A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition GDCh Chemie

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Accepted Article

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To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.202111860

Link to VoR: https://doi.org/10.1002/anie.202111860

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10.1002/anie.202111860

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Rhodium-Catalyzed Atroposelective Access to Axially Chiral Olefins via C-H Bond Activation and Directing Group Migration

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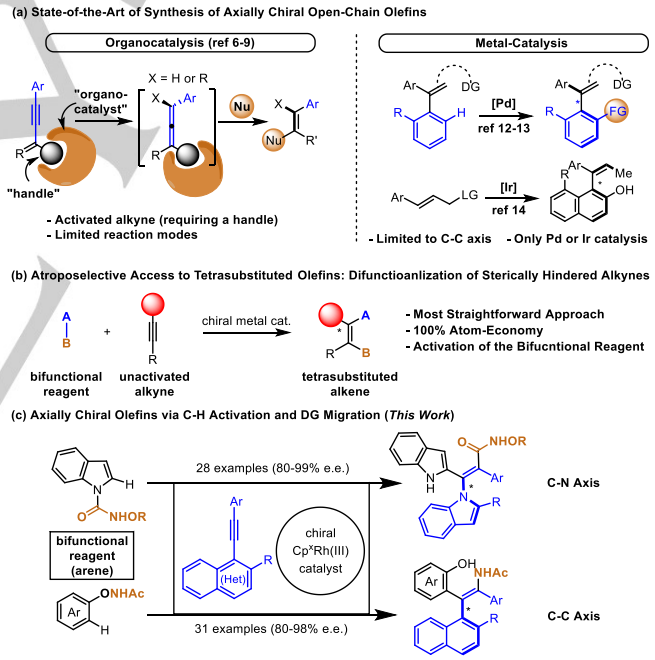
Abstract: Axially chiral open-chain olefins represent an underexplored class of chiral platform. In this report, two classes of tetrasubstituted axially chiral acyclic olefins have been accessed in excellent enantioselectivity and regioselectivity via C-H activation of (hetero)arenes assisted by a migratable directing group en route to coupling with sterically hindered alkynes. The coupling of indoles bearing an *N*-aminocarbonyl directing group afforded C-N axially chiral acrylamides with assistance of a racemic zinc carboxylate additive. DFT studies suggest a *β*-nitrogen elimination-reinsertion pathway for the directing group migration. Meanwhile, the employment of *N*-phenoxycarboxamide delivered C-C axially chiral enamides *via* migration of the oxidizing directing group. Experimental studies suggest that in both cases the (hetero)arene substrate adopts a well-defined orientation during the C-H activation, which in turn determines the disposition of alkyne in migratory insertion. Synthetic applications of representative chiral olefins have been demonstrated.

Introduction

Atropisomerism arises from hindered rotation along a single bond due to steric hindrance of the moieties around this bond.[1] The resulting axially chiral molecules represent a large family that plays important roles as chiral building blocks, chiral ligands or catalysts, and pharmaceuticals.[2] Considerable efforts have been made toward construction of axial chirality. Biaryls are a predominant motif among axially chiral molecules due to their synthetic feasibility.[3] Depending on the nature of the moieties that make the chiral axis, axially chiral amides and olefins also add to the repertoire of axial chirality.[4] In particular, axially chiral olefins defined by a C(olefinic)-E axis are largely underexplored,[5] which seems to be ascribed to the synthetic challenges assosicated with tetrasubstituted acyclic olefins, and the relatively low atropostability also adds to the challenge since deformation of the four bonds around the C=C bond may offset the steric repulsion. Given increasing importance of axially chiral olefins in syntheis, catalysis, and material studies, novel enantioselective synthetic methods are under great demand.



Scheme 1 Axially Chiral Olefins and the Directing Group Migration Strategy

Organocatalysis has offered a facile approach to address the synthetic challenges, and most systems are based on nucleophilic functionalization of activated/functionalized alkynes via formation of an allene intermediate assisted by a tethered handle (Scheme 1a). In 2017, Tan[6] realized synthesis of trisubstititued acroleins via nucleophilic addition to alkynylaldehydes. By resorting to vinylidene *o*-quinone methide intermediates, Yan[7] accomplished addition of diverse nucleophiles to 1-alkynylnaphthols, affording tri/tetrasubstituted styrenes. Related strategies have been employed by Zhao, Tan, and Shi in construction of cyclic[8] or open-chain[9] olefins. On the other hand, metal catalysis provided important alternative solutions (Scheme 1a). Gu[10] reported atroposelective synthesis of cyclic olefins via Pd-catalyzed coupling of arylbromide and hydrazones. The C-H activation

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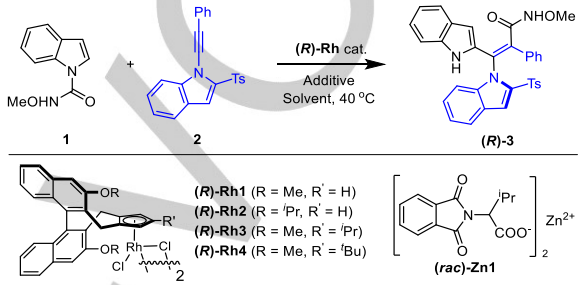
strategy has been recently employed in constructions of chirl axis.[11] Shi reported Pd-catalyzed activation of C(aryl)-H bond proximal to an olefin unit assisted by a permanent or transient directing group (Scheme 1a).[12] The same strategy was recently adopted by Wang using a carboxyl directing group.[13] Very recently, the group of You and the group of Yi, Liu, and He[14] reported Ir(I)-catalyzed enantioselective synthesis of naphthol-based trisubstituted olefins via allylic substitutiuon and chirality transfer. Thus, existing metal-catalyzed systems remain limited to two reaction patterns using functionalizd alkenes and have also been mostly limited to trisbustituted C-C axially chiral olefins.

Catalytic direct 1,2-difunctionalization of sterically hindered, unactivated alkynes represents one of the most straightforward approaches to provide tetrasubstituted olefins (Scheme 1b). While this is appealing, atroposelective systems are underdeveloped possibly due to limited reactivity of the sterically hindered alkynes. Our strategy is the activation of the bifunctional reagent, and we rationalized that the C-H activation strategy[15] can be further elaborated toward atroposelective conctruction of olefins *via* insertion of bulky arylalkynes. Our[16] recent catalytic C-H activation-annulation reactions using sterically hindered alkynes[17] allowed atroposelective construction of biaryls and other cyclic products. However, moving to open-chain olefin targets carries considerable challenges, and we envisioned a substrate activation strategy using an arene bearing a migratable directing group[18] as a bifucntional reagent, which couples with sterically hindered alkynes to directly afford tetrasubstituted olefins in a single step in 100% atom-economy (Scheme 1c). In fact, racemic examples of C-H activation with migration of an oxidizing or electrophilic directing group have been deveopled under Rh(III),[19,20] Co(III),[21] and Mn(I)[22] catalysis. Despite the reports on racemic systems of migration of an oxidizing directing group,[19,21d] very few asymmetric systems have been developed. Thus, Cramer[23] and Yi[24] accomplished Rh/Co-catalyzed asymmetric coupling of *N*-phenoxyacetamides with olefins/dienes through migration of the amide group. In case of migration of an electrophilic directing group,[20-22] no asymmetric system has been developed. Clearly, existing asymmetric systems have been extremely limited in reaction patterns and are also limited to creation of point-chirality using olefin substrates. We now report enantioselective coupling of (hetero)arenes and readily available alkynes toward construction of tetrasubstituted chiral olefins via migration of two classes of bifunctional directing group (Scheme 1c).

Results and Discussion

N-Aminocarbonylindoles (**1**) have been recently demonstrated as heteroarenes that undergo C-H activation together with migration of the aminocarbonyl group in the coupling with simple alkynes.[20] Thus, we intitated our studies with the optimization of the coupling of this indole and a 1-alkynylindole (**2**, Table 1) using Cramer's 2nd generation chiral Rh(III) cyclopentadienyl catalyst,[25] which have demonstrated great power in creation of axial chirality[16,26] via asymmetric C-H bond activation.[27] The coupling did occur to afford the desired C-N axially chiral acrylamide **3** in high efficiency and good enantioselectivity when catalyzed by the **(*R*)-Rh1** catalyst (40 °C in PhMe, entry 1). Switching to other **(*R*)-Rh2-4** catalysts only led to inferior results (entries 2-4). Solvent screening revealed that toluene and $PhCF_3$ outperformed other common solvents. Investigation of base additives showed that common carboxylates of sodium, potassium, zinc, and silver all failed to improve the enantioselectivity (entires 8-11). After extensive screening, a catalytic ammount of racemic phthalimide-based zinc carboxylate ((*rac*)-**Zn1**) was indentified as a superior additive,[26c,28] affording excellent efficiency and enantioselectivity (entry 12, 98% e.e., conditions A,). Essentially the same result was observed when (*R*)-**Zn1**, (*S*)-**Zn1**, or (*rac*)-**Zn1** was used. Therefore, the configuration of this additive does not contribute to the enantioselective control. Employment of the sodium salt of this racemic acid only gave 76% e.e. Therefore, both the zinc and the carboxylate played an important role. Lowering the amount of the **Zn1** or the reaction temperature tends to give slightly lower efficiency (entries 13 and 14).

Table 1. Optimization Studies[a,b]



Entry	Catalyst	Solvent	Additive	Yield[b] (%)	e.e.
1	**(*R*)-Rh1**	PhMe	NaOAc	85	80
2	**(*R*)-Rh2**	PhMe	NaOAc	42	76
3	**(*R*)-Rh3**	PhMe	NaOAc	< 3	-
4	**(*R*)-Rh4**	PhMe	NaOAc	< 3	-
5	**(*R*)-Rh1**	DCE	NaOAc	70	50
6	**(*R*)-Rh1**	TFE	NaOAc	< 3	-
7	**(*R*)-Rh1**	$PhCF_3$	NaOAc	82	80
8	**(*R*)-Rh1**	PhMe	NaOPiv	75	78
9	**(*R*)-Rh1**	PhMe	KOAc	81	78
10	**(*R*)-Rh1**	PhMe	AgOAc	86	70
11	**(*R*)-Rh1**	PhMe	$Zn(OAc)_2$	84	76
12	**(*R*)-Rh1**	PhMe	**(*rac*)-Zn1**	91	98
13[c]	**(*R*)-Rh1**	PhMe	**(*rac*)-Zn1**	75	98
14[d]	**(*R*)-Rh1**	PhMe	**(*rac*)-Zn1**	86	98

[a] Reactions were carried out using **1** (0.05 mmol), **2** (0.06 mmol), **(*R*)-Rh** cat. (4 mol%) and an additive (0.5 equiv) in a solvent (0.3 mL) for 24 h under N_2. [b] Isolated yields. [c] 0.2 equiv of (*rac*)-**Zn1** was used. [d] 30 °C.

Following the optimized reaction conditions A, the scope and limitation of this coupling system was next explored (Scheme 2). The scope of the indole subtrate was explored using alkyne **2** as a coupling reagent. It was found that introduction of 4-Me, -ester, and -halogen groups into the indole ring all gave excellent enantiosectivity (**4-7**, 95-97% e.e.). The absolute configuration of product (*R*)-**4** was secured by X-ary crystallographic analysis (CCDC 2100665). The same senario was also observed for indoles bearing diverse electron-donating, -withdrawing, and halogen groups at the 5-, 6-, and 7- positions (**8-17**, 85-99% e.e.). The compatibility of different 7-groups manifested the tolerance of steric effect during the C-H activation. In addition, 5, 6-disubstituted indoles also proved viable (**18** and **19**). The migrating directing group has also been extended to several *N*-alkoxycarbonyls with high to excellent enantioselectivity (**20** and **21**). A decent scope of alkyne has also been established. The coupling proceeded smoothly when the alkyne terminus was extended to several *para*-substituted phenyls (**22-24**), and electron-donating and halogen groups at different positions of

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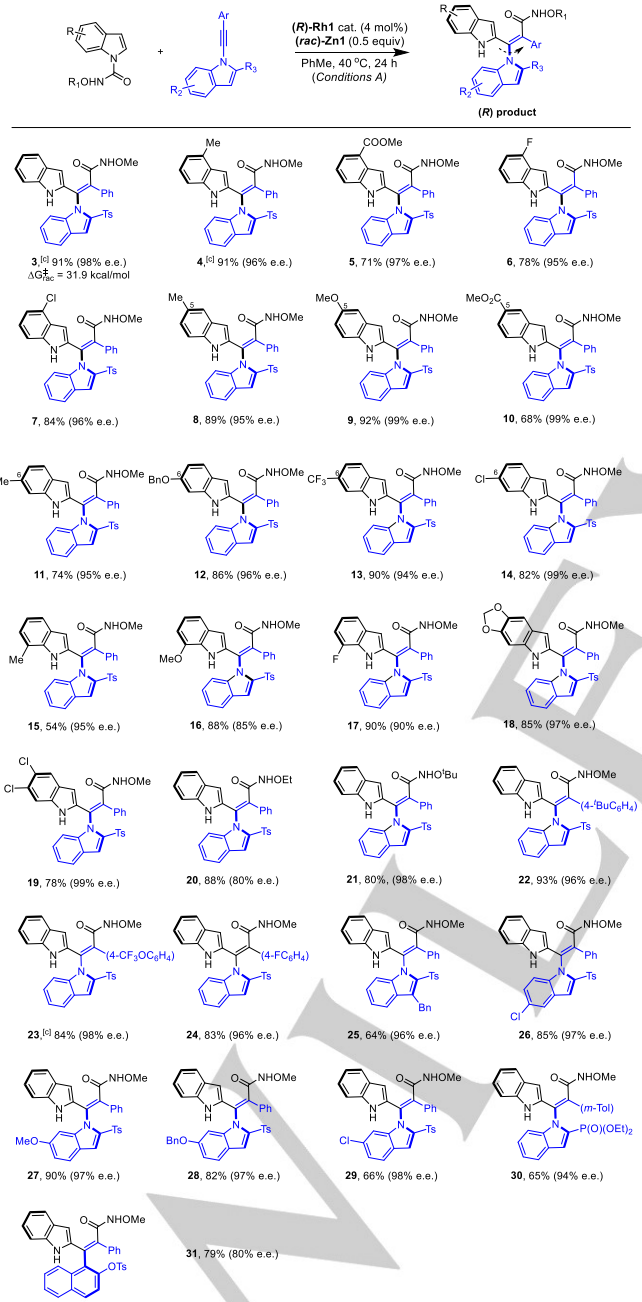
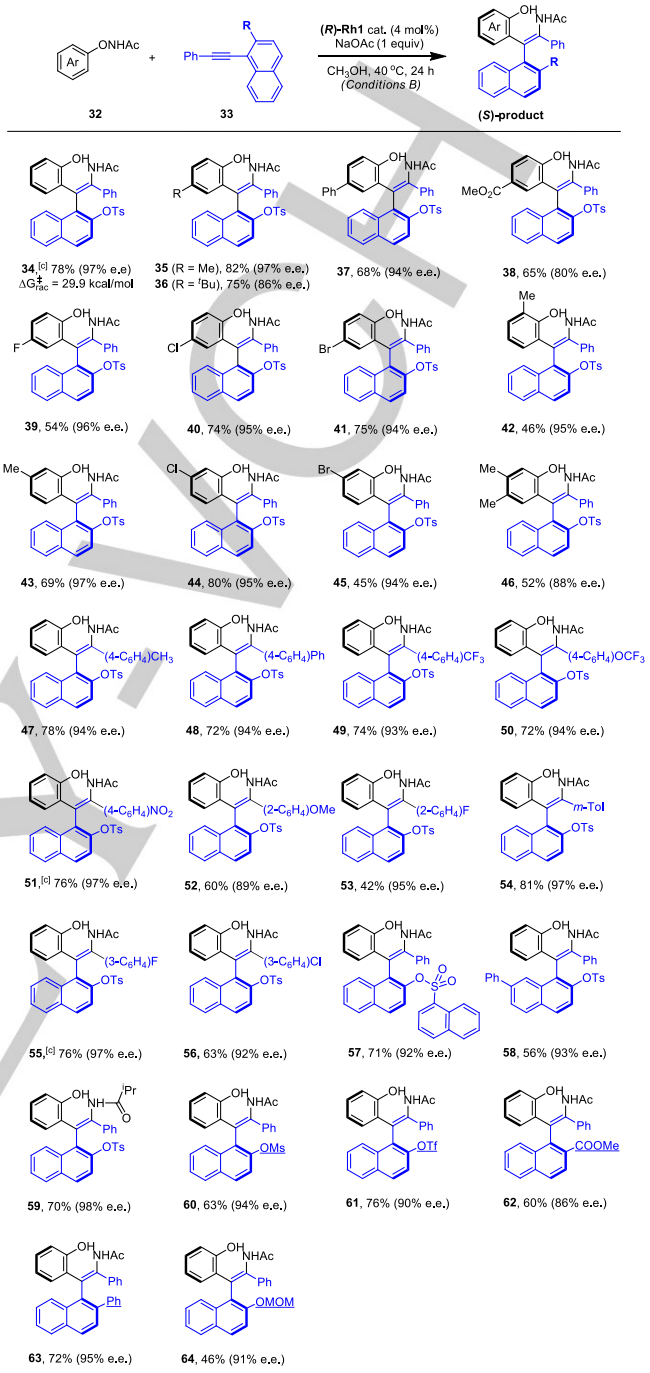
the indole ring was also compatible (**25-29**, 96-98% e.e.). The bulky 2-substituent in the indole was not restricted to a sulfonyl group, and *N*-alkynylindoles bearing a 2-phosphate ester also reacted in excellent enantioselectivity under the same reaction conditions (**30**). In contrast to these aryl-substituted alkynes, the corresponding alkyl-substituted alkynes failed to undergo any desired coupling, and 1-naphthyl-alkyne reacted with lower enantioselectivity (**31**, 80% e.e.). In all cases, no redox-neutral [4+2]-type annulation product has been detected.[16a] In addition, racemization studies of product **3** gave $\Delta G^{\neq}_{rac}$ = 31.9 kcal/mol in PhOMe at 100 °C.



Scheme 2. [a] Reactions were carried out using *N*-aminocarbonylindole (0.1 mmol), alkyne (0.12 mmol), (*R*)-**Rh1** catalyst (4 mol%), and (*rac*)-**Zn1** (0.5 equiv) at 40 °C in PhMe (1 mL) for 24 h under air. [b] Isolated yields. [c] Average of two runs.



Scheme 3. [a] Reactions were carried out using *N*-phenoxyacetamide (0.1 mmol), alkyne (0.12 mmol), (*R*)-**Rh1** (4 mol%), and NaOAc (1.0 equiv) at 40 °C in CH_3OH (1 mL) for 24 h under air. [b] Isolated yields. [c] Average of two runs.

To better define the scope of the arene substrate, we further indentified arenes bearing an oxidizing N-O bond since migration of an oxidizing directing group has been disclosed in Rh(III)-catalyzed C-H activation since 2013.[19] An attactive example is the coupling of PhONHAc and internal alkyne reported by Lu and Liu in 2013.[19a] Nevertheless, asymmetric coupling that delivers axial chirality has not been reported. It was found that *N*-phenoxyacetamide (**32**) coupled with alkyne **2** in high efficiency (see Supporting Information). However, the

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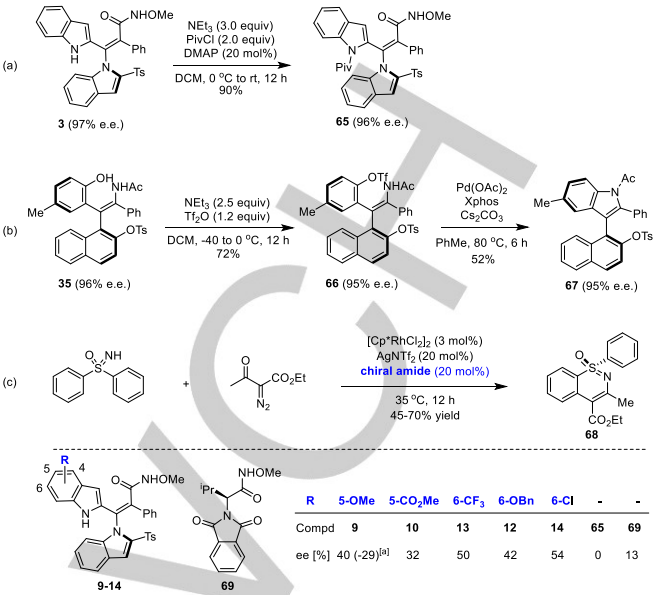
enantioselectivity was less satisfactory after extensive studies (80% e.e.). To our delight, switching the alkyne to 1-alkynylnaphthalene **33** afforded enamide **34** in excellent enantioselectivity under operationally simple conditions uisng the same rhodium catalyst in MeOH (Conditions B, Scheme 3). The scope of the *N*-phenoxycarboxamides was also found to be broad. Thus, introduction of diverse electron-donating and -withdrawing groups into the 4-positions allowed smooth coupling in mostly excellent enanioselectivity (**35-41**, 80-97% e.e.), wih the lowest enantioselectivity being observed for a 4-ester substituted *N*-phenoxyacetamide (**38**). The (*S*) configuration of the product **41** was confirmed by X-ray cryslallography (CCDC 2100749), which bears the same spacial orientation as the chiral acrylamide products (but with different priority order of the substituents). An *ortho*-methyl susbstituted substrate still underwent coupling in excellent enantioselectivity albeit with reduced enfficiency (**42**), likely due to the steric effect. The coupling of several *meta*-substituted *N*-phenoxyacetamides also proceeded smoothly (**43-46**, 88-97% e.e.). Alkynes bearing a large array of substituents at the *ortho*, *meta* and *para* positions of the phenyl terminus all underwent smooth coupling (**47-56**, 89-97% e.e.), including a *para*-nitro substituted alkyne substrate (**51**). Extension of the 2-sulfonyl group to a bulkier 2-naphthylsulfonyl group met with no difficulty (**57**). The presence of a 7-phenyl group also had marginal influence on the reaction efficiency or enantioselectivity (**58**). The amide group was extendable to a bulkier carboxamide (**59**, 98% e.e.). The 2-substituent in the naphthylene ring of the alkyne was successfully expanded to other sulfonyloxy groups such as OMs (product **60**) and OTf (product **61**) with excellent enantioselectivity. Moreover, other carbon- or oxygen-based groups such as ester (**62**), phenyl (**63**), and OMOM (**64**) were all compatible (86-95% e.e.), indicating overall excellent functional group compatibility. In all cases, essentially no [3+2]-type annulative coupling has been observed.[19a] In line with our previous observations, no reaction occurred when the corresponding alkyl-terminated alkyne was used. A slightly lower barrier of $\Delta G^{\neq}_{rac}$ = 29.9 kcal/mol (PhOMe, 100 °C) was measured for **34**.

Synthetical applications of representative products have been conducted (Scheme 4). *N*-protection of **3** using PivCl afforded **65** (Scheme 4a). Triflation of the OH group in **36** followed by palladium-catalyzed intramolecular amination provided indole **67** in excellent enantioselectivity (Scheme 4b). Applications of chiral carboxamides as an additve to control the enantioselectivity of C-H activation were also explored. The model desymmetrization-annulative coupling of diphenylsulfoximine with α-diazo acetylacetate[29] was examined with different carboxamides as a chiral additive (Scheme 4b). When catalyzed by [RhCp*Cl$_2$]$_2$, the reaction occurred smoothly to give **68** in 32-57% e.e. in the presence of an NH unprotected indole additive (Scheme 4c). However, only racemic product was obtained when *N*-protected amide **65** was used, and a point-chiral amide **69** also afforded poor enantioselectivity. Despite the moderate enantioselectivity, this represents the first example of employment of chiral carboxamide additive in asymmetric C-H bond activation. In addition, product **35** also exhibited significant aggregation-induced emmision properties (Supporting Information).



Scheme 4. Synthetic Applications of Representative Products. [a] Ru(*p*-cymene)Cl$_2$]$_2$ was used (with opposite product configuration).

The mechanism of the coupling of *N*-methoxy-indolecarboxamide (**1**) and an alkyne was next scrutinized by a combination of experimental and computational methods (Schemes 5 and 6). Stoichiometric C-H activation-coordinative saturation reaction of indole **1** with (*R*)-**Rh1** afforded complex **70** in 58% yield as a single stereoisomer (**Scheme 5a**). The orientation of the arene moiety was assigned based on our reports of a closely analogous chiral Rh(III) complex derived from *N*-methoxybenzamide,[30] and our DFT calculations further supported the assignment (Supporting Information), where the bulkier urea direacting group is disposed frontward away from the chiral ligand for minimized interaction. Complex **70** proved to be a catalyst precursor for the coupling of indole **1** and alkyne **2** at 60 °C (69% yield and 80% e.e.), suggesting relavance of C-H bond activation. Following formation of a rhodacyclic intermediate (**A**), the resulting Rh-aryl bond is proposed to undergo regioselective and enantio-determining migratory insertion into the alkyne (**Scheme 5b**). In this process, the Ts group of the alkyne is preferably pointed downward for minimized steric repulsion with the Cp ring, and this stereochemisty of alkyne insertion eventually affords the major (*R*) product. The validity of this stereochemical model has been further supported by control experiements using several 3-substituted indoles, which all coupeld with much lower enantioselectivity (**Scheme 5c**). The reduced enantioselectivity is likely ascribed to poor control of the initial orientation of the indole substrate druing the C-H activation, in additon to the pronounced steric effect in subsequent alkyne insertion. With the enhanced steric repulsion between the 3-group and the flanking chiral ligand, the arene orientation in the structure **A** is no longer predominating, and **A** and **A'** are less biased or possibly even inverted in energetics. It is possible that the presence of the **Zn1** additive may serve to stablize the structure **B** via chelation of the Ts and the amide group to the Zn center with possible π-π stacking between the alkyne-phenyl ring and the phthalimide in **Zn1** (Scheme **5b**).

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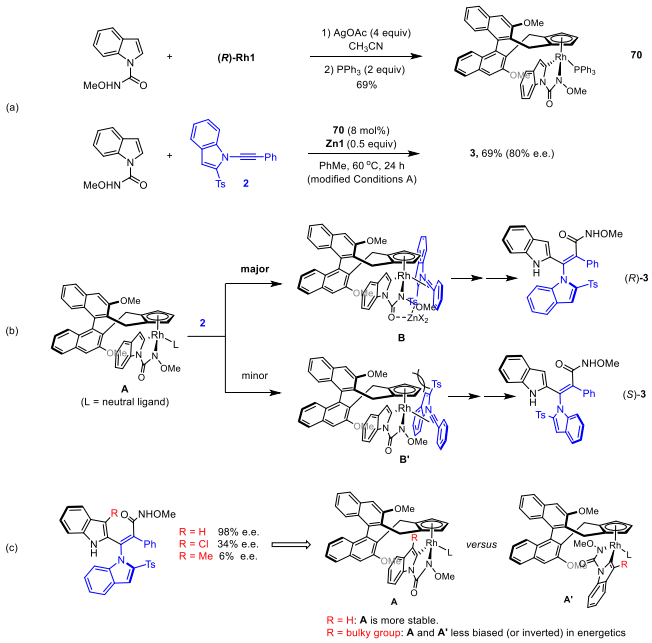
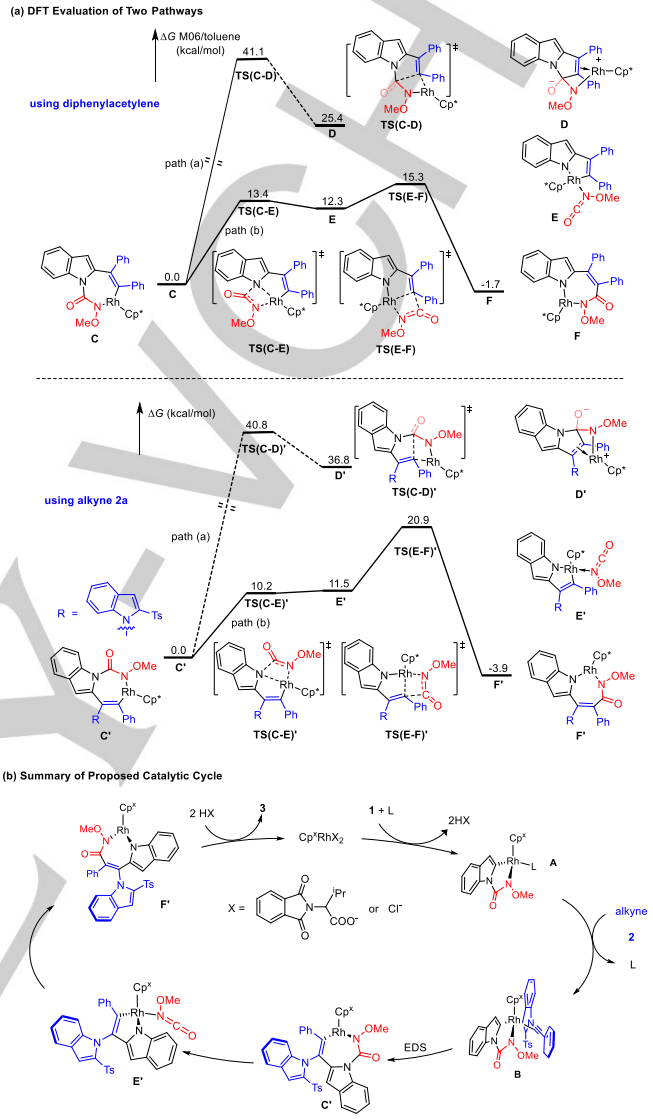


Scheme 5. Mechanistic Studies of the Coupling of *N*-Aminocarbonylindoles.

Following the alkyne insertion, the formation of the C(alkenyl)-C(O)NHOMe bond constitutes a key step. Two possible pathways can be envisionsed (Scheme 6a). In the pathway a), the Rh(III)-alkenyl bond in intermediate **C** nucleophilically adds to the urea carbonyl group to give intermediate **D**,[21] and elimination of the indolide is proposed to give intermeduate **F**. Twofold protonolyisis eventually furnished the final prouct. Although this pathway has been widely proposed in $[RhCp^*Cl_2]_2$-catalyzed coupling of **1** and diphenylacetylene,[20] we reasoned that the urea carbonyl is poorly electrophilic, and the addition is kinetically challenging. Alternatively (path b), intermediate **C** may undergo β-nitrogen elimination to generate a rhodacycle stabilized with a ligated isocyanate intermediate (**E**),[31] which is proposed to undergo reinsertion into the Rh-C bond to give the same intermediate **F**. Theoretical studies on the $[RhCp^*Cl_2]_2$-catalyzed coupling of *N*-methoxy-indolecarboxamide and diphenylacetylene (PhMe, 298 K) have been conducted to weigh over these two possible pathways. It was found that the β-nitrogen elimination of alkenyl intermediate **C** proceeds through a late transition state with only 13.4 kcal/mol activation free energy. The subsequent insertion of the isocyanate was found to be highly feasible with a calculated $\Delta G^{\neq}$ of only 3.0 kcal/mol. Therefore, this β-nitrogen elimination–insertion process is kinetically feasible and reversible. In stark contrast, the nucleophilic addition to the urea carbonyl occurs with a significantly higher activation barrier (41.1 kcal/mol). In addition, the same trend was also consistently observed when the indolyl alkyne **2** was employed, indicating that the electronic effect of the alkyne does not affect the opreration of this pathway (Scheme 6a). The calculated higher barrier using alkyne **2** is also consistent with the low reactivity of $Cp^*RhCl_2]_2$ in catalyzing this racemic reaction. To further probe this mechanism, a crossover experiement has been performed using two analogous indole substrates in equimolar ratio in the coupling with the allkyne **2**, which gave no crossover in the product mixture (see Supporting Information). This likely suggests that the isocyanate species is metal-bound throughout the catalysis so that no isocyanate ligand exchange occurs.. Accordingly, the overall β-elimination–insertion pathway for the asymmetric coupling using strically hindered alkyne **2** is given in Scheme 6b.



Scheme 6. DFT Studies of the Reaction Pathways of the Coupling of *N*-Aminocarbonylindoles and Summary of the Plausible Mechanism (EDS = enantiodetermining step). DFT calculation was computed at the M06/def2-TZVP/SMD(toluene)//M06/def2-SVP/SMD(toluene) level.

The mechanism of the coupling of *N*-phenoxycarboxamide was also briefly explored. A rhodacycle **71** was prepared by following a recent report[24] (Scheme 7). Complex **71** was designated as a catalyst for the coupling of *N*-phenoxyisobutyramide and alkyne **33,** from which the coupled product **59** was isolated in 65% yield and 98% ee. To further explore this C-H activation event, the coupling of *N*-phenoxyacetamide and alkyne **33** was conducted in the presence of CD_3OD. The coupled product **34**-D_n was appreciably deuterated (25% D) at the *ortho* position, suggesting reversibility of the C-H activation. Kinetic isotope effect was then measured from two parallel expeiments, and KIE = 2.0 at a low conversion suggests that the C-H bond activation occurs during or prior

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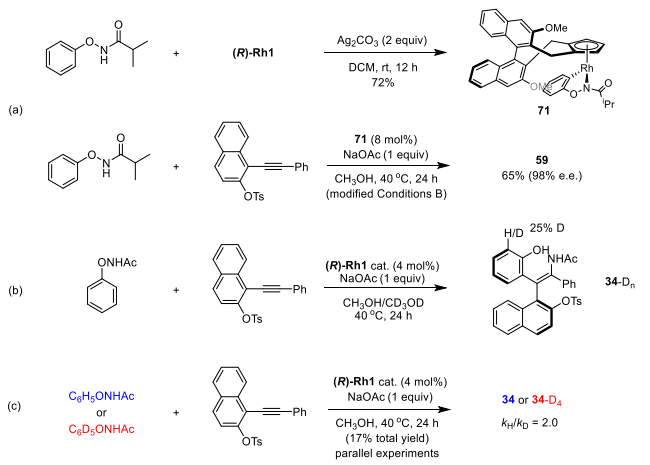
to the turnover-limiting step. Thus, this coupling possibly proceeds through a pathway that inolves C-H bond activation, alkyne insertion, O-N oxidative addition, and nitrene insertions although a Rh(III)-Rh(I) pathway is also possible.[19a,21d] Given the directly analogous rhodacyclic intermediates and the same stereochemistry of the coupled products, the enantio-determining alkyne insertion likely proceeds with the same orientations of the arene and the alkyne.



Scheme 7. Mechanistic Studies on the Coupling of *N*-Phenoxyacetamide.

Conclusion

In summary, we have developed highly enantioselective synthesis of two classes of tetrasubstituted olefins based on Rh(III)-catalyzed C-H activation of different arenes and coupling with sterically hindered alkynes. These transformations have been enabled by a migratable directing group as a result of interactions between the polarized Rh(III)-alkenyl bond and a bifunctional directing group. Indoles bearing a weakly and formally electrophilic *N*-aminocarbonyl group coupled to give C-N axially chiral acrylamides, and the enantioselectivity was further promoted by a racemic zinc carboxylate additive. DFT studies suggest that migration of the *N*-aminocarbonyl group is likely fulfilled by a *β*-nitrogen elimination pathway that generates an isocyanate intermediate. Meanwhile, the reaction of *N*-phenoxyacetamides afforded C-C axially chiral enamides via migration of the oxidizing directing group. In both systems, the enantioselectivity control was realized by a combination of chiral Rh(III) catayst, proper choice of the arene with a migratable directing group, and sterically hindered alkynes. Synthetic applications of representative products have been explored, which show promise as a chiral additive in enantioselective C-H activation. Development of other axially chiral platforms are underway in our laboratory and will be reported in due course.

Acknowledgements

Financial support from the NSFC (22101167) and the SNNU is gratefully acknowledged.

Keywords: axially chiral olefin • rhodium • C-H activation • directing group migration • alkyne

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10.1002/anie.202111860

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RESEARCH ARTICLE

Rhodium-Catalyzed Atroposelective Access to Axially Chiral Olefins via C-H Bond Activation and Directing Group Migration

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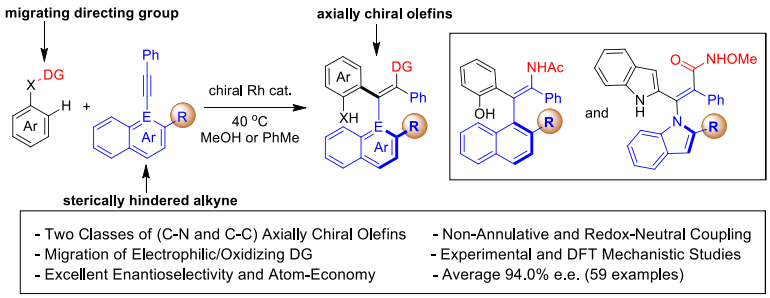

Two classes of terasubstituted axially chiral olefins have been accessed in excellent enantioselectivity via Rh(III)-catalyzed asymmetric C-H activation assisted by a migratable directing group.