAc = 10/1); ¹H NMR (400 MHz, CDCl₃): δ 8.27 (s, 1 H), 7.96 (d, *J* = 16.0 Hz, 1 H); 7.93-7.92 (m, 1 H); 7.36-7.34 (m, 1 H), 7.24-7.21 (m, 2 H), 6.48 (d, *J* = 16.0 Hz, 1 H), 5.74 (t, *J* = 7.4 Hz, 1 H), 4.20 (t, *J* = 6.6 Hz, 2 H), 2.46 (t, *J* = 7.4 Hz, 2 H), 2.27 (q, *J* = 7.3 Hz, 2 H), 1.71-1.66 (m, 2 H), 1.56-1.43 (m, 4 H), 1.39-1.34 (m, 2 H), 1.01 (t, *J* = 7.3 Hz, 3 H), 0.97 (t, *J* = 7.4 Hz, 3 H), 0.89 (t, *J* = 7.3 Hz, 3 H); ¹³C NMR (100 MHz, CDCl₃): δ 168.6, 145.5, 138.8, 137.8, 135.6, 130.3, 126.3, 122.9, 121.4, 120.6, 113.1, 111.0, 110.0, 63.9, 32.6, 30.9, 30.6, 22.8, 21.9, 19.3, 13.9, 13.84, 13.76; HRMS (ESI) Calcd for C₂₃H₃₂NO₂ [M + H]⁺ 354.2433, found 354.2430.

(*E*)-butyl 3-(2-((*E*)-1,2-diphenylvinyl)-1*H*-indol-3-yl)acrylate (7ak): Obtained as a 2:1 mixture with its stereoisomer (*E*)-butyl 3-(2-((*Z*)-1,2-diphenylvinyl)-1*H*-indol-3-yl)acrylate (**7ak'**) (stereochemistry is tentatively assigned); 70% yield; A brown oil; *R_f* 0.19 (hexane/EtOAc = 10/1); ¹H NMR (400 MHz, CDCl₃): δ 8.32 (s, 1 H, **7ak'**), 8.05 (d, *J* = 16.0 Hz, 1 H, **7ak**), 8.06 (s, 1 H, **7ak**), 8.00-7.98 (m, 1 H, **7ak**), 7.95-7.92 (m, 1 H, **7ak'**), 7.60 (d, *J* = 16.0 Hz, 1 H, **7ak'**), 7.37-7.32 (m, 4 H, **7ak** and **7ak'**), 7.27-7.22 (m, 4 H, **7ak** and **7ak'**), 7.17-7.08 (m, 4 H, **7ak** and **7ak'**), 7.05-7.04 (m, 1 H, **7ak** and **7ak'**), 6.94 (s, 1 H, **7ak**), 6.58 (d, *J* = 16.0 Hz, 1 H, **7ak**), 6.32 (d, *J* = 16.0 Hz, 1 H, **7ak'**), 4.15 (t, *J* = 6.6 Hz, 2 H, **7ak**), 4.05 (t, *J* = 6.6 Hz, 2 H, **7ak'**), 1.64-1.56 (m, 2 H, **7ak** and **7ak'**), 1.39-1.31 (m, 2 H, **7ak** and **7ak'**), 0.92

(t, $J = 7.4$ Hz, 3 H, **7ak'**), 0.88 (t, $J = 7.4$ Hz, 3 H, **7ak**); ^{13}C NMR (100 MHz, CDCl_3): δ 168.3, 167.9, 143.5, 140.8, 138.3, 138.0, 137.4, 136.0, 135.9, 135.1, 133.6, 131.9, 131.1, 130.3, 129.8, 129.08, 129.05, 128.8, 128.7, 128.5, 128.4, 128.22, 128.17, 128.1, 127.7, 127.1, 126.4, 123.6, 123.3, 121.8, 121.7, 121.54, 121.50, 120.8, 119.3, 114.8, 114.3, 111.9, 111.7, 111.6, 111.5, 111.2, 64.7, 63.9, 30.83, 30.78, 19.22, 19.16, 13.74, 13.69; HRMS (ESI) Calcd for $\text{C}_{29}\text{H}_{28}\text{NO}_2$ $[\text{M} + \text{H}]^+$ 422.2120, found 422.2122.

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Chapter 4 Cobalt-Catalyzed C2-Alkylation of *N*-Pyrimidylindole with Vinylsilane

4.1 Introduction

Indole represents a privileged core structural motif that occurs in biologically active natural and synthetic products.¹ Consequently, there has been a strong demand for synthetic methods that allow efficient and regioselective functionalization of indole nucleus.² In the past decade, transition-metal-catalyzed C–H bond functionalization has emerged as a powerful strategy for the direct introduction of alkenyl and aryl groups to the C2 and C3 positions of indole.³ However, there still remains a challenge when it comes to direct C–H alkylation.⁴ While direct C3-alkylation can be achieved by the Friedel-Crafts reaction, C2-alkylation has conventionally required indol-2-yl radicals generated from 2-halogenated indoles or 2-lithioindoles generated by C2-lithiation with a stoichiometric lithium base (Scheme 4.1).^{5,6}

Scheme 4.1 Conventional methods for C2-alkylated indole

With the above situation, examples of direct catalytic C2-alkylation of indole via

transition-metal-catalyzed C–H activation have been limited.⁷ In 2008, Nakao and Hiyama reported a nickel-catalyzed addition reaction of azoles and related heteroarenes to vinylarenes, which allowed introduction of a 1-arylethyl group to the C2 position of indoles bearing electron-withdrawing groups on the C3 position (Scheme 4.2a).^a Shibata and coworkers also investigated C2-alkylation of indole with alkene catalyzed by Ir complex.^c During the present study, a more general method for C2-alkylation of indole was reported by Jiao and Bach, who elegantly exploited Catellani's palladium/norbornene chemistry to introduce various primary alkyl groups using alkyl bromides (Scheme 4.2b).^d

Scheme 4.2 C2-alkylation of indole via transition-metal-catalyzed C–H activation

In the past few years, cobalt catalysts have been developed as inexpensive catalysts for C–H functionalization reactions by our group and others.⁸ The cobalt catalysis often shows mild reaction conditions and unique regioselectivities.⁹ As described in Chapter 3, we have developed a cobalt-pyridylphosphine catalyst system for the C2-alkenylation reaction of *N*-pyrimidylindoles with internal alkynes (Scheme 4.3a), in which the pyrimidyl group serves as a readily removable directing group.¹⁰ In addition, our group also developed an *ortho*-alkylation of aromatic imines with vinylsilanes and

simple olefins catalyzed by a cobalt-phenanthroline complex (Scheme 4.3b).¹¹ Based on these studies, we have developed a C2-alkylation reaction of *N*-pyrimidylindoles with vinylsilanes using a cobalt-bathocuproine catalyst, which is described herein (Scheme 4.3c).

Scheme 4.3 (a) Cobalt-catalyzed C2-alkenylation of *N*-pyrimidylindole, (b) ortho-alkylation of aryl imine, and (c) C2-alkylation of *N*-pyrimidylindole.

4.2 Results and Discussion

Our study started with the optimization of reaction conditions for the addition of *N*-pyrimidylindole **1a** to vinyltrimethylsilane **2a**. The catalytic system consisting of CoBr₂ (10 mol%), 1,10-phenanthroline (phen, 10 mol%) and neopentylmagnesium bromide (100 mol%), which was effective for the ortho-alkylation of aromatic imines, afforded the desired product **3aa** only in 17% yield along with a small amount of a C2-neopentylated product **4** (Table 4.1, entry 1). Screening of phenanthroline and bipyridine-type ligands (entries 2-5) showed that the use of 2,9-dimethyl-1,10-phenanthroline (neocuproine) and 2,9-dimethyl-4,7-diphenylphenanthroline (bathocuproine) improved the yield of **3aa**, while the byproduct **4** could not be suppressed (entries 3 and 4). The *P,N*-bidentate ligand pyphos that we previously employed for the C2-alkenylation of indoles,¹² was poorly effective (entry 6). There was no improvement of catalytic efficiency with *N*-heterocyclic carbene (NHC) and phosphine ligands (entries 7-9). The reaction was sensitive to the amount of the Grignard reagent, as the yield of **3aa** was improved by reducing of the amount Grignard reagent from 100 to 60 mol% with suppression of the byproduct **4** (entry 10).

Table 4.1 Screening of ligands^a

entry	ligand (mol%)	yield (%) ^b	
		3aa	4
1	phen (10 mol%)	17	7
2	bathophen (10 mol%)	11	7
3	neocup (10 mol%)	32	12
4	bathocup (10 mol%)	34	20
5	dtbpy (10 mol%)	1	3
6	pyphos (10 mol%)	2	3
7	IMes•HCl (10 mol%)	4	2
8	PPh_3 (20 mol%)	9	5
9	$\text{P}(\text{3-ClC}_6\text{H}_4)_3$ (20 mol%)	23	11
10 ^c	bathocup (10 mol%)	50	10

^a Reaction was performed on a 0.3 mmol scale. ^b Determined by GC using *n*-tridecane as internal standard. ^c 60 mol% of $t\text{BuCH}_2\text{MgBr}$ was used.

We next screened Grignard reagents by using bathocuproine as the ligand. Among Grignard reagents without β -hydrogen atoms, neopentyl- and phenylmagnesium bromides afforded the product **3aa** in modest yields (Table 4.2, entries 1 and 4), while trimethylsilylmethyl- and methylmagnesium chlorides gave much lower yields (entries 2 and 3). Primary and secondary alkyl Grignard reagents were also effective, while the efficiency of the reaction was strongly dependent on the alkyl group (entries 5-10). Cyclohexylmagnesium bromide was found to be the optimum Grignard reagent, which

afforded the product **3aa** in 69% isolated yield without formation of the cross-coupling product **4** between **1a** and the Grignard reagent.

Table 4.2 Screening of Grignard reagents^a

entry	RMgX	3aa	yield (%) ^b
1	<i>t</i> BuCH ₂ MgBr	50	10
2	Me ₃ SiCH ₂ MgCl	26	5
3	MeMgCl	14	4
4	PhMgBr	46	5
5	EtMgBr	28	3
6	<i>n</i> BuMgBr	45	0
7	<i>i</i> PrMgBr	49	3
8	<i>o</i> -C ₃ H ₅ MgBr	13	0
9	<i>o</i> -C ₅ H ₉ MgBr	46	0
10 ^c	<i>o</i> -C ₆ H ₁₁ MgBr	67 (69) ^c	0

^a Reaction was performed on a 0.3 mmol scale. ^b Determined by GC using *n*-tridecane as internal standard. ^c Isolated yield.

With the optimized reaction conditions in hand, we investigated the substrate scope of the reaction (Figure 4.1). Various *N*-pyrimidinylindoles underwent the alkylation reaction with vinyltrimethylsilane to afford the products **3ba-3fa** in moderate yields, with tolerance of both electron-withdrawing (F and Cl) and electron-donating (OMe) substituents. The *N*-pyrimidinylindoles with steric hindrance at the C3 and C7 positions

also participated in the reaction and gave the alkylated products **3ga-3ia** in moderate to good yields. Unlike the cobalt-catalyzed C2-alkenylation reaction (Scheme 4.1a), a cyano group was not tolerated in this reaction. In addition, *N*-pyrimidyl benzimidazole, a good substrate for the C2-alkenylation reaction, did not participate in the present alkylation reaction. The alkylation reaction was achieved efficiently by using a pyridyl group as a directing group instead of the pyrimidyl group. On the other hand, an *N,N*-dimethylcarbamoyl group, which was previously used as a directing group for rhodium-catalyzed C2-alkenylation reaction,¹³ was entirely ineffective. Vinylsilanes bearing dimethylphenylsilyl and triphenylsilyl groups reacted with **1a** to afford the products **3ab** and **3ac** in moderate yields. Vinyltriethoxysilane also participated in the reaction and gave the alkylation product in 20% yield, although the product could not be separated in a pure form.

Figure 4.1 Addition of *N*-pyrimidylindoles to vinylsilanes. Reaction was performed on a 0.3 mmol scale, and yields of isolated products are shown.

Unfortunately, the present catalytic system was not very effective for the C2-alkylation with simple olefins. The reaction of **1a** with norbornene **2d** was sluggish, affording the alkylation product **3ad** in 30% yield (Scheme 4.4a). The reaction was even more sluggish with 1-octene **2e**, which afforded the product **3ae** in only 9% yield (Scheme 4.4b). The reaction of styrene with **1a** afforded only a small amount of the alkylation product (3% as estimated by GC and GCMS), the regiochemistry (branched versus linear) of which was not determined. An acrylate ester was not tolerated in this reaction because of the presence of an excess amount of Grignard reagent.

Scheme 4.4 Addition of *N*-pyrimidylindole to (a) norbornene and (b) 1-octene

The alkylation reaction of **1a** could be performed on a 5 mmol scale by using 1.2 equiv of vinyltrimethylsilane **2a** without decrease in the product yield (Scheme 4.5). Furthermore, the pyrimidyl group on the alkylated product **3aa** could be easily removed by treatment with NaOEt in dimethylsulfoxide (DMSO) at 100 °C, affording the free indole product **4aa** in 85% yield.

Scheme 4.5 Gram-scale reaction and deprotection of *N*-pyrimidyl group

4.3 Conclusion

In summary, we have developed a cobalt-bathocuproine catalytic system for the C2-alkylation of *N*-pyrimidylindoles with vinylsilanes. The reaction proceeds at a mild temperature of 60 °C, and is applicable to alkylation on a gram scale. However, the scope of olefins is largely limited to the vinylsilanes, and simple olefins exhibit poor reactivity. Further investigation should be focused on the development of more broadly applicable catalytic systems for the direct alkylation of indole and other heterocycles.

4.4 Experimental Section

C2-Alkylation of *N*-pyrimidyl Indole with Vinylsilane

Typical Procedure: 1-(Pyrimidin-2-yl)-2-(2-(trimethylsilyl)ethyl)-1*H*-indole (3aa). In a Schlenk tube were placed 1-(pyrimidin-2-yl)-1*H*-indole (58.6 mg, 0.3 mmol), CoBr₂ (6.6 mg, 0.03 mmol), and bathocuproine (10.8 mg, 0.03 mmol), which were then dissolved in THF (1.3 mL). To the solution was added cyclohexylmagnesium bromide (0.60 M in THF, 0.3 mL, 0.18 mmol) at 0 °C. After stirring for 30 min at this temperature, vinyltrimethylsilane (66 μL, 0.45 mmol) was added. The reaction mixture was stirred at 60 °C for 12 h, and then quenched with saturated aqueous solution of NH₄Cl (1.5 mL). The resulting mixture was extracted with ethyl acetate (10 mL × 3). The combined organic layer was dried over Na₂SO₄ and concentrated under reduced pressure. Purification of the crude product by silica gel chromatography (eluent: hexane/EtOAc = 100/1) afforded the title compound as a colorless oil (61.2 mg, 69%). The 5 mmol-scale reaction was performed according to a similar procedure using 100 mL Schlenk tube to afford the same product in 68% yield.

R_f 0.39 (hexane/EtOAc = 10/1); ¹H NMR (400 MHz, CDCl₃): δ 8.80 (d, J = 4.8 Hz, 2 H), 8.24 (d, J = 8.0 Hz, 1 H), 7.54-7.52 (m, 1 H), 7.23-7.13 (m, 3 H), 6.50 (s, 1 H), 3.20-3.16 (m, 2 H), 0.86-0.82 (m, 2 H), 0.02 (s, 9 H); ¹³C NMR (100 MHz, CDCl₃): δ 158.3, 158.1, 145.0, 137.1, 129.4, 122.3, 121.7, 119.6, 117.0, 113.7, 105.1, 23.8, 16.5, -1.8; HRMS (ESI) Calcd for C₁₇H₂₂N₃Si [M + H]⁺ 296.1583, found 296.1584.

5-Fluoro-1-(pyrimidin-2-yl)-2-(2-(trimethylsilyl)ethyl)-1H-indole (3ba): 55% yield; colorless oil; R_f 0.37 (hexane/EtOAc = 10/1); ^1H NMR (400 MHz, CDCl_3): δ 8.78 (d, J = 4.8 Hz, 2 H), 8.23-8.19 (m, 1 H), 7.18-7.14 (m, 2 H), 6.95-6.90 (m, 1 H), 6.45 (s, 1 H), 3.19-3.15 (m, 2 H), 0.85-0.81 (m, 2 H), 0.02 (s, 9 H); ^{13}C NMR (100 MHz, CDCl_3): δ 158.9 (d, $^1J_{\text{C-F}}$ = 236 Hz), 158.2, 158.1, 146.8, 133.4, 130.1 (d, $^3J_{\text{C-F}}$ = 10.0 Hz), 117.1, 114.8 (d, $^3J_{\text{C-F}}$ = 9.1 Hz), 109.9 (d, $^2J_{\text{C-F}}$ = 24.8 Hz), 104.9, 104.8 (d, $^2J_{\text{C-F}}$ = 27.0 Hz), 24.1, 16.5, -1.8; HRMS (ESI) Calcd for $\text{C}_{17}\text{H}_{21}\text{FN}_3\text{Si}$ $[\text{M} + \text{H}]^+$ 314.1489, found 314.1491.

5-Chloro-1-(pyrimidin-2-yl)-2-(2-(trimethylsilyl)ethyl)-1H-indole (3ca): 39% yield; yellow oil; R_f 0.38 (hexane/EtOAc = 10/1); ^1H NMR (400 MHz, CDCl_3): δ 8.79 (d, J = 4.8 Hz, 2 H), 8.17 (d, J = 8.8 Hz, 1 H), 7.47 (d, J = 2.1 Hz, 1 H), 7.19-7.13 (m, 2 H), 6.43 (s, 1 H), 3.18-3.14 (m, 2 H), 0.84-0.80 (m, 2 H), 0.01 (s, 9 H); ^{13}C NMR (100 MHz, CDCl_3): δ 158.14, 158.09, 146.5, 135.4, 130.5, 127.1, 122.3, 119.1, 117.2, 114.9, 104.5, 24.0, 16.4, -1.8; HRMS (ESI) Calcd for $\text{C}_{17}\text{H}_{21}\text{ClN}_3\text{Si}$ $[\text{M} + \text{H}]^+$ 330.1193, found 330.1190.

5-Methoxy-1-(pyrimidin-2-yl)-2-(2-(trimethylsilyl)ethyl)-1H-indole (3da): 62% yield; colorless oil; R_f 0.32 (hexane/EtOAc = 10/1); ^1H NMR (400 MHz, CDCl_3): δ 8.75 (d, J = 4.8 Hz, 2 H), 8.22 (d, J = 9.0 Hz, 1 H), 7.09 (t, J = 4.8 Hz, 1 H), 7.01 (d, J = 2.5 Hz, 1 H), 6.87-6.84 (m, 1 H), 6.43 (s, 1 H), 3.87 (s, 3 H), 3.21-3.17 (m, 2 H), 0.87-0.83 (m, 2 H), 0.03 (s, 9 H); ^{13}C NMR (100 MHz, CDCl_3): δ 158.3, 157.9, 155.3, 145.8, 132.0, 130.1, 116.6, 114.9, 111.1, 105.1, 102.2, 55.7, 24.1, 16.6, -1.8; HRMS (ESI) Calcd for $\text{C}_{18}\text{H}_{24}\text{N}_3\text{OSi}$ $[\text{M} + \text{H}]^+$ 326.1689, found 326.1690.

6-Fluoro-1-(pyrimidin-2-yl)-2-(2-(trimethylsilyl)ethyl)-1H-indole (3ea): 52% yield; colorless oil; R_f 0.47 (hexane/EtOAc = 10/1); ^1H NMR (400 MHz, CDCl_3): δ 8.78 (d, J = 4.8 Hz, 2 H), 8.08-8.04 (m, 1 H), 7.44-7.40 (m, 1 H), 7.15 (t, J = 4.8 Hz, 1 H), 6.97-6.92 (m, 1 H), 6.46 (s, 1 H), 3.19-3.15 (m, 2 H), 0.85-0.81 (m, 2 H), 0.02 (s, 9 H); ^{13}C NMR (100 MHz, CDCl_3): δ 160.0 (d, $^1J_{\text{C-F}}$ = 235 Hz), 158.2, 158.1, 145.5 (d, $^4J_{\text{C-F}}$ = 3.8 Hz), 137.1 (d, $^3J_{\text{C-F}}$ = 12.5 Hz), 125.6, 119.9 (d, $^3J_{\text{C-F}}$ = 9.9 Hz), 117.1, 109.8 (d, $^2J_{\text{C-F}}$ = 24.0 Hz), 104.8, 101.3 (d, $^2J_{\text{C-F}}$ = 28.4 Hz), 24.0, 16.5, -1.8; HRMS (ESI) Calcd for $\text{C}_{17}\text{H}_{21}\text{FN}_3\text{Si}$ $[\text{M} + \text{H}]^+$ 314.1489, found 314.1494.

6-Chloro-1-(pyrimidin-2-yl)-2-(2-(trimethylsilyl)ethyl)-1H-indole (3fa): 43% yield; colorless oil; R_f 0.44 (hexane/EtOAc = 10/1); ^1H NMR (400 MHz, CDCl_3): δ 8.81 (d, J = 4.8 Hz, 2 H), 8.29 (s, 1 H), 7.41 (d, J = 8.3 Hz, 1 H), 7.20-7.13 (m, 2 H), 6.45 (s, 1 H), 3.18-3.13 (m, 2 H), 0.83-0.79 (m, 2 H), 0.01 (s, 9 H); ^{13}C NMR (100 MHz, CDCl_3): δ 158.2, 158.1, 145.9, 137.4, 128.1, 127.9, 122.2, 120.2, 117.3, 114.1, 104.8, 23.9, 16.5, -1.8; HRMS (ESI) Calcd for $\text{C}_{17}\text{H}_{21}\text{ClN}_3\text{Si}$ [$\text{M} + \text{H}$] $^+$ 330.1193, found 330.1192.

3-Methyl-1-(pyrimidin-2-yl)-2-(2-(trimethylsilyl)ethyl)-1H-indole (3ga): 42% yield; white solid; R_f 0.42 (hexane/EtOAc = 10/1); ^1H NMR (400 MHz, CDCl_3): δ 8.77 (d, J = 4.8 Hz, 2 H), 8.26-8.24 (m, 1 H), 7.50-7.48 (m, 1 H), 7.22-7.20 (m, 2 H), 7.11 (t, J = 4.8 Hz, 1 H), 3.18-3.14 (m, 2 H), 2.29 (s, 3 H), 0.73-0.69 (m, 2 H), 0.01 (s, 9 H); ^{13}C NMR (100 MHz, CDCl_3): δ 158.4, 158.0, 139.9, 136.1, 130.6, 122.5, 121.4, 117.8, 116.6, 113.5, 111.6, 20.4, 17.3, 8.7, -1.9; HRMS (ESI) Calcd for $\text{C}_{18}\text{H}_{24}\text{N}_3\text{Si}$ [$\text{M} + \text{H}$] $^+$ 310.1740, found 310.1743.

7-Methyl-1-(pyrimidin-2-yl)-2-(2-(trimethylsilyl)ethyl)-1H-indole (3ha): 71% yield;

colorless oil; R_f 0.19 (hexane/EtOAc = 10/1); ^1H NMR (400 MHz, CDCl_3): δ 8.86 (d, J = 4.8 Hz, 2 H), 7.45 (d, J = 7.7 Hz, 1 H), 7.28 (t, J = 4.8 Hz, 1 H), 7.09 (t, J = 7.4 Hz, 1 H), 6.95 (d, J = 7.2 Hz, 1 H), 6.46 (s, 1 H), 2.74-2.69 (m, 2 H), 1.96 (s, 3 H), 0.82-0.78 (m, 2 H), -0.02 (s, 9 H); ^{13}C NMR (100 MHz, CDCl_3): δ 159.0, 158.3, 144.9, 136.6, 129.6, 124.7, 121.4, 121.0, 119.0, 117.8, 102.3, 21.8, 19.9, 15.8, -1.9; HRMS (ESI) Calcd for $\text{C}_{18}\text{H}_{24}\text{N}_3\text{Si}$ $[\text{M} + \text{H}]^+$ 310.1740, found 310.1738.

7-Ethyl-1-(pyrimidin-2-yl)-2-(2-(trimethylsilyl)ethyl)-1H-indole (3ia): 58% yield; colorless oil; R_f 0.27 (hexane/EtOAc = 10/1); ^1H NMR (400 MHz, CDCl_3): δ 8.86 (d, J = 4.8 Hz, 2 H), 7.44 (d, J = 6.9 Hz, 1 H), 7.30 (t, J = 4.8 Hz, 1 H), 7.13 (t, J = 7.5 Hz, 1 H), 7.02 (d, J = 7.3 Hz, 1 H), 6.47 (s, 1 H), 2.70-2.65 (m, 2 H), 2.30 (q, J = 7.5 Hz, 2 H), 0.98 (t, J = 7.5 Hz, 3 H), 0.81-0.76 (m, 2 H), -0.04 (s, 9 H); ^{13}C NMR (100 MHz, CDCl_3): δ 159.5, 158.3, 145.1, 136.0, 129.9, 127.8, 122.5, 121.2, 119.2, 117.9, 102.5, 25.7, 21.9, 15.8, 13.9, -1.9; HRMS (ESI) Calcd for $\text{C}_{19}\text{H}_{26}\text{N}_3\text{Si}$ $[\text{M} + \text{H}]^+$ 324.1896, found 324.1892.

1-(Pyridin-2-yl)-2-(2-(trimethylsilyl)ethyl)-1H-indole (3ka): 80% yield; colorless oil; R_f 0.42 (hexane/EtOAc = 10/1); ^1H NMR (400 MHz, CDCl_3): δ 8.69-8.67 (m, 1 H), 7.91-7.87 (m, 1 H), 7.62-7.60 (m, 1 H), 7.46 (d, J = 8.0 Hz, 1 H), 7.38-7.31 (m, 2 H),

7.17-7.14 (m, 2 H), 6.50 (s, 1 H), 2.92-2.88 (m, 2 H), 0.82-0.78 (m, 2 H), -0.02 (s, 9 H); ^{13}C NMR (100 MHz, CDCl_3): δ 151.6, 149.5, 144.2, 138.2, 137.3, 128.6, 121.9, 121.5, 120.9, 120.5, 119.9, 109.9, 101.7, 21.9, 15.9, -1.9; HRMS (ESI) Calcd for $\text{C}_{18}\text{H}_{23}\text{N}_2\text{Si}$ $[\text{M} + \text{H}]^+$ 295.1631, found 295.1631.

2-(2-(Dimethyl(phenyl)silyl)ethyl)-1-(pyrimidin-2-yl)-1H-indole (3ab): 50% yield; colorless oil; R_f 0.33 (hexane/EtOAc = 10/1); ^1H NMR (400 MHz, CDCl_3): δ 8.70 (d, J = 4.8 Hz, 2 H), 8.29 (d, J = 8.0 Hz, 1 H), 7.57-7.55 (m, 3 H), 7.42-7.39 (m, 3 H), 7.26-7.22 (m, 2 H), 7.09 (t, J = 4.8 Hz, 1 H), 6.52 (s, 1 H), 3.27-3.23 (m, 2 H), 1.16-1.12 (m, 2 H), 0.34 (s, 6 H); ^{13}C NMR (100 MHz, CDCl_3): δ 158.2, 158.0, 144.7, 139.0, 137.0, 133.6, 129.3, 128.9, 127.7, 122.4, 121.7, 119.6, 116.9, 113.8, 105.2, 23.9, 15.9, -3.2; HRMS (ESI) Calcd for $\text{C}_{22}\text{H}_{24}\text{N}_3\text{Si}$ $[\text{M} + \text{H}]^+$ 358.1740, found 358.1738.

1-(Pyrimidin-2-yl)-2-(2-(triphenylsilyl)ethyl)-1H-indole (3ac): 31% yield; white solid; m.p. 124.8-125.7 °C; R_f 0.25 (hexane/EtOAc = 10/1); ^1H NMR (400 MHz, CDCl_3): δ 8.60 (d, J = 4.8 Hz, 2 H), 8.36-8.34 (m, 1 H), 7.64-7.57 (m, 7 H), 7.50-7.41 (m, 9 H), 7.28-7.24 (m, 2 H), 7.07 (t, J = 4.8 Hz, 1 H), 6.58 (s, 1 H), 3.45-3.41 (m, 2 H), 1.84-1.80 (m, 2 H); ^{13}C NMR (100 MHz, CDCl_3): δ 158.1, 157.9, 144.6, 137.0, 135.7, 134.8, 129.5,

129.3, 127.9, 122.5, 121.8, 119.7, 116.8, 113.9, 105.3, 24.1, 13.8; HRMS (ESI) Calcd for $C_{32}H_{28}N_3Si$ $[M + H]^+$ 482.2053, found 482.2051.

2-(Bicyclo[2.2.1]heptan-2-yl)-1-(pyrimidin-2-yl)-1H-indole (3ad): 30% yield; colorless oil; R_f 0.33 (hexane/EtOAc = 10/1); 1H NMR (400 MHz, $CDCl_3$): δ 8.82 (d, J = 4.8 Hz, 2 H), 8.08-8.06 (m, 1 H), 7.56-7.53 (m, 1 H), 7.21-7.15 (m, 3 H), 6.49 (s, 1 H), 3.71-3.67 (m, 1 H), 2.38-2.29 (m, 2 H), 1.65-1.63 (m, 1 H), 1.58-1.53 (m, 4 H), 1.38-1.34 (m, 1 H), 1.27-1.24 (m, 1 H), 1.17-1.15 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.4, 158.2, 146.9, 137.2, 129.1, 122.3, 121.5, 119.8, 117.3, 112.9, 103.3, 42.3, 40.6, 38.1, 36.8, 36.1, 29.7, 28.9; HRMS (ESI) Calcd for $C_{19}H_{20}N_3$ $[M + H]^+$ 290.1657, found 290.1655.

Removal of the Pyrimidyl Group

2-(2-(Trimethylsilyl)ethyl)-1H-indole (4aa): A mixture of 1-(pyrimidin-2-yl)-2-(2-(trimethylsilyl)ethyl)-1H-indole (**3aa**, 886 mg, 3 mmol) and freshly prepared sodium ethoxide (408 mg, 6 mmol) in DMSO (5 mL) was stirred at 100 °C under nitrogen atmosphere for 20 h. After cooling to ambient temperature, the reaction mixture was extracted with EtOAc (20 $\times$ 2 mL), and the combined organic phase was

dried over Na₂SO₄. After filtration and evaporation of the solvents under reduced pressure, the crude product was purified by column chromatography on silica gel (hexane/EtOAc = 50/1) to yield the title product (554 mg, 85%) as a yellow solid.

M.p. 93.5-94.3 °C; *R_f* 0.38 (hexane/EtOAc = 10/1); ¹H NMR (400 MHz, CDCl₃): δ 7.87 (brs, 1 H), 7.53 (d, *J* = 7.6 Hz, 1 H), 7.29 (d, *J* = 7.2 Hz, 1 H), 7.14-7.05 (m, 2 H), 6.25 (s, 1 H), 2.80-2.76 (m, 2 H), 1.01-0.96 (m, 2 H), 0.06 (s, 9 H); ¹³C NMR (100 MHz, CDCl₃): δ 142.2, 135.9, 128.8, 120.9, 119.7, 119.5, 110.2, 98.8, 22.5, 15.9, -1.8; HRMS (ESI) Calcd for C₁₃H₂₀NSi [M + H]⁺ 218.1365, found 218.1363.

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Chapter 5 Cobalt-Catalyzed Intramolecular Alkylation Leading to Dihydropyrroloindoles and Tetrahydropyridoindoles

5.1 Introduction

The dihydropyrroloindole and tetrahydropyridoindole core skeletons are present in drug candidates and natural products such as L-888,607 and MK-7246 (Figure 5.1). The former compound is a potent agonist at the human recombinant CRTH2 receptor,¹ and the latter is a CRTH2 antagonist for the potential treatment of respiratory disease.² Consequently, the development of efficient and selective reactions allowing construction of such fused tricyclic indoles is highly desirable.

Figure 5.1 Biologically active compounds containing dihydropyrroloindole or tetrahydropyridoindole moieties

Catalytic intramolecular insertion of an olefin into a C–H bond enables atom-economical construction of cyclic systems. While the Murai group reported seminal studies on rhodium- and ruthenium-catalyzed intramolecular cyclization of 1,5- and 1,6-diene derivatives through chelation-assisted olefin C–H activation (Scheme 5.1a),³ Bergman and Ellman have extensively studied the rhodium-catalyzed C–H activation

reactions of aromatic, heteroaromatic, and olefinic substrates bearing alkene tethers (Scheme 5.1b)^{4,5,6,7} and demonstrated their utility in target-oriented synthesis of carbo- and heterocycles.⁸ Among these studies, they achieved the synthesis of biologically active dihydropyrroloindole derivatives via rhodium-catalyzed C–H activation/intramolecular hydroarylation of *N*-allylindoles (Scheme 5.1c).⁹

(a) Intramolecular cyclization of 1,5- and 1,6-diene derivatives

(b) C–H activation reaction of substrates bearing alkene tethers

(c) Synthesis of biologically active dihydropyrroloindole derivatives

Scheme 5.1 Rh- or Ru-catalyzed intramolecular C–H bond functionalization

As is the case in Scheme 5.1, the rhodium catalysis works most efficiently for 5-*endo*-type cyclization with substrates bearing allylic tethers. On the other hand, homoallylic tethers exhibit a regioselectivity issue because of the two intrinsically feasible modes of cyclization (i.e., 5-*exo* vs. 6-*endo*) as well as facile olefin isomerization

prior to hydroarylation, and have not been employed on the indole platform. Alkene tethers longer than a homoallyl group have never been used on any aromatic or heteroaromatic platforms.¹⁰

In this chapter, we report on our development of cobalt-*N*-heterocyclic carbene (NHC)-catalyzed intramolecular olefin hydroarylation of indole derivatives bearing homoallyl or bishomoallyl tethers (Scheme 5.2). The reaction occurs under mild conditions to afford a series of dihydropyrroloindole and tetrahydropyridoindole derivatives and makes a useful addition to the repertoire of methods for intramolecular olefin hydroarylation. The present study has led to a couple of notable findings, such as (1) regiodivergent formation of five- and six-membered rings by the choice of the NHC ligand and (2) formation of quaternary carbon center, which have been hitherto unknown for olefin hydroarylation through chelation-assisted C–H activation.

Scheme 5.2 Co-catalyzed intramolecular hydroarylation leading to dihydropyrroloindole and tetrahydropyridoindole

5.2 Results and Discussion

We began our study with the intramolecular cyclization of indole **1a** bearing an aldimine moiety on C3 position and a homoallyl group on the nitrogen atom (Table 5.1). In light of our recent work on cobalt-catalyzed, chelation-assisted intermolecular olefin hydroarylation,^{11,12} we screened reaction conditions by using 10 mol% of CoBr₂, 10-20 mol% of a ligand, and 100 mol% of Me₃SiCH₂MgCl at room temperature. Preliminary experiments performed at the relatively high concentration of 0.2 M, identified SIMes•HCl as promising preligand, affording the expected five- and six-membered cyclization products **2a** and **3a** in 39% overall yields with a ratio of 4:1 (entry 1). The reactions became much more sluggish by using other types of ligands, such as mono- and bidentate phosphines (PPh₃, dppe, DPEphos) and phenanthroline (entries 2-5).

Table 5.1 Screening of reaction conditions ^a

Entry	Conc. [M]	Ligand (mol%)	Yield [%] (2a:3a) ^b
1	0.2	SIMes•HCl (10)	39 (4:1)
2	0.2	PPh ₃ (20)	9 (1:1)
3	0.2	dppf (10)	0
4	0.2	DPEphos (10)	6 (1:5)
5	0.2	phen (10)	4 (< 1:20)
6	0.05	SIMes•HCl (10)	84 (8:1) ^c
7	0.05	IMes•HCl (10)	45 (2:1)
8	0.05	SIPr•HCl (10)	46 (1:5)
9	0.05	IPr•HCl (10)	63 (1:5) ^c
10 ^d	0.05	RhCl(PPh ₃) ₃ (10)	37 (1:2)
11 ^e	0.05	[RhCl(coe)] ₂ /PCy ₃ (10)	8 (1:2)

^a The reaction was performed on a 0.3 mmol scale. ^b Determined by GC using *n*-tridecane as an internal standard. ^c Yield and selectivity are based on isolation. ^d The reaction was performed using RhCl(PPh₃)₃ (10 mol%) at 150 °C in toluene. ^e The reaction was performed using [RhCl(coe)]₂ (10 mol%) and PCy₃ (10 mol%) at 150 °C in toluene.

Reducing the concentration to 0.05 M improved the reaction significantly using the SIMes ligand to afford **2a** and **3a**, which were separable by routine chromatography, in 84% overall yields with an 8:1 ratio (entry 6). During examination of other NHC preligands, we found significant effects of their saturation/unsaturation and *N*-substituents on the catalytic activity and regioselectivity. The use of IMes•HCl resulted in a decrease in the product yield and regioselectivity, yet affording **2a** as the major product (entry 7). In contrast, the regioselectivity was reversed when more sterically congested SIPr•HCl and IPr•HCl were employed, the latter affording **2a** and **3a** in 63% overall yields with a 1:5 ratio (entries 8 and 9). In our hands, the reaction of **1a** using a rhodium(I) catalyst

such as $\text{RhCl}(\text{PPh}_3)_3$ or $[\text{RhCl}(\text{coe})_2]_2/\text{PCy}_3$ was sluggish at an elevated temperature of 150 °C with regioselectivity of 1:2 (entries 10 and 11).

With the effective Co-SIMes and Co-IPr catalytic systems in hand, we first examined the reaction of *N*-homoallylindoles bearing different substituents on the indole nucleus (Table 5.2). As a result, regiodivergent cyclization was achieved in moderate to good yields for the substrates **1b-1e** bearing 5-methoxy, 5-chloro, 6-fluoro, and 7-methyl substituents, respectively (entries 3-10). Five-membered ring formation with the Co-SIMes catalyst was achieved with a reasonable level of regioselectivity (4:1 or greater; entries 3, 5, 7, and 9), while the selectivity toward six-membered ring formation with the Co-IPr catalytic system was generally modest (ca. 1:2; entries 4, 6, 8, and 10). For some of the substrates, gentle warming at 40 °C was necessary for the desired cyclization (entries 5, 6, and 8-10). They cyclized rather sluggishly or underwent undesirable isomerization of the homoallyl group to an unreactive allylic group at room temperature.

Table 5.2 Regiodivergent cyclization of *N*-homoallylindoles ^a

Entry	R	Ligand (mol%)	Yield [%] (2 : 3) ^b
1	H (1a)	SIMes•HCl (10)	84 (8:1)
2	H (1a)	IPr•HCl (10)	63 (1:5)
3	5-OMe (1b)	SIMes•HCl (10)	56 (5.2:1)
4	5-OMe (1b)	IPr•HCl (10)	45 (1:2.2)
5 ^c	5-Cl (1c)	SIMes•HCl (10)	55 (4.5:1)
6 ^c	5-Cl (1c)	IPr•HCl (10)	51 (1:2.3)
7	6-F (1d)	SIMes•HCl (10)	82 (9:1)
8 ^c	6-F (1d)	IPr•HCl (10)	71 (1:2.5)
9 ^c	7-Me (1e)	SIMes•HCl (10)	62 (4.1:1)
10 ^c	7-Me (1e)	IPr•HCl (10)	59 (1:2.3)

^a The reaction was performed on a 0.3 mmol scale. ^b Yield and regioisomer ratio are based on isolation. ^c The reaction temperature was 40 °C.

We next investigated cyclization of indole substrates bearing substituted homoallyl or other olefin tethers on the nitrogen atom (Table 5.3). The substrate **1f** with a *gem*-disubstituted olefin moiety smoothly underwent cyclization under Co-IPr catalysis to afford the six-membered ring **3f** with near complete regioselectivity (entry 1), presumably because formation of quaternary carbon center through five-membered ring formation is unfavorable.^c Even with this steric bias, consistent with the regioselectivity trend observed with **1a**, the reaction of **1f** with the Co-SIMes catalyst afforded significant amount of the five-membered ring isomer **2f** (**3f**:**2f** = 1.2:1; entry 2). With an alkyl substituent on the homoallylic terminus, the reaction afforded the five-membered cyclic product (**2g-2i**) in the preference to the six-membered isomer regardless of the ligand used (entries 3-6).

Both the *E*- and *Z*-olefin moieties smoothly participated in the reaction (entries 3 and 6), demonstrating a relatively minor effect of the double bond geometry on the reactivity and the regioselectivity. Given these results, it was rather surprising that the substrate **1j** bearing two methyl groups on the homoallylic terminus cyclized exclusively to the six-membered ring product **3j** under Co-IPr catalysis, albeit in a modest yield (entry 7). Note that the same selectivity was also observed with the Co-SIMes catalyst. To our knowledge, this and the formation of **2f** (entry 2) are the first examples of the formation of a quaternary carbon center by olefin hydroarylation through chelation-assisted C-H activation. Exclusive six-membered ring formation was also observed with the substrate **1k**, which bears a substituent at the allylic position (entry 8). In the same manner, the geometrically more constrained substrate **1l** with a cyclohexenyl moiety afforded the tetracyclic product **3l** having a bicyclo[3.3.1] skeleton (entry 9).

Besides the *N*-homoallylindole substrates, the substrate **1m** with a 2-vinylphenyl group also took part in six-membered ring formation to afford the angular fused tetracyclic product **3m** in 63% yield (entry 10). Furthermore, the substrate **1n** with a bishomoallyl group smoothly cyclized in a 6-*endo* fashion to afford tetrahydropyridoindole **3n**, along with a minor seven-membered ring isomer (entry 11; ratio = 9:1). Note that, unlike the rhodium-catalyzed reaction, *N*-allylindole and *N*-methallylindole derivatives did not cyclize to the corresponding five-membered ring products under either Co-IPr or Co-SIMes catalysis. The Co-IPr catalyst caused isomerization of the allyl group of *N*-allylindole to a 1-propenyl group, other cases resulted in recovery of the starting material. These observations indicate that

five-membered ring formation from the *N*-homoallylindole substrates (e.g., Table 5.2, odd number entries) goes directly through 5-*exo*-type cyclization rather than through isomerization of the olefin moiety followed by 5-*endo*-type cyclization.

Table 5.3 Cyclization of indoles with various olefin tethers ^a

Entry	Substrate	Ligand	Major product	Yield [%] (r.r) ^b
1		IPr		99 (48:1) ^c
2	1f	SIMes		75 (1.2:1) ^c

3	1g (R = Et)	SIMes	2g	78 (9:1) ^d
4	1h (R = (CH ₂) ₂ Ph)	IPr	2h	51 (9:1) ^d
5	1i (R = <i>c</i> -C ₆ H ₁₁)	SIMes	2i	51
6		SIMes	2g	70 (3:1) ^d
	1g'	IPr		65 (8:1) ^d
7 ^e		IPr		40
	1j		3j	
8		IPr		43
	1k		3k	
9 ^f		IPr		43
	1l		3l	
10 ^e		IPr		63
	1m		3m	
11		IPr		73 (9:1) ^g
	1n		3n	

^a Unless otherwise noted, the reaction was performed on a 0.3 mmol scale under conditions described in Table 5.2.

^b Isolated yield except for entry 6 (GC yield). The regioisomer ratio (r.r) was determined by ¹H NMR except for entries 2 and 11 (each isomer separated) and entry 6 (determined by GC). ^c The minor isomer was a five-membered ring. ^d The minor isomer was a six-membered ring. ^e The reaction was performed at 60 °C. ^f The reaction was performed at 40 °C. ^g The minor isomer was a seven-membered ring.

In order to gain insight into the reaction pathways, the C2-deuterated substrate **1a-d** was subjected to Co-SIMes and Co-IPr catalysis (Scheme 5.3). Unlike the case of the parent substrate **1a**, the reaction of **1a-d** was rather sluggish at room temperature (< 10% yield, > 70% recovery). Both of the catalytic systems promoted the reaction at 40 °C to afford the cyclization products **2a-d** and **3a-d** in ca. 60% overall yield with the same regioselectivity as was observed for **1a**. These observations suggest that the rate-limiting step of the present reaction involves cleavage of C2–H bond, while C–C reductive elimination has often been proposed to be rate-determining in the rhodium-catalyzed hydroarylation reaction.¹³ Analysis of the cyclization products showed that the deuterium atom on the C2 position of **1a-d** was largely transferred to the methyl moiety of **2a-d** and C8-methylene moiety of **3a-d**, and that deuterium incorporation into other moieties was almost negligible. These observations are also in contrast to significant H/D scrambling observed for related rhodium-catalyzed intramolecular cyclization reactions.^{b,a}

Scheme 5.3 Deuterium-labeling experiments

In light of the above observations and our previous studies on cobalt-catalyzed

intermolecular olefin hydroarylation, we propose the reaction pathways outlined in Scheme 5.4. First, the C2–H bond of the indole substrate undergoes chelation-assisted oxidative addition to a low-valent cobalt species to afford a cobaltacycle intermediate **A**. Subsequent insertion of the olefin moiety into the Co–H bond leads to either six-membered (**B**) or seven-membered (**C**) cobaltacycle intermediates,¹⁴ which is followed by reductive elimination to afford the product **2a** or **3a**, respectively. Judging from the lack of significant H/D scrambling in the deuterium-labeling experiments, we consider that the C–H oxidative addition and olefin insertion steps are practically irreversible. Thus, the regioselectivity of the reaction is probably determined in the olefin insertion step.

Scheme 5.4 Proposed reaction pathway

Preliminary experiments have shown induction of enantioselectivity in the

intramolecular hydroarylation by chiral nonracemic NHC ligands (Scheme 5.5). Thus, NHC ligands bearing chirality on the backbone or the *N*-substituent promoted cyclization of **1f** to **3f** in modest yield with low but measurable enantiomeric excess, which should have arisen from face-selective insertion of the olefin moiety into the Co-H bond (see Scheme 5.4). Note that asymmetric induction was also observed with other privileged chiral ligands (e.g., BINAP, DuPhos), although the reactivity and enantioselectivity have not reached a practically attractive level (see Experiment Section). Exploration of enantioselective cyclization of **1f** and other substrates deserves further study.

Scheme 5.5 Attempts on enantioselective cyclization of **1f** to **3f**

The present reaction could be scaled up to allow further synthetic transformations of the cyclization product (Scheme 5.6). Thus, cyclization of **1f** to **3f** was achieved on a 3 mmol scale in 92% yield (average of two runs). The formyl group of **3f** was removed according to a palladium-catalyzed decarbonylation protocol, affording product **4** in 88% yield.¹⁵ Reduction of **3f** with NaBH₄ and subsequent aqueous workup resulted in a clean formation of bisindole **5** in 83% yield without any trace of an alcohol intermediate.¹⁶

Finally, **3f** was converted to 3-(2-aminoethyl)indole derivatives **6** through a sequence of Henry reaction with nitromethane, reduction with LiAlH_4 , and protection with a Cbz group.

Scheme 5.6 Transformation of tetrahydropyridoindole product. Reaction conditions: a) $\text{Pd}(\text{OAc})_2$, MS $4\text{\AA}$, cyclohexane, $140\text{ }^\circ\text{C}$, 88%; b) NaBH_4 , MeOH, then 1 M HCl, 83%; c) (i) CH_3NO_2 , NH_4OAc , (ii) LiAlH_4 , (iii) CbzCl , 91% (three steps).

5.3 Conclusion

In summary, we have developed a cobalt-NHC-catalyzed intramolecular olefin hydroarylation reaction on an indole platform, which allows preparation of dihydropyrroloindole and tetrahydropyridoindole derivatives under mild reaction conditions. Importantly, construction of a quaternary carbon center and a bicyclo[3.3.1] skeleton and use of a bis-homoallyl tether have been achieved for the first time in the manifold of intramolecular hydroarylation via C–H activation. The regioselectivity of the cyclization reaction primarily depends on the structure of the olefin tether, but can be controlled by the steric nature of the NHC ligand when the tether is a parent homoallyl group, which represents an example of catalytic regiodivergent synthesis.^{17,18} The origin of the substrate- and ligand-dependent regioselectivity deserves further investigation. In addition, asymmetric induction observed with chiral NHC ligands also holds promise for further studies.

5.4 Experimental Section

Preparation of Substrates for Cobalt-Catalyzed Reaction

A Typical Procedure: (*E*)-*N*-((1-(but-3-en-1-yl)-1*H*-indol-3-yl)methylene)-4-methoxyaniline (**1a**). Sodium hydride (1.2 g, 30 mmol) was added to the solution of 1*H*-indole-3-carbaldehyde (2.90 g, 20 mmol) in DMF (25 mL) at 0 °C. 4-Bromo-1-butene (3.0 mL, 30 mmol) was added dropwise, and the resulting mixture was stirred at room temperature for 12 h. The reaction was quenched by the addition of water at 0 °C, and the resulting mixture was extracted with EtOAc (20 mL $\times$ 3). The combined organic layer was dried over Na₂SO₄ and concentrated under reduced pressure. Purification of the crude product by silica gel chromatography (eluent: hexane/EtOAc = 4/1) afforded 1-(but-3-en-1-yl)-1*H*-indole-3-carbaldehyde as a yellow oil (3.36 g, 84%). ¹H NMR (400 MHz, CDCl₃): δ 9.99 (s, 1 H), 8.34-8.26 (m, 1 H), 7.70 (s, 1 H), 7.42-7.27 (m, 3 H), 5.87-5.67 (m, 1 H), 5.11-5.04 (m, 2 H), 4.24 (t, *J* = 7.1 Hz, 2 H), 2.70-2.55 (m, 2 H). ¹³C NMR (100 MHz, CDCl₃): δ 184.5, 138.3, 137.1, 133.5, 125.5, 124.0, 122.9, 122.2, 118.5, 118.1, 110.0, 46.8, 33.9.

In a 100 mL round bottom flask were added 1-(but-3-en-1-yl)-1*H*-indole-3-carbaldehyde (3.36 g, 16.8 mmol), 4Å molecular sieve (15 g), *p*-anisidine (2.28 g, 18.5 mmol) and toluene (25 mL). The reaction mixture was stirred at room temperature for 12 h. The resulting mixture was filtered and the filtrate was concentrated under reduced pressure. Purification of the crude product by silica gel chromatography (eluent: hexane/EtOAc/Et₃N = 20/1/1) afforded the title compound as a yellow solid (4.45 g, 87%).

m.p. 68.0-68.9 °C; R_f 0.27 (hexane/EtOAc/Et₃N = 5/1/0.5); ¹H NMR (400 MHz, CDCl₃): δ 8.64 (s, 1 H), 8.48-8.46 (m, 1 H), 7.54 (s, 1 H), 7.38-7.36 (m, 1 H), 7.33-7.27 (m, 2 H), 7.24-7.20 (m, 2 H), 6.95-6.91 (m, 2 H), 5.82-5.75 (m, 1 H), 5.11-5.06 (m, 2 H), 4.21 (t, J = 7.1 Hz, 2 H), 3.83 (s, 3 H), 2.64-2.59 (m, 2 H); ¹³C NMR (100 MHz, CDCl₃): δ 159.3, 152.8, 146.6, 137.0, 134.0, 132.7, 126.2, 123.1, 122.2, 121.8, 121.4, 118.0, 115.1, 114.3, 109.6, 55.5, 46.4, 34.2; HRMS (ESI) Calcd for C₂₀H₂₁N₂O [M + H]⁺ 305.1654, found 305.1656.

(*E*)-*N*-((1-(But-3-en-1-yl)-5-methoxy-1*H*-indol-3-yl)methylene)-4-methoxyaniline

(1b): 83% yield; A white solid; m.p. 74.8-75.9 °C; R_f 0.36 (hexane/EtOAc/Et₃N = 5/1/0.5); ¹H NMR (400 MHz, CDCl₃): δ 8.61 (s, 1 H), 8.00 (d, J = 2.5 Hz, 1 H), 7.48 (s, 1 H), 7.26-7.21 (m, 3 H), 6.97-6.91 (m, 3 H), 5.80-5.71 (m, 1 H), 5.09-5.05 (m, 2 H), 4.17 (t, J = 7.1 Hz, 2 H), 3.91 (s, 3 H), 3.83 (s, 3 H), 2.60 (q, J = 7.0 Hz, 2 H); ¹³C NMR (100 MHz, CDCl₃): δ 157.2, 155.6, 152.9, 146.8, 134.0, 133.2, 132.1, 126.7, 121.8, 118.0, 114.7, 114.3, 113.4, 110.4, 103.8, 55.8, 55.5, 46.5, 34.3; HRMS (ESI) Calcd for C₂₁H₂₃N₂O₂ [M + H]⁺ 335.1760, found 335.1781.

(E)-N-((1-(But-3-en-1-yl)-5-chloro-1H-indol-3-yl)methylene)-4-methoxyaniline (1c):

73% yield; A yellow solid; m.p. 73.1-74.5 °C; R_f 0.23 (hexane/EtOAc/Et₃N = 5/1/0.5); ¹H NMR (400 MHz, CDCl₃): δ 8.56 (s, 1 H), 8.50 (s, 1 H), 7.48 (s, 1 H), 7.25-7.20 (m, 4 H), 6.93-6.91 (m, 2 H), 5.79-5.69 (m, 1 H), 5.07-5.03 (m, 2 H), 4.16 (t, J = 7.1 Hz, 2 H), 3.82 (s, 3 H), 2.60-2.55 (m, 2 H); ¹³C NMR (100 MHz, CDCl₃): δ 157.5, 152.1, 146.3, 135.5, 133.8, 133.75, 127.4, 127.1, 123.5, 122.1, 121.9, 118.3, 114.8, 114.3, 110.7, 55.5, 46.6, 34.2; HRMS (ESI) Calcd for C₂₀H₂₀N₂OCl [M + H]⁺ 339.1264, found 339.1261.

(E)-N-((1-(But-3-en-1-yl)-6-fluoro-1H-indol-3-yl)methylene)-4-methoxyaniline (1d):

81% yield; A yellow solid; m.p. 103.7-104.5 °C; R_f 0.33 (hexane/EtOAc/Et₃N = 5/1/0.5); ¹H NMR (400 MHz, CDCl₃): δ 8.59 (s, 1 H), 8.47-8.43 (m, 1 H), 7.49 (s, 1 H), 7.21 (app. d, J = 8.8 Hz, 2 H), 7.05-7.00 (m, 2 H), 6.93 (app. d, J = 8.9 Hz, 2 H), 5.81-5.74 (m, 1 H), 5.11-5.06 (m, 2 H), 4.16 (t, J = 7.0 Hz, 2 H), 3.83 (s, 3 H), 2.61 (app. q, J = 7.0 Hz, 2 H); ¹³C NMR (100 MHz, CDCl₃): δ 160.4 (d, ¹ J_{C-F} = 239 Hz), 157.4, 152.4, 146.4, 137.3 (d, ³ J_{C-F} = 11.6 Hz), 133.7, 133.3 (d, ⁴ J_{C-F} = 2.8 Hz), 123.6 (d, ³ J_{C-F} = 9.8 Hz), 122.5, 121.8, 118.2, 115.4, 114.3, 110.0 (d, ² J_{C-F} = 23.7 Hz), 96.2 (d, ² J_{C-F} = 26.2

Hz), 55.5, 46.5, 34.1; HRMS (ESI) Calcd for $C_{20}H_{20}N_2OF$ $[M + H]^+$ 323.1560, found 323.1566.

(E)-N-((1-(But-3-en-1-yl)-7-methyl-1H-indol-3-yl)methylene)-4-methoxyaniline (1e):

67% yield; A yellow solid; m.p. 104.6-105.5 °C; R_f 0.26 (hexane/EtOAc/Et₃N = 5/1/0.5); 1H NMR (400 MHz, CDCl₃): δ 8.62 (s, 1 H), 8.34 (d, J = 7.9 Hz, 1 H), 7.48 (s, 1 H), 7.21 (app. d, J = 8.8 Hz, 2 H), 7.16-7.13 (m, 1 H), 7.02 (d, J = 7.1 Hz, 1 H), 6.92 (app. d, J = 8.8 Hz, 2 H), 5.83-5.73 (m, 1 H), 5.12-5.07 (m, 2 H), 4.41 (t, J = 7.2 Hz, 2 H), 3.82 (s, 3 H), 2.73 (s, 3 H), 2.57 (q, J = 7.1 Hz, 2 H); ^{13}C NMR (100 MHz, CDCl₃): δ 157.3, 152.7, 146.7, 135.7, 134.3, 133.7, 127.4, 126.4, 121.9, 121.6, 120.8, 120.1, 118.1, 115.0, 114.3, 55.5, 48.8, 36.6, 19.9; HRMS (ESI) Calcd for $C_{21}H_{23}N_2O$ $[M + H]^+$ 319.1810, found 319.1816.

(E)-4-Methoxy-N-((1-(3-methylbut-3-en-1-yl)-1H-indol-3-yl)methylene)aniline (1f):

The precursor 1-(3-methylbut-3-en-1-yl)-1H-indole-3-carbaldehyde was prepared from indole-3-carboxaldehyde and 3-methylbut-3-en-1-yl 4-methylbenzenesulfonate in the presence of NaH in DMF; 82% yield; A yellow solid; m.p. 88.5-89.6 °C; R_f 0.33 (hexane/EtOAc/Et₃N = 5/1/0.5); 1H NMR (400 MHz, CDCl₃): δ 8.63 (s, 1 H), 8.48-8.46

(m, 1 H), 7.53 (s, 1 H), 7.38-7.36 (m, 1 H), 7.33-7.27 (m, 2 H), 7.23-7.21 (m, 2 H), 6.93-6.91 (m, 2 H), 4.83 (s, 1 H), 4.70 (s, 1 H), 4.26 (t, $J = 7.4$ Hz, 2 H), 3.82 (s, 3 H), 2.56 (t, $J = 7.3$ Hz, 2 H), 1.78 (s, 3 H); ^{13}C NMR (100 MHz, CDCl_3): δ 157.3, 152.7, 146.6, 141.6, 137.0, 132.7, 126.2, 123.1, 122.2, 121.8, 121.4, 115.1, 114.3, 113.0, 109.5, 55.5, 45.4, 37.9, 22.5; HRMS (ESI) Calcd for $\text{C}_{21}\text{H}_{23}\text{N}_2\text{O}$ $[\text{M} + \text{H}]^+$ 319.1810, found 319.1804.

(*E*)-*N*-((1-((*E*)-Hex-3-en-1-yl)-1*H*-indol-3-yl)methylene)-4-methoxyaniline (1g): The precursor (*E*)-1-(hex-3-en-1-yl)-1*H*-indole-3-carbaldehyde was prepared from indole-3-carboxaldehyde and (*E*)-hex-3-en-1-yl 4-methylbenzenesulfonate in the presence of NaH in DMF; 72% yield; A yellow solid; m.p. 63.7-65.0 °C; R_f 0.37 (hexane/EtOAc/Et₃N = 5/1/0.5); ^1H NMR (400 MHz, CDCl_3): δ 8.64 (s, 1 H), 8.48-8.45 (m, 1 H), 7.53 (s, 1 H), 7.38-7.36 (m, 1 H), 7.32-7.26 (m, 2 H), 7.22 (app. d, $J = 8.9$ Hz, 2 H), 6.93 (app. d, $J = 8.9$ Hz, 2 H), 5.51-5.46 (m, 1 H), 5.40-5.36 (m, 1 H), 4.16 (t, $J = 7.1$ Hz, 2 H), 3.83 (s, 3 H), 2.54 (q, $J = 6.8$ Hz, 2 H), 2.00-1.93 (m, 2 H), 0.91 (t, $J = 7.4$ Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3): δ 157.3, 152.9, 146.8, 137.1, 135.9, 132.9, 126.2, 124.3, 123.0, 122.2, 121.9, 121.4, 115.0, 114.3, 109.8, 55.5, 47.0, 33.2, 25.6, 13.6; HRMS (ESI) Calcd for $\text{C}_{22}\text{H}_{25}\text{N}_2\text{O}$ $[\text{M} + \text{H}]^+$ 333.1967, found 333.1964.

(E)-N-((1-((Z)-hex-3-en-1-yl)-1H-indol-3-yl)methylene)-4-methoxyaniline (1g'): The precursor (Z)-1-(hex-3-en-1-yl)-1H-indole-3-carbaldehyde was prepared from indole-3-carboxaldehyde and (Z)-hex-3-en-1-yl 4-methylbenzenesulfonate in the presence of NaH in DMF; 70% yield; A yellow oil; R_f 0.37 (hexane/EtOAc/Et₃N = 5/1/0.5); ¹H NMR (400 MHz, CDCl₃): δ 8.64 (s, 1 H), 8.47-8.45 (m, 1 H), 7.55 (s, 1 H), 7.40-7.35 (m, 1 H), 7.33-7.27 (m, 2 H), 7.22 (app. d, J = 8.9 Hz, 2 H), 6.92 (app. d, J = 8.9 Hz, 2 H), 5.56-5.42 (m, 1 H), 5.38-5.26 (m, 1 H), 4.16 (t, J = 7.1 Hz, 2 H), 3.83 (s, 3 H), 2.60 (q, J = 7.2 Hz, 2 H), 1.97-1.86 (m, 2 H), 0.87 (t, J = 7.5 Hz, 3 H); ¹³C NMR (100 MHz, CDCl₃): δ 157.3, 152.8, 146.7, 137.0, 135.3, 132.8, 126.2, 123.8, 123.0, 122.2, 121.9, 121.4, 115.0, 114.3, 109.6, 55.5, 46.7, 27.8, 20.5, 14.0; HRMS (ESI) Calcd for C₂₂H₂₅N₂O [M + H]⁺ 333.1967, found 333.1966.

(E)-4-Methoxy-N-((1-((E)-6-phenylhex-3-en-1-yl)-1H-indol-3-yl)methylene)aniline

(1h): The precursor (E)-1-(6-phenylhex-3-en-1-yl)-1H-indole-3-carbaldehyde was prepared from indole-3-carboxaldehyde and (E)-6-phenylhex-3-en-1-yl 4-methylbenzenesulfonate in the presence of NaH in DMF; 58% yield; A yellow oil; R_f 0.23 (hexane/EtOAc/Et₃N = 5/1/0.5); ¹H NMR (400 MHz, CDCl₃): δ 8.55 (s, 1 H),

8.50-8.48 (m, 1 H), 7.30 (s, 1 H), 7.24-7.18 (m, 7 H), 7.14-7.10 (m, 1 H), 7.02-7.00 (m, 2 H), 6.88 (app. d, $J = 8.8$ Hz, 2 H), 5.47-5.40 (m, 1 H), 5.29-5.23 (m, 1 H), 3.84 (t, $J = 7.0$ Hz, 2 H), 3.73 (s, 3 H), 2.45-2.37 (m, 4 H), 2.13 (q, $J = 7.4$ Hz, 2 H); ^{13}C NMR (100 MHz, CDCl_3): δ 157.5, 152.9, 146.8, 141.8, 137.2, 133.3, 132.4, 128.7, 128.4, 126.4, 126.1, 125.5, 123.2, 122.6, 122.1, 121.6, 115.2, 114.5, 109.9, 55.6, 46.5, 35.6, 29.3, 28.0; HRMS (ESI) Calcd for $\text{C}_{28}\text{H}_{29}\text{N}_2\text{O}$ $[\text{M} + \text{H}]^+$ 409.2280, found 409.2283.

(*E*)-*N*-(1-((*E*)-4-Cyclohexylbut-3-en-1-yl)-1*H*-indol-3-yl)methylene-4-methoxyaniline

(1i): The precursor (*E*)-1-(4-cyclohexylbut-3-en-1-yl)-1*H*-indole-3-carbaldehyde was prepared from indole-3-carboxaldehyde and (*E*)-4-cyclohexylbut-3-en-1-yl 4-methylbenzenesulfonate in the presence of NaH in DMF; 78% yield; A yellow solid; m.p. 76.5-77.4 °C; R_f 0.24 (hexane/EtOAc/Et₃N = 5/1/0.5); ^1H NMR (400 MHz, CDCl_3): δ 8.64 (s, 1 H), 8.45-8.43 (m, 1 H), 7.56 (s, 1 H), 7.39-7.37 (m, 1 H), 7.33-7.26 (m, 2 H), 7.23-7.21 (m, 2 H), 6.94-6.92 (m, 2 H), 5.35-5.23 (m, 2 H), 4.17 (t, $J = 7.1$ Hz, 2 H), 3.83 (s, 3 H), 2.62 (q, $J = 7.3$ Hz, 2 H), 2.07-1.98 (m, 1 H), 1.64-1.60 (m, 3 H), 1.42-1.38 (m, 2 H), 1.21-1.07 (m, 3 H), 1.01-0.92 (m, 2 H); ^{13}C NMR (100 MHz, CDCl_3): δ 157.3, 152.7, 146.7, 139.7, 137.0, 132.7, 126.3, 123.0, 122.4, 122.2, 121.8, 121.4, 115.0, 114.3, 109.6, 55.5, 46.9, 36.5, 33.1, 28.1, 25.9, 25.8; HRMS (ESI) Calcd for $\text{C}_{26}\text{H}_{31}\text{N}_2\text{O}$ $[\text{M} + \text{H}]^+$ 387.2436, found 387.2433.

(E)-4-Methoxy-N-((1-(4-methylpent-3-en-1-yl)-1H-indol-3-yl)methylene)aniline (1j):

83% yield; A yellow solid; m.p. 79.5-80.6 °C; R_f 0.23 (hexane/EtOAc/Et₃N = 5/1/0.5); ¹H NMR (400 MHz, CDCl₃): δ 8.64 (s, 1 H), 8.47-8.45 (m, 1 H), 7.53 (s, 1 H), 7.38-7.36 (m, 1 H), 7.33-7.27 (m, 2 H), 7.23 (app. d, J = 8.8 Hz, 2 H), 6.93 (app. d, J = 8.9 Hz, 2 H), 5.13 (app. t, J = 7.4 Hz, 1 H), 4.13 (t, J = 7.1 Hz, 2 H), 3.83 (s, 3 H), 2.54 (q, J = 7.0 Hz, 2 H), 1.67 (s, 3 H), 1.47 (s, 3 H); ¹³C NMR (100 MHz, CDCl₃): δ 157.3, 152.8, 146.7, 137.1, 135.5, 132.8, 126.2, 123.0, 122.2, 121.9, 121.4, 119.5, 115.0, 114.3, 109.6, 55.5, 46.7, 28.8, 25.7, 17.6; HRMS (ESI) Calcd for C₂₂H₂₅N₂O [M + H]⁺ 333.1967, found 333.1969.

(E)-4-Methoxy-N-((1-(2-methylbut-3-en-1-yl)-1H-indol-3-yl)methylene)aniline (1k):

The precursor 1-(2-methylbut-3-en-1-yl)-1H-indole-3-carbaldehyde was prepared from indole-3-carboxaldehyde and 2-methylbut-3-en-1-yl 4-methylbenzenesulfonate in the presence of NaH in DMF; 97% yield; A yellow oil; R_f 0.24 (hexane/EtOAc/Et₃N = 5/1/0.5); ¹H NMR (400 MHz, CDCl₃): δ 8.65 (s, 1 H), 8.48-8.46 (m, 1 H), 7.52 (s, 1 H), 7.36-7.27 (m, 3 H), 7.23 (app. d, J = 8.8 Hz, 2 H), 6.93 (app. d, J = 8.8 Hz, 2 H), 5.83-5.74 (m, 1 H), 5.07-5.03 (m, 2 H), 4.15-4.01 (m, 2 H), 3.86 (s, 3 H), 2.86-2.80 (m, 1

H), 1.08 (d, $J = 6.8$ Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3): δ 157.3, 152.8, 146.7, 140.0, 137.3, 133.4, 126.1, 123.0, 122.2, 121.8, 121.4, 115.7, 114.9, 114.3, 109.8, 55.5, 52.6, 38.4, 17.4; HRMS (ESI) Calcd for $\text{C}_{21}\text{H}_{23}\text{N}_2\text{O}$ $[\text{M} + \text{H}]^+$ 319.1810, found 319.1801.

(*E*)-*N*-((1-(Cyclohex-2-en-1-ylmethyl)-1*H*-indol-3-yl)methylene)-4-methoxyaniline

(11): The precursor 1-(cyclohex-2-en-1-ylmethyl)-1*H*-indole-3-carbaldehyde was prepared from indole-3-carboxaldehyde and cyclohex-2-en-1-ylmethyl 4-methylbenzenesulfonate in the presence of NaH in DMF; 88% yield; A yellow solid; m.p. 97.9-99.0 °C; R_f 0.33 (hexane/EtOAc/Et₃N = 5/1/0.5); ^1H NMR (400 MHz, CDCl_3): δ 8.66 (s, 1 H), 8.47-8.45 (m, 1 H), 7.56 (s, 1 H), 7.39-7.37 (m, 1 H), 7.33-7.27 (m, 2 H), 7.23 (app. d, $J = 8.9$ Hz, 2 H), 6.93 (app. d, $J = 8.9$ Hz, 2 H), 5.84-5.81 (m, 1 H), 5.53-5.50 (m, 1 H), 4.15-3.99 (m, 2 H), 3.83 (s, 3 H), 2.76-2.72 (m, 1 H), 2.03-2.02 (m, 2 H), 1.73-1.68 (m, 2 H), 1.57-1.48 (m, 1 H), 1.35-1.28 (m, 1 H); ^{13}C NMR (100 MHz, CDCl_3): δ 157.4, 152.8, 146.8, 137.5, 133.1, 129.8, 127.3, 126.2, 123.1, 122.2, 121.9, 121.4, 115.1, 114.3, 109.9, 55.5, 51.9, 36.1, 26.8, 25.2, 20.5; HRMS (ESI) Calcd for $\text{C}_{23}\text{H}_{25}\text{N}_2\text{O}$ $[\text{M} + \text{H}]^+$ 345.1967, found 345.1966.

(*E*)-4-Methoxy-*N*-((1-(2-vinylphenyl)-1*H*-indol-3-yl)methylene)aniline (1m): The precursor 1-(2-vinylphenyl)-1*H*-indole-3-carbaldehyde was prepared from indole through copper-catalyzed *N*-arylation with 1-bromo-2-vinylbenzene¹⁹ and the Vilsmeier–Haack reaction; 68% yield; A yellow solid; m.p. 119.1-119.8 °C; *R_f* 0.35 (hexane/EtOAc/Et₃N = 5/1/0.5); ¹H NMR (400 MHz, CDCl₃): δ 8.71 (s, 1 H), 8.58 (d, *J* = 7.7 Hz, 1 H), 7.78-7.76 (m, 1 H), 7.60 (s, 1 H), 7.50-7.40 (m, 2 H), 7.36-7.29 (m, 2 H), 7.28-7.24 (m, 3 H), 7.08 (d, *J* = 8.1 Hz, 1 H), 6.95-6.93 (m, 2 H), 6.31 (dd, *J*₁ = 11.0 Hz, *J*₂ = 17.5 Hz, 1 H), 5.75 (d, *J* = 17.4 Hz, 1 H), 5.21 (d, *J* = 11.3 Hz, 1 H), 3.83 (s, 3 H); ¹³C NMR (100 MHz, CDCl₃): δ 157.5, 152.7, 146.5, 138.7, 136.1, 135.1, 134.1, 131.6, 128.9, 128.7, 128.1, 126.4, 125.7, 123.8, 122.4, 122.0, 121.9, 117.0, 116.8, 114.3, 111.1, 55.5; HRMS (ESI) Calcd for C₂₄H₂₁N₂O [M + H]⁺ 353.1654, found 353.1647.

(*E*)-4-Methoxy-*N*-((1-(pent-4-en-1-yl)-1*H*-indol-3-yl)methylene)aniline (1n): 86% yield; A yellow oil; *R_f* 0.28 (hexane/EtOAc/Et₃N = 5/1/0.5); ¹H NMR (400 MHz, CDCl₃): δ 8.64 (s, 1 H), 8.47-8.45 (m, 1 H), 7.55 (s, 1 H), 7.37-7.35 (m, 1 H), 7.32-7.27 (m, 2 H), 7.22 (app. d, *J* = 8.8 Hz, 2 H), 6.93 (app. d, *J* = 8.9 Hz, 2 H), 5.83-5.77 (m, 1 H), 5.08-5.03 (m, 2 H), 4.16 (t, *J* = 7.0 Hz, 2 H), 3.83 (s, 3 H), 2.13-2.07 (m, 2 H), 2.02-1.96 (m, 2 H); ¹³C NMR (100 MHz, CDCl₃): δ 157.3, 152.8, 146.7, 137.2, 137.0, 132.7, 126.2, 123.1, 122.2, 121.9, 121.5, 116.0, 115.1, 114.3, 109.7, 55.5, 46.0, 30.7, 29.0; HRMS (ESI) Calcd for C₂₁H₂₃N₂O [M + H]⁺ 319.1810, found 319.1807.

(*E*)-*N*-((1-(but-3-en-1-yl)-2-deuterio-1*H*-indol-3-yl)methylene)-4-methoxyaniline

(1a-d): Phosphorus oxychloride (0.51 g, 3.3 mmol) was added dropwise to DMF (7 mL) at 0 °C. The mixture was stirred for 20 min, followed by the dropwise addition of a solution of 2-deuterio-1*H*-indole (0.35 g, 3.0 mmol, 90% D content, prepared according to the literature procedure²⁰) in DMF (3 mL). The resulting mixture was stirred at 35 °C for 1 h, followed by the addition of pieces of ice and 20% NaOH aqueous solution. The reaction mixture was refluxed for 6 h, and then allowed to room temperature and poured into ice water. The precipitate, 2-deuterio-1*H*-indole-3-carbaldehyde, was collected and dried under vacuum (0.32 g, 73%). This crude product, without further purification, was subjected to *N*-homoallylation and condensation with *p*-anisidine according to the typical procedure to afford the title compound. ¹H NMR (400 MHz, CDCl₃): δ 8.65 (s, 1 H), 8.46 (dd, *J*₁ = 6.9, *J*₂ = 1.4 Hz, 1 H), 7.55 (s, 0.1 H), 7.41-7.35 (m, 1 H), 7.34-7.27 (m, 2 H), 7.24-7.18 (m, 2 H), 6.96-6.89 (m, 2 H), 5.79 (ddt, *J*₁ = 11.1, *J*₂ = 9.7, *J*₃ = 6.9 Hz, 1 H), 5.14-4.99 (m, 2 H), 4.23 (t, *J* = 7.1 Hz, 2 H), 3.83 (s, 3 H), 2.63 (q, *J* = 7.0 Hz, 2 H).

Cobalt-Catalyzed Intramolecular Alkylation Reaction

A Typical Procedure: 1-methyl-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole-9-carbaldehyde (**2a**). In a Schlenk tube were placed CoBr₂ (6.6 mg, 0.03 mmol), SiMes•HCl (10.3 mg, 0.03 mmol), **1a** (91.3 mg, 0.3 mmol), and THF (5.7 mL). To the

solution was added $\text{Me}_3\text{SiCH}_2\text{MgCl}$ (1.03 M in THF, 0.29 mL, 0.3 mmol) at 0 °C. After stirring for 30 min, the reaction mixture was allowed to warm to room temperature and stirred for 12 h. The reaction was quenched by the addition of 3 M HCl (1.5 mL). The resulting mixture was stirred at room temperature for 2 h, and then extracted with ethyl acetate (10 mL $\times$ 3). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the crude product by silica gel chromatography (eluent: hexane/EtOAc = 5/1) afforded the title compound **2a** as a pale yellow solid (50.2 mg, 84%) along with its isomer 6,7,8,9-tetrahydropyrido[1,2-*a*]indole-10-carbaldehyde (**3a**, 5.6 mg, 9%).

m.p. 147.3-148.1 °C; R_f 0.46 (hexane/EtOAc = 1/1); ^1H NMR (400 MHz, CDCl_3): δ 10.08 (s, 1 H), 8.22-8.20 (m, 1 H), 7.27-7.20 (m, 3 H), 4.16-4.10 (m, 1 H), 4.05-3.99 (m, 1 H), 3.69-3.64 (m, 1 H), 2.88-2.83 (m, 1 H), 2.28-2.23 (m, 1 H), 1.48 (d, J = 7.1 Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3): δ 183.1, 159.3, 132.6, 129.9, 122.8, 122.6, 121.5, 110.0, 109.9, 43.7, 35.5, 33.0, 20.2; HRMS (ESI) Calcd for $\text{C}_{13}\text{H}_{14}\text{NO}$ $[\text{M} + \text{H}]^+$ 200.1075, found 200.1071.

6,7,8,9-Tetrahydropyrido[1,2-*a*]indole-10-carbaldehyde (3a, Table 5.2, entry 2): 63% overall yield (**2a**:**3a** = 1:5.0, two isomers separated); A yellow solid; m.p. 124.7-125.7 °C;

R_f 0.43 (hexane/EtOAc = 1/1); ^1H NMR (400 MHz, CDCl_3): δ 10.09 (s, 1 H); 8.18 (d, J = 7.2 Hz, 1 H), 7.30-7.24 (m, 3 H), 4.03 (t, J = 6.2 Hz, 2 H), 3.24 (t, J = 6.4 Hz, 2 H), 2.14-2.08 (m, 2 H), 1.98-1.92 (m, 2 H); ^{13}C NMR (100 MHz, CDCl_3): δ 183.4, 148.2, 136.4, 125.8, 123.0, 122.6, 120.5, 112.8, 109.1, 42.3, 22.6, 22.3, 19.5; HRMS (ESI) Calcd for $\text{C}_{13}\text{H}_{14}\text{NO}$ $[\text{M} + \text{H}]^+$ 200.1075, found 200.1077.

7-Methoxy-1-methyl-2,3-dihydro-1H-pyrrolo[1,2-a]indole-9-carbaldehyde (2b, Table 5.2, entry 3): 56% overall yield (**2b:3b** = 5.2:1, two isomers separated); A yellow solid; m.p. 119.4-120.2 °C; R_f 0.41 (hexane/EtOAc = 1/1); ^1H NMR (400 MHz, CDCl_3): δ 10.05 (s, 1 H), 7.75 (d, J = 2.1 Hz, 1 H), 7.10 (d, J = 8.7 Hz, 1 H), 6.85 (dd, J_1 = 8.8 Hz, J_2 = 2.4 Hz, 1 H), 4.16-4.10 (m, 1 H), 4.05-3.99 (m, 1 H), 3.88 (s, 3 H), 3.71-3.65 (m, 1 H), 2.91-2.82 (m, 1 H), 2.30-2.22 (m, 1 H), 1.49 (d, J = 7.0 Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3): δ 183.0, 159.5, 156.5, 130.7, 127.6, 112.8, 110.7, 110.0, 103.7, 55.8, 44.0, 35.6, 33.2, 20.4.; HRMS (ESI) Calcd for $\text{C}_{14}\text{H}_{16}\text{NO}_2$ $[\text{M} + \text{H}]^+$ 230.1181, found 230.1177.

2-Methoxy-6,7,8,9-tetrahydropyrido[1,2-a]indole-10-carbaldehyde (3b, Table 5.2, entry 4): 45% overall yield (**2b:3b** = 1:2.2, two isomers separated); A white solid; m.p.

148.5-148.6 °C; R_f 0.35 (hexane/EtOAc = 1/1); ^1H NMR (400 MHz, CDCl_3): δ 10.07 (s, 1 H), 7.73 (s, 1 H), 7.15 (d, J = 8.8 Hz, 1 H), 6.89-6.86 (m, 1 H), 4.03 (t, J = 6.1 Hz, 2 H), 3.89 (s, 3 H), 3.25 (t, J = 6.4 Hz, 2 H), 2.13-2.10 (m, 2 H), 1.97-1.94 (m, 2 H); ^{13}C NMR (100 MHz, CDCl_3): δ 183.2, 156.9, 131.4, 126.6, 114.6, 112.9, 112.6, 109.8, 102.8, 55.8, 42.4, 22.5, 22.4, 19.5; HRMS (ESI) Calcd for $\text{C}_{14}\text{H}_{16}\text{NO}_2$ $[\text{M} + \text{H}]^+$ 230.1181, found 230.1182.

7-Chloro-1-methyl-2,3-dihydro-1H-pyrrolo[1,2-a]indole-9-carbaldehyde (2c, Table 5.2, entry 5): 55% overall yield (**2c:3c** = 4.5:1, two isomers separated); A yellow solid; m.p. 114.9-115.2 °C; R_f 0.40 (hexane/EtOAc = 1/1); ^1H NMR (400 MHz, CDCl_3): δ 10.03 (s, 1 H), 8.18 (d, J = 1.7 Hz, 1 H), 7.17-7.09 (m, 2 H), 4.18-4.12 (m, 1 H), 4.08-4.02 (m, 1 H), 3.72-3.67 (m, 1 H), 2.94-2.88 (m, 1 H), 2.32-2.27 (m, 1 H), 1.51 (d, J = 7.1 Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3): δ 182.9, 160.1, 131.1, 131.0, 128.6, 123.2, 121.3, 110.9, 109.7, 44.0, 35.7, 33.3, 20.3; HRMS (ESI) Calcd for $\text{C}_{13}\text{H}_{13}\text{NOCl}$ $[\text{M} + \text{H}]^+$ 234.0686, found 234.0691.

2-Chloro-6,7,8,9-tetrahydropyrido[1,2-a]indole-10-carbaldehyde (3c, Table 5.2, entry 6): 51% overall yield (**2c:3c** = 1:2.3, two isomers separated); A yellow solid; m.p.

135.3-136.1 °C; R_f 0.35 (hexane/EtOAc = 1/1); ^1H NMR (400 MHz, CDCl_3): δ 10.06 (s, 1 H), 8.17 (s, 1 H), 7.18-7.14 (m, 2 H), 4.05 (t, J = 6.1 Hz, 2 H), 3.27 (t, J = 6.4 Hz, 2 H), 2.16-2.13 (m, 2 H), 2.01-1.97 (m, 2 H); ^{13}C NMR (100 MHz, CDCl_3): δ 183.2, 149.0, 134.9, 129.0, 126.8, 123.0, 120.3, 112.5, 110.1, 42.5, 22.6, 22.3, 19.4; HRMS (ESI) Calcd for $\text{C}_{13}\text{H}_{13}\text{NOCl}$ $[\text{M} + \text{H}]^+$ 234.0686, found 234.0681.

6-Fluoro-1-methyl-2,3-dihydro-1H-pyrrolo[1,2-a]indole-9-carbaldehyde (2d, Table 5.2, entry 7): 82% overall yield (**2d:3d** = 9:1, two isomers separated); A yellow solid; m.p. 102.5-103.4 °C; R_f 0.50 (hexane/EtOAc = 1/1); ^1H NMR (400 MHz, CDCl_3): δ 10.06 (s, 1 H), 8.15-8.12 (m, 1 H), 7.02-6.96 (m, 1 H), 6.90-6.88 (m, 1 H), 4.15-4.09 (m, 1 H), 4.04-3.98 (m, 1 H), 3.72-3.67 (m, 1 H), 2.92-2.86 (m, 1 H), 2.33-2.26 (m, 1 H), 1.51 (d, J = 7.0 Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3): δ 183.0, 159.9 (d, $^1J_{\text{C-F}}$ = 239 Hz), 159.86, 132.8 (d, $^3J_{\text{C-F}}$ = 12.0 Hz), 126.1, 122.7 (d, $^3J_{\text{C-F}}$ = 9.9 Hz), 110.8 (d, $^2J_{\text{C-F}}$ = 23.5 Hz), 110.0, 96.8 (d, $^2J_{\text{C-F}}$ = 26.2 Hz), 43.8, 35.6, 33.0, 20.3; HRMS (ESI) Calcd for $\text{C}_{13}\text{H}_{13}\text{NOF}$ $[\text{M} + \text{H}]^+$ 218.0981, found 218.0981.

3-Fluoro-6,7,8,9-tetrahydropyrido[1,2-a]indole-10-carbaldehyde (3d, Table 5.2, entry 8): 71% overall yield (**2d:3d** = 1:2.5, two isomers separated); A yellow solid; m.p.

160.0-161.2 °C; R_f 0.39 (hexane/EtOAc = 1/1); ^1H NMR (400 MHz, CDCl_3): δ 10.04 (s, 1 H), 8.12-8.09 (m, 1 H), 7.02-6.97 (m, 1 H), 6.91-6.89 (m, 1 H), 3.96 (t, J = 6.2 Hz, 2 H), 3.22 (t, J = 6.4 Hz, 2 H), 2.15-2.09 (m, 2 H), 1.98-1.94 (m, 2 H); ^{13}C NMR (100 MHz, CDCl_3): δ 183.2, 159.9 (d, $^1J_{\text{C-F}}$ = 238 Hz), 148.8, 136.6 (d, $^3J_{\text{C-F}}$ = 11.5 Hz), 121.9, 121.6 (d, $^3J_{\text{C-F}}$ = 9.4 Hz), 112.8, 111.1 (d, $^2J_{\text{C-F}}$ = 23.6 Hz), 96.0 (d, $^2J_{\text{C-F}}$ = 26.1 Hz), 42.4, 22.4, 22.2, 19.4; HRMS (ESI) Calcd for $\text{C}_{13}\text{H}_{13}\text{NOF}$ $[\text{M} + \text{H}]^+$ 218.0981, found 218.0980.

1,5-Dimethyl-2,3-dihydro-1H-pyrrolo[1,2-a]indole-9-carbaldehyde (2e, Table 5.2, entry 9): 62% overall yield (**2e:3e** = 4.1:1, two isomers separated); A white solid; m.p. 136.8-137.6 °C; R_f 0.46 (hexane/EtOAc = 1/1); ^1H NMR (400 MHz, CDCl_3): δ 10.09 (s, 1 H), 8.05 (d, J = 7.9 Hz, 1 H), 7.12 (t, J = 7.5 Hz, 1 H), 6.96 (d, J = 7.3 Hz, 1 H), 4.49-4.42 (m, 1 H), 4.38-4.32 (m, 1 H), 3.68-3.63 (m, 1 H), 2.88-2.82 (m, 1 H), 2.62 (s, 3 H), 2.28-2.23 (m, 1 H), 1.48 (d, J = 7.0 Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3): δ 183.3, 159.7, 132.3, 130.3, 124.7, 122.9, 121.0, 119.3, 109.9, 46.9, 35.8, 32.3, 20.5, 17.9; HRMS (ESI) Calcd for $\text{C}_{14}\text{H}_{16}\text{NO}$ $[\text{M} + \text{H}]^+$ 214.1232, found 214.1237.

4-Methyl-6,7,8,9-tetrahydropyrido[1,2-a]indole-10-carbaldehyde (3e, Table 5.2,

entry 10): 59% overall yield (**2e:3e** = 1:2.3, two isomers separated); A yellow solid; m.p. 163.3-164.4 °C; R_f 0.40 (hexane/EtOAc = 1/1); ^1H NMR (400 MHz, CDCl_3): δ 10.12 (s, 1 H), 8.07 (d, J = 7.8 Hz, 1 H), 7.12 (t, J = 7.5 Hz, 1 H), 6.94 (d, J = 7.2 Hz, 1 H), 4.47 (t, J = 6.2 Hz, 2 H), 3.27 (t, J = 6.5 Hz, 2 H), 2.72 (s, 3 H), 2.12-2.06 (m, 2 H), 1.94-1.88 (m, 2 H); ^{13}C NMR (100 MHz, CDCl_3): δ 183.6, 148.2, 135.6, 126.8, 126.0, 122.9, 121.3, 118.4, 112.8, 46.1, 23.3, 23.1, 20.4, 19.0; HRMS (ESI) Calcd for $\text{C}_{14}\text{H}_{16}\text{NO}$ $[\text{M} + \text{H}]^+$ 214.1232, found 214.1230.

8-Methyl-6,7,8,9-tetrahydropyrido[1,2-*a*]indole-10-carbaldehyde (3f, Table 5.3, entry 1): 99% yield (**2f:3f** = 1:48, obtained as a mixture); A yellow solid; m.p. 142.1-143.4 °C; R_f 0.24 (hexane/EtOAc = 3/1); ^1H NMR (400 MHz, CDCl_3): δ 9.93 (s, 1 H), 8.08 (d, J = 7.3 Hz, 1 H), 7.19-7.12 (m, 3 H), 4.08-4.03 (m, 1 H), 3.78-3.70 (m, 1 H), 3.29-3.24 (m, 1 H), 2.52-2.45 (m, 1 H), 2.05-1.99 (m, 1 H), 1.92-1.86 (m, 1 H), 1.66-1.55 (m, 1 H), 1.07 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3): δ 183.2, 148.2, 136.2, 125.8, 122.9, 122.5, 120.4, 112.5, 109.1, 41.7, 30.4, 30.0, 26.2, 21.0; HRMS (ESI) Calcd for $\text{C}_{14}\text{H}_{16}\text{NO}$ $[\text{M} + \text{H}]^+$ 214.1232, found 214.1231.

1,1-Dimethyl-2,3-dihydro-1H-pyrrolo[1,2-*a*]indole-9-carbaldehyde (2f, Table 5.3,

entry 2): 75% overall yield (**2f:3f** = 1:1.2, two isomers separated); A yellow solid; m.p. 119.3-120.5 °C; R_f 0.21 (hexane/EtOAc = 5/1); ^1H NMR (400 MHz, CDCl_3): δ 10.23 (s, 1 H), 8.25-8.23 (m, 1 H), 7.28-7.24 (m, 3 H), 4.15 (t, J = 7.0 Hz, 2 H), 2.51 (t, J = 7.1 Hz, 2 H), 1.60 (s, 6 H); ^{13}C NMR (100 MHz, CDCl_3): δ 182.9, 161.9, 132.4, 130.2, 122.9, 122.8, 121.9, 110.0, 109.3, 43.5, 43.3, 40.8, 28.2; HRMS (ESI) Calcd for $\text{C}_{14}\text{H}_{16}\text{NO}$ [$\text{M} + \text{H}$] $^+$ 214.1232, found 214.1234.

1-Propyl-2,3-dihydro-1H-pyrrolo[1,2-a]indole-9-carbaldehyde (2g, Table 5.3, entry 3): 78% overall yield (**2g:3g** = 9:1, obtained as a mixture); A yellow solid; R_f 0.33 (hexane/EtOAc = 3/1); ^1H NMR (400 MHz, CDCl_3): δ 10.15 (s, 1 H), 8.24-8.21 (m, 1 H), 7.30-7.22 (m, 3 H), 4.22-4.17 (m, 1 H), 3.89-3.82 (m, 1 H), 3.47-3.44 (m, 1 H), 2.20-2.13 (m, 1 H), 2.07-2.00 (m, 2 H), 1.92-1.83 (m, 2 H), 1.76-1.68 (m, 1 H), 1.06 (t, J = 7.4 Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3): δ 183.5, 152.6, 136.2, 126.0, 123.0, 122.7, 120.6, 112.4, 109.2, 42.4, 33.3, 29.1, 22.6, 17.7, 12.2; HRMS (ESI) Calcd for $\text{C}_{15}\text{H}_{18}\text{NO}$ [$\text{M} + \text{H}$] $^+$ 228.1388, found 228.1404.

1-(3-Phenylpropyl)-2,3-dihydro-1H-pyrrolo[1,2-a]indole-9-carbaldehyde (2h, Table 5.3, entry 4): 51% overall yield (**2h:3h** = 9:1, obtained as a mixture); A yellow solid; R_f

0.33 (hexane/EtOAc = 3/1); ^1H NMR (400 MHz, CDCl_3): δ 10.08 (s, 1 H), 8.23-8.20 (m, 1 H), 7.31-7.26 (m, 5 H), 7.22-7.20 (m, 3 H), 4.27-4.22 (m, 1 H), 3.94-3.86 (m, 1 H), 3.65-3.60 (m, 1 H), 2.85-2.76 (m, 2 H), 2.26-2.03 (m, 5 H), 1.96-1.92 (m, 1 H); ^{13}C NMR (100 MHz, CDCl_3): δ 183.5, 152.0, 141.0, 136.3, 128.5, 128.4, 128.3, 126.1, 123.1, 122.8, 120.7, 112.4, 109.2, 42.4, 37.6, 33.8, 31.3, 23.0, 17.8; HRMS (ESI) Calcd for $\text{C}_{21}\text{H}_{22}\text{NO}$ $[\text{M} + \text{H}]^+$ 304.1701, found 304.1698.

1-(Cyclohexylmethyl)-2,3-dihydro-1H-pyrrolo[1,2-a]indole-9-carbaldehyde (2i,

Table 5.3, entry 5): 51% yield; A yellow solid; m.p. 138.7-139.5 °C; R_f 0.30 (hexane/EtOAc = 5/1); ^1H NMR (400 MHz, CDCl_3): δ 10.04 (s, 1 H), 8.24-8.22 (m, 1 H), 7.26-7.21 (m, 3 H), 4.16-4.01 (m, 2 H), 3.66-3.62 (m, 1 H), 2.82-2.77 (m, 1 H), 2.37-2.31 (m, 1 H), 1.86-1.67 (m, 6 H), 1.55-1.48 (m, 1 H), 1.44-1.39 (m, 1 H), 1.30-1.17 (m, 3 H), 1.05-0.97 (m, 2 H); ^{13}C NMR (100 MHz, CDCl_3): δ 183.3, 159.2, 132.9, 129.9, 122.8, 122.7, 121.7, 110.0, 109.9, 43.6, 42.6, 35.8, 35.6, 34.0, 33.4, 32.3, 26.4, 26.2, 26.0; HRMS (ESI) Calcd for $\text{C}_{19}\text{H}_{24}\text{NO}$ $[\text{M} + \text{H}]^+$ 282.1858, found 282.1855. Recrystallization from hexane/EtOAc (2:1) afforded single crystals suitable for X-ray diffraction analysis, which confirmed the five-membered ring structure (see below).²¹

Figure 5.2 Structure of **2i**

9,9-Dimethyl-6,7,8,9-tetrahydropyrido[1,2-*a*]indole-10-carbaldehyde (3j, Table 5.3, entry 7): 40% yield; A yellow oil; R_f 0.27 (hexane/EtOAc = 5/1); ^1H NMR (400 MHz, CDCl_3): δ 10.51 (s, 1 H), 8.36-8.34 (m, 1 H), 7.30-7.27 (m, 3 H), 4.06 (t, J = 6.1 Hz, 2 H), 2.12-2.09 (m, 2 H), 1.87-1.84 (m, 2 H), 1.63 (s, 6 H); ^{13}C NMR (100 MHz, CDCl_3): δ 184.8, 155.1, 135.6, 126.6, 123.2, 122.9, 121.5, 112.9, 109.2, 43.0, 37.9, 33.8, 31.5, 19.1; HRMS (ESI) Calcd for $\text{C}_{15}\text{H}_{18}\text{NO}$ [$\text{M} + \text{H}$] $^+$ 228.1388, found 228.1389.

7-Methyl-6,7,8,9-tetrahydropyrido[1,2-*a*]indole-10-carbaldehyde (3k, Table 5.3, entry 8): 43% yield; A yellow solid; m.p. 162.5-163.3 °C; R_f 0.20 (hexane/EtOAc = 3/1); ^1H NMR (400 MHz, CDCl_3): δ 10.01 (s, 1 H), 8.10 (d, J = 7.1 Hz, 1 H), 7.22-7.15 (m, 3 H), 4.09-4.05 (m, 1 H), 3.42-3.32 (m, 2 H), 3.01-2.92 (m, 1 H), 2.12-2.06 (m, 1 H), 2.00-1.95 (m, 1 H), 1.50-1.40 (m, 1 H), 1.11 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3): δ 183.4, 147.7, 136.1, 126.0, 123.0, 122.6, 120.5, 112.6, 109.1, 48.9, 28.5, 27.7,

22.1, 18.9; HRMS (ESI) Calcd for $C_{14}H_{16}NO$ $[M + H]^+$ 214.1232, found 214.1230.

6,7,8,9,10,11-hexahydro-7,11-methanoazocino[1,2-*a*]indole-12-carbaldehyde (3l,

Table 5.3, entry 9): 1H NMR analysis indicated that the title compound contained a small amount of a byproduct arising from olefin isomerization of **1l**; 43% yield; A yellow oil; R_f 0.26 (hexane/EtOAc = 3/1); 1H NMR (400 MHz, $CDCl_3$): δ 10.13 (s, 1 H), 8.25 (d, J = 8.0 Hz, 1 H), 7.33-7.26 (m, 3 H), 4.25-4.22 (m, 1 H), 4.08-4.05 (m, 1 H), 3.87-3.85 (m, 1 H), 2.56-2.54 (m, 1 H), 2.06-1.77 (m, 6 H), 1.58-1.54 (m, 1 H), 1.22-1.11 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 183.2, 136.4, 126.1, 125.0, 123.1, 122.8, 121.0, 111.7, 109.2, 48.2, 33.1, 32.6, 28.9, 28.0, 26.6, 19.3; HRMS (ESI) Calcd for $C_{16}H_{18}NO$ $[M + H]^+$ 240.1388, found 240.1387. Upon being left in EtOAc/hexane, **3l** was oxidized to a carboxylic acid in the form of single crystals, which was subjected to X-ray diffraction analysis to confirm the bicyclo[3.3.1] skeleton (see below).²²

Figure 5.3 Structure of carboxylic acid obtained from **3l**

5,6-Dihydroindolo[1,2-*a*]quinoline-7-carbaldehyde (3m, Table 5.3, entry 10): 63% yield; A yellow solid; m.p. 118.5-119.4 °C; R_f 0.27 (hexane/EtOAc = 3/1); ^1H NMR (400 MHz, CDCl_3): δ 10.27 (s, 1 H), 8.36-8.33 (m, 1 H), 7.94-7.88 (m, 2 H), 7.44-7.37 (m, 2 H), 7.35-7.32 (m, 2 H), 7.24-7.20 (m, 1 H), 3.36 (t, J = 7.0 Hz, 2 H), 2.94 (t, J = 7.1 Hz, 2 H); ^{13}C NMR (100 MHz, CDCl_3): δ 184.3, 148.1, 135.5, 134.4, 129.9, 129.0, 127.7, 127.0, 125.3, 123.9, 123.5, 121.4, 118.2, 113.3, 111.7, 25.8, 21.6; HRMS (ESI) Calcd for $\text{C}_{17}\text{H}_{14}\text{NO}$ $[\text{M} + \text{H}]^+$ 248.1075, found 248.1071.

9-Methyl-6,7,8,9-tetrahydropyrido[1,2-*a*]indole-10-carbaldehyde (3n, Table 5.3, entry 11): The title compound and its seven-membered ring isomer, 7,8,9,10-tetrahydro-6*H*-azepino[1,2-*a*]indole-11-carbaldehyde (**3n'**), were isolated (ratio = 9:1, 73% overall yield). The title compound contained a small amount of a byproduct arising from olefin isomerization; A yellow oil; R_f 0.20 (hexane/EtOAc = 3/1); R_f 0.20 (hexane/EtOAc = 3/1); ^1H NMR (400 MHz, CDCl_3): δ 10.22 (s, 1 H), 8.22-8.20 (m, 1 H), 7.31-7.26 (m, 3 H), 4.27-4.22 (m, 1 H), 3.92-3.85 (m, 1 H), 3.82-3.78 (m, 1 H), 2.28-2.20 (m, 1 H), 2.11-2.00 (m, 2 H), 1.91-1.85 (m, 1 H), 1.50 (d, J = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3): δ 183.6, 152.9, 136.2, 126.2, 123.1, 122.8, 120.6, 112.2, 109.3, 42.5,

27.0, 26.8, 22.9, 17.9; HRMS (ESI) Calcd for $C_{14}H_{16}NO$ $[M + H]^+$ 214.1232, found 214.1234.

Because of the limited amount, only 1H NMR spectrum was taken for **3n'**: 1H NMR (400 MHz, $CDCl_3$): δ 10.17 (s, 1 H), 8.38-8.24 (m, 1 H), 7.37-7.20 (m, 3 H), 4.29-4.18 (m, 2 H), 3.34-3.18 (m, 2 H), 1.96-1.92 (m, 2 H), 1.87-1.74 (m, 4 H).

Deuterium-labeling Experiments

1a-d (45.8 mg, 0.15 mmol, 90% D) was subjected to the standard reaction conditions ($CoBr_2$ (10 mol%), $SIMes \cdot HCl$ (10 mol%) or $IPr \cdot HCl$ (10 mol%), Me_3SiCH_2MgCl (100 mol%)) at 40 °C for 12 h. After hydrolysis, the crude products was purified by column chromatography on silica gel (hexane/EtOAc = 5/1) to afford products **2a-d** and **3a-d**. The distribution of the deuterium atoms in the major product was analyzed by 1H NMR.

Screening Chiral Ligands for Enantioselective Cyclization of **1f**.

The enantiomeric excess was determined by chiral HPLC (Chiralpak OD-H, 10% *i*-PrOH/hexane, flow rate 1.0 mL/min, $\lambda = 254$ nm). Copies of HPLC traces of racemic and enantioenriched (33% ee, obtained with the NHC ligand in the box) samples of **3f** are shown below.

Transformations of Intramolecular Hydroarylation Product

8-Methyl-6,7,8,9-tetrahydropyrido[1,2-*a*]indole (**4**): The decarbonylation reaction was performed according to the literature procedure. A mixture of palladium acetate (5.0 mg, 0.022 mmol, 15 mol%), molecular sieves 4Å (50 mg) and **3f** (32.0 mg, 0.15 mmol) in cyclohexane (0.5 mL) was stirred at 140 °C for 24 h. The reaction mixture was cooled to room temperature and filtered through Celite and washed with ethyl acetate. The filtrate was concentrated and the crude product was purified by column chromatography on silica gel (hexane/EtOAc = 50/1) to yield the title compound (24.4 mg, 88 %) as a yellow solid. m.p. 79-80 °C; *R_f* 0.55 (hexane/EtOAc = 10/1); ¹H NMR (400 MHz, CDCl₃): δ 7.55 (d, *J* = 7.5 Hz, 1 H), 7.28 (d, *J* = 7.9 Hz, 1 H), 7.20-7.05 (m, 2 H), 6.19 (s, 1 H), 4.27 (ddd, *J*₁ = 11.7, *J*₂ = 5.7, *J*₃ = 3.0 Hz, 1 H), 3.89 (td, *J*₁ = 11.5, *J*₂ = 5.0 Hz, 1 H), 3.09 (ddd, *J*₁ = 16.1, *J*₂ = 4.3, *J*₃ = 1.4 Hz, 1 H), 2.56 (dd, *J*₁ = 16.1, *J*₂ = 10.7 Hz, 1 H), 2.21-2.06 (m, 1 H), 2.05-1.94 (m, 1 H), 1.76 (dtd, *J*₁ = 13.1, *J*₂ = 11.1, *J*₃ = 5.7 Hz, 1 H), 1.16 (d, *J* = 6.6 Hz, 3 H); ¹³C NMR (100 MHz, CDCl₃): δ 137.2, 136.1, 128.4, 120.1, 119.6, 119.5, 108.6, 97.3, 41.7, 32.5, 31.3, 27.8, 21.3; HRMS (ESI) Calcd for C₁₃H₁₆N [M + H]⁺ 186.1283, found 186.1290.

8-Methyl-10-((8-methyl-4a,6,7,8,9,10a-hexahydropyrido[1,2-a]indol-10-yl)methyl)-6,

7,8,9-tetrahydropyrido[1,2-a]indole (5): NaBH₄ (11.4 mg, 0.3 mmol) was added to the solution of **3f** (32.0 mg, 0.15 mmol) in methanol (1.0 mL) at 0 °C and the resulting mixture was stirred at room temperature for 1 h. The reaction was quenched by the addition of 1 M HCl (1.5 mL) and then extracted with ethyl acetate (10 mL × 3). The combined organic layer was dried over MgSO₄ and concentrated under reduced pressure. Purification of the crude product by silica gel chromatography (eluent: hexane/EtOAc = 50/1) afforded the title compound as a white solid (23.9 mg, 83%).

m.p. 144-145 °C; *R_f* 0.23 (hexane/EtOAc = 25/1); ¹H NMR (400 MHz, CDCl₃): δ 7.40 (d, *J* = 7.8 Hz, 2 H), 7.20 (d, *J* = 8.1 Hz, 2 H), 7.06 (t, *J* = 7.5 Hz, 2 H), 6.96 (t, *J* = 7.4 Hz, 2 H), 4.21 (ddd, *J*₁ = 11.6, *J*₂ = 5.5, *J*₃ = 3.2 Hz, 2 H), 4.06 (t, *J* = 5.7 Hz, 2 H), 3.84 (td, *J*₁ = 11.4, *J*₂ = 4.9 Hz, 2 H), 3.04 (dd, *J*₁ = 16.0, *J*₂ = 4.1 Hz, 2 H), 2.43-2.27 (m, 2 H), 2.14-1.99 (m, 2 H), 2.00-1.89 (m, 2 H), 1.80-1.63 (m, 2 H), 1.11 (d, *J* = 6.6 Hz, 6 H); ¹³C NMR (100 MHz, CDCl₃): δ 135.9, 133.1, 128.5, 119.9, 118.8, 118.4, 108.7, 108.3, 41.6, 31.3, 31.1, 31.08, 27.8, 21.5, 18.9; HRMS (ESI) Calcd for C₂₇H₃₁N₂ [M + H]⁺ 383.2487, found 383.2489.

Benzyl(2-(8-methyl-6,7,8,9,9a,10-hexahydropyrido[1,2-*a*]indol-10-yl)ethyl)carbamate (6):

e (6): Ammonium acetate (346.9 mg, 4.5 mmol) was added to the solution of **3f** (319.9 mg, 1.5 mmol) in CH₃NO₂ (2 mL). The resulting mixture was stirred at 105 °C for 1 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was diluted with CH₂Cl₂ (20 mL), washed with water (2 × 5 mL) and saturated aqueous NaCl. The organic layer was dried over MgSO₄ and concentrated under reduced pressure to afford the product (*E*)-8-methyl-10-(2-nitrovinyl)-6,7,8,9-tetrahydropyrido[1,2-*a*]indole as a yellow solid (384 mg, quant), which was carried over to the next step without further purification. ¹H NMR (400 MHz, CDCl₃): δ 8.34 (d, *J* = 13.2 Hz, 1 H), 7.77-7.67 (m, 2 H), 7.34-7.26 (m, 3 H), 4.32-4.27 (m, 1 H), 4.03-3.88 (m, 1 H), 3.33 (ddd, *J*₁ = 17.3, *J*₂ = 4.7, *J*₃ = 1.6 Hz, 1 H), 2.62 (dd, *J*₁ = 17.3, *J*₂ = 10.4 Hz, 1 H), 2.26-2.16 (m, 1 H), 2.10-2.08 (m, 1 H), 1.85-1.75 (m, 1 H), 1.24 (d, *J* = 6.6 Hz, 3 H).

A solution of (*E*)-8-methyl-10-(2-nitrovinyl)-6,7,8,9-tetrahydropyrido[1,2-*a*]indole (384 mg, 1.5 mmol) in THF (3 mL) was added dropwise to a suspension of LiAlH₄ (342 mg, 9 mmol) in anhydrous THF (20 mL) at 0 °C. The resulting mixture was heated under reflux for 2 h. The reaction mixture was cooled to room temperature and the excess hydride was destroyed by dropwise addition of saturated aqueous Na₂SO₄ at 0 °C. The resulting mixture was filtered through Celite. The filtrate was dried over MgSO₄ and concentrated under reduced pressure to afford the product

2-(8-methyl-6,7,8,9-tetrahydropyrido[1,2-*a*]indol-10-yl)ethanamine as a yellow oil (342 mg, quant), which was carried over to the next step without further purification. ^1H NMR (400 MHz, CDCl_3): δ 7.53 (d, $J = 7.6$ Hz, 1 H), 7.24-7.08 (m, 3 H), 4.27-4.22 (m, 1 H), 3.89-3.82 (m, 1 H), 3.10-3.04 (m, 1 H), 2.96 (d, $J = 6.8$ Hz, 2 H), 2.87-2.81 (m, 2 H), 2.46-2.39 (m, 1 H), 2.13-2.08 (m, 1 H), 1.99-1.95 (m, 1 H), 1.76-1.67 (m, 1 H), 1.16 (d, $J = 6.6$ Hz, 3 H).

2-(8-Methyl-6,7,8,9-tetrahydropyrido[1,2-*a*]indol-10-yl)ethanamine (342.5 mg, 1.5 mmol) was suspended in a 1:1 (v/v) mixture of aqueous NaOH solution (2 M, 10 mL) and CH_2Cl_2 (10 mL). After cooling to 0 °C, benzyl chloroformate (281 mg, 1.65 mmol) was added dropwise and the resulting mixture was stirred at room temperature for 2 h. After the reaction was complete, the phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2×10 mL). The combined organic layer was washed with brine, dried over MgSO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (hexane/EtOAc = 10/1) to afford the title compound (494.8 mg, 91 %) as a yellow solid.

m.p. 105-106 °C; R_f 0.41 (hexane/EtOAc = 3/1); ^1H NMR (400 MHz, CDCl_3): δ 7.49 (d, $J = 7.6$ Hz, 1 H), 7.33 (s, 5 H), 7.22 (s, 1 H), 7.13 (t, $J = 7.2$ Hz, 1 H), 7.07 (t, $J = 7.3$ Hz, 1 H), 5.09 (s, 2 H), 4.80 (s, 1 H), 4.23-4.18 (m, 1 H), 3.82 (td, $J_1 = 11.4$, $J_2 = 4.9$ Hz, 1 H), 3.43 (dd, $J_1 = 12.8$, $J_2 = 6.4$ Hz, 2 H), 3.02-2.97 (m, 1 H), 2.88 (dt, $J_1 = 14.4$, $J_2 = 7.1$ Hz, 2 H), 2.37 (dd, $J_1 = 15.9$, $J_2 = 10.7$ Hz, 1 H), 2.16-2.00 (m, 1 H), 1.97-1.86 (m, 1 H), 1.69 (ddd, $J_1 = 24.2$, $J_2 = 11.2$, $J_3 = 5.7$ Hz, 1 H), 1.11 (d, $J = 6.5$ Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3): δ 156.5, 136.8, 136.0, 134.3, 128.5, 128.1, 120.4, 119.4, 117.7, 108.7,

105.9, 66.5, 41.7, 41.5, 31.3, 30.7, 27.8, 24.4, 21.4; HRMS (ESI) Calcd for $C_{23}H_{27}N_2O_2$
[M + H]⁺ 363.2073, found 363.2074.

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²¹ CCDC 943911 contains supplementary crystallographic data for the compound **2i**. The data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

²² CCDC 943912 contains the supplementary crystallographic data for the carboxylic acid. The data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

List of Publications

1. Cobalt-Catalyzed Addition of Azoles to Alkynes, Ding, Z.; Yoshikai, N. *Org. Lett.* **2010**, *12*, 4180-4183.
2. Cobalt-Catalyzed Alkenylation of Thiazoles with Alkynes via C–H Bond Functionalization, Ding, Z.; Yoshikai, N. *Synthesis* **2011**, 2561-2566.
3. Mild and Efficient C2-Alkenylation of Indoles with Alkynes Catalyzed by a Cobalt Complex, Ding, Z.; Yoshikai, N. *Angew. Chem. Int. Ed.* **2012**, *51*, 4698-4701.
4. C2-Alkylation of N-Pyrimidyl Indole with Vinylsilane via Cobalt-Catalyzed C–H Bond Activation, Ding, Z.; Yoshikai, N. *Beilstein J. Org. Chem.* **2012**, *8*, 1536-1542.
5. Cobalt-Catalyzed Intramolecular Olefin Hydroarylation Leading to Dihydropyrroloindoles and Tetrahydropyridindoles, Ding, Z.; Yoshikai, N. *Angew. Chem. Int. Ed.* **2013**, *52*, 8574-8578.