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Nickel Catalyzed Enantioselective 1,4-Hydroamination of 1,3-Dienes

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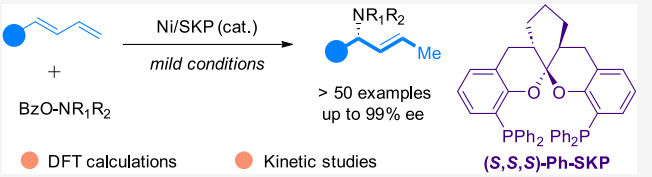
ABSTRACT: Transition metal-catalyzed enantioselective hydroamination of 1,3-dienes provides a direct methodology for the construction of chiral allylamines. So far, all of the reported examples used nucleophilic amines and proceeded with 3,4-regioselectivity. Herein, we describe the first example of nickel-catalyzed enantioselective 1,4-hydroamination of 1,3-dienes using trimethoxysilane and hydroxylamines with a structurally adaptable aromatic spiroketal based chiral diphosphine (SKP) as the ligand, affording a wide array of α-substituted chiral allylamines in high yields with excellent regio- and enantioselectivities. This operationally simple protocol demonstrated a broad substrate scope and excellent functional group compatibility, significantly expanding the chemical space for chiral allylamines. Experimental and DFT studies were performed to elucidate the mechanism and to rationalize the regio- and enantioselectivities of the reaction.



1. INTRODUCTION

Chiral amines are occurring extensively as substructures in numerous pharmaceuticals and biologically active molecules (Figure 1a).[1] Consequently, the development of efficient strategies for the stereocontrolled construction of C−N bonds has been an active endeavor in the synthetic community, and transition-metal catalyzed olefin asymmetric hydroamination constitutes one of the most straightforward approaches to various amines.[2,3] In this context, the catalytic asymmetric intermolecular hydroamination of conjugated dienes has attracted much attention due to the ready availability of the raw materials and the synthetic versatility of the allylamine products in fine chemical synthesis.[4−8] On the other hand, the control of regio- and stereoselectivities in catalytic asymmetric intermolecular hydroamination of 1,3-dienes is challenging, since up to 16 isomers of the corresponding products might be produced, depending on the nature and substitution pattern of the diene, as well as the reagents and catalysts (Figure 1b).[9−11] Over the last two decades, some transition metal-catalyzed asymmetric intermolecular hydroamination reactions of conjugated dienes have been reported from the elegant work from the groups of Hartwig,[12] Malcolmson,[13,14] Dong,[11,15] Mazet,[16] and Yin,[17] providing efficient access to a variety of optically active cyclic or acyclic allylamines (Figure 1c).[11−17] Despite these advances, only 3,4-addition hydroamination products were obtained in all of these cases, whereas the 1,4-regioselective asymmetric hydroamination reaction of acyclic dienes still remains elusive. As most of the developed diene hydroamination protocols involve the use of a nucleophilic amine, we envisioned that by employing an umpolung strategy in diene asymmetric hydroamination (Figure 1d), i.e., via interception of a nucleophilic allyl metal intermediate with an electrophilic amination reagent, may lead to a different regioselectivity complementary to the current methods.[18−20] To the best of our knowledge, there has been no precedent on metal-catalyzed enantioselective 1,4-hydroamination of 1,3-dienes so far.[10]

Herein we report the first example of nickel-catalyzed enantioselective 1,4-hydroamination of 1,3-dienes by using SKP as a chiral ligand to afford 1-aryl-substituted (*E*)-allylic amines with stereogenic center at the more sterically hindered carbon in high yields with excellent enantiomeric excesses (Figure 1e). The underlying mechanism was also investigated by using a combined array of experimental and DFT studies, to rationalize the regio- and enantioselectivities of SKP/Ni-catalyzed enantioselective hydroamination of conjugated dienes.

2. RESULTS AND DISCUSSION

2.1. Reaction Development. Recently, metal hydride-catalyzed hydrofunctionalization of alkenes has attracted considerable attention.[18−27] It has been reported that some NiH complexes demonstrate robust catalytic activity for enantioselective C−N bond-forming processes,[27−36] wherein O-benzoyl hydroxylamines ($BzO-NR_2$) are used as electrophilic amination reagent which is compatible to the presence of reductant reagents in the reaction system.[37] Accordingly, we commenced our studies on the Ni-catalyzed model reaction of phenylbutadiene **1a** and morpholino benzoate **2a**, and a preliminary parameter survey revealed that the reaction was best run at rt in 2-Me-THF with $Ni(COD)_2$ as the Ni source in

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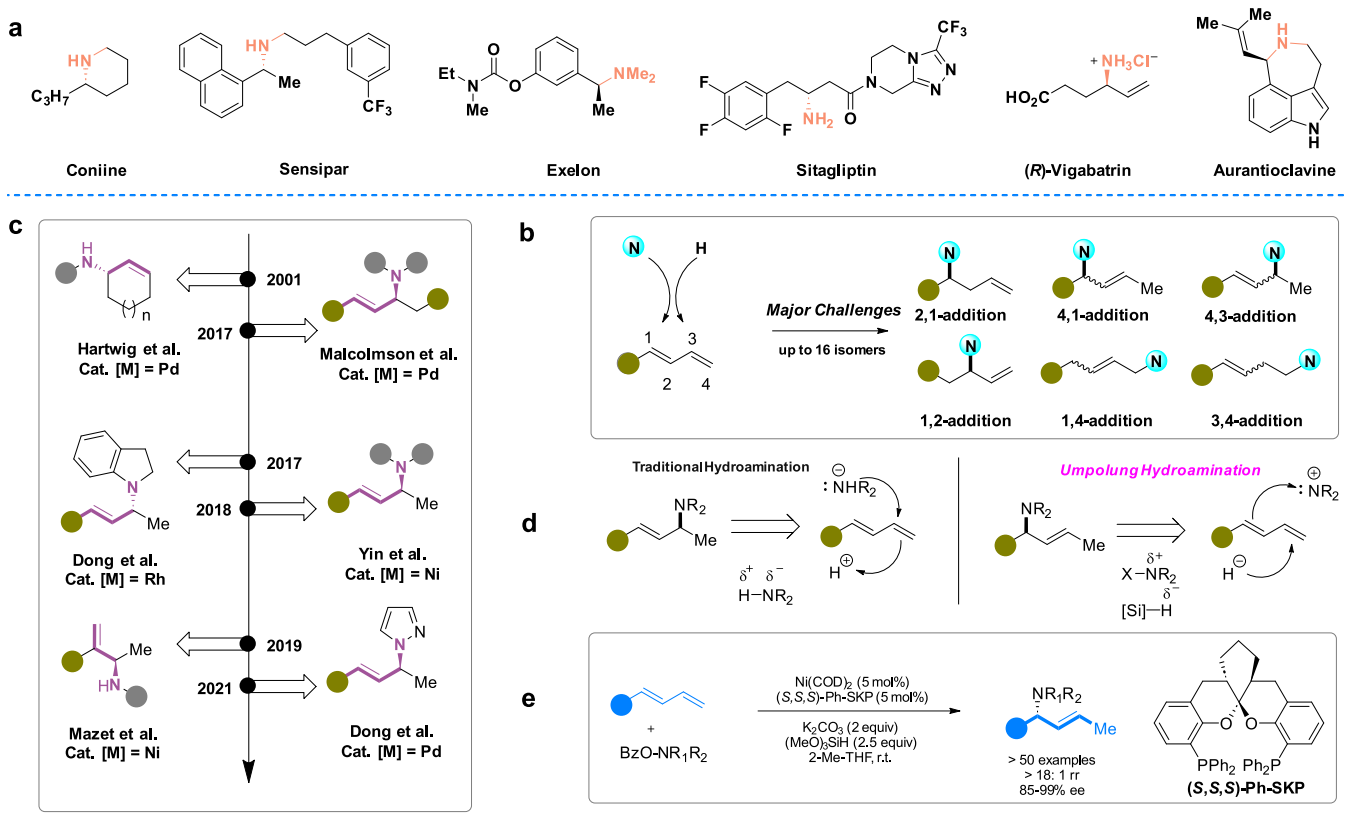

Figure 1. Catalytic asymmetric hydroamination of 1,3-dienes. (a) Selected examples of natural products and pharmaceuticals containing an alkylamine moiety. (b) Major challenges in regioselectivity control for the asymmetric hydroamination of 1,3-dienes. (c) Development of metal-catalyzed enantioselective hydroamination of 1,3-dienes. (d) Traditional hydroamination and umpolung polarity strategy. (e) This work: Ni/SKP catalyzed the asymmetric 1,4-hydroamination of 1,3-dienes.

the presence of trimethoxysilane and K_2CO_3 (for details, see SI). Under these conditions, catalysts modified by diverse chiral ligands were further assayed (Table 1). Notably, in all reactive cases the product **3a** was generated as the predominant regioisomer (rr = **3a**/**3a**′ > 19/1), with 1,4-hydroamination regioselectivity in sharp contrast to that of 3,4-amination achieved using nucleophilic amines (Figure 1c),[11−17] attesting umpolung-enabled regioselectivity control in this reaction.[18] However, both the catalytic activity and stereoselectivity control differed substantially in each case, depending on the identity of the chiral ligand. The reactions using several *N*,*N*-bidentate chiral ligands (**L1**−**L5**) commonly used in NiH chemistry provided **3a** only in low yields (29−49%) with poor enantioselectivities (1−30% ee). The chiral *P*,*N*-bidentate ligand (**L6**) also proved to be inefficient for this transformation, giving **3a** in 19% yield with a 13% ee. A variety of representative chiral phosphine ligands[38] were further surveyed in this reaction, including diphosphines with an atropisomeric (**L7**-**L9**), spirobisindanyl (**L10**), P-stereogenic (**L11**), planar stereogenic (**L12**) or ferrocenyl (**L13**) backbone. Unfortunately, none of them delivered **3a** in satisfactory yields (≤50%), and only very poor enantiocontrol (≤3% ee) was achieved in each case. Monodentate chiral phosphoramidite ligands (**L14**-**L15**) were also tested in the reaction, however, affording **3a** in nearly racemic forms (<6% ee). To our delight, the spiroketal-based chiral diphosphine ligands (*S*,*S*,*S*)-Ar-SKP (**L16**-**L19**), developed by our group and featured by hemilabile coordination tendency and a flexible backbone,[39,40] turned out to be superior in terms of both activity and enantioselectivity for this reaction, affording *E*-**3a** in good to high yields (74−92%) with excellent enantioselectivities (91−95% ee). Control experiments indicated that under otherwise identical conditions, no **3a** was detected in the reaction without the use of a ligand (see SI), a clear manifestation of the ligand-accelerated catalysis in the present reaction.[41] These ligand screening results indicated that the prevailing 1,4-regioselectivity is primarily determined by the nature of hydroamination reagents and almost irrelevant to the ligand types, while both the reactivity and enantioselectivity of the catalysis are highly dependent on the donor atoms and steric features of the chiral ligands, among which (*S*,*S*,*S*)-Ph-SKP (**L16**) was identified as optimal to give *E*-**3a** in 92% yield with 95% ee. While the use of a nickel(II) salt instead of $Ni(COD)_2$ as the catalyst precursor generally resulted in a lower yield with somehow declined ee values, hydrosilanes with different substituents differ much in the reactivity to afford **3a** in varying yields, albeit with almost the same ee and rr values suggesting the involvement of one or more common intermediate(s) in the catalysis (see the SI).

2.2. Substrate Scope with Respect to Amination Reagents. Under the optimized conditions, the Ni/**L16** catalyzed regio- and enantioselective processes were applied to a range of electrophilic O-benzoyl hydroxylamines (BzO−NR_2) **2a**−**t** in reactions with 1-phenylbutadiene **1a** or its analogue **1b** (Table 2). High reactivity (**3a**−**e**, 78−93%) and outstanding regio- and enantiocontrol (>28:1 rr, 93−95% ee) were achieved in the reaction of amination reagents derived from common cyclic amines (morpholine **2a**, thiomorpholine **2b** and piperidines **2c**−**d**, acetal-protected piperidone **2e**). This method was also compatible with acyclic dialkylamine-

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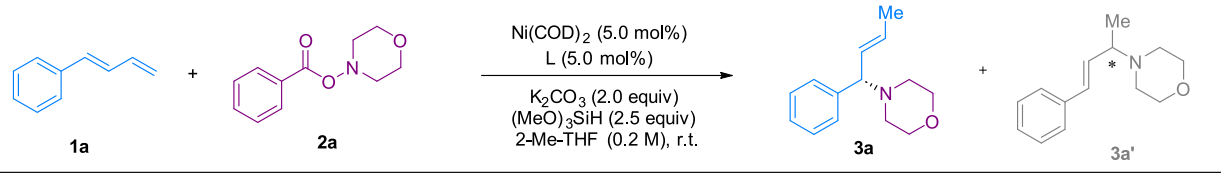
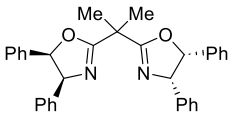
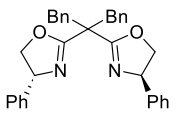
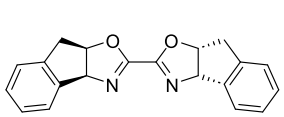
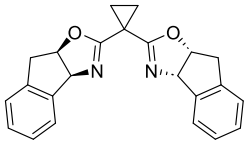
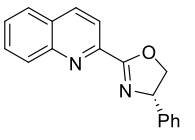
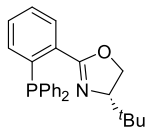
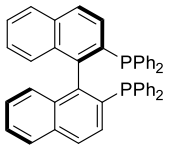
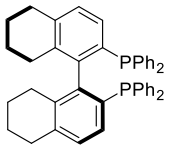
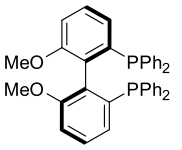
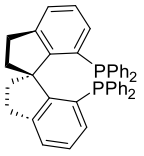
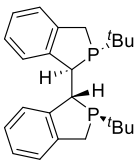
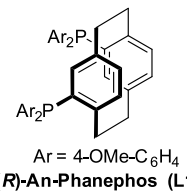
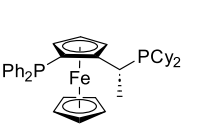
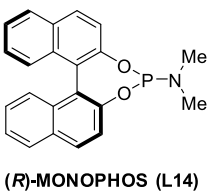
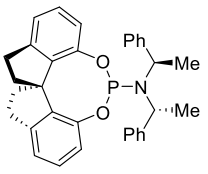
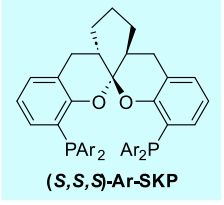
Table 1. Optimization of the Reaction Conditions[a]



				
L1	**(*S*,*S*)-BnPh-Sabox (L2)**	**L3**	**L4**	**(*S*)-Ph-Quinox (L5)**
49% yield 27:1 rr 2% ee	44% yield 21:1 rr 7% ee	29% yield 19:1 rr 30% ee	34% yield 19:1 rr -2% ee	30% yield 30:1 rr 1% ee
				
(*S*)-^{t}BuPhox (L6)	**(*R*)-BINAP (L7)**	**(*S*)-H8-BINAP (L8)**	**(*R*)-MeO-BIPHEP (L9)**	**(*R*)-SDP (L10)**
19% yield 29: 1 rr -13% ee	40% yield 24:1 rr 1% ee	43% yield 25:1 rr -2% ee	50% yield 27:1 rr 2% ee	49% yield 19:1 rr -3% ee
				
(*Rc*,*Sp*)-DuanPhos (L11)	**(*R*)-An-Phanephos (L12)**	**(*R*)-(*S*)-Josiphos (L13)**	**(*R*)-MONOPHOS (L14)**	**(*R*)-SIPHOS-PE (L15)**
n.d.	Ar = 4-OMe-C$_6$H$_4$ 43% yield 24:1 rr 3% ee	n.d.	26% yield 25:1 rr -6% ee	52% yield 24:1 rr 4% ee



(*S*,*S*,*S*)-Ar-SKP

L16, Ar = Ph, 92% yield, 31:1 rr, 95% ee
L17, Ar = *p*-MeC$_6$H$_4$, 78% yield, 31:1 rr, 94% ee
L18, Ar = 3,5-Me$_2$C$_6$H$_3$, 74% yield, 32:1 rr, 92% ee
L19, Ar = 3,5-^{t}Bu$_2$-4-OMe-C$_6$H$_2$, 83% yield, 32:1 rr, 91% ee

[a]Conditions: all the reactions were carried out with Ni(COD)$_2$ (5.0 mol %), ligand (5.0 mol %), **1a** (0.10 mmol), **2a** (0.15 mmol), K_2CO_3 (0.20 mmol), $(MeO)_3SiH$ (0.25 mmol) in 2-Me-THF (0.5 mL) for 24 h at rt under N_2. Yield and regioisomeric ratio (rr = **3a**/**3a**′) values were measured by GC analysis of the crude reaction mixture using *n*-decane as an internal standard. Enantiomeric excess (ee) values of **3a** were determined using HPLC analysis, n.d. = **3a** not detected.

based O-benzoyl hydroxylamines **2f**–**j**, giving the corresponding tertiary allylic amines **3f**–**j** in 76–94% yields with >18/1 rr and 93–98% ee. To our delight, the secondary amine product **3k** can also be obtained directly using the protocol with >20/1 rr and 95% ee, albeit in a moderate yield, probably as a result of the weak reactivity or nonproductive consumption of the corresponding amination precursor **2k**.[42] Since piperazines are ubiquitous in nature and one class of the most prevalent N-heterocycles in biologically active molecules and drugs,[43] an array of O-benzoyl hydroxylamines derived from piperazines (**2l**–**s**) bearing various substituents were further examined in the reactions with **1a**, giving the corresponding 1,4-hydroamination products (**3l**–**3s**) in good yields (58–96%) with excellent regio- and enantioselectivities (>18:1 rr, 92–96% ee). The configuration of product **3r** has been established as (*S*, *E*) by X-ray crystallographic analysis. Furthermore, homopiperazine derived **2t** was also compatible with the procedure, giving the corresponding product **3t** in 96% yield with >20/1 rr and 94% ee.

2.3. Substrate Scope with Respect to 1,3-Dienes. To further evaluate the generality of this strategy, we proceeded to investigate the hydroamination of various 1,3-dienes with morpholino benzoate **2a** under standard conditions (Table 3). For the reactions of 1-aryl-substituted dienes **1b**–**s**, high levels of enantio- and 1,4-regioselectivity were observed (≥20/1 rr, 85–99% ee). A variety of 1-phenyl substituted 1,3-dienes (**1b**–**m**), bearing electron-withdrawing or electron-donating groups at the phenyl *ortho*-, *para*-, or *meta*-positions, were efficiently converted to the corresponding 1,4-hydroamination products (**4b**–**m**) in good to high yields with excellent selectivities (71–

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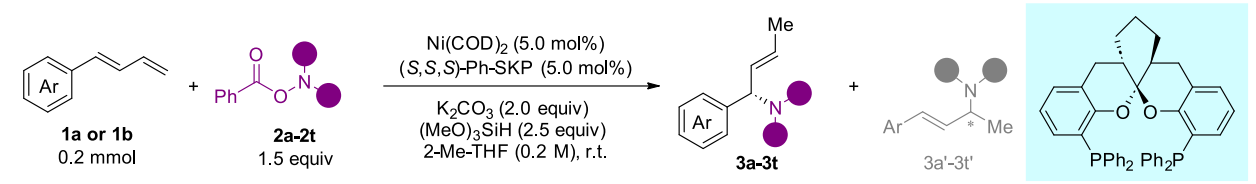
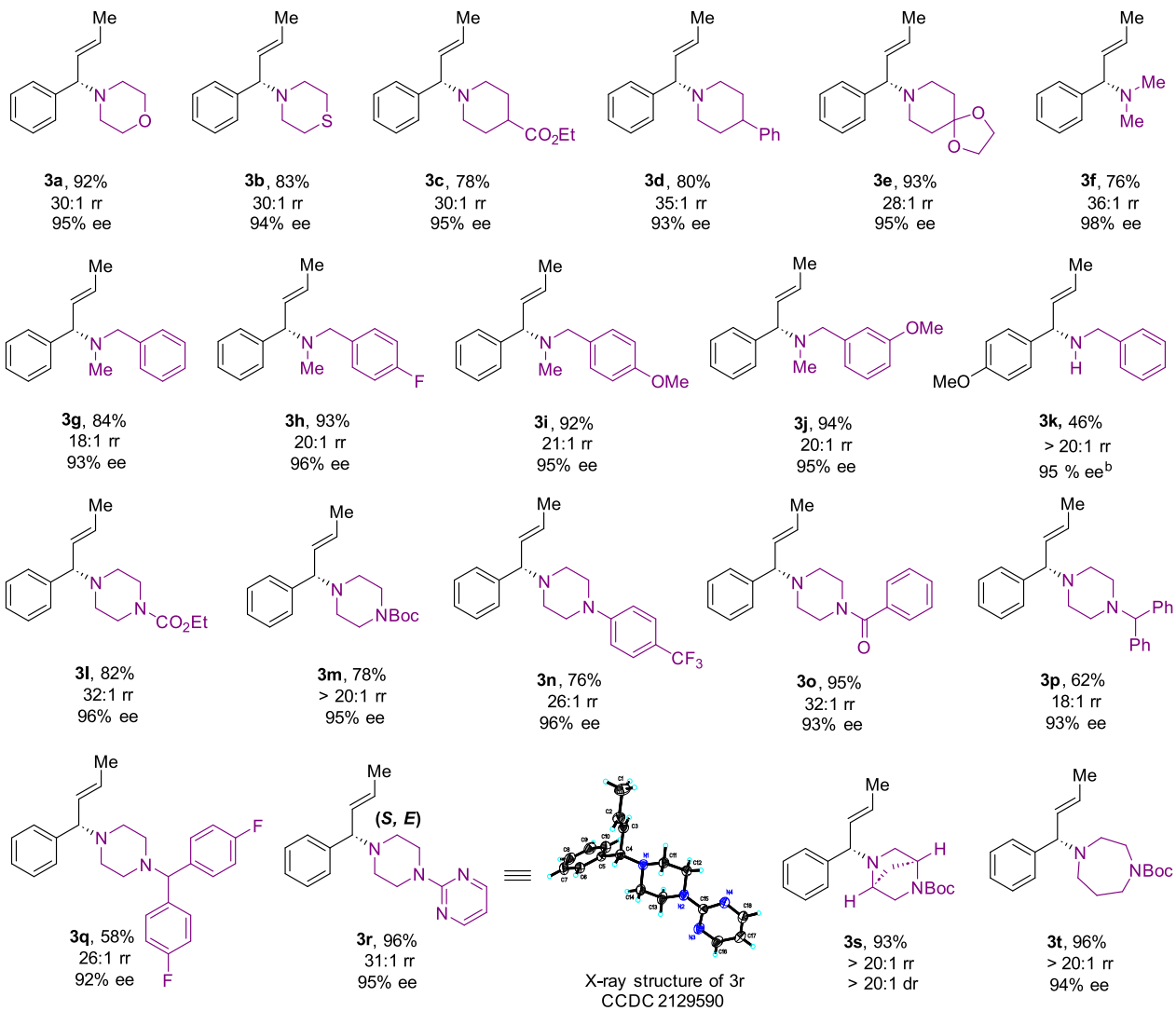
Table 2. Scope with Respect to the Hydroxylamine Electrophiles[a]





[a]Conditions: all the reactions were carried out with $Ni(COD)_2$ (5.0 mol %), (*S*,*S*,*S*)-Ph-SKP (5.0 mol %), **1a** (0.20 mmol), **2** (0.30 mmol), K_2CO_3 (0.40 mmol), $(MeO)_3SiH$ (0.50 mmol) in 2-Me-THF (1.0 mL) for 36 h at rt under N_2. Regioisomeric ratio (rr) values were determined by GC analysis of the crude reaction mixture using *n*-decane as an internal standard. Yields are for the isolated products. Enantiomeric excess (ee) values were determined using HPLC analysis (see Supporting Information for full details). [b]**1b** was used instead of **1a**.

94%, ≥ 20/1 rr, 85−96% ee). Moreover, the reactions of dialkoxy-substituted 1-phenyl-1,3-dienes (**1n** and **1o**) also proceeded well to furnish the corresponding allyl amines **4n** and **4o** in high yields and 96% and 95% ee, respectively. 1-Aryl-substituted dienes that contain different types of medicinally relevant heterocycles, including benzodioxole (**1p**), dihydrobenzofuran (**1q**), benzothiophene (**1r**) and quinoline (**1s**), also proved to be viable substrates for the reaction, producing the corresponding hydroamination products **4p**−**s** in good yields with excellent enantioselectivity (91−99% ee). To our gratification, 1,2-disubstituted diene **1t** proved also a viable substrate in this reaction, delivering the corresponding 1,4-hydroamination product **4t** in 59% yield with 28/1 rr and 80% ee. However, a substantially diminished regioselectivity level was observed in the reaction of 1-alkyl-substituted diene **1u**, wherein both 1,4- and 3,4-hydroamination products **4u** and **4u'** were obtained in moderate yields with good enantioselectivity (86% and 87% ee, respectively), without an obvious preferential regioselectivity (**4u:4u'** = 1.14:1). The poor regioselectivity contrasts sharply with the excellent regiocontrol in reactions of 1-aryldienes using the same catalyst, and the strong inclination in the latter dienes for preferred amination

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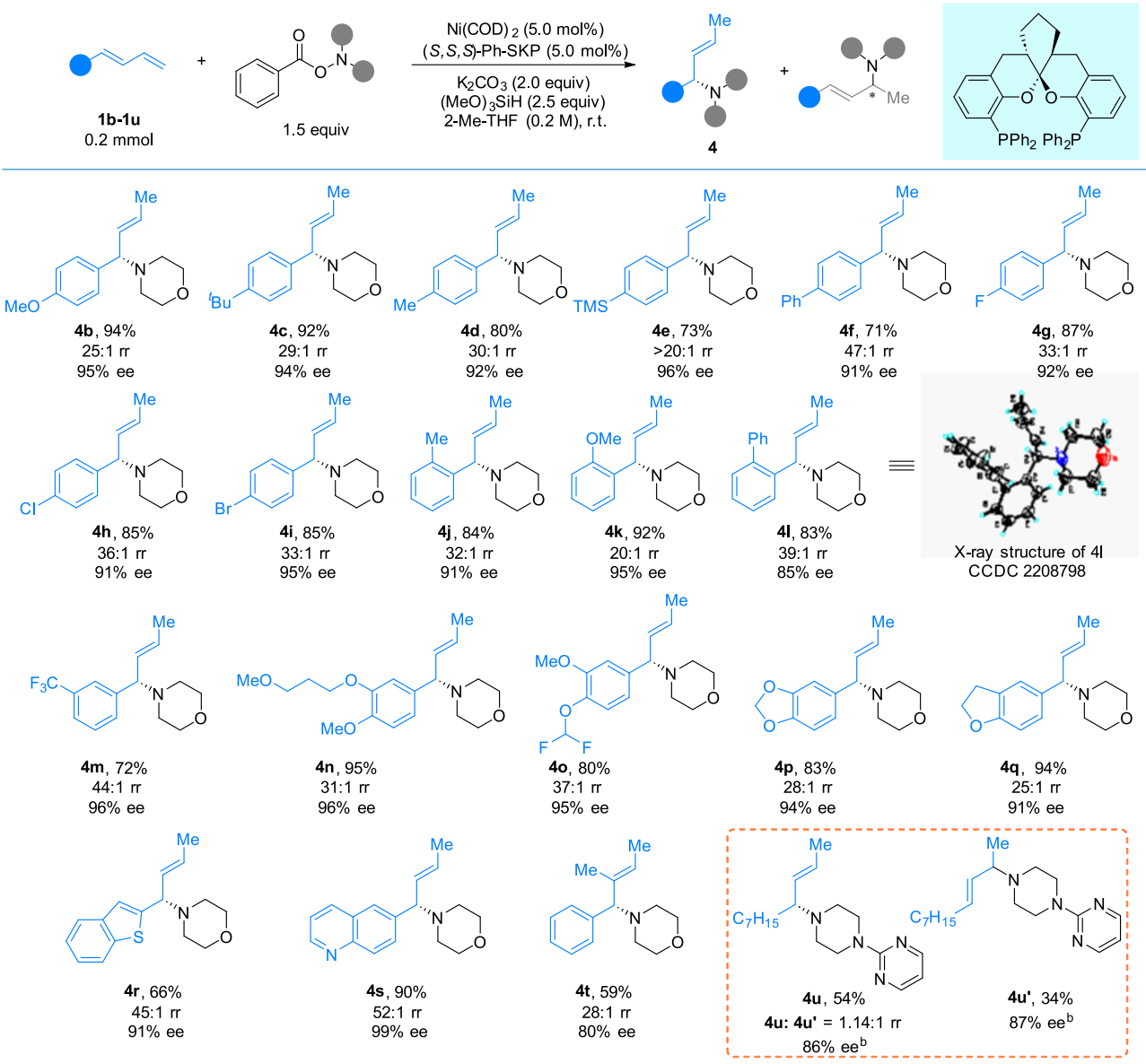
Table 3. Scope with Respect to 1,3-Dienes[a]



[a]Conditions: all the reactions were carried out with $Ni(COD)_2$ (5.0 mol %), (*S,S,S*)-Ph-SKP (5.0 mol %), 1,3-dienes (0.20 mmol), **2a** (0.30 mmol), K_2CO_3 (0.40 mmol), $(MeO)_3SiH$ (0.50 mmol) in 2-Me-THF (1.0 mL) for 36 h at rt under N_2. Regioisomeric ratio (rr) values were determined by GC analysis of the crude reaction mixture using *n*-decane as an internal standard. Yields are for the isolated products. Enantiomeric excess (ee) values were determined using HPLC analysis. [b]0.2 mmol **2q** was used instead of **2a**, 0.3 mmol **1u** was used (see the Supporting Information for full details).

to the sterically more hindered C1 site implies that the aryl group can exert a profound influence on the regioselectivity, most likely on electronic grounds.[44]

2.4. Synthetic Applications. To demonstrate the utility of the operationally simple method in the late-stage synthetic manipulation of complex molecular structures, dienes substrates derived from some pharmaceuticals were submitted to the asymmetric hydroamination reaction with **2a** under standard conditions, providing products containing a Vitamin E (**4v**), Febuxostat intermediate (**4w**), Canagliflozin intermediate (**4x**), or Empagliflozin intermediate (**4y**) in high yields with excellent regio- and enantioselectivities (Figure 2a). Furthermore, the practicality of this transformation was further highlighted by the gram-scale synthesis of **3e**, produced using a lower catalyst loading without compromising the yield or the selectivities (Figure 2b). By taking advantage of the alkenyl moiety, allylamine **3e** was readily converted into chiral cyclopropane **3ea** or corresponding epoxide **3eb**, respectively, both in good yields with high stereoselectivities (Figure 2c and 2d). To our delight, as an especially attractive abundant feedstock, 1,3-butadiene **1ad** also worked well in the reaction with **2q** and afforded the corresponding 1,4-hydroamination product **3qy** smoothly. Furthermore, 2,3-dimethyl-1,3-butadiene **1ae** was also a suitable coupling partner in this reaction, giving the corresponding product **3qz** in a good yield (Figure 2e).

2.5. Mechanistic Investigations. In order to shed some light on the mechanism, a deuterium labeling experiment was

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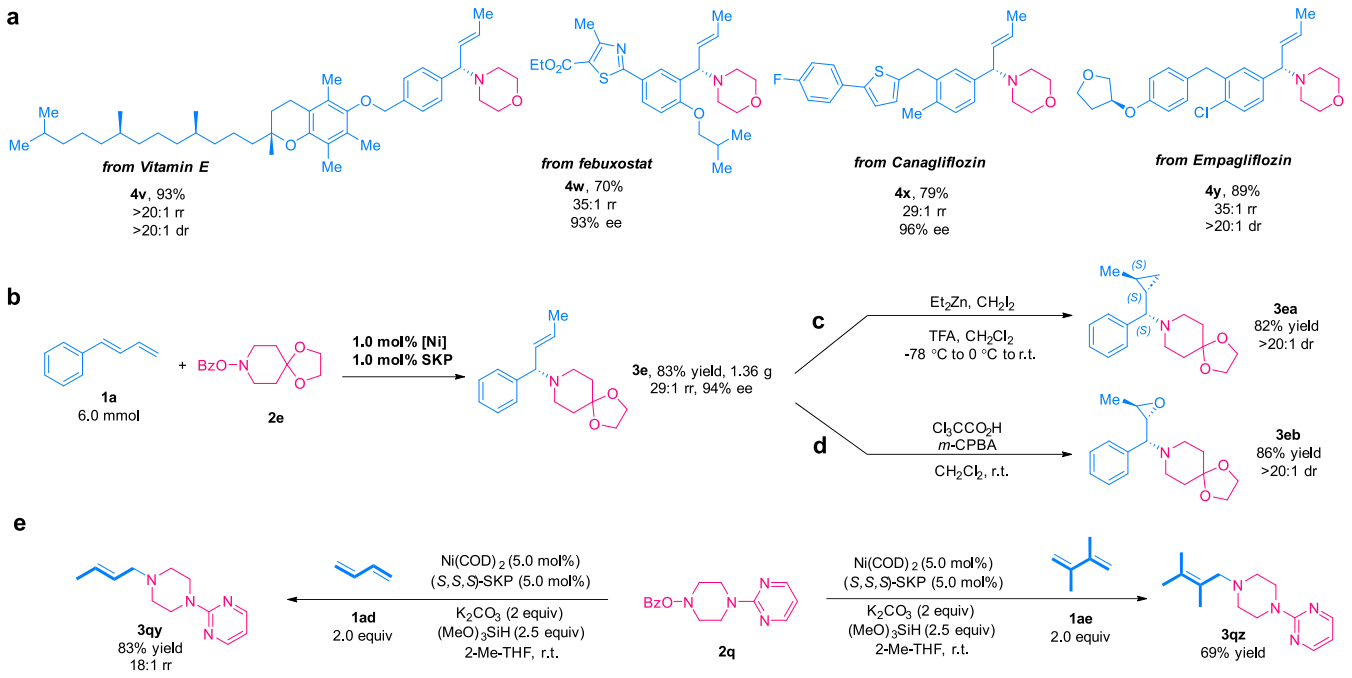

Figure 2. Synthetic applications. (a) Functionalization of drug-derived 1,3-dienes. (b) Gram-scale hydroamination under a lower catalyst loading. (c) Conversion of the allylamine **3e** into the chiral cyclopropane **3ea**. (d) Conversion of the allylamine **3e** into the chiral epoxide **3eb**. (e) Transformation of 1,3-butadienes **1ad** and **1ae** into the corresponding allylamines **3qy** and **3qz** (see the Supporting Information for full details).

carried out on the reaction of **1za** and **2a** using a deuterated silane (Ph_2SiD_2) as the hydride source (Figure 3a). More than 99% deuterium incorporation at the ending methyl group was observed, indicating that NiH addition should be an irreversible process.[45] The presence of butylated hydroxytoluene (BHT, a radical scavenger) demonstrated no significant impact on the reaction results, suggesting that a radical intermediate is unlikely to be involved in the transformation (Figure 3b).[46] When dienes with opposite configured inner C=C bond (i.e., *E*-**1za** vs *Z*-**1zb**) were submitted to the reaction with **2a**, only *E*-configured products **6b** were obtained as opposite enantiomers in high optical purities, respectively (Figure 3c). The observation of opposite enantiomers formed from the same chiral catalyst with these two diene stereoisomers (*E*-**1za** and *Z*-**1zb**) suggested that migratory insertion should have occurred to opposite faces of the two substrates, and the enantiomers produced are presumably caused by stereoselective migratory insertion of (SKP)NiH into the terminal C−C double bond of the diene. To further probe into the factors influencing the regioselectivity, the reaction of conjugated trienes **1ab** with **2q** was performed under standard conditions, to deliver the 1,4-adduct **6c** as the major regioisomer in high regioselectivity (Figure 3d). This is in sharp contrast to the reaction of **1u**, an alkyl-substituted conjugated diene, wherein the corresponding regioisomeric hydroamination products **4u** and **4u′** were only obtained without clear preference (rr close to 1:1, Table 3). Taking together, these results indicated that the inner alkenyl group in **1ab**, like those aryl substituents in dienes **1a**−**t**, may exert a profound effect on the regiochemical outcome of the reaction, e.g., via directing the formation of an allyl nickel intermediate that can be stabilized further by the neighboring alkenyl or aryl groups.[47] This is further attested by the reaction results of the aryl-conjugated triene **1ac** with **2a** wherein a regioisomeric mixture of hydroamination products **6d**/**6e**/**6f** was obtained, and the 1,4- and the 1,6-adduct **6e** and **6d** were generated as the major products in almost equal amounts (rr **6d**:**6e**:**6f** = 23:21:1, Figure 3e). NLE study on the reaction of **1a** and **2e** revealed a linear relationship between the ee values of the SKP ligand and those of the product **3e** (Figure 3f), indicating that the enantioselectivity-determining step of the asymmetric hydroamination should involve a monomeric nickel complex bearing a single SKP ligand.[48] Furthermore, the kinetic profile for the model reaction of **1a** and **2a** under the standard conditions showed no induction period in the process, indicating a rapid generation of active SKP/Ni species in the catalysis (Figure 3g). To gain some insight into the turnover-limiting step, kinetic studies for each reaction component were performed on the reaction of 1,3-diene **1a** and hydroxylamine ester **2a** (Figure 3h). The kinetics for the reaction was found to be zeroth-order-dependent on both **1a** and **2a**, while the rate demonstrated first-order dependence on both $Ni(COD)_2$ and $(MeO)_3SiH$, suggesting that the Ni catalyst and the hydrosilane were involved in the turnover-limiting step. In addition, Hammett studies were also performed on the reactions of *para*-substituted dienes with **2a** and *para*-substituted N−O-benzoates with **1a**, respectively (Figure 3i).[49] The Hammett plot shown in the left of Figure 3i revealed a very small ρ value of ca. 0.02, indicating that the dienes are unlikely to be involved in the turnover-limiting step of the process. The second Hammett study with *para*-substituted N−O-benzoates had an impact on the rate of dienes hydroamination, indicating that the use of amine electrophiles bearing a more electron-withdrawing carboxylate leaving group led to an increase in the reaction rate (ρ = 0.55). These results further support that the regeneration of NiH is likely to be the turnover-limiting step in the titled reaction.[29,30]

2.6. Density Functional Theory Calculations. To gain further insights into the mechanism and to rationalize the origin of regio- and enantioselectivity, we performed density functional theory (DFT) calculations on the hydroamination of dienes **1a** with morpholino benzoate **2a** using the SKP-

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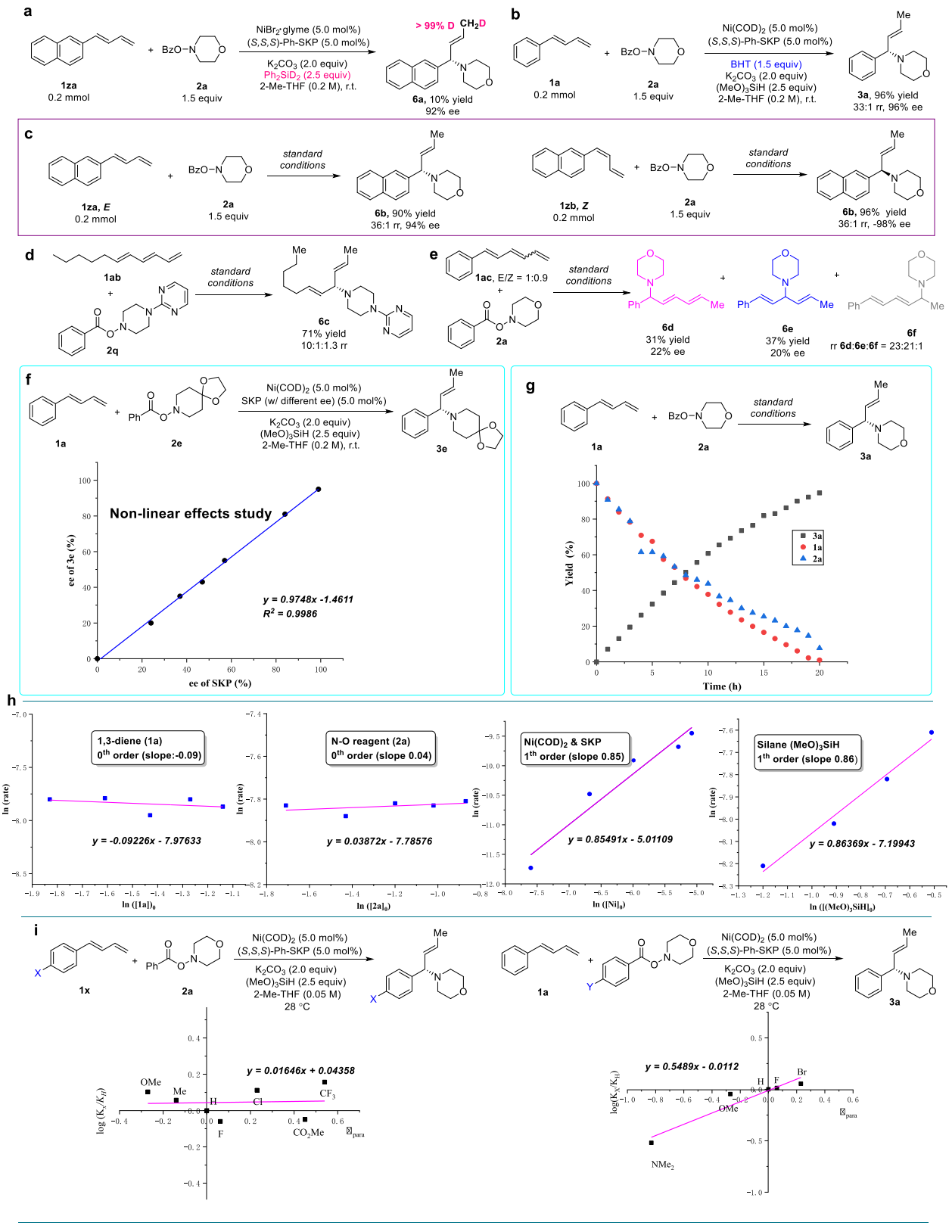

Figure 3. Preliminary mechanistic study. (a) Deuterium incorporation experiment. (b) Reaction in the presence of radical scavengers. (c), Reactions of (*E*)- and (*Z*)-1,3-diene **1za** and **1zb** with **2a**. (d) The reaction of the alkyl-substituted triene **1ab** with **2q**. (e) The reaction of the aryl-substituted triene **1ac** participates with **2a**. (f) Nonlinear effect study. (g) Kinetic profiles of the reaction of **1a** and **2a** under the standard conditions. (h) Kinetic studies of reaction components. (i) Hammett plots of reaction components. (see the Supporting Information for full detail).

supported Ni catalyst. Figure 4a depicts the energy profile calculated for the regio- and enantiodetermining steps of the reaction mechanism (see the Supporting Information for Computational Details). The hydronickelation of diene **1a**

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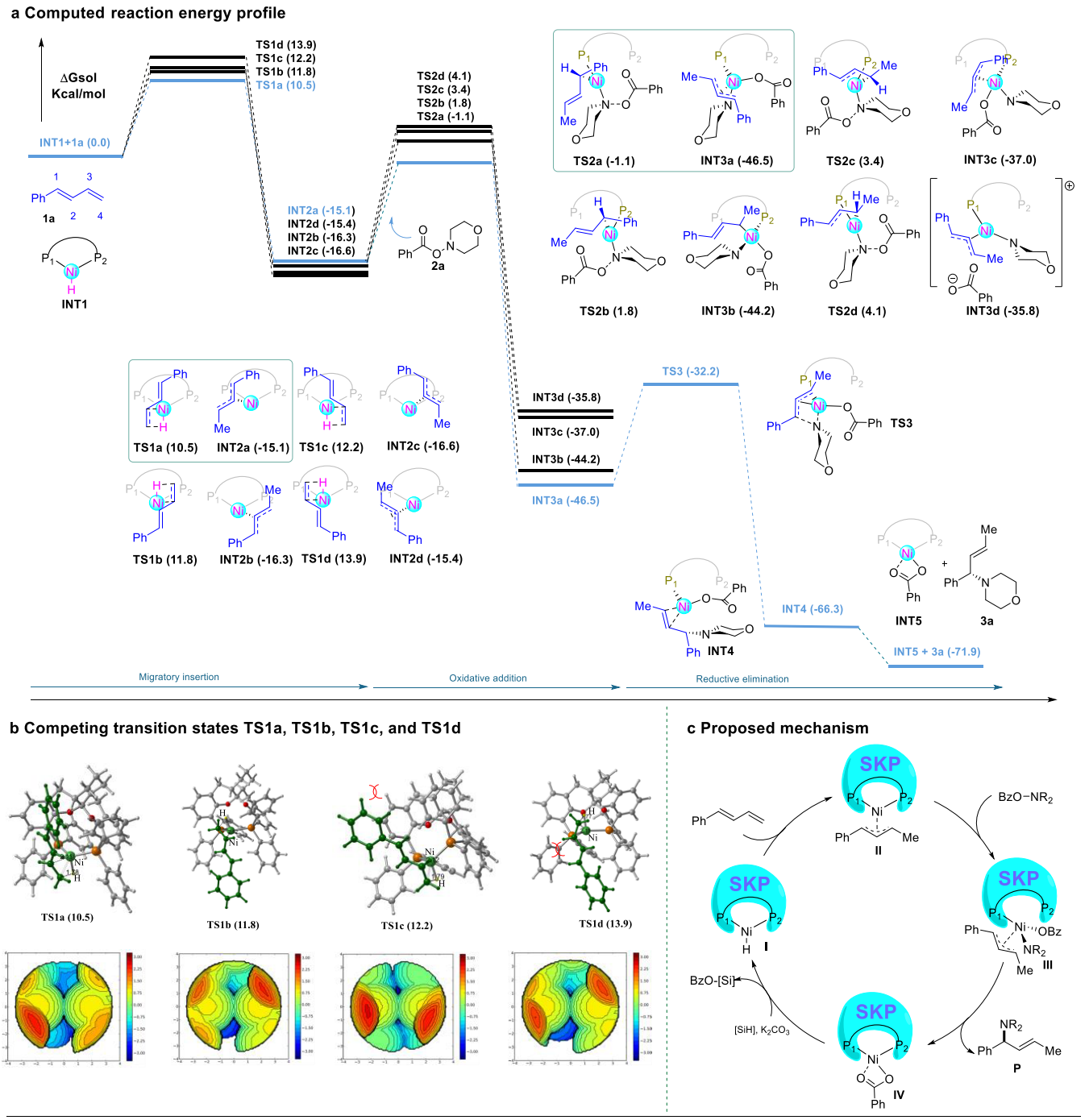

Figure 4. Density functional theory calculations. (a) Gibbs free energy profile calculated for the Ni/SKP-catalyzed hydroamination of 1,3-dienes with hydroxylamines. (b) Competing transition states and steric contour maps. (c) Proposed mechanism. The relative Gibbs free energies (in parentheses) are given in kcal mol^{-1}. Calculated by DFT at the B3LYP-D3(BJ)/6-311++G(d,p)-LANL2DZ/SMD(THF)//B3LYP-D3(BJ)/6-311G(d,p)-LANL2DZ level of theory.

with the SKP-NiH catalyst **INT1** through **TS-1** was found to be exergonic and kinetically controlled. Due to the unsymmetrical nature of the SKP ligand, there are four conceivable competing pathways for the hydronickelation of dienes **1a** with transition states denoted by **TS1a-d**, among which the kinetic barrier to (*Si*)-facial attack **TS1a** (10.5 kcal/mol) was found lower than all the other three pathways (11.8−13.9 kcal/mol). Furthermore, both (*Si*)-facial attack pathways (**TS1a**/**TS1b**) were found to be more favorable than the (*Re*)-facial ones (**TS1c**/**TS 1d**), hence leading to the preferential formation of **INT2a** and ultimately to (*S*)-**3a** given the irreversible nature of the process. The subsequent reaction of **INT2a** with amine electrophile **2a** can also proceed via four competing transition states (**Ts2a-d**), respectively, resulting in the formation of Ni(III) species **INT3a-d** via N−O bond cleavage. Noteworthily, due to the severe steric congestion caused by these bulky ligands on the Ni center, in these species, SKP was found to bind with Ni species in an κ^1-fashion as a monodentate phosphine ligand. In the four TS structures **Ts2a-d**, the (κ^1-SKP)Ni moiety ligates simultaneously with the C1 or C3 site

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of the 1-Ph-3-Me-disubstituted allyl group, as well as the N atom of morpholino benzoate. The free-energy profiles indicated that the N−O bond cleavage via η^1-C1 bound **TS2a** is the most favorable. It is also notable that both η^1-C1 bound **TS2a** and **TS2b** are more stable than η^1-C3 bound **TS2c** and **TS2d**, respectively, probably owing to the more effective delocalization of electron density by neighboring Ph and allyl π-systems, which is consistent with our experimental results. Calculations also revealed that all the four located pathways (**TS2a-d**) are strongly exergonic by 20.7−31.4 kcal/mol and hence irreversible, therefore the pathway via the most favorable **TS2a** will dictate the regioselectivity for diene 1,4-hydroamination. The resulting (κ^1-SKP)-ligated Ni(III) species **INT3a** subsequently undergo a facile C−N bond-forming reductive elimination via **TS3** to deliver **INT4a**, which on intramolecular ligand exchange can be readily transformed into (SKP)Ni(I) benzoate **INT5** with release of the hydroamination product **3a**. Finally, the Ni(I) hydride species **INT1** is regenerated in situ from **INT5** by transmetalation with the hydrosilane reagent and a base.

Steric contour maps (Figure 4b) provided a rationale for the predominant formation of **TS1a** in the hydronickelation step.[50,51] In this case, the incoming diene **1a** binds with the SKP-ligated Ni(I) center via the (*Si*)-face of the terminal C═C bond, wherein the diene skeleton is roughly in alignment with the north to south groove shaped by the two PPh_2 donors, and the bulkier phenyl of **1a** situates in the less hindered northern hemisphere of the pocket. Similarly, **TS1b** wherein Ni attacks **1a** via its (*Si*)-face is also favored, albeit to a lesser extent. On the other hand, the steric clashes between **1a** and the SKP ligand in **TS1c-d** are deemed unfavorable.

According to the above results and literature,[26−36] a plausible reaction mechanism was proposed (Figure 4c). The nickel(I) hydride species **I**, generated from SKP-bound Ni precursor with a silane in the presence of a base,[52,53] would insert into the terminal double bond of the 1,3-diene, generating the corresponding π-allyl-Ni(I) intermediate **II**. Subsequent coordination and N−O bond cleavage of the amine electrophile on the Ni(I) center of intermediate **II** would afford high-valent Ni(III) intermediate **III**, wherein SKP binds with Ni in a monodentate fashion. The following reductive elimination would deliver the corresponding hydroamination product **P** together with benzoate-ligated nickel(I) species **IV**. Finally, the transmetalation of **IV** with hydrosilane assisted by a base would regenerate NiH (**I**) for the next catalytic cycle.

3. SUMMARY AND CONCLUSIONS

In summary, we have developed a Ni/SKP-catalyzed regio- and enantioselective hydroamination of 1,3-dienes. The protocol is featured by good functional group tolerance and mild reaction conditions, enabling the construction of an array of enantioenriched allylamines (>50 examples) from simple dienes with excellent 1,4-regioselectivity and high levels of enantiocontrol (up to 99% ee, > 20:1 rr). The successful functionalization of drug derivatives further showcased the preparative utility of the reaction. A mechanism to rationalize the observed regio- and enantioselectivities was proposed on the basis of combined experimental and theoretical studies. We anticipate that this report may trigger more studies on the use of chiral diphosphine ligands and earth-abundant transition metals in asymmetric catalytic chemistry. Further studies on SKP/Ni catalysis are underway.

■ ASSOCIATED CONTENT

Supporting Information

This material is available free of charge on the ACS Publications Web site. The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.4c03854.

Experimental procedures, complete characterization data, and copies of NMR spectra (PDF)

Accession Codes

CCDC 2129590 and 2208798 contain the supplementary crystallographic data for 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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