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Article

O-Allylhydroxyamine: A Bifunctional Olefin for Construction of Axially and Centrally Chiral Amino Alcohols via Asymmetric Carboamidation

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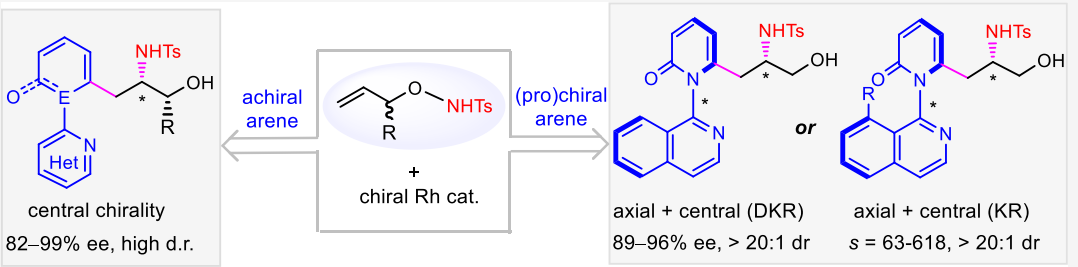

ABSTRACT: Difunctionalization of olefins offers an attractive approach to access complex chiral structures. Reported herein is the design of *N*-protected *O*-allylhydroxyamines as bifunctional olefins that undergo catalytic asymmetric 1,2-carboamidation with three classes of (hetero)arenes to afford chiral amino alcohols via C−H activation. The C═C bond in *O*-allylhydroxyamine is activated by the intramolecular electrophilic amidating moiety as well as a migrating directing group. The asymmetric carboamidation reaction pattern depends on the nature of the (hetero)arene reagent. Simple achiral (hetero)arenes reacted to give centrally chiral *β*-amino alcohols in excellent enantioselectivity. The employment of axially prochiral or axially racemic heteroarenes afforded amino alcohols with both axial and central chirality in excellent enantio- and diastereoselectivity. In the case of axially racemic heteroarenes, the coupling follows a kinetic resolution pattern with an *s*-factor of up to >600. A nitrene-based reaction mechanism has been suggested based on experimental studies, and a unique mode of induction of enantio- and diastereoselectivity has been proposed. Applications of the amino alcohol products have been demonstrated.

INTRODUCTION

Olefins serve as abundant feedstock chemicals in a large range of catalytic transformations, and they typically undergo hydrofunctionalization[1] and difunctionalization,[2] allowing ready access to a plethora of value-added chemicals. Difunctionalization of olefins, which simultaneously introduces two functional groups across the double bond, represents a highly important transformation. The key issue of this reaction resides in the reaction reactivity and selectivity, especially regio- and enantioselectivity. To enhance the reactivity and selectivity, directing group (DG)-assisted, metal-catalyzed functionalization of olefins has been established as a dominant strategy via formation of a five- or six-membered metalacyclic intermediate.[3] By following this strategy, difunctionalization of olefins has been realized with a nucleophile and an electrophile under redox-neutral conditions,[4] with two nucleophiles under oxidative conditions,[5] or with two electrophiles under reductive conditions (Scheme 1a).[6] Asymmetric protocols of olefin difunctionalization have been developed by the groups of Engle, Fu, Kong, Wang, Shu, Diao, Morken, Nevado, and others using nickel[7] or palladium catalysts.[8] However, the reaction pattern is mostly limited to dicarbofunctionalization, and the role of a DG is essentially limited to the chelating effect. However, removal or functionalization of the DG may not be a trivial task.

Arene C−H bonds are an intrinsically nucleophilic carbon source, and their abundance in the nature calls for efficient synthetic utilization. Indeed, functionalization of olefins with arenes has provided numerous synthetic methods to access complex organic scaffolds without prefunctionalization.[9] In recent years, two-component[10] 1,2- or 1,1-difunctionalization of olefins has been independently developed by Cramer and You via C−H activation of specific arenes with a built-in electrophilic amidating reagent (Scheme 1b). The related three-component[11] difunctionalization of olefins (Scheme 1b) with arenes has been reported by Ellman, Cramer, Glorius, and Rovis, relying on the employment of reactive electrophiles

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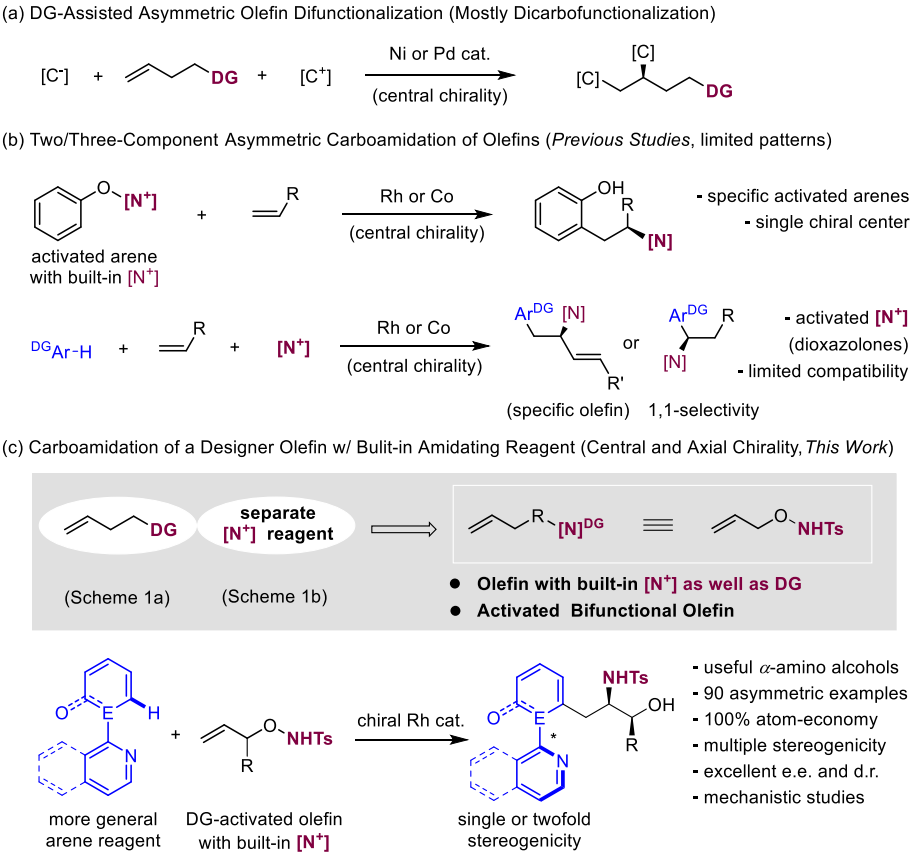
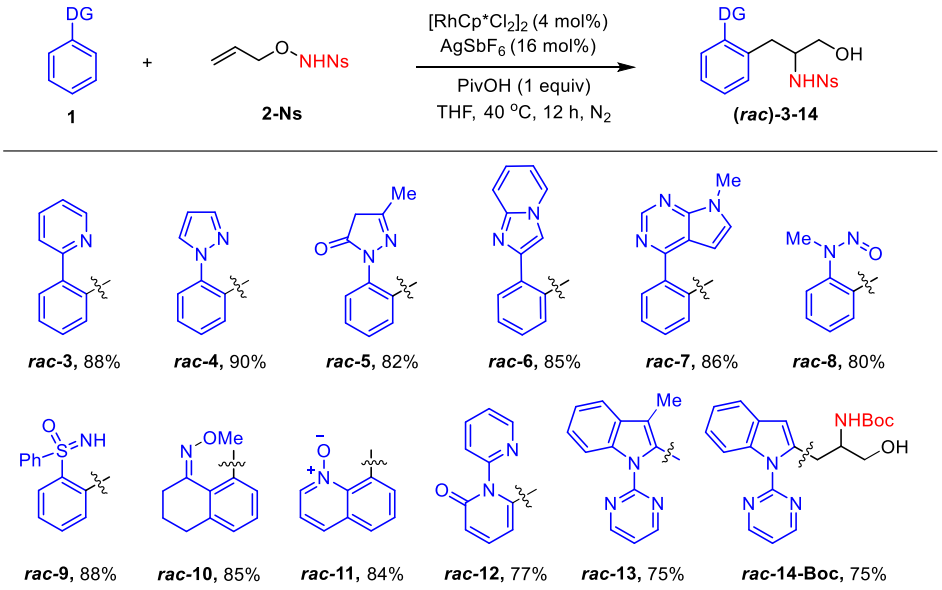
Scheme 1. Asymmetric Difunctionalization of Olefins



Scheme 2. Scope of Arenes in Racemic Carboamidation[a]



[a]Reaction conditions: arene (0.1 mmol), olefin **2-Ns** (0.15 mmol), $[RhCp^*Cl_2]_2$ (4 mol %), $AgSbF_6$ (16 mol %), and PivOH (0.1 mmol) in THF (1 mL) at 40 °C under N_2 for 12 h. Isolated yield.

(mostly aldehyde or amidating reagents).[11,12] These difunctionalization systems have been mostly limited to racemic synthesis.[12] While there are related rhodium- or cobalt-catalyzed 1,2-asymmetric difunctionalizations, the reaction patterns remain monotonous, with the olefins being restricted to activated ones such as acrylate esters, strained bicyclic olefins,[10e,12h] and 1,3-dienes.[10f,11b] In addition, the product is limited to central chirality.

The generation of multiple chiral elements in one shot offers an attractive strategy to enhance molecular complexity. While 1,2-difunctionalization of olefins with arenes allows access to two contiguous chiral centers, the asymmetric control seems

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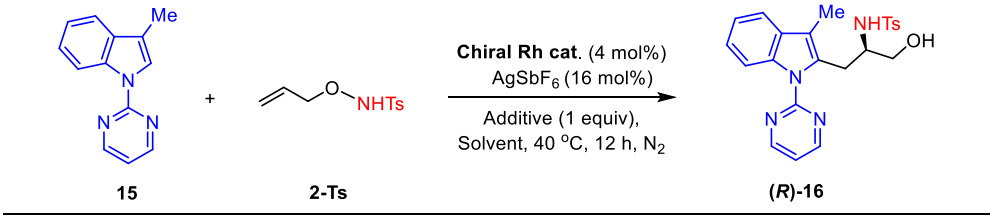
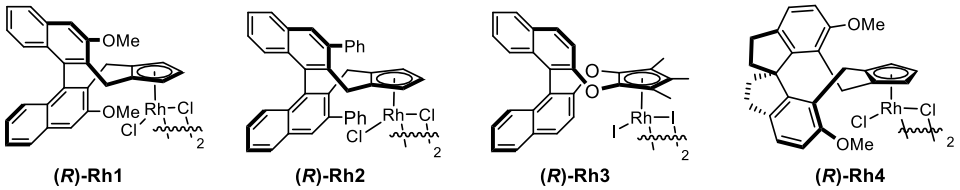
Table 1. Optimization Studies[a,b]





entry	Rh cat.	additive	solvent	yield (%)	Ee (%)
1	**Rh1**	PivOH	1,2-dichloroethane (DCE)	79	−58
2	**Rh2**	PivOH	DCE	35	−50
3	**Rh3**	PivOH	DCE	41	−48
4	**Rh4**	PivOH	DCE	80	93
5	**Rh4**	PivOH	dichloromethane (DCM)	76	91
6	**Rh4**	PivOH	methanol (MeOH)	39	85
7	**Rh4**	PivOH	trifluoroethanol (TFE)	55	92
8	**Rh4**	PivOH	1,4-dioxane	24	82
9	**Rh4**	PivOH	toluene (PhMe)	74	84
10	**Rh4**	PivOH	trifluorotoluene ($PhCF_3$)	84	92
11	**Rh4**	PivOH	2-methyl tetrahydrofuran (2-Me-THF)	89	96
12	**Rh4**	**PivOH**	**THF**	**91**	**98**
13	**Rh4**	acetic acid (HOAc)	THF	82	94
14	**Rh4**	adamantane 1-carboxylic acid (1-$AdCO_2H$)	THF	55	95
15	**Rh4**	2,4,6-trimethylphenylbenzoic acid ($MesCO_2H$)	THF	72	96

[a]Reactions were carried out using indole **15** (0.1 mmol), **2-Ts** (1.5 equiv), chiral Rh catalyst (4 mol %), and additive (1.0 equiv) at 40 °C in a solvent (1 mL) for 12 h under N_2. [b]Isolated yields.

relatively less challenging due to the correlated nature of the two chiral centers.[10e,13] In contrast, asymmetric construction of both a chiral axis and a chiral center is more challenging.[14] In this context, branch-selective hydroarylation of olefins has been applied to the construction of both axial and central chirality, although linear selectivity is more common.[15] Notably, the Lassaletta group reported palladium- or iridium-catalyzed branch-selective C−X or C−H alkylation via dynamic kinetic resolution of arenes in high enantio- and diastereoselectivity.[16] Remarkably, the Ackermann group realized the Ru-catalyzed version using a chiral carboxylic acid as the chiral source.[17] It will be more challenging to apply olefin difunctionalization for this purpose, where the bifunctionality in the final products allows rich chemistry. Inspired by prior studies by the groups of Chang,[18] Ellman,[11a] Cramer,[10e,11c] Glorius,[12g] Yu,[19] and Meggers[20] on related functionalization using electrophilic amidating reagents, we designed *N*-protected *O*-allylhydroxylamines as novel olefins with a built-in amidating reagent as well as a DG (Scheme 1c). We now report the asymmetric coupling of this olefin with more general classes of arenes, affording synthetically useful centrally and axially chiral amino alcohols in excellent regio-, enantio-, and diastereoselectivity (if applicable) in 100% atom economy.

RESULTS AND DISCUSSION

Racemic Coupling. The racemic coupling of arenes and *N*-(allyloxy)-4-nitrobenzenesulfonamide (**2-Ns**) was initially investigated to explore the reactivity of the new olefin reagent. Brief optimization indicated applicability of a broad spectrum of arenes bearing a readily installed DG under unified reaction conditions using $[Cp^*RhCl_2]_2/AgSbF_6$ as a catalyst and pivalic acid (PivOH) as an additive, affording the racemic amino alcohols as a result of olefin carboamidation (Scheme 2). Various arenes all reacted in excellent yield and regioselectivity (*rac*-**3**-**10**) under N-chelation assistance. Quinoline *N*-oxides were also viable (product *rac*-**11**). In addition, heteroarenes such as *N*-pyridylpyridone (*rac*-**12**) and *N*-pyrimidylindoles (*rac*-**13**, 75% yield) were also applicable under the reaction conditions. The *N*-substituent in the alkene was not restricted to a sulfonyl group, and an *N*-Boc-protected olefin also reacted in comparable efficiency under the same reaction conditions (*rac*-**14-Boc**). These observations suggest the generally high reactivity of *O*-allylhydroxyamines, which bodes well for the development of asymmetric carboamidation systems.

Asymmetric Optimization Studies. We next focused on the asymmetric version of the carboamidation reaction. *N*-pyrimidyl-3-methylindoles (**15**) and *N*-(allyloxy)-4-methylbenzenesulfonamide were selected as the model substrates for optimization studies (Table 1). The desired carboamidation reaction occurred in the presence of Cramer's second generation catalyst[21a,b] (*R*)-**Rh1**/$AgSbF_6$ with PivOH as an additive in DCE, and product **16** was isolated in a promising yield and moderate enantioselectivity (entry 1). While an inferior yield and enantioselectivity were found for binaph-

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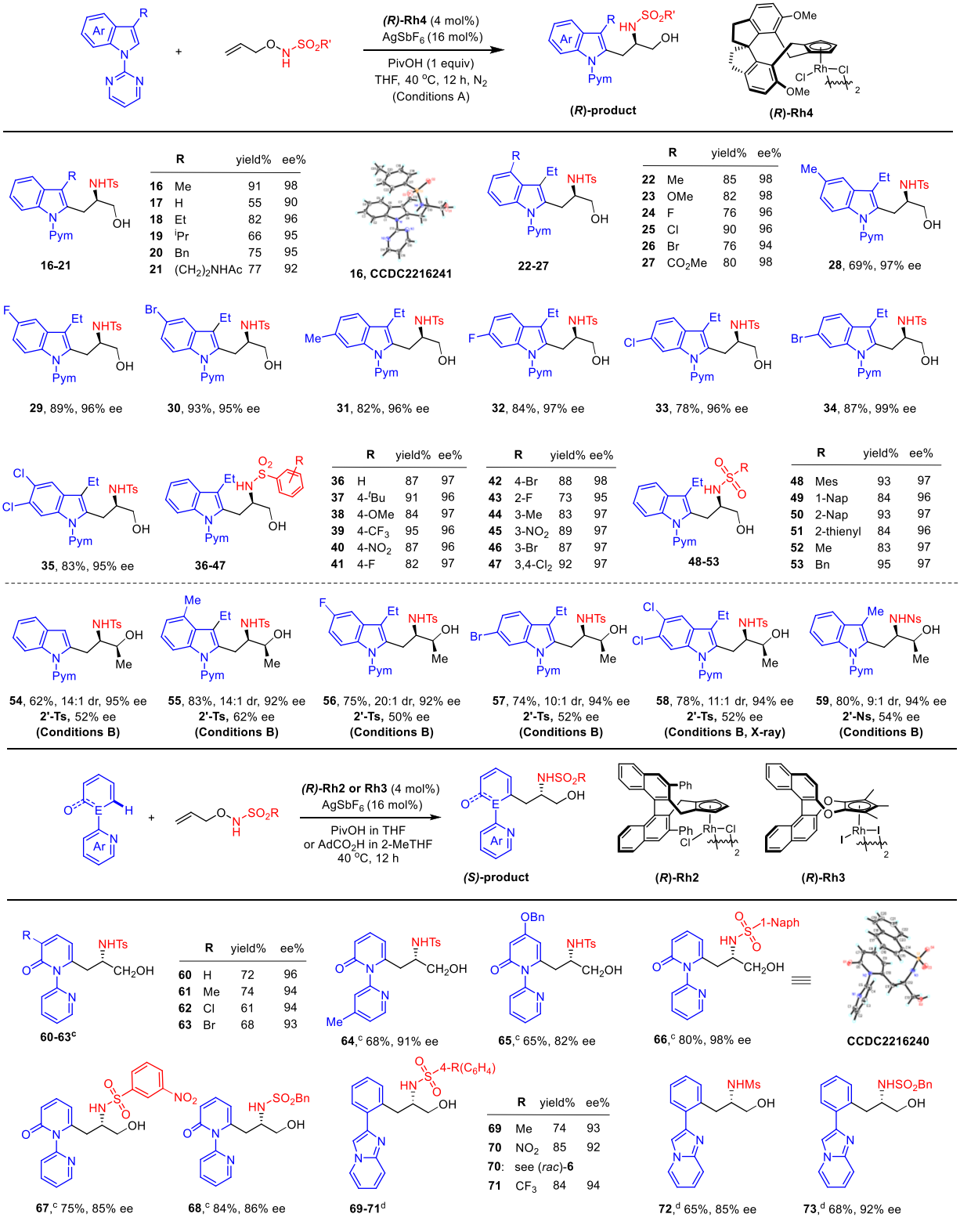
Scheme 3. Central Chirality via Asymmetric Carboamidation Using Five- and Six-Membered Arenes[a]



	R	yield%	ee%
16	Me	91	98
17	H	55	90
18	Et	82	96
19	^{i}Pr	66	95
20	Bn	75	95
21	$(CH_2)_2NHAc$	77	92

	R	yield%	ee%
22	Me	85	98
23	OMe	82	98
24	F	76	96
25	Cl	90	96
26	Br	76	94
27	CO_2Me	80	98

	R	yield%	ee%
36	H	87	97
37	4-^{t}Bu	91	96
38	4-OMe	84	97
39	4-CF_3	95	96
40	4-NO_2	87	96
41	4-F	82	97

	R	yield%	ee%
42	4-Br	88	98
43	2-F	73	95
44	3-Me	83	97
45	3-NO_2	89	97
46	3-Br	87	97
47	3,4-Cl_2	92	97

	R	yield%	ee%
48	Mes	93	97
49	1-Nap	84	96
50	2-Nap	93	97
51	2-thienyl	84	96
52	Me	83	97
53	Bn	95	97

	R	yield%	ee%
60	H	72	96
61	Me	74	94
62	Cl	61	94
63	Br	68	93

	R	yield%	ee%
69	Me	74	93
70	NO_2	85	92
70:	see (*rac*)-6		
71	CF_3	84	94

[a]Reaction conditions A: indole (0.1 mmol), alkene (0.15 mmol), (*R*)-**Rh4** (4 mol %), $AgSbF_6$ (16 mol %) and PivOH (0.1 mmol) in THF (1 mL) at 40 °C under N_2 for 12 h, Isolated yields. [b]Reaction conditions B: indole (0.1 mmol), alkene (0.2 mmol), (*R*)-**Rh4** (4 mol %), $AgPF_6$ (16 mol %), and 1-$AdCO_2H$ (0.1 mmol) in MeOH (1 mL) at 40 °C under N_2 for 12 h. [c]Reaction conditions C: arene (0.1 mmol), alkene (0.15 mmol), (*R*)-**Rh2** (4 mol %), $AgSbF_6$ (16 mol %), and PivOH (0.1 mmol) in THF (1 mL) at 40 °C under N_2 for 12 h. Isolated yields. [d]Reaction conditions D: arene (0.1 mmol), alkene (0.15 mmol), (**R**)-**Rh3** (4 mol %), $AgSbF_6$ (16 mol %), and 1-$AdCO_2H$ (0.1 mmol) in 2-Me-THF (1 mL) at 40 °C under N_2 for 12 h.

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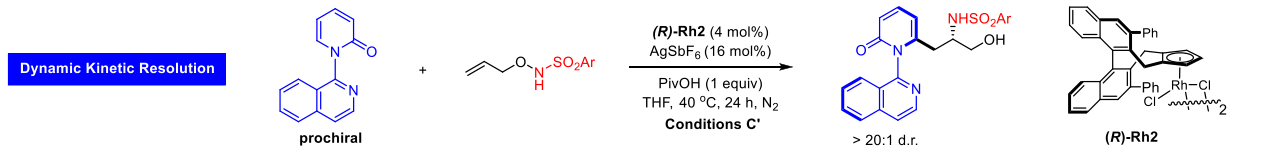
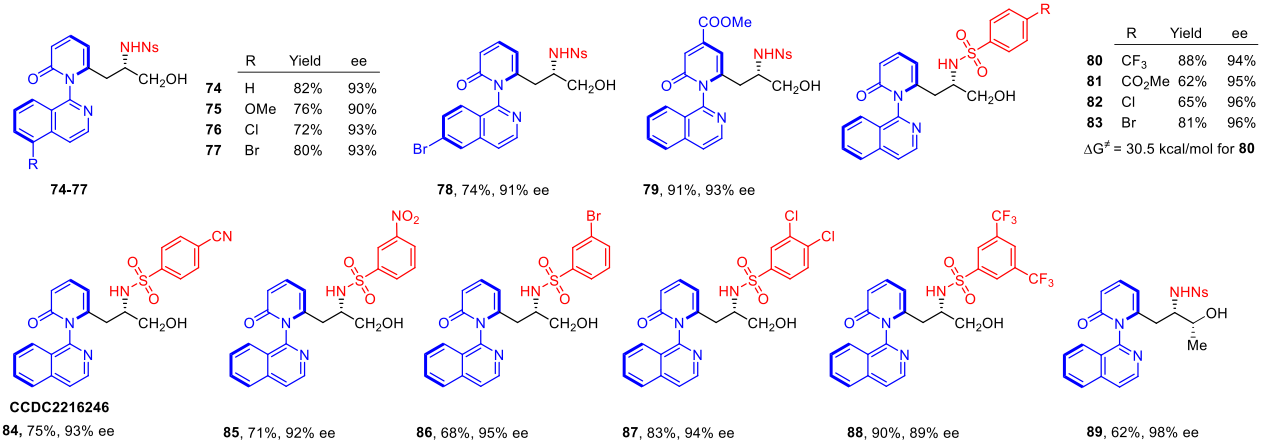
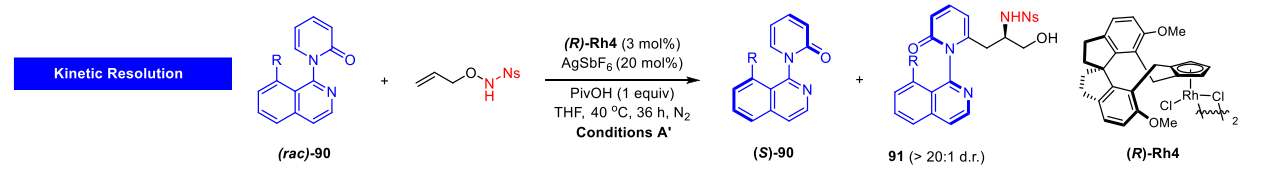
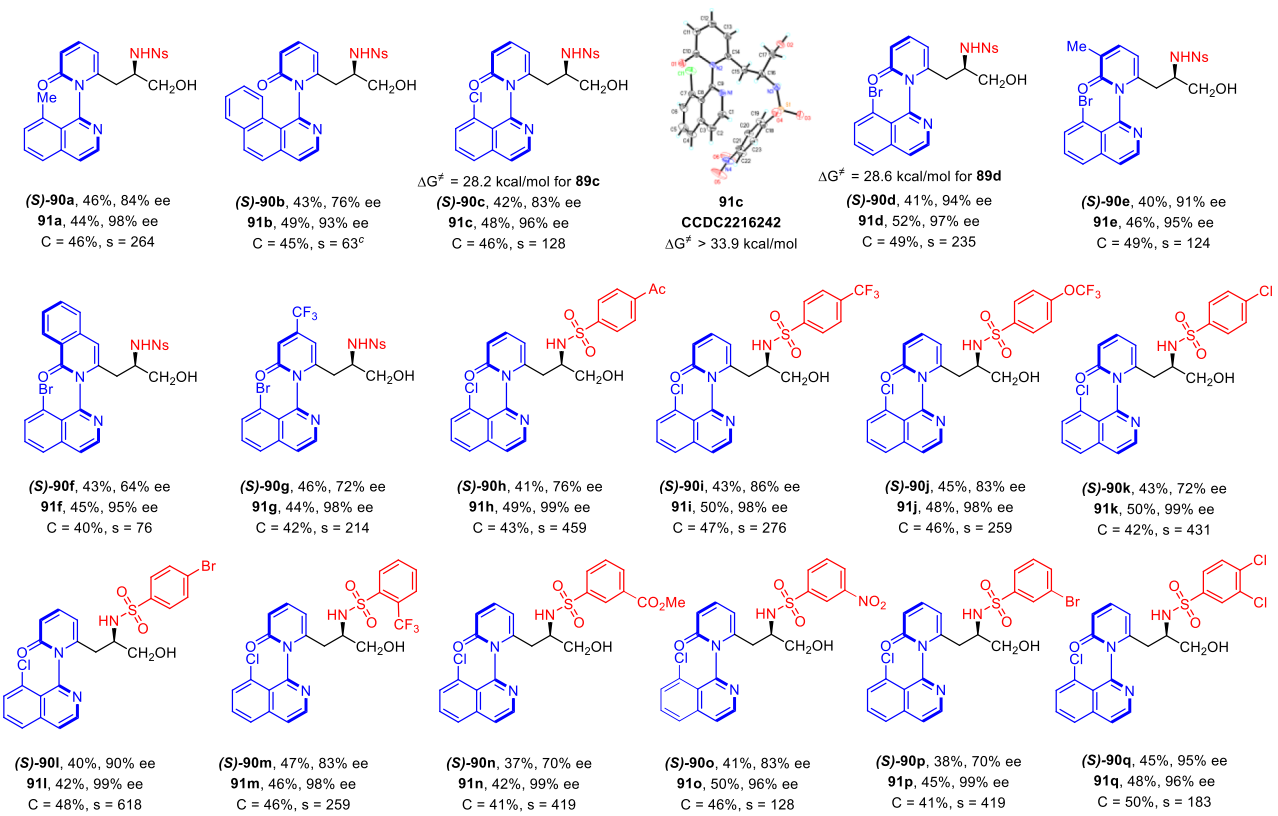
Scheme 4. Scope of Synthesis of Axially and Centrally Chiral Amino Alcohols[a]









[a]DKR (modified conditions C): arene (0.1 mmol), alkene (0.15 mmol), (*R*)-**Rh2** (4 mol %), $AgSbF_6$ (16 mol %), and PivOH (0.1 mmol) in THF (1 mL) at 40 °C under N_2 for 24 h. Isolated yields. [b]KR (modified conditions A): (*rac*)-**90** (0.1 mmol), alkene (0.06 mmol), (*R*)-**Rh4** (3 mol %), $AgSbF_6$ (20 mol %), and PivOH (0.1 mmol) in THF (1 mL) at 40 °C under N_2 for 36 h. Isolated yields. [c]At 15 °C.

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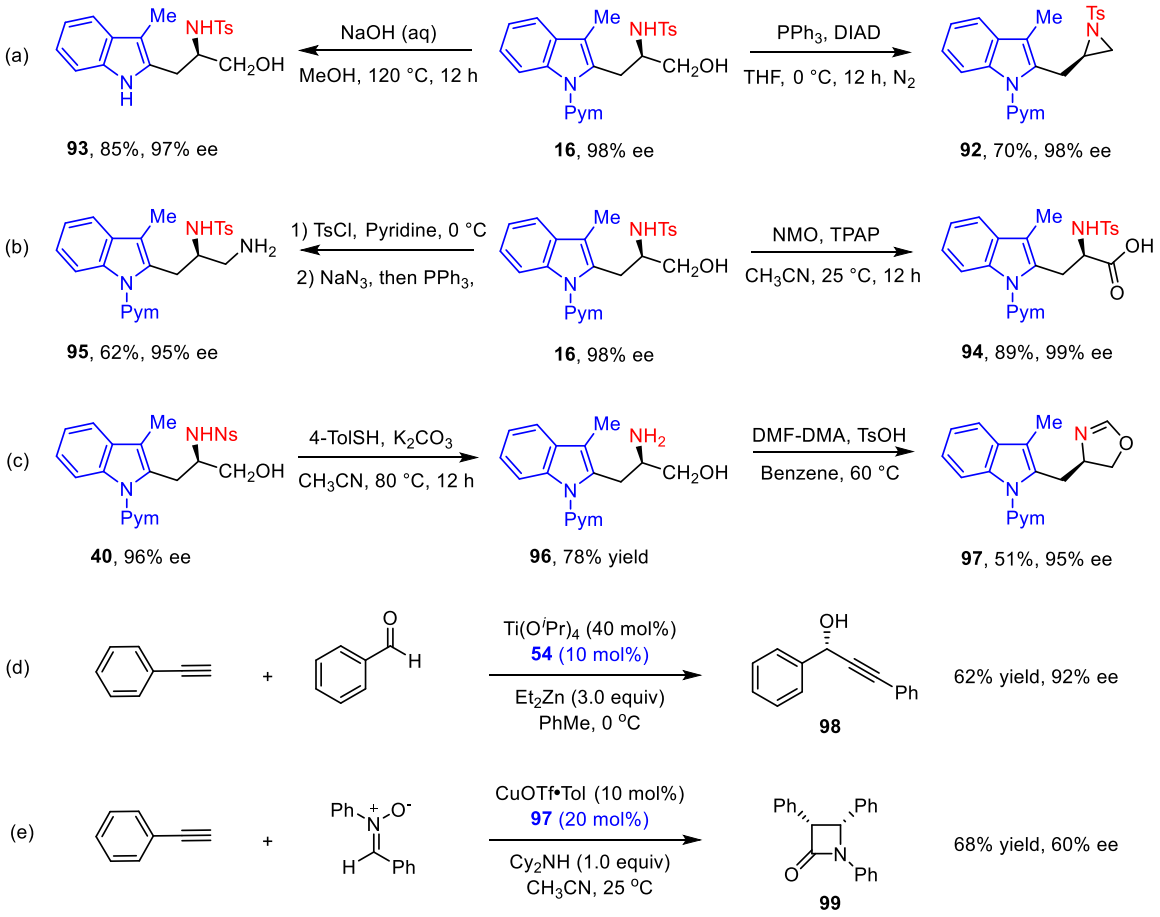
Scheme 5. Synthetic Applications of Representative Products



thalene-based chiral catalysts (*R*)-**Rh2** and (*R*)-**Rh3** (entries 2 and 3), switching to a spirocyclic (*R*)-**Rh4** catalyst, which was originally developed by You,[22] significantly improved the yield (80%) and enantioselectivity (93% ee, entry 4). The observed opposite configuration is due to the opposite spatial orientation of the chiral ligand despite the same nomenclature. Solvent screening indicated the superiority of THF (entries 6−12), as in the racemic coupling system. Investigation of the additives returned PivOH as the optimal acid additive.

Scope Studies of Central Chirality. With the optimal reaction conditions in hand, we next examined the scope of asymmetric synthesis of centrally chiral *β*-amino alcohols (Scheme 3). The scope of the indole substrates was first explored using the *N*-sulfonyl-*O*-allylhydroxyamine **2-Ts** as a coupling reagent. While high enantioselectivity was observed when a 3-unsubstituted indole was used (product **17**), installation of a 3-substituent (Me, Et, ^{i}Pr, Bn, CH_2CH_2NHAc) increased the enantioselectivity and reaction efficiency, and the corresponding products **18-21** were obtained in 66−82% yields with excellent enantioselectivity, indicating insensitivity to the steric effect. The absolute configuration of product **16** (CCDC2216241) was determined to be (*R*) by X-ray crystallography. Further examination revealed that introduction of a Me, OMe, ester, and halogen group at the 4-, 5- or 6-position of the indole ring all allowed isolation of the products in excellent enantioselectivity (**22-34**, 94−99% e.e.). The scope of the olefin substrate was next examined. A large range of electron-donating and -withdrawing and halogen groups at different positions of the benzene ring of the *N*-arenesulfonyl group was fully compatible, affording products **36-48** in good yield and excellent enantioselectivity (95−98% ee.). Other *N*-(hetero)arenesulfonyl groups also underwent efficient coupling to afford the corresponding *β*-amino alcohols **49−51** with ≥96% ee. Extension to several *N*-alkanesulfonyl-substituted *O*-allyl hydoxyamines was also successful (**52** and **53**). Significantly, a representative class of racemic olefins (2 equiv) bearing an allylic methyl group was also amenable to the coupling reaction except that modified reaction conditions were adopted (**54−59**, Conditions B). In this case, the coupling afforded amino alcohols with two contiguous chiral centers as a result of kinetic resolution (KR) of the racemic olefin. Under these modified conditions, indoles with diverse substituents at the 4-, 5-, and 6-positions all underwent smooth coupling in 10 to 20:1 d.r. and in 92−95% ee (**54−58**). The major product of **58** was determined to be (R_{C2}, S_{C1}) configuration by X-ray crystallographic analysis (CCDC 2235765), and the rest of the products were assigned by analogy. In this series of methyl-substituted olefins, the presence of an *N*-Ns group was also compatible (product **59**).

To better define the arene scope, we next examined other classes of carbo- or heterocycles. Under different modified reaction conditions using Cramer's chiral catalyst (*R*)-**Rh2** (Conditions C), 2-pyridylpyridones bearing various substituents in the pyridine or the pyridone ring all proved to be effective substrates (**60−65**). Alkenes bearing different benzenesulfonyl groups also coupled smoothly with 2-pyridylpyridone. In all cases, the amino alcohols were isolated in consistently high enantioselectivity (**60−68**, 82−98% ee).

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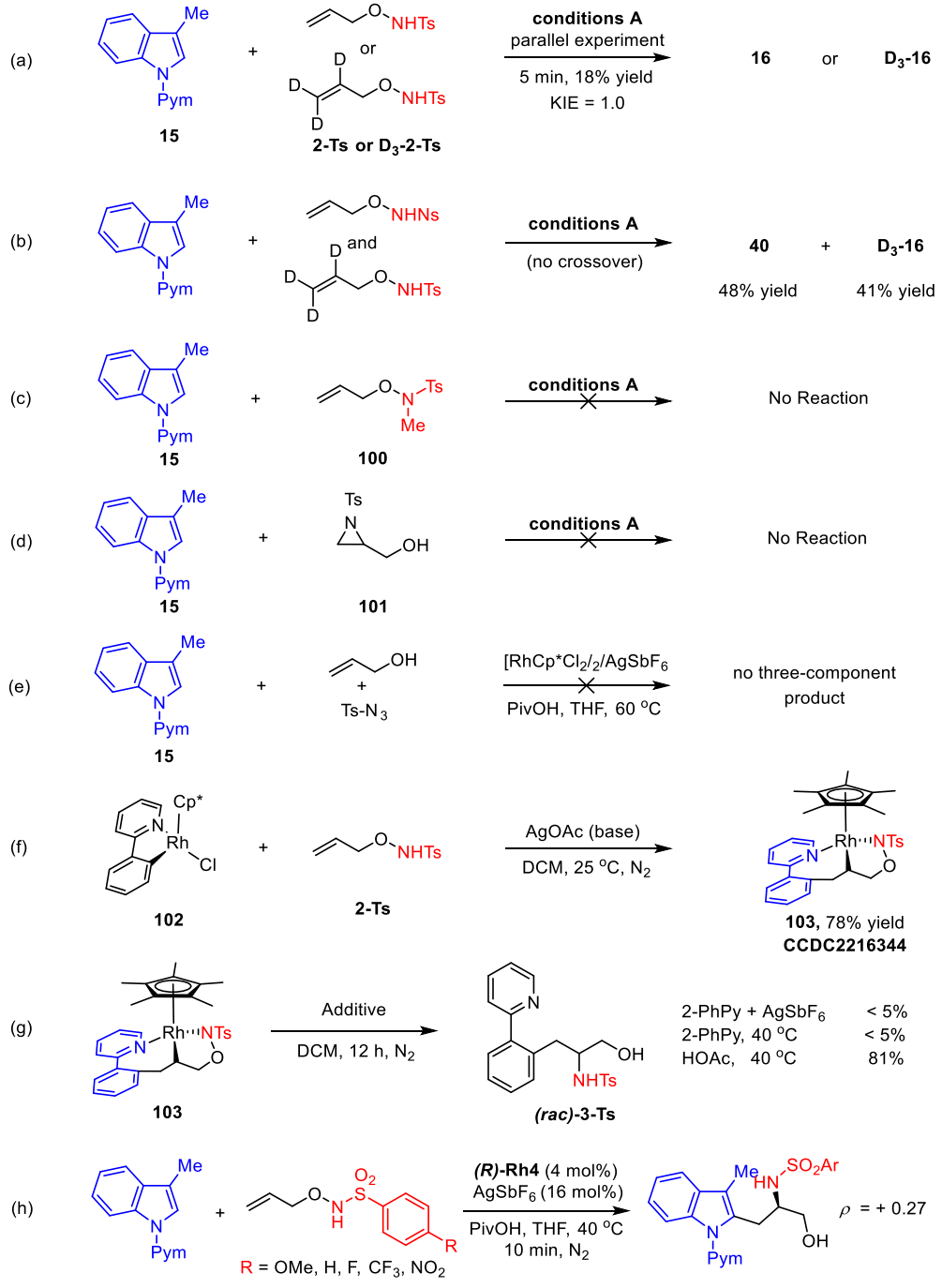
Scheme 6. Experimental Mechanistic Studies



The (*S*) configuration of the product **66** was confirmed by X-ray crystallography (CCDC 2216240). Successful coupling of 2-phenylimidazo[1,2-*a*]pyridine as an arene further verified the generality of this reaction system. Thus, 2-phenylimidazo[1,2-*a*]pyridine reacted smoothly with the *O*-allylhydroxyamine reagent using (*R*)-**Rh3** as the catalyst and $AdCO_2H$ as the additive in 2-MeTHF (Conditions D), where a similar set of *N*-sulfonyl-*O*-allylhydroxyamine reagent also proved viable (**69**−**73**).

Scope of Products with Twofold Stereogenicity. The excellent enantioselectivity in the synthesis of centrally chiral products **60**−**68** promise well for the generation of both axial and central chirality when more sterically hindered 2-pyridones are used. In fact, partially hindered C−N rotation was suggested by ^{13}C NMR spectroscopy of **60**−**68**. Indeed, both dynamic kinetic transformation and kinetic resolution have been realized (Scheme 4), depending on the steric size of the pyridones with a bulky N-DG. 2-Pyridones bearing an 8-unsubstituted *N*-isoquinolyl DG reacted smoothly to produce the corresponding chiral product with an additional C−N chiral axis (Scheme 4, top). The scope of this reaction was briefly explored using (*R*)-**Rh2** as the optimal chiral catalyst, and the presence of electron-withdrawing or -donating groups at different positions of the isoquinoline ring only had marginal influence on the reactivity or enantioselectivity (**74**−**79**). Moreover, variations of substituents in the arenesulfonyl group allowed smooth isolation of products **80**-**88** in moderate to good yield and excellent enantioselectivity (89−96% ee). The

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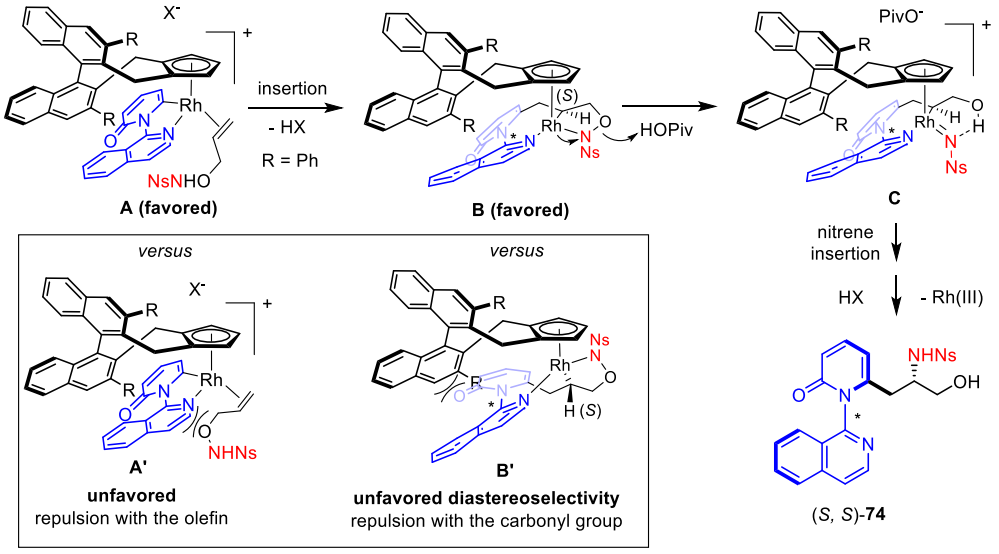
Scheme 7. Induction of Enantio- and Diastereoselectivity via a Single Insertion Step



absolute configuration of product **84** has been determined to be (a*S*, c*S*) by X-ray crystallography (CCDC 2216246). In all cases, excellent diastereoselectivity was observed (>20:1 dr). As for 2-pyridone bearing a bulkier 8-substituted isoquinolyl DG, axial chirality exists in the pyridone substrate and such racemic arene coupled with the olefin with a kinetic resolution pattern (Scheme 4, bottom). The scope of this kinetic resolution system was then explored. It was found that the (*R*)-**Rh4** catalyst outperformed others in terms of enantioselectivity. Thus, introduction of Me, Cl, and Br groups or a fused ring into the 8-position of the isoquinoline ring all gave smooth reactions (products **91a−d**). Generally high enantiopurity (76−94% ee) of the recovered arene and consistently excellent enantioselectivity of the product (93−98% ee) were obtained, which corresponds to an *s*-value of 63−264. The absolute configuration of the product **91c** was determined by X-ray crystallography (CCDC 2216242) to be (a*R*, c*R*), consistent with the configuration of product **84** due to employment of a spatially inverted chiral ligand. The rotational barrier of representative products (**91c**) along the C−N axis has been experimentally determined to be $\Delta G^{\neq}$ > 33.9 kcal/mol, while the recovered substrate (*S*)-**90c** only carries a rotational barrier of 28.2 kcal/mol. 2-Pyridone rings functionalized with various groups were all effective substrates, affording the coupled products in excellent enantioselectivity (**91e−g**, 95−98% ee). The olefins bearing a range of substituents at different positions of the benzene ring in the *N*-sulfonyl group were fully compatible, affording **91h−q** in a good yield and high ee (96−99% ee). Meanwhile, comparable ee values were also obtained for the recovered arenes, which corresponds to *s*-values of 128−618. In all cases, the products were generated as a single diastereomer (>20:1 d.r.).

Synthetic Applications. Synthetic transformations and catalytic applications of our representative chiral amino alcohols have been explored (Scheme 5). Treatment of product **16** with PPh_3/DIAD afforded aziridine **92** in a 70% yield. The *N*-pyrimidyl DG in **16** was selectively cleaved when treated with NaOH/MeOH (**93**, Scheme 5a). Oxidation of **16** gave amino acid **94** in an excellent yield. The OH group in product **16** could be protected by Ts, and azidation-reduction afforded the diamine **95** (Scheme 5b). Removal of the Ns group in **40** gave free amine **96** in a good yield; further treatment of **96** with DMF-DMA/TsOH afforded oxazoline **97** in an acceptable yield (Scheme 5c). In all cases, only slight erosion of the enantiopurity was detected. Chiral amino alcohol **54** was further applied as a ligand in Ti-catalyzed nucleophilic addition between benzaldehyde and alkynylzinc,[23] affording alcohol **98** in 92% ee (Scheme 5d). We also applied **97** as a chiral ligand in Cu-catalyzed asymmetric Kinugasa reaction between phenylacetylene and an arylnitrone, affording **99** with promising enantioselectivity (Scheme 5e),[24] indicating potentiality of both chiral amino alcohol and related oxazoline as chiral ligands in asymmetric catalysis.

Mechanistic Studies. A series of experiments have been conducted to explore the mechanism of this (asymmetric) coupling system (Scheme 6). To probe the olefin insertion event, we conducted kinetic isotope effect studies using protio and deuterated olefins, and a KIE = 1.0 was obtained (Scheme 6a), suggesting that the olefin insertion should not be rate-limiting, otherwise an inverse KIE would be expected.[25] A crossover experiment using indole **15** and two distinguishable alkenes verified the intramolecularity of the formal migration of sulfonamide group since only two corresponding products were generated without crossover (Scheme 6b). Control experiments using an *N*,*N*-disubstituted *O*-allyl hydroxyamine **100** or an aziridine **101** as a coupling reagent all failed to give any cross-coupling product (Scheme 6c,d). These outcomes may suggest intermediacy of a nitrene species,[17−19] which is inaccessible using olefin **100**, or suggest the lack of chelation assistance in **100** that is crucial for migratory insertion. It is also unlikely that our *O*-allylhydroxyamine reagent undergoes isomerization to a hydroxymethyl-functionalized aziridine[26] as an intermediate. To explore the chelation effect in the olefin reagent, a three-component control reaction between an indole, allyl alcohol, and TsN_3 was conducted (Scheme 6e). No desired three-component carboamidation product was detected, and only a small amount of the direct C−H amidation side-product was observed, indicating that the olefin reagent is chelation-activated toward insertion. To further explore the mechanistic details, especially the olefin insertion, an equimolar mixture of rhodacycle **102**, 2-phenylpyridine, and AgOAc was stirred at 25 °C, from which complex (*rac*)-**103**

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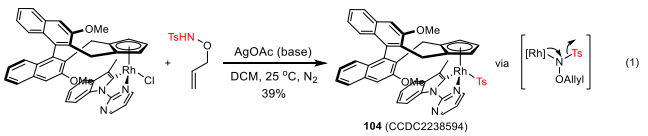
was isolated as the single diastereomer in a high yield (Scheme 6f) as a result of selective olefin insertion-nitrogen chelation with deprotonation. Complex **103** was fully characterized by X-ray crystallography (CCDC 2216344). Heating a solution of **103** in the presence 2-phenylpyridine (2 equiv) and $AgSbF_6$ afforded no coupled product. In contrast, introduction of AcOH or PivOH (2 equiv) in the absence of 2-phenylpyridine readily gave the carboamidation product (*rac*)-**3-Ts** (40 °C), highlighting the significant role of the acid in the catalytic cycle (Scheme 6g). Besides facilitating the C−H bond activation, carboxylic acid promoted the cleavage of the N−O bond with concomitant formation of a nitrene species,[27] which is proposed to undergo insertion into the Rh−C(alkyl) bond to build the C−N bond (see Scheme 7 and the Supporting Information). To probe the electronic effect of the *N*-sulfonyl group in the olefin, a Hammett plot has been constructed for the coupling of an indole substrate and an *N*-(allyloxy)-4-arenesulfonamide bearing a different 4-substituent in the benzene ring under the asymmetric reaction conditions (Scheme 6h). The Hammett plot revealed a slight buildup of negative charge in the transition state (ρ = +0.27). Thus, this coupling system likely proceeds through a pathway that involves C−H activation, chelation-assisted alkene insertion, acid-assisted nitrene formation, nitrene insertions, and eventual protodemetalation (see Scheme 7 and the Supporting Information), and the Hammett plot seems to suggest that the nitrene formation or its insertion is probably turnover-limiting.

To explore the stoichiometric interactions between the chiral rhodacyclic species and the olefin, an enantiomeric pure rhodacycle that is derived from C−H activation of an indole was allowed to react with olefin **2-Ts** in the presence of AgOAc. To our surprise, a Rh(III) sulfinate complex (**104**) was isolated as the major product as a result of N−S bond cleavage (eq 1). Although this species seems irrelevant to the



catalytic cycle, we may conclude that the basic conditions strongly favor sulfonamide ligation (instead of the olefin coordination that is required for migratory insertion). Subsequently, it undergoes elimination of the sulfinate group which then re-coordinates after decomposition of the nitrene species. This observation also seems consistent with our observation that the alternative N−O bond cleavage does not occur easily and needs acid-assistance (Scheme 6g).

Chiral Induction and Key Steps. The key elementary steps and the enantio- and diastereo-induction have been rationalized for the asymmetric coupling between a 2-pyridone and *N*-Ns-*O*-allylhydroxyamine (Scheme 7). Based on the chiral induction model initially proposed by the Cramer group and experimentally supported by our group,[21a,b,28] the C−H bond activation is proposed to give a rhodacyclic intermediate with a well-defined orientation of the arene, where the bulky isoquinolinyl DG is pointed frontward for minimized steric interactions with the chiral ligand. The olefin then approaches with a well-controlled orientation to minimize the steric interactions between the arene moiety and the CH_2ONHNs segment of the olefin (**A** vs **A′**). Subsequent migratory insertion into the olefin generates a chelation-stabilized (*S*)-configured alkyl group in the intermediate **B**, which is analogous to the complex **103** in our stoichiometric studies, and the β-hydrogenation of **B** is also suppressed by the chelation effect. Significantly, this migratory insertion is also diastereo-determining because upon migratory insertion, the C−N chiral axis in the rhodacyclic intermediate **B** is created and is carried forward. It is proposed that the steric repulsions between the R (R = Ph) group in the chiral ligand the carbonyl group in 2-pyridone pushed the carbonyl group downward (see also **B′**), which corresponds to the formation of an (*S*)-configured chiral axis. PivOH-assisted N−O bond cleavage (oxygen elimination) then gives a nitrene intermediate **C** with intramolecular hydrogen bonding, and a sequence of nitrene insertion and Rh−N bond protonolysis eventually furnishes the (*S*,*S*)-**74** product. In this system, the enantioselectivity and diastereoselectivity have been simultaneously induced by a single elementary step, which accounts for the excellent enantio- and diastereoselectivity throughout the entire study. Previously, single-step induction of both enantio- and diastereoselectivity has been relatively rare.[29]

CONCLUSIONS

In conclusion, *N*-protected *O*-allylhydroxyamines have been designed as bifunctional olefins that undergo Rh-catalyzed 1,2-carboamidation in three asymmetric reaction patterns, depending on the nature of the arene substrates. The coupling of achiral (hetero)arenes bearing a small DG gave centrally chiral amino alcohols in excellent enantioselectivity. With the increase of the size of the DG, dynamic kinetic transformation has been realized for axially prochiral arenes, affording corresponding amino alcohols with axial as well as central chirality in excellent enantioselectivity and diastereoselectivity. In the case of axially racemic 2-pyridones bearing a large 8-substituted isoquinolyl DG, the coupling follows a kinetic resolution pattern, where the 2-pyridone substrates were effectively resolved together with the formation of axially and centrally chiral products with an *s*-factor of up to >600. Synthetic applications of representative amino alcohols have been explored, which showed promise as a chiral additive or ligand in enantioselective asymmetric catalytic reactions. Mechanistic studies have been extensively performed, and a rhodacycle was isolated as an intermediate which is proposed to be a nitrene precursor. The current *O*-allylhydroxyamine reagent exhibited a complementary role in asymmetric olefin difunctionalization, and further studies on the rich chemistry of this olefin in other metal-catalyzed complex coupling systems are underway in our laboratory.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.3c01162.

Experimental procedures, computational details, characterization of new compounds, NMR spectra, HPLC chromatograms, and crystal structures of **16** (CCDC2216241), **58** (CCDC2235765), **66** (CCDC2216240), **84** (CCDC2216246), **91c** (CCDC2216242), **103** (CCDC2216344), and **104** (CCDC2238594) (PDF)

Accession Codes

CCDC 2216240−2216242, 2216246, 2216344, 2235765, and 2238594 contain the supplementary crystallographic data for

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this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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