Nickel-Catalyzed Asymmetric (3 + 2) Annulations of Propargylic Carbonates and Vinylogous Donors via an Alkenylation Pathway

Zhi Zhao,[§] Lei Zhu,[§] Zhao-Li Song, Keji Qubi, Qin Ouyang,* Wei Du,* and Ying-Chun Chen*

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ABSTRACT: The transition-metal-catalyzed alkenylation strategy of propargylic alcohol derivatives provides an efficient protocol to access multifunctional products in a double-nucleophilic attack pattern. While limited relevant asymmetric examples have been reported via palladium catalysis, here we first demonstrate that a nonprecious Ni(0)-based chiral complex can efficiently promote the tandem substitution process between propargylic carbonates and *N*-trifluoroethyl ketimines via consecutive aza-vinylogous activations, finally accomplishing a (3 + 2) annulation reaction to afford products embedding a 4-methylene-3,4-dihydro-2*H*-pyrrole framework with high regio-, diastereo-, and enantiocontrol. Their assemblies with a few all-carbon-based vinylogous precursors are also successful, and enantioenriched adducts containing a 3-methylenecyclopentene scaffold are furnished effectively. The substitution patterns for both types of substrates are substantial, and an array of synthetic elaborations is conducted to deliver more versatile architectures with high application potential. In addition, density functional theory calculations and control experiments have been conducted to rationalize the catalytic pathways and regio- and enantioselectivity control.
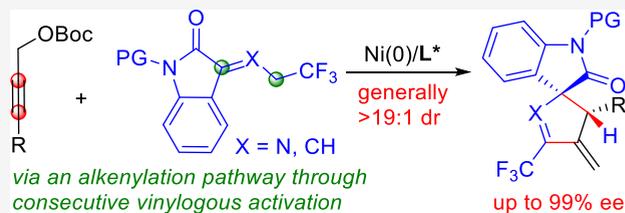
INTRODUCTION

Propargylic alcohol and their derivatives, easily accessible from terminal alkynes and carbonyls, are extensively applied as important staring materials in organic synthesis, as they can undergo versatile transformations via organo- or metal catalysis.[1] Remarkably, unique propargylic electrophiles can be generated through oxidative addition with transition metals, which enable diverse transformative patterns, though sometimes lower reactivity is observed compared to the allylic variants.[2] As summarized in Scheme 1a, different products (propargylation,[3] allenylation,[4] and dienylation[5]) can be constructed via palladium or nickel catalysis, depending on the different sites attacked by various nucleophiles. In addition, π-allylpalladium species can be formed after nucleophilic attack at central carbon, followed by protonation, which can be further trapped by another nucleophile to afford the formal alkenylation products.[6] Undoubtedly, the latter strategy would be more attractive but synthetically more challenging, as a higher structural complexity would be realized by embedding two functional groups into the products. Nevertheless, limited progress has been made in this area, probably due to the existence of other competitive pathways and difficulties in simultaneously controlling the chemo-, regio-, and stereoselectivity. As a result, only a few palladium-catalyzed asymmetric alkenylation reactions of propargylic esters have been disclosed to furnish some annulated products to date, and all of them relied on employing reactive bisnucleophilic counterparts, as outlined in Scheme 1b.[7] Therefore, the development of other catalytic systems, especially using earth-abundant nonprecious transition metals, are highly desirable

for the asymmetric alkenylation reaction of propargylic alcohol derivatives.[8]

On the other hand, the design and application of novel bisnucleophilic partners in the assembly with propargylic electrophiles are also crucial for the creation of some unique frameworks. The ketimines **2** condensed from trifluoroethyl-amine and isatins are versatile reagents for the construction of CF₃-containing molecules with potential bioactivity,[9] and they were extensively employed as 2-azaallyl anion or azomethine ylide precursors in organic synthesis (Scheme 1c).[10] Here, we first uncovered that ketimines **2** could perform as bisnucleophilic species via consecutive aza-vinylogous-type activations[11] and participate in the asymmetric alkenylation reaction with propargylic carbonates **1**, finally furnishing multifunctional spirooxindole architectures **3** with a 4-methylene-3,4-dihydro-2*H*-pyrrole motif in a (3 + 2) annulation pattern. Notably, a Ni(0) catalytic system is demonstrated to be well compatible and even showed much superior catalytic efficacy to that of Pd(0) catalysis, though a number of challenging issues, as suggested in Scheme 1c, need to be conquered simultaneously in such a complicated cascade reaction.

Scheme 1. Transition-Metal-Catalyzed Transformations of Propargylic Alcohol Derivatives
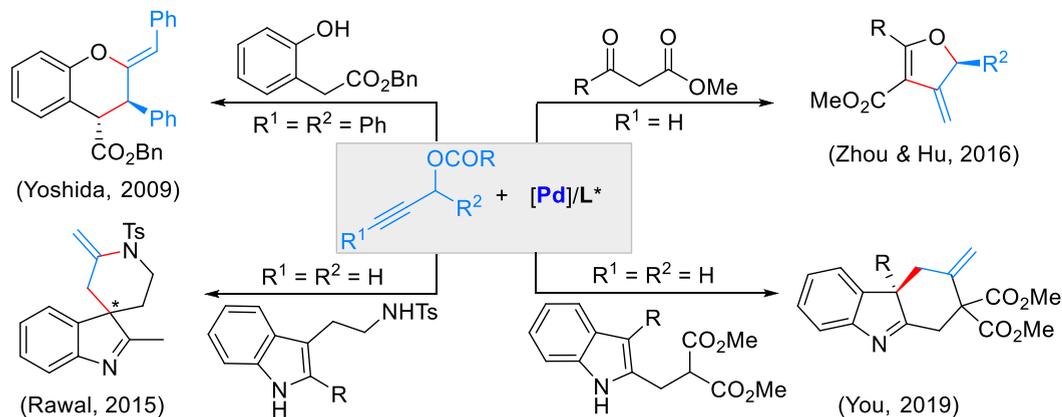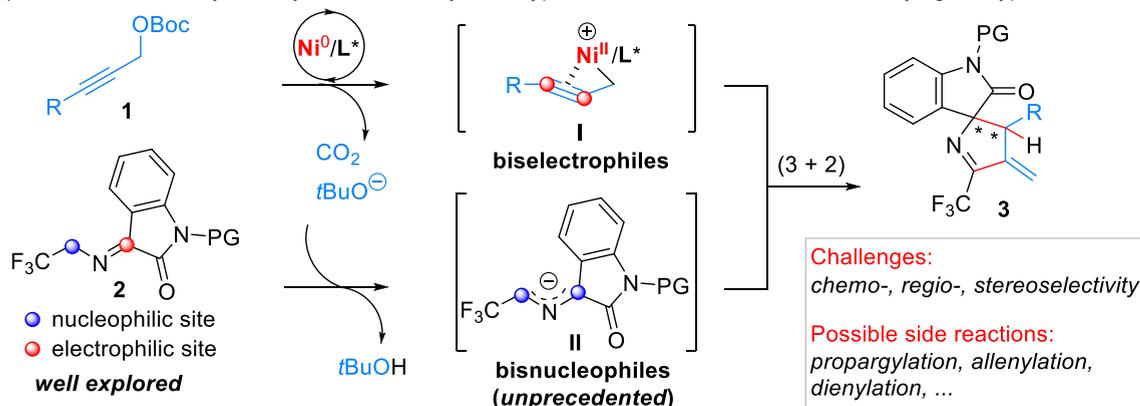
a) Summary of transformations of propargylic alcohol derivatives
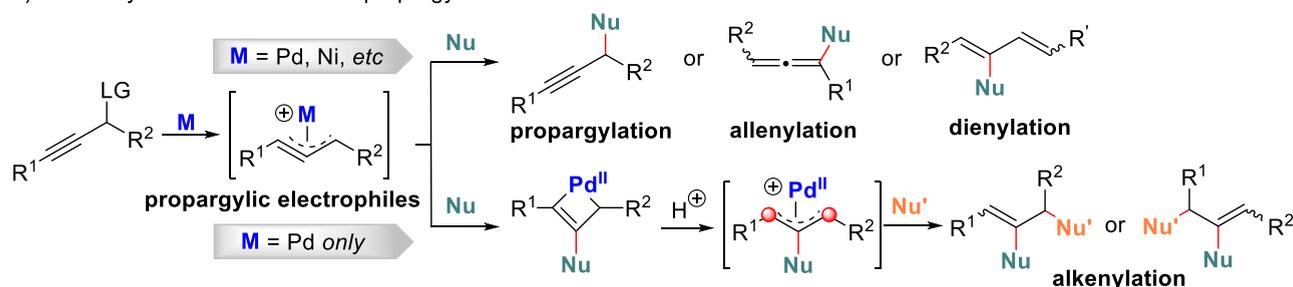
b) Pd-catalyzed asymmetric alkenylation-type annulations of propargylic alcohol derivatives with bisnucleophiles

c) This work: Ni-catalyzed asymmetric alkenylation-type annulations via cascade aza-vinylogous-type activation


RESULTS AND DISCUSSION

Reaction Optimizations. The initial attempt was carried out with propargylic carbonate **1a** and isatin ketimine **2a**. No reaction occurred in THF at 80 °C catalyzed by Ni($^{4-tBu}$stb)$_3$ in the absence of other ligands (Table 1, entry 1).[12] While adding PPh$_3$ as the ligand resulted in no success, pleasingly, the expected alkenylation reaction indeed occurred by employing a bisphosphine ligand dppe, and cycloadduct **3a** was produced in a fair yield but with excellent regio- and diastereoselectivity (entry 2). Inspired by these results, a variety of commercially available chiral bisphosphine ligands in combination with Ni($^{4-tBu}$stb)$_3$ were explored to realize the potential asymmetric version. Commonly used (S)-BINAP **L1** showed no activity (entry 3), whereas smooth conversions were observed by using ligands **L2−4**, and good enantioselectivity was obtained for product **3a** (entries 4−6). In order to further improve the enantiocontrol, other parameters involving solvents were evaluated under the catalysis of Ni($^{4-tBu}$stb)$_3$ and **L4** (entries

7−10), and EtOAc proved to be a better choice (entry 7). Conducting the reaction at 60 °C improved the enantioselectivity, and a similar yield was attained by extending the reaction time (entry 11). Nevertheless, lower yields were observed by using Ni($^{4-CF3}$stb)$_3$ or Ni(COD)$_2$ as the precursor (entries 12 and 13). To our delight, the yield was enhanced significantly by reducing the reaction concentration (entry 14). In addition, slightly inferior data were yielded by using a branched carbonate **1a′** (entry 15).[7d] It should be noted that an apparently decreased efficacy was observed by replacing the metal source with Pd$_2$(dba)$_3$,[7] mostly because of the formation of dienylation byproducts (entries 16 and 17).[13]

Substrate Scope Investigation. Consequently, we turned to investigate the scope and limitations of this new (3 + 2) annulation reaction. We first explored the substitution patterns of N-trifluoroethyl isatin ketimines **2** in the reactions with propargylic carbonate **1a**. As summarized in Scheme 2a, the ones with diverse N-protecting groups were well applied under

Table 1. Optimizations for Catalytic Conditions of Asymmetric (3 + 2) Annulation of Carbonate 1a and Ketimine 2a[a]
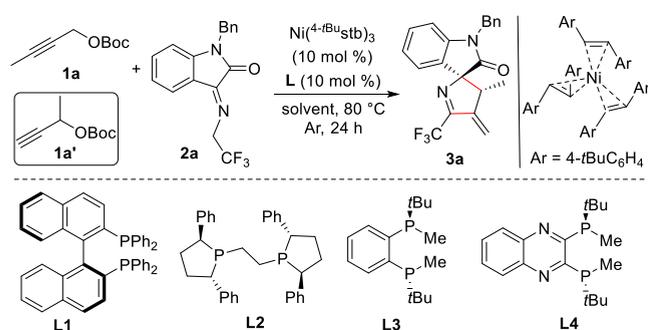
entry	metal source	L	solvent	yield (%)[b]	ee (%)[c]
1	Ni($^{4-tBu}$stb)$_3$		THF	NR	
2	Ni($^{4-tBu}$stb)$_3$	dppe	THF	47	
3	Ni($^{4-tBu}$stb)$_3$	L1	THF	NR	
4	Ni($^{4-tBu}$stb)$_3$	L2	THF	42	82
5	Ni($^{4-tBu}$stb)$_3$	L3	THF	49	80
6	Ni($^{4-tBu}$stb)$_3$	L4	THF	65	81
7	Ni($^{4-tBu}$stb)$_3$	L4	EtOAc	62	86
8	Ni($^{4-tBu}$stb)$_3$	L4	toluene	58	77
9	Ni($^{4-tBu}$stb)$_3$	L4	DCM	32	86
10	Ni($^{4-tBu}$stb)$_3$	L4	DMF	64	66
11[d]	Ni($^{4-tBu}$stb)$_3$	L4	EtOAc	65	90
12[d]	Ni($^{4-CF3}$stb)$_3$	L4	EtOAc	41	90
13[d]	Ni(COD)$_2$	L4	EtOAc	43	89
14[de]	Ni($^{4-tBu}$stb)$_3$	L4	EtOAc	81	90
15[def]	Ni($^{4-tBu}$stb)$_3$	L4	EtOAc	64	88
16[de]	Pd$_2$(dba)$_3$	L2	EtOAc	34	80
17[de]	Pd$_2$(dba)$_3$	L4	EtOAc	11	66

[a]Unless noted otherwise, reactions were performed with 1a (0.06 mmol), 2a (0.05 mmol), metal (10 mol %), and L (10 mol %) in solvent (0.5 mL) at 80 °C for 24 h. [b]Yield of the isolated 3a. [c]Determined by HPLC analysis on a chiral stationary phase; >19:1 dr by ^{1}H NMR analysis. [d]At 60 °C for 48 h. [e]In EtOAc (1.0 mL). [f]With carbonate 1a′.
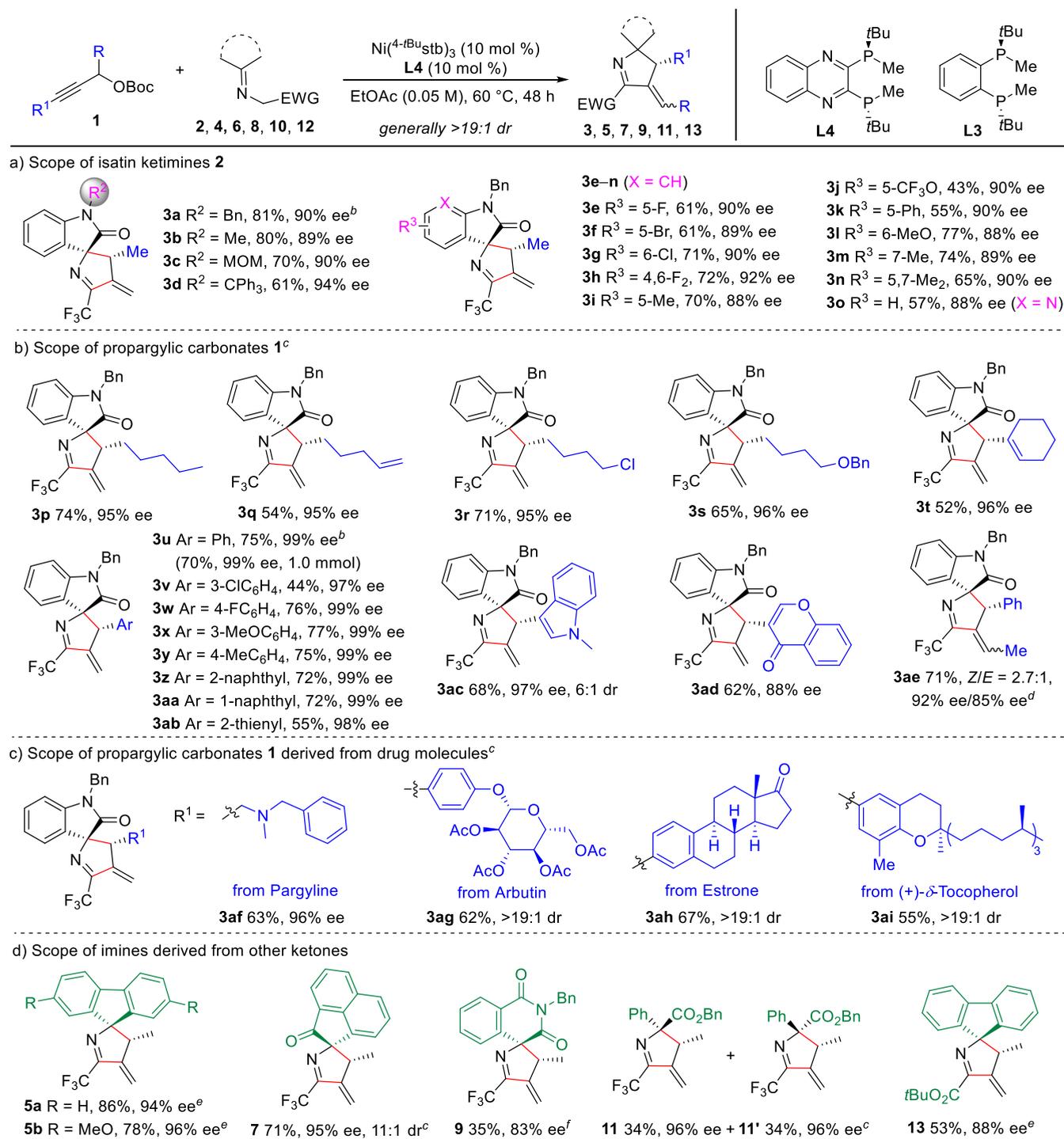
the catalysis of Ni($^{4-tBu}$stb)$_3$ and L4 in EtOAc at 60 °C for 48 h, and high enantioselectivity was obtained for desired products 3b–d. In addition, the introduction of diverse groups into the oxindole ring of substrates 2 has little effect on the reaction, and moderate yields with high levels of enantiocontrol were consistently attained for corresponding products 3e–n, and good data were also gained for a 7-azaisatin-derived product 3o. Nevertheless, the combination of Ni($^{4-tBu}$stb)$_3$ and L3 proved to be more reliable for the reactions of propargylic carbonates 1 with bulkier substituents, and 1,3-dioxolane was selected as the solvent at 80 °C. It was found that those bearing different alkyl groups, even functionalized ones, underwent the cascade transformations smoothly, delivering products 3p–s in moderate yields with excellent enantioselectivity. Moreover, a 1-cyclohexenyl-substituted substrate also showed good reactivity and chemoselectivity (product 3t). It was pleasing that a spectrum of propargylic carbonates 1 having diversely substituted aryl and heteroaryl groups were compatible in the reactions with ketimine 2a, and moderate yields with remarkable ee values were generally afforded for corresponding products 3u–ab, even on a larger scale (for 3u), whereas a minor diastereomer was generated for a 3-indolyl product 3ac. Notably, product 3ad having a 2-chromone

scaffold could be obtained efficiently (Scheme 2b). Nevertheless, the current Ni(0)-based catalyst showed poor reactivity when a disubstituted propargylic carbonate was used, whereas the corresponding product 3ae with high enantioselectivity could be obtained under the catalysis of Pd$_2$(dba)$_3$ and L4, albeit with a low Z/E ratio. Interestingly, a few drug derivatives embedding a propargylic motif exhibited good tolerance in the annulation reactions with ketimine 2a, furnishing complex architectures 3af–ai with high levels of stereoselectivity, demonstrating that the current strategy is applicable for the late-stage modifications of multifunctional pharmaceuticals (Scheme 2c).

The above success encouraged us to introduce more valuable scaffolds into the multifunctional 2H-pyrrole architectures by employing the imines derived from other types of activated carbonyls and trifluoroethylamine. As illustrated in Scheme 2d, fluorenone-derived imines 4 were well applied in the reactions with carbonate 1a,[14] and adding DABCO was found to be important to the high conversions, probably by enhancing the deprotonation process (products 5a and 5b). Monoketimine 6 from acenaphthylene-1,2-dione showed good reactivity, though trace amounts of diastereomer were observed (product 7). In addition, imine 8 derived from isoquinoline-1,3,4(2H)-trione was also applicable, albeit in a fair yield (product 9). Although poor diastereoselectivity was observed in the reaction of imine 10 from benzyl benzoylformate,[15] both isomers 11 and 11′ with outstanding ee values could be well separated. Furthermore, the fluorenone imine 12 of tert-butyl glycinate was tolerated to furnish product 13 in a moderate yield with high enantioselectivity.[16]

Apart from aza-vinylogous precursors, we intended to expand the nucleophiles to all-carbon-based ones; thus, unique 3-methylene-1-cyclopentene scaffolds would be effectively constructed. As illustrated in Scheme 3, inspiringly, the newly designed 3-trifluoropropylidene-2-oxindole 14 undertook similar alkenylation reaction with diverse propargylic carbonates 1 under the catalysis of Ni($^{4-tBu}$stb)$_3$ and L3 in 1,4-dioxane, affording spirooxindoles 15a–d in fair to moderate yields with high to excellent enantioselectivity. Nevertheless, acyclic substrate 16 gave a mixture of products in the assembly with carbonate 1a, which could be isolated as separable alcohols 17 and 17′ with good enantiocontrol after facile reduction.[18] In addition, both vinylogous precursors 18[17] and 20[18] successfully participated in the annulations, and high enantioselectivity was guaranteed by using Ni($^{4-tBu}$stb)$_3$/ligand L5 in THF (products 19 and 21, respectively), whereas slightly altered catalytic conditions were adopted for a chroman-4-one-derived substrate 22, furnishing a tricyclic framework 23 in a moderate yield with an excellent ee value.

Synthetic Elaborations. We further conducted diverse synthetic transformations with the multifunctional cycloadducts to exhibit high potential in future application. As illustrated in Scheme 4A, the exo-double bond of product 3u could easily isomerize to an endo-fashion by simple treatment with DBU at rt, affording spirooxindole 24 incorporating a 2H-pyrrole motif. In addition, highly diastereoselective dihydroxylation of 3u was realized to give product 25 in a moderate yield via osmium-based oxidation. Moreover, chemoselective attack on the imine group of 3u with a Grignard reagent was successful, and product 26 was obtained in a moderate yield with excellent diastereoselectivity. Importantly, owing to the electron-withdrawing effect of the CF$_3$-containing imine group, a sulfur-Michael addition to the exo-alkene occurred efficiently
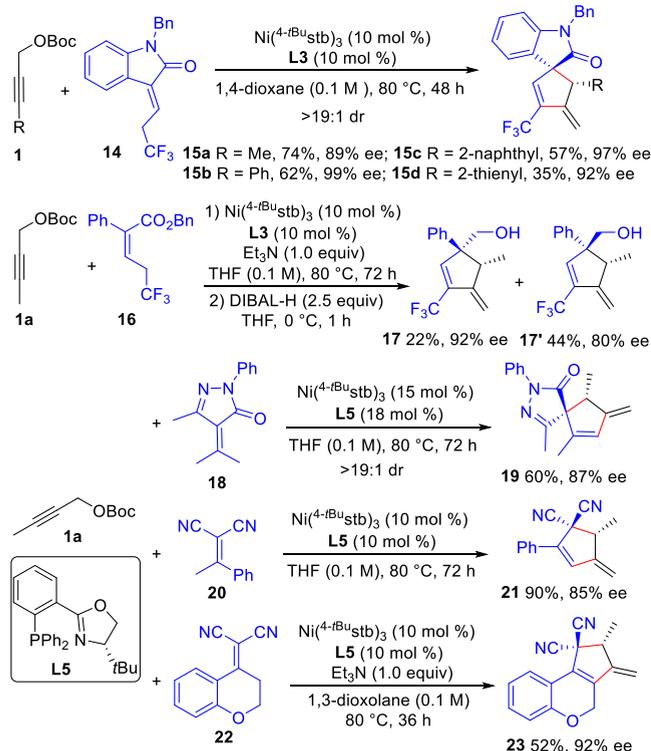
Scheme 2. Substrate Scope Studies[a]

a) Scope of isatin ketimines **2**

3a R[2] = Bn, 81%, 90% ee[b]	**3j** R[3] = 5-CF$_3$O, 43%, 90% ee
3b R[2] = Me, 80%, 89% ee	**3k** R[3] = 5-Ph, 55%, 90% ee
3c R[2] = MOM, 70%, 90% ee	**3l** R[3] = 6-MeO, 77%, 88% ee
3d R[2] = CPh$_3$, 61%, 94% ee	**3m** R[3] = 7-Me, 74%, 89% ee

3e–n (X = CH)

3e R[3] = 5-F, 61%, 90% ee
3f R[3] = 5-Br, 61%, 89% ee
3g R[3] = 6-Cl, 71%, 90% ee
3h R[3] = 4,6-F$_2$, 72%, 92% ee
3i R[3] = 5-Me, 70%, 88% ee

3n R[3] = 5,7-Me$_2$, 65%, 90% ee
3o R[3] = H, 57%, 88% ee (X = N)

b) Scope of propargylic carbonates **1**[c]

3p 74%, 95% ee

3q 54%, 95% ee

3r 71%, 95% ee

3s 65%, 96% ee

3t 52%, 96% ee

3u Ar = Ph, 75%, 99% ee[b]
(70%, 99% ee, 1.0 mmol)
3v Ar = 3-ClC$_6$H$_4$, 44%, 97% ee
3w Ar = 4-FC$_6$H$_4$, 76%, 99% ee
3x Ar = 3-MeOC$_6$H$_4$, 77%, 99% ee
3y Ar = 4-MeC$_6$H$_4$, 75%, 99% ee
3z Ar = 2-naphthyl, 72%, 99% ee
3aa Ar = 1-naphthyl, 72%, 99% ee
3ab Ar = 2-thienyl, 55%, 98% ee

3ac 68%, 97% ee, 6:1 dr

3ad 62%, 88% ee

3ae 71%, Z/E = 2.7:1,
92% ee/85% ee[d]

c) Scope of propargylic carbonates **1** derived from drug molecules[c]

R[1] =

from Pargyline
3af 63%, 96% ee

from Arbutin
3ag 62%, >19:1 dr

from Estrone
3ah 67%, >19:1 dr

from (+)-δ-Tocopherol
3ai 55%, >19:1 dr

d) Scope of imines derived from other ketones

5a R = H, 86%, 94% ee[e]
5b R = MeO, 78%, 96% ee[e]

7 71%, 95% ee, 11:1 dr[c]

9 35%, 83% ee[f]

11 34%, 96% ee + **11'** 34%, 96% ee[c]

13 53%, 88% ee[e]

[a]Unless noted otherwise, reactions were performed with carbonate **1** (0.12 mmol), imine **2** (or **4**, **6**, **8**, **10**, and **12**, 0.10 mmol), Ni(4-tBustb)$_3$ (10 mol %), and **L4** (10 mol %) in EtOAc (2.0 mL) at 60 °C for 48 h; yield referred to the isolated data; ee value was determined by HPLC analysis on a chiral stationary phase; dr was determined by ^{1}H NMR analysis. [b]The absolute configuration of enantiopure **3a** and **3u** was determined by X-ray analysis. The other products were assigned by analogy. [c]With **L3** (10 mol %) in 1,3-dioxolane (1.0 mL) at 80 °C for 36 h. [d]With Pd$_2$(dba)$_3$ (5 mol %) and **L4** (10 mol %) in DME (1.0 mL) at 80 °C. [e]With **L3** (10 mol %) and DABCO (1.0 equiv) in THF (1.0 mL) at 80 °C. [f]In 1,3-dioxolane (1.0 mL) at 80 °C.

under mild base conditions,[19] and exclusive diastereocontrol for product **27** was attained in the protonation process. Furthermore, a dipolar cycloaddition reaction of **3u** was tested, and a bisspirocyclic framework **28** was produced in a high yield, which could be chemoselectively converted to amine **29**

with exclusive diastereocontrol by reduction of NaBH$_3$CN. Alternatively, both amide and imine groups of **28** were reduced by NaBH$_4$, and a dehydroxylation reaction of the resultant hemiaminal motif succeeded to furnish triamine product **30** by further treatment with NaBH$_3$CN. In addition, the 3-

Scheme 3. Construction of 3-Methylenecyclopentene Frameworks with All-Carbon-Based Vinylogous Precursors[a]

Scheme 4. Synthetic Transformations of Multifunctional Products

A) Transformations of product **3u**

B) Transformations of product **15b**

(a) DBU (20 mol %), DCM, rt, 24 h. (b) K₂OsO₄·2H₂O (10 mol %), NMO (5.0 equiv), THF/H₂O, rt, 48 h. (c) BnMgBr (1.5 equiv), THF, THF, 0 °C. (d) Ronglite (2.0 equiv), K₂CO₃ (1.0 equiv), PhSSPh (0.6 equiv), DMF, rt, 2 h. (e) LiF (4.5 equiv), MeCN, 80 °C, 48 h. (f) NaBH₃CN (4.0 equiv), AcOH (4.0 equiv), MeCN, rt, 17 h. (g) NaBH₄ (5.0 equiv), MeOH/THF, 0 °C, 12 h, then NaBH₃CN (10.0 equiv), AcOH (10.0 equiv), MeCN, rt, 2 h. (h) Pd/C (20 wt %), H₂ (1 atm), MeOH, rt, 2 h. (i) *m*-CPBA (3.0 equiv), DCM, rt, 72 h.

methylene-1-cyclopentene motif of product **15b** can undergo different elaborations. As outlined in Scheme 4B, product **31** with a tetrasubstituted alkene moiety was obtained via a hydrogenation and isomerization process. Furthermore, a diastereoselective epoxidation reaction was realized by using *m*-CPBA, and product **32** was furnished in a fair yield due to incomplete conversions. Such enantioenriched spirocyclic architectures might find high interest in drug discovery field.[20]

Mechanism Studies. To gain more insights into the regio- and stereoselective (3 + 2) annulation reaction, density functional theory (DFT) calculations were conducted. As depicted in Scheme 5a, carbonate **1a** first underwent an oxidative addition in the presence of Ni(0)/**L4**, generating the cationic π-propargyl nickel complex **I** and a *tert*-butoxide anion. The latter would deprotonate compound **2a** to afford 2-azaallyl anion **II**. Theoretically, the nucleophilic attack of **II** on intermediate **I** might involve three reaction pathways to generate distinct products since it has several active sites (C₁, C₂, and C₃).[3−5] The calculations of the current case indicated that the attack on C₂ (**TS-1**, 9.8 kcal/mol), which would deliver nickellacyclobutene **III**, was more favorable than that on C₁ (**TS-3**, 13.0 kcal/mol) or on C₃ (**TS-4**, 27.0 kcal/mol). These findings aligned with our experimental observations as no propargylation product (via **TS-3**) or allenylation product (via **TS-4**) was detected. Due to the high acidity of the α-CH group of intermediate **III**, a 1,3-proton shift process would easily occur to afford the more stable *cis*-configured π-allylnickel intermediate **IV** with a significant exotherm of 25.0 kcal/mol.[21] Finally, an outer-sphere allylic alkylation would produce the branched (3 + 2) annulated species **V** via **TS-2** with an energy barrier of 18.8 kcal/mol, and Ni(0) was regenerated simultaneously.[22] It should be noted that the *trans*-configured π-allylnickel intermediate **VI** would also be
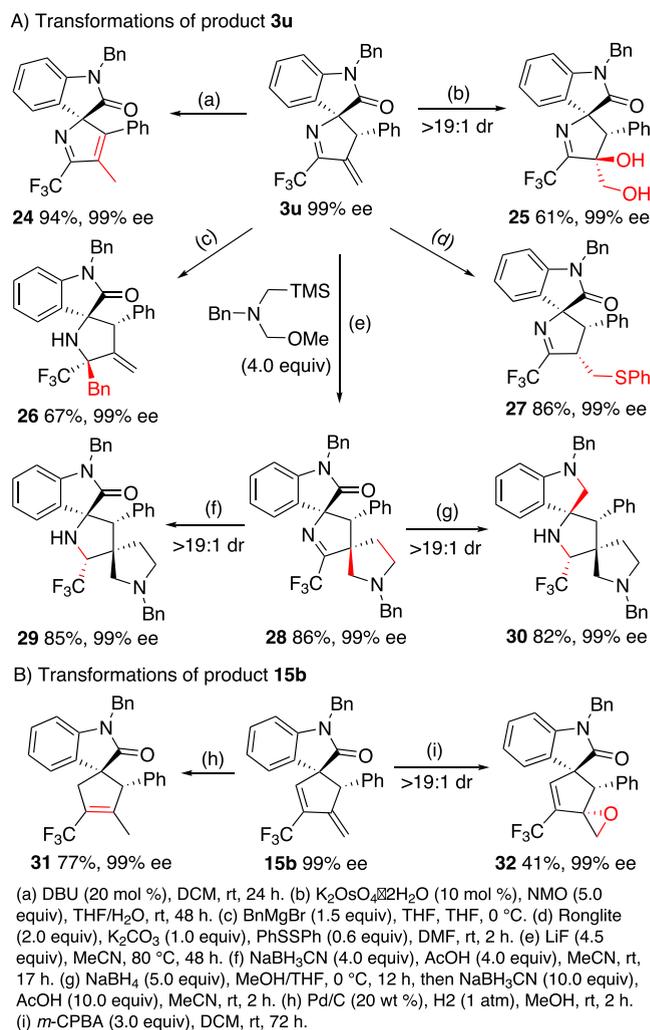
possibly generated after protonation;[7d] however, both **VI** and the relevant transition state **TS-5** for allylic alkylation step possess apparently higher energies, suggesting such a pathway would not be favored.

The proposed mechanism was partially supported by the control experiments. As illustrated in Scheme 5b, *d*-**2a** was applied to the reaction with carbonate **1g** under the standard conditions, and product *d*-**3u** with deuterium incorporation at the α-position of the phenyl group was obtained, consistent with the suggested formation of analogous intermediate **IV′**. Furthermore, intermediate **IV′** (or **III′**) could be successfully detected by high-resolution mass spectrometry (HRMS) analysis in the reaction of substrates **1g** and **2a** under the catalysis of Ni(0)/**L3** (Scheme 5c), which also supported the proposed catalytic cycle.

The origin of the enantioselectivity was also investigated. The stereogenic centers are formed in the final allylic alkylation step; thus, transition states **TS-2** and **TS-2**-*ent*, leading to product **3a** and **3a**-*ent*, respectively, were analyzed (Scheme 5d). The activation free energy of **TS-2**-*ent* is 2.1 kcal/mol higher than that of **TS-2**, which aligns with the experimental observation that **3a** is the major product. Structural analysis revealed that the steric hindrance between the methyl group at the allyl moiety and the *tert*-butyl group at ligand **L4** increases
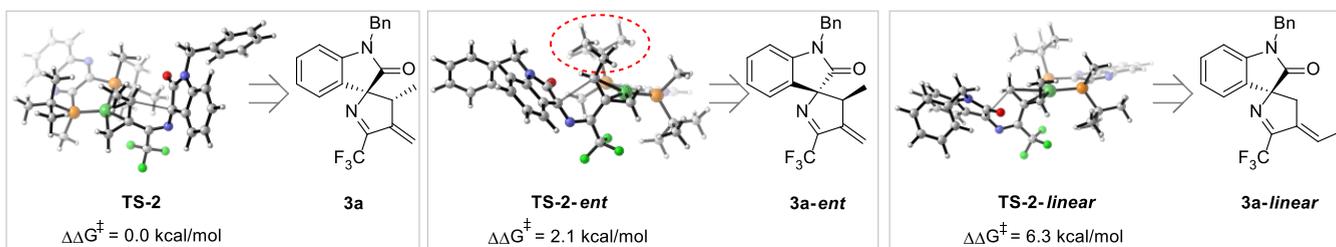
Scheme 5. Mechanism Studies

a) Free-energy profiles for Ni-catalyzed asymmetric (3 + 2) annulation
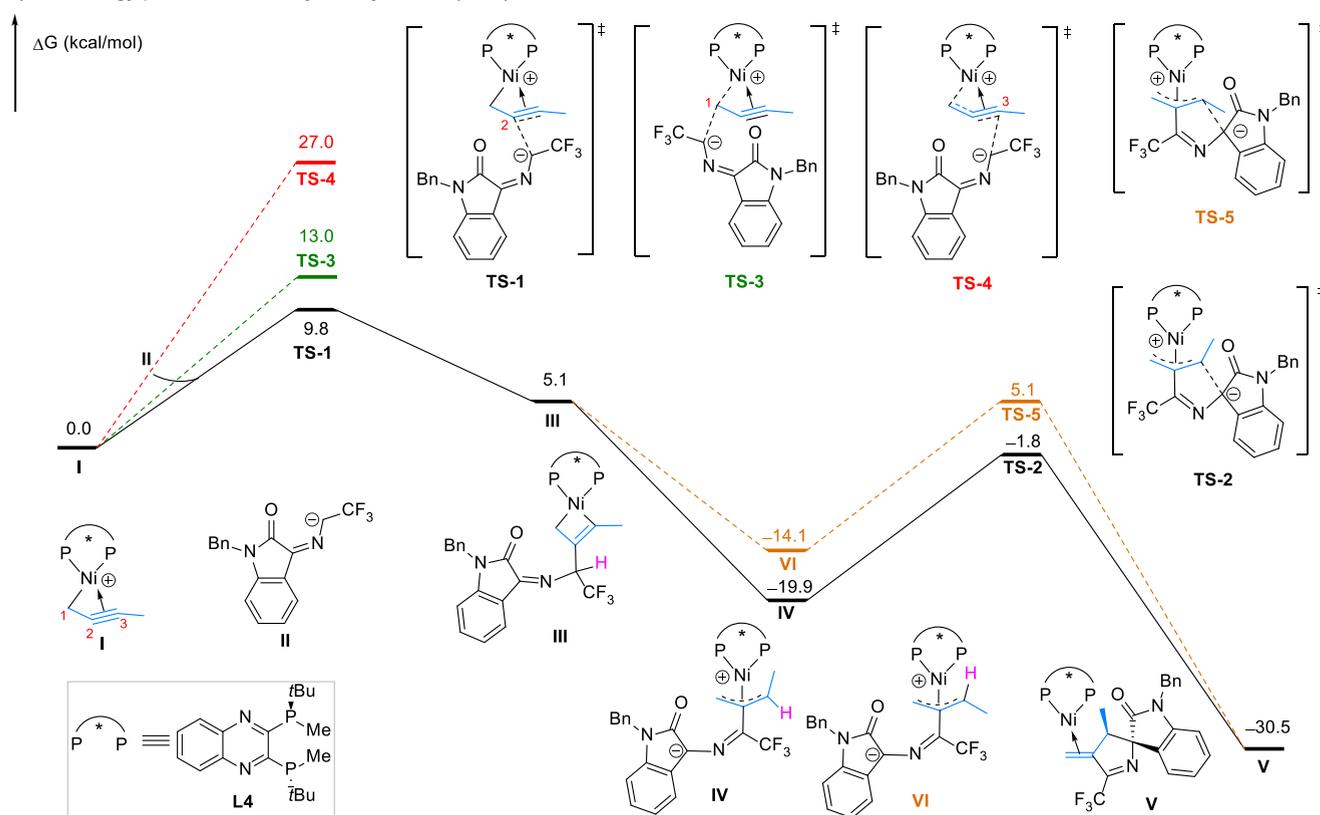
b) Deuterium-labeling study
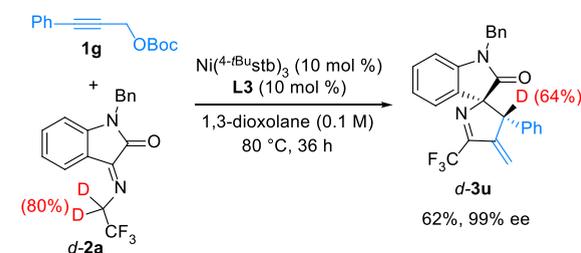
c) HRMS study on the reaction of 1g and 2a

HRMS for **III'** or **IV'** [M + H]⁺
Calcd 773.2542; Found 773.2543
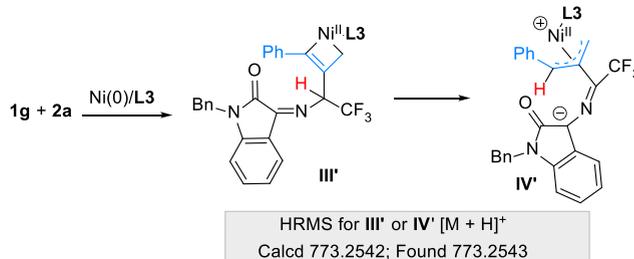
d) Enantioselectivity and regioselectivity investigation

the energy of **TS-2**-*ent*, thus dominating the π-facial selectivity control. Additionally, the plausible linear regioselectivity in the allylic alkylation step was compared. In fact, regioisomer **3a**-*linear* would be less favored since a higher energy (6.3 kcal/mol) was observed in transition state **TS-2**-*linear* in comparison with **TS-2**.[23]

■ CONCLUSIONS

In summary, we demonstrated that a chiral Ni(0) complex, derived from bench-stable Ni(⁴-*tBu*stb)₃ and commercially available bisphosphine ligand, could efficiently promote the

alkenylation reaction between propargylic carbonates and N-trifluoroethyl ketimines, furnishing (3 + 2) annulation products in a high chemo-, regio-, and stereoselective manner. The substrate scope for both partners was substantial, and a broad spectrum of frameworks, especially challenging spirocyclic architectures incorporating a 4-methylene-3,4-dihydro-2H-pyrrole motif, were generally constructed with good to excellent diastereo- and enantioselectivity. Moreover, a few all-carbon-based vinylogous nucleophiles were successfully utilized in the annulations with propargylic carbonates via similar Ni(0) catalysis, and diverse 3-methylene-1-cyclo-

pentene derivatives were afforded with high stereocontrol. Further elaborations with the multifunctional cycloadducts well exhibited their potential in organic and medicinal chemistry. The DFT study and control experiments supported that the in situ generated π-propargyl nickel complexes from propargylic carbonates were chemo- and regioselectively assembled with 2-azaallylic anion intermediates via consecutive aza-vinylogous activation, probably involving nickellacyclobutene as the key intermediates. We believe that earth-abundant Ni(0) catalysis would find more application in the asymmetric transformations of readily accessible propargylic substrates.

■ ASSOCIATED CONTENT

ⓢ Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.4c12664.

> More screening conditions, complete experimental procedures, characterization of new products, mechanism discussion including DFT calculations, NMR, HRMS spectra, and HPLC chromatograms (PDF). Crystallographic data of enantiopure **3a** and **3u** (CIF) (PDF)

Accession Codes

Accession Codes CCDC 2323940 and 2382905 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.

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Notes

The authors declare no competing financial interest.

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(23) Some inconsistence was unfortunately noted in the DFT calculation study on the diastereoselective formation of the observed product **3a** at current stage, and more factors still remain to be figured out and considered in the mechanism elucidations. See the Supporting Information for more details.

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