Nickel-Catalyzed Domino Cross-Electrophile Coupling Dicarbofunctionalization Reaction to Afford Vinylcyclopropanes

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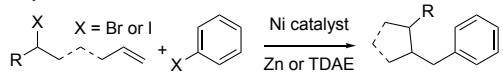
ABSTRACT: We have established a nickel-catalyzed domino reaction that harnesses sulfonamide, alkyl chloride, and alkyne functionalities in a multistep sequence to afford vinylcyclopropanes bearing tetrasubstituted olefins. Starting materials are prepared by iron-promoted aza-Prins reactions of ynals. This method provides rapid synthetic access to valuable building blocks with applications in medicinal chemistry. Experimental and computational results support initiation of the catalytic cycle by oxidative addition of the propargylic sulfonamide and a key ambiphilic allenylnickel intermediate leads to a bifurcated reaction pathway that generates olefin isomers

Domino reactions provide powerful strategies to build molecular complexity by forging multiple C–C bonds and stereogenic centers in a single reaction flask.[1] Development of these reactions typically builds on mechanistic understanding of discrete elementary steps, established in simpler transformations. Incorporation of cross-electrophile coupling (XEC) reactions into domino sequences is in its early stages.[2] Recent efforts have established nickel-catalyzed conjunctive XEC reactions where two organohalides are utilized to functionalize an alkene in the presence of a reducing agent (Scheme 1a).[3,4,5,6] These reactions intersect traditional XEC reaction mechanisms because they involve two oxidative addition events and, frequently, alkyl radical intermediates.[7] *Domino methods that combine XEC reactions with additional C–C bond-forming reactions have not been reported.*

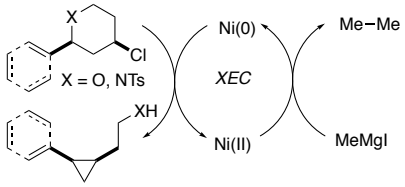
We sought to develop a domino reaction building on our nickel-catalyzed XEC reactions of ethers and sulfonamides (Scheme 1b).[8,9] In contrast with other XEC mechanisms, these reactions avoid radical intermediates, initiate with a polar oxidative addition of an activated C–O or C–N bond,[10] and cascade forward via an intramolecular S_N2-type reaction. Based on the calculated reaction coordinate, catalyst turnover by reduction of Ni(II) to Ni(0) with formation of ethane is rate-determining. Therefore, this catalytic cycle presents an opportunity to develop new domino transformations by inserting elementary steps known for Ni(II) intermediates.[11,12,13] In this manuscript, we disclose a nickel-catalyzed domino reaction that combines intramolecular XEC and dicarbofunctionalization reactions to produce substituted vinylcyclopropanes (Scheme 1c). This multicomponent transformation produces three new carbon–carbon bonds and a strained ring. The cyclopropane moiety is produced with high stereochemical fidelity. In addition, we provide experimental and computational evidence that the mechanism involves a single oxidative addition, an intramolecular S_N2-type reaction and a single reductive elimination. All elementary steps are stereospecific; product isomers result from divergent pathways from a key allenylnickel intermediate.

Scheme 1. Nickel-Catalyzed Domino XEC Reactions

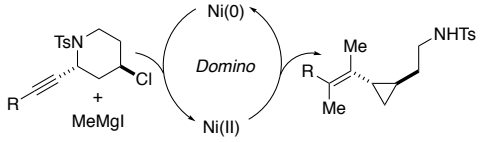
a. Conjunctive XEC reactions



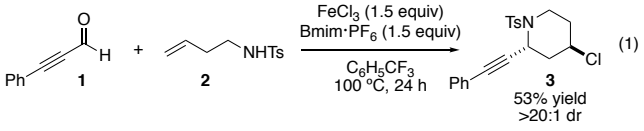
b. Intramolecular XEC Reaction



c. **This work:** XEC-Dicarbofunctionalization Domino Reaction

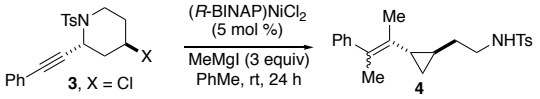


At the outset, we recognized that a critical component of our approach would be the rapid and efficient synthesis of the requisite starting materials. We envisioned that an aza-Prins reaction could generate 4-halo-2-alkynyl piperidines directly from ynals. [14] Unfortunately, there were no Prins or aza-Prins reactions of simple ynals in the literature. The closest precedence was a cobalt-mediated reaction, where the cobalt complex serves to mask the alkyne to produce protected 2-alkynyl tetrahydropyrans.[15] We were encouraged, however, by iron-promoted aza-Prins reactions of enals for synthesis of 2-vinyl piperidines.[16] We applied similar conditions for the aza-Prins reaction of ynals (eq 1). Gratifyingly, this reaction afforded the desired 2-alkynyl-4-chloropiperidine in 53% yield and as a single diastereomer. As expected, the *trans* diastereomer was preferred due to minimization of A(1,3)-strain.[17] This transformation proved to be robust across a range of aryl- and alkyl-substituted ynals (*vide infra*).[18]



We investigated the feasibility of the proposed domino reaction employing *N*-tosyl piperidine **3**.[19] We began with the previously developed conditions for the XEC reaction of aryl and vinyl sulfonamides with (*R*-BINAP)$NiCl_2$ as the precatalyst (Table 1, entry 1).[8c,20] We evaluated two halide leaving groups, and the chloride produced the functionalized cyclopropane in greater yield as compared to the fluoride (entries 1 and 2).[21] We determined by NMR analysis that the cyclopropane moiety is exclusively produced as the *trans* configuration while the olefin is generated as a mixture of (*E*)- and (*Z*)-alkene isomers.[18] In an attempt to improve diastereoselectivity, we cooled the reaction to 0 °C, however, no product was formed and 98% starting material was recovered (entry 3). Previously, our laboratory has found that Lewis acidic MgI_2 can accelerate the rate of oxidative addition of sluggish electrophiles,[9,22] however, the yield of the domino reaction did not improve with the addition of one equivalent of MgI_2 (entry 4). When the number of equivalents of the Grignard reagent was lowered, the yield improved (entries 5 and 6). Next, we evaluated alternative precatalysts. The commercially available Jamison catalyst, *cis*-(*R*-BINAP)Ni(o-tolyl)Cl, afforded similar yield and *E*:*Z* ratios (entry 7).[20a] $Ni(cod)_2$ and racemic BINAP provided decreased yield, consistent with our prior observation that cod inhibits XEC reactions of sulfonamides.[8c] Other precursors also afforded modest yields (entries 9 and 10).[23] Finally, we observed that the nickel catalyst was essential for the domino reaction to take place. In the absence of catalyst, simple propargylic displacement by the Grignard reagent occurred in 15% yield (entry 11).[24,25] We hypothesized that allenylcopper intermediates could potentially engage in an XEC reaction.[26,27,28] However, in preliminary investigations, when the nickel precatalyst was replaced with a copper salt no reaction was observed (entry 12). Therefore, we concluded that the optimal domino conditions employ a nickel(II) precatalyst, BINAP as the ligand, and two equivalents of methylmagnesium iodide.

Table 1. Optimization of Nickel-Catalyzed Domino Reaction



Entry	Deviation from Standard Conditions	Yield (%)[a]	*E*:*Z*
1	none	61	1.5 : 1
2	X = F	51	1.1 : 1
3	0 °C instead of rt	<5	–
4	1.0 equiv of MgI_2 added	61	1.7 : 1
5	2.5 equiv MeMgI	68	1.5 : 1
6	**2 equiv MeMgI**	**72 (71)[b]**	**1.7 : 1**
	(R-BINAP)NiCl2 replaced with 5 mol% of:		
7	*cis*-(*R*-BINAP)Ni(*o*-tolyl)Cl	74	1.2 : 1
8	$Ni(cod)_2$, *rac*-BINAP	30	1 : 2
9[c]	Ni(cod)(DQ), *rac*-BINAP	42	1 : 1.2
10[c]	$Ni(acac)_2$, *rac*-BINAP	52	1 : 1.6
11	No Nickel Catalyst	<5	–
12[d]	$Cu(CH_3CN)_4OTf$	<5	–

[a]Determined by ^1H NMR based on comparison to PhTMS as an internal standard. [b]Isolated yield. [c]2 equiv of methylmagnesium iodide. [d] PhMe replaced with DCM.

To determine the functional group compatibility of this reaction, a series of experiments to probe the reaction robustness were performed (Figure 1).[29] Since this transformation employs a nucleophilic Grignard reagent, we first targeted functional groups that are sensitive to methylmagnesium iodide. We began by evaluating acidic moieties. Phenol, thiophenol, and aniline were all tolerated under the reaction conditions, given excess Grignard reagent to account for proton transfer, allowing for moderate to good yields of cyclopropane **4**. We were also pleased to note that a silyl ether was well tolerated. Nitrobenzene inhibited the nickel catalyst and poor yields of cyclopropane **4** were observed. With excess Grignard reagent, a nitrile and an aldehyde were cleanly converted to the amine and alcohol, respectively, and these moieties did not interfere with nickel catalyst: cyclopropane **4** was generated in good yields.

Next, we targeted additives with functional groups that can react with or serve as ligands for nickel catalysts (Figure 1). Aryl and alkyl chlorides did not outcompete the propargyl sulfonamide; the substituted vinylcyclopropane was observed in good yield. Alkenes strongly ligate nickel catalysts, so we evaluated two alkenes: cyclohexene and styrene. Cyclohexene was well-tolerated and did not inhibit the reaction, however, styrene inhibited the domino reaction likely due to strong ligation to the active catalyst. Finally, we evaluated nitrogen-containing heterocycles, common ligands for transition metals. In the presence of pyridine and a substituted pyridine the yield of cyclopropane **4** was lowered. Interestingly, when pyridine

was the additive, (*Z*)-alkene **4** was the major product.[18] Indole and *N*-methyl indole did not affect the yields of the domino transformation. Finally, *N*-methylmorpholine inhibited the domino reaction resulting in diminished yield of cyclopropane **4**. Taken together, numerous functional groups are tolerated under our reaction conditions providing a robust domino reaction.

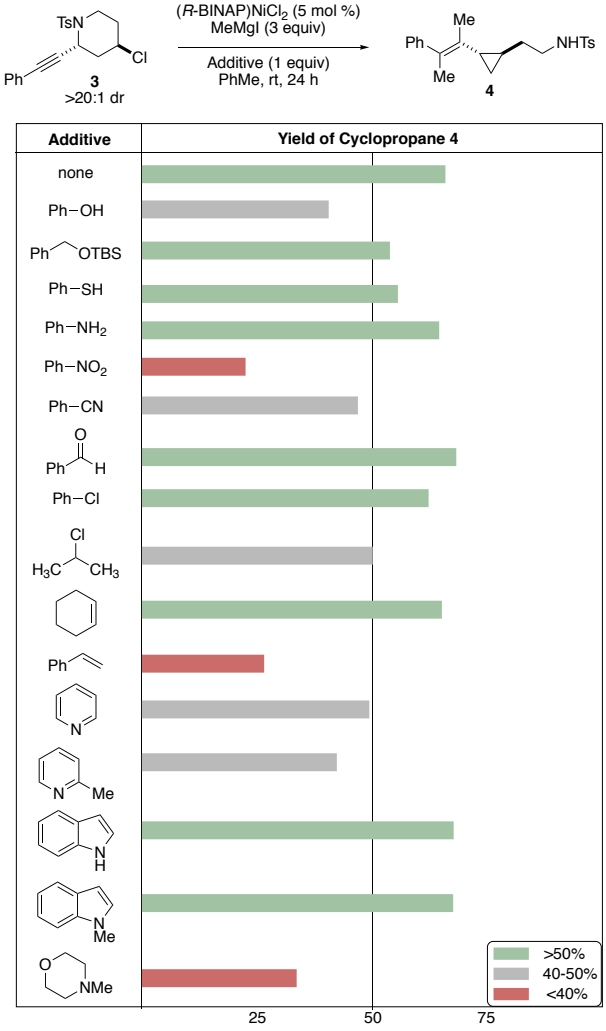
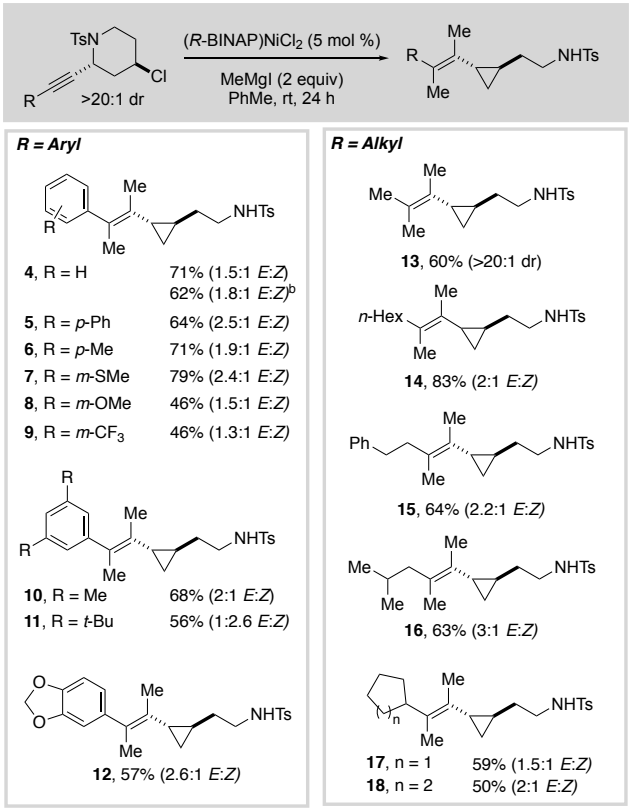


Figure 1. Robustness screen to establish functional group compatibility. (a) Yield of cyclopropane **4** determined by ^{1}H NMR based on comparison to PhTMS as an internal standard. (b) Unless otherwise noted, products were observed as ~1.5:1 mixture of (*E*)- and (*Z*)-alkene isomers. Employing pyridine and 2-methylpyridine as additives provided a slight preference for formation of the (*Z*)-alkene isomer (1:1.6 and 1:1.2 *E*:*Z* respectively).

Next, we evaluated the scope of the domino reaction (Scheme 2). Historically, cyclopropanes have been synthesized via Simmons–Smith reactions, transition metal-catalyzed carbene insertions, cycloisomerizations, and nucleophilic displacement reactions.[30] This method establishes an alternative to these strategies, while also providing a rapid synthesis of highly substituted vinylcyclopropanes.[31,32,33] First, we evaluated substituted aromatic rings (**4**–**12**). We found that electron donating groups were well tolerated in the domino reaction, producing the desired product in excellent yields and moderate *E*:*Z* ratios. Interestingly, this reaction could be scaled up tenfold (to 1.0 mmol) and still retain good yield. The electron withdrawing CF_3 group provided the desired product albeit in moderate yield and diastereoselectivity. Interestingly, the sterically bulky *t*-Bu substrate provided (*Z*)-alkene **11** as the major product. We hypothesize that the *t*-Bu groups hinder the carbometallation step and favor the intramolecular transmetalation leading to (*Z*)-vinylcyclopropane as the major product (*vide infra*). We were delighted to observe that aromatic groups were not necessary and alkyl substrates were able to undergo the transformation in excellent yields (**13**–**18**). It is important to note that cyclopropane **13** derived from propyne is obtained in excellent diastereoselectivity (>20:1) further confirming that cyclopropane formation is highly stereoselective.

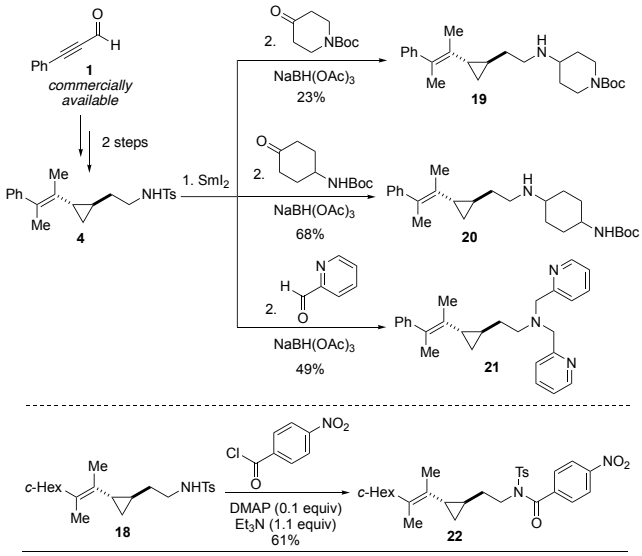
Scheme 2. Substrate Scope[a]



[a]Reactions performed on 0.1–0.2 mmol scale. Isolated yields.
[b]Reaction performed on 1.0 mmol scale.

Vinylcyclopropane and amine-substituted cyclopropane moieties are present in numerous biologically active compounds, natural products and pharmaceutical agents.[34,35] For example, amino-substituted vinylcyclopropanes have been established as lysine specific demethylase (LSD1) inhibitors with potent anti-leukemia activity.[36] To demonstrate the synthetic potential of our domino reaction, we synthesized a series of analogs of LSD1 inhibitors (Scheme 3). First, we performed a SmI_2 deprotection of the pendant sulfonamide.[37] The resulting primary amine was subjected to three different reductive amination reactions to produce **19, 20,** and **21**. Alternatively, the sulfonamide moiety could be functionalized directly via acylation to afford imide **22** in 61% yield. Interestingly, amine **20** demonstrated significant cell death against colon cancer cell lines (COLO-205 and HCC-2998) and imide **22** is active against a non-small cell lung cancer cell line (HOP-92).[38] Therefore, this domino reaction provides rapid access to bioactive structural motifs in four steps from commercially available materials.

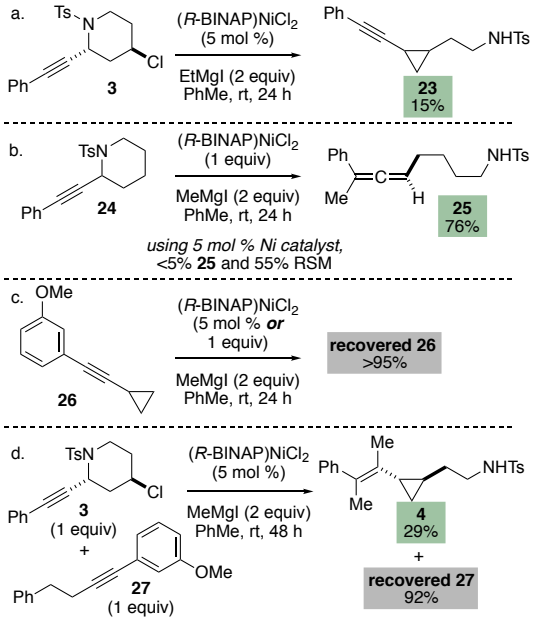
Scheme 3. Derivatization of Cyclopropane Products[a,b,c]



[a]SmI_2 (10 equiv), pyrrolidine (4 equiv), H_2O (5 equiv), rt, 5 min [b]$NaBH(OAc)_3$ (2 equiv), DCE, rt, 30 min. [c]Yield over two steps.

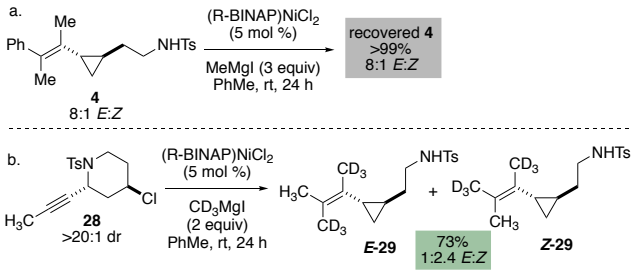
Next, we aimed to elucidate the mechanism of this multicomponent reaction. A series of control experiments were consistent with initiation of the catalytic cycle by oxidative addition of the nickel catalyst with the propargylic sulfonamide moiety. First, employing an alternative Grignard reagent, EtMgI, led to formation of alkynylcyclopropane **23** in 15% yield (Scheme 4a). This observation is consistent with oxidative addition of the propargylic sulfonamide to produce an allenylnickel complex that proceeds through an XEC pathway. A simple propargylic sulfonamide, **24**, lacking a pendant alkyl halide, underwent substitution to form allene **25**. This further supports that the mechanism initiates by oxidative addition of the propargylic sulfonamide. Additionally, simple alkynes did not undergo dicarbofunctionalization under standard reaction conditions (Scheme 4c and d). Alkynyl cyclopropane **26** did not undergo a 1,2-dicarbofunctionalization under standard reaction conditions, employing catalytic or stoichiometric quantities of nickel complex. Similarly, in a competition experiment, propargylic sulfonamide **3** reacted while alkyne **27** was not functionalized. Therefore, even in the presence of relevant catalytically active organonickel intermediates, a simple alkyne was not engaged. Taken together, these experiments support initiation of the domino reaction by oxidative addition of the propargylic sulfonamide moiety.

Scheme 4. Mechanistic Control Experiments



Next, we examined subsequent steps in the catalytic cycle, with a particular focus on the steps that would bifurcate to afford (*E*)- and (*Z*)-isomers of the alkene. To ensure that the product distribution was a kinetic distribution, we performed a control experiment (Scheme 5a). Resubjecting vinylcyclopropane **4** (8:1 *E*:*Z*) to the reaction conditions resulted in no isomerization. To determine whether the relative stability of product diastereomers is reflected in key transition states, we examined a substrate devoid of a steric preference for product formation (Scheme 5b). Employing a deuterated Grignard reagent provided vinylcyclopropane **29** as a 1:2.4 mixture (*E*:*Z*). Therefore, we concluded that the relative stability of product isomers does not impact the selectivity of the reaction.

Scheme 5. Kinetic and Thermodynamic Stability of Products



We next evaluated the reaction mechanism and origins of selectivity using density functional theory (DFT) calculations. The DFT-computed free energy changes of the catalytic cycle of (*Z*)-vinylcyclopropane **4** formation are shown in Figure 2. From the substrate-coordinated complex **INT1**, oxidative addition of the propargylic C–N bond can occur via **TS2** to generate the allenylnickel(II) intermediate **INT3**. This step is analogous to the S_N2-type oxidative addition mechanism identified in our previous mechanistic studies of Ni-catalyzed Kumada and XEC reactions of benzylic and allylic ethers and sulfonamides.[9,10b] It also follows the known propensity of propargylic electrophiles to undergo oxidative addition with low-valent nickel complexes.[39] Additionally, consistent with our prior mechanistic studies,[8c,9] the Lewis acid plays an important role in promoting oxidative addition. Lewis acidic

MgI_2, present in solution due to Schlenk equilibrium of the Grignard reagent, [40] coordinates to the oxygen of the sulfonamide, which activates the substrate for oxidative addition. The barrier for the same Ni(0)-mediated oxidative addition increases by 14.6 kcal/mol without the assistance of MgI_2 (Figure S5).

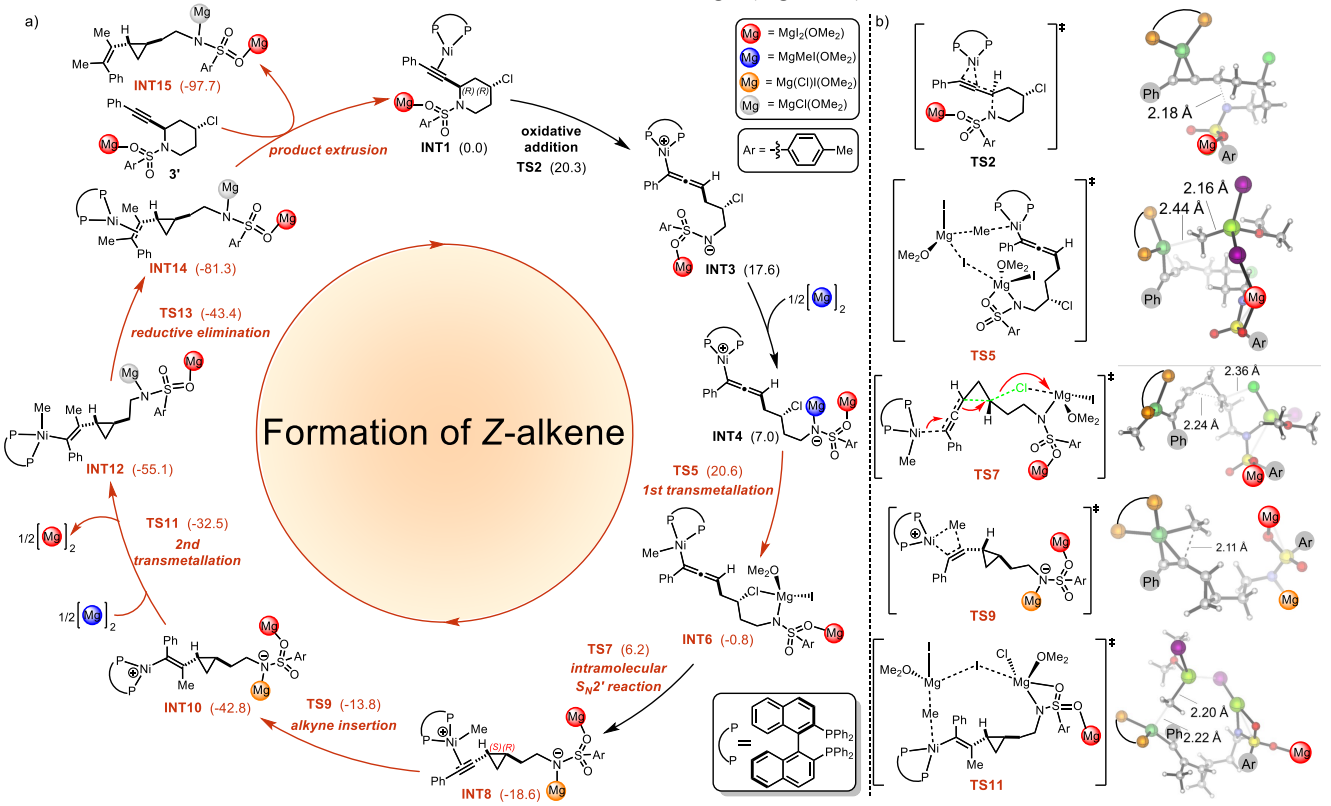


Figure 2. a) DFT-computed free energy changes of the catalytic cycle of nickel-catalyzed domino cross-electrophile coupling dicarbofunctionalization reaction for formation of (*Z*)-alkene, at the M06/def2-TZVPP-SMD(toluene)//B3LYP-D3(BJ)/def2-SVP-SMD(toluene) level of theory. b) Optimized structures of key transition states. All free energies are in kcal/mol.

After oxidative addition, allenylnickel complex **INT3** cascades through the catalytic cycle. First, zwitterionic allenylnickel(II) species **INT3** complexes with the Grignard reagent to afford intermediate **INT4**. Subsequent intramolecular transmellation proceeds via **TS5** to generate the allenylnickel(II) methyl intermediate **INT6**. This transmetallation increases the nucleophilicity of the allene moiety and allows the facile intramolecular S_N2'-type reaction via **TS7** to produce the cyclopropane ring (**INT8**). We also considered the direct S_N2'-type reaction of **INT4**, which is less favorable as compared to the transmetallation via **TS5** due to the poor nucleophilicity of the cationic allenylnickel(II) moiety (Figure S6). From **INT8**, *syn*-migratory alkyne insertion of the methylnickel complex via **TS9** generates the (*Z*)-alkenylnickel(II) intermediate **INT10**. Subsequent transmetallation and reductive elimination generates the alkene moiety as the (*Z*)-isomer. Final product extrusion liberates the (*Z*)-vinylcyclopropane product and regenerates the reactive intermediate **INT1** for the next catalytic cycle.

This mechanism could account for formation of the (*E*)-isomer of vinylcyclopropane product **4** if isomerization of the vinylnickel intermediate was feasible. Related isomerization reactions have been proposed to account for olefin isomers generated via vinylnickel species. [41] However, calculated barriers demonstrate that the transmetallation of **INT10** is significantly faster than the *E*:*Z* isomerization to **INT17** (10.3 kcal/mol vs 15.7 kcal/mol, **TS11** vs. **TS16**, Figure 3). Therefore, the facile transmetallation of the cationic vinylnickel species prevents *E*:*Z* isomerization, and the catalytic cycle for formation of (*Z*)-vinylcyclopropane formation does not account for the formation of (*E*)-vinylcyclopropane.

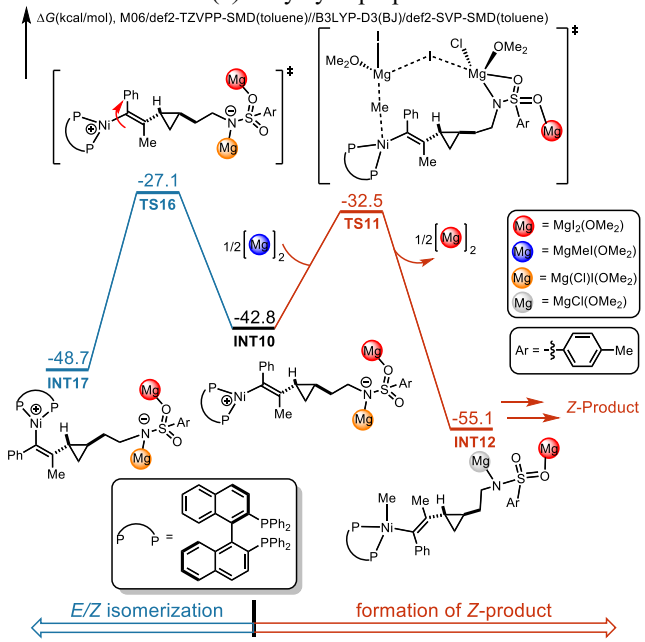


Figure 3. DFT-computed free energy barriers of the competing transmetallation and *E*:*Z*-isomerization of vinylnickel species.

The DFT-computed free energy profile of the (*E*)-vinylcyclopropane formation is shown in Figure 4. The catalytic cycle initates with the same oxidative addition of the

propargylic sulfonamide to afford the zwitterionic allenylnickel(II) complex **INT3**, and this complex coordinates an equivalent of the Grignard reagent to afford **INT4**. At this point, the mechanism diverges. From **INT4**, instead of transmetallation which leads to (*Z*)-vinylcyclopropane, the Grignard reagent can attack the internal carbon of the allenylnickel moiety to generate nickellacyclobutene **INT19**. This anti carbometallation reaction occurs via **TS18**. Similar nucleophilic additions to the internal carbon of an allene have been identified in related transformations. [42]

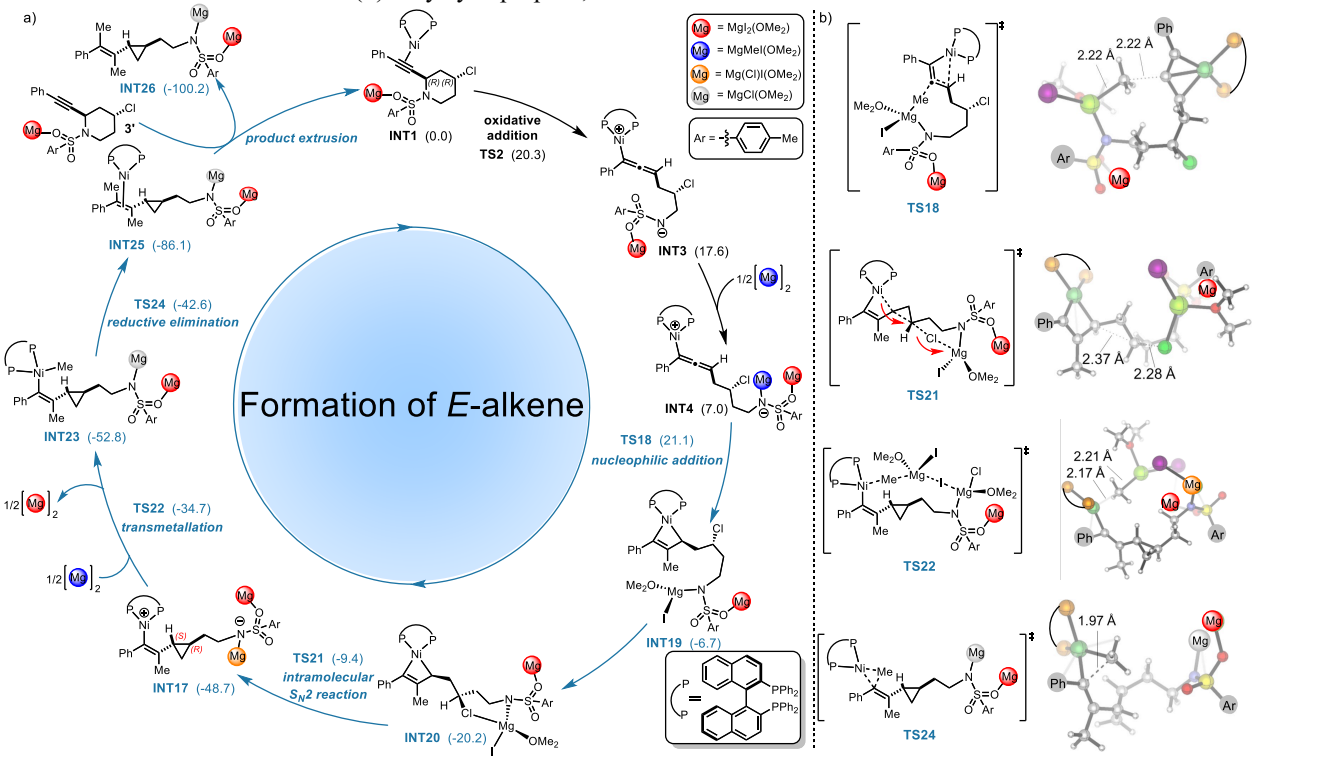


Figure 4. a) DFT-computed free energy changes of the catalytic cycle of nickel-catalyzed domino cross-electrophile coupling dicarbofunctionalization reaction for formation of (*E*)-alkene, at the M06/def2-TZVPP-SMD(toluene)//B3LYP-D3(BJ)/def2-SVP-SMD(toluene) level of theory. b) Optimized structures of key transition states. All free energies are in kcal/mol.

Subsequent steps in the catalytic cycle mirror those for formation of (*Z*)-vinylcyclopropane. Coordination of the alkyl halide to the tethered Grignard reagent provides **INT20**. A facile intramolecular S_N2-type reaction via **TS21** generates the cyclopropane moiety of **INT17**. In **TS21**, the nucleophilic allylic position of the metallocyclobutene attacks the pendant alkyl chloride. In addition to generating the new C–C bond of the cyclopropane, this step provides a vinylnickel(II) moiety in **INT17**. Finally, transmetallation via **TS22** and subsequent C–C reductive elimination via **TS24** generates the tetrasubstituted olefin as the (*E*)-isomer. Product extrusion liberates the (*E*)-vinylcyclopropane product and regenerates the reactive intermediate **INT1**.

Based on the DFT-computed free energy profiles, the pathways for synthesis of (*Z*)- and (*E*)-vinylcyclopropane share the same oxidative addition step, and the chemoselectivity is determined by the competing transformations of zwitterionic allenylnickel(II) intermediate **INT4** (Figure 5). The classical transmetallation to nickel via **TS5** generates the LNi(allenyl)(methyl) intermediate **INT6**, which irreversibly undergoes subsequent transformations to produce the (*Z*)-vinylcyclopropane product. The alternative carbometallation involves the attack of the internal carbon of the allene with the Grignard reagent. This step leads to the nickellacyclobutene intermediate **INT19** and eventually produces the (*E*)-vinylcyclopropane product. The *E*:*Z*-selectivity is determined by the competition between **TS5** and **TS18**, which only have a 0.5 kcal/mol free energy difference. This competition is consistent with the observed low *E*:*Z*-selectivity of the vinylcyclopropane formation.

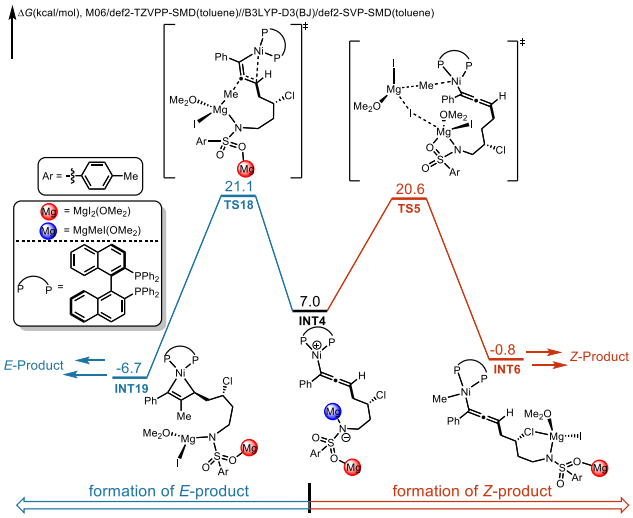
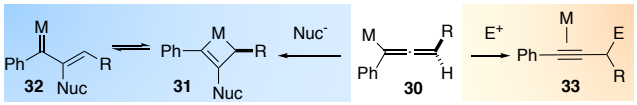


Figure 5. Mechanistic pathways that are responsible for the *E*:*Z*-selectivity.

Interestingly, this proposed bifurcated mechanism is consistent with the known ambiphilic reactivity of allenylmetal intermediates (Scheme 6).[42] Nucleophiles tend to add to the central carbon, leading to formation of metallocyclobutene intermediates **31**. These metallocyclobutenes can equilibrate with vinylcarbene complexes **32**. In contrast, electrophiles tend to add to the terminal carbon. In our system, allenylmetal

complex **INT4** reacts with coordinated nucleophilic Grignard reagent to form metallocyclobutene **INT19**. However, if transmetallation proceeds, the resultant electron-rich allenylnickel moiety of **INT6** quickly attacks the pendant electrophilic alkyl chloride.



Scheme 6. Ambiphilic Pathways for Allenylmetal Species

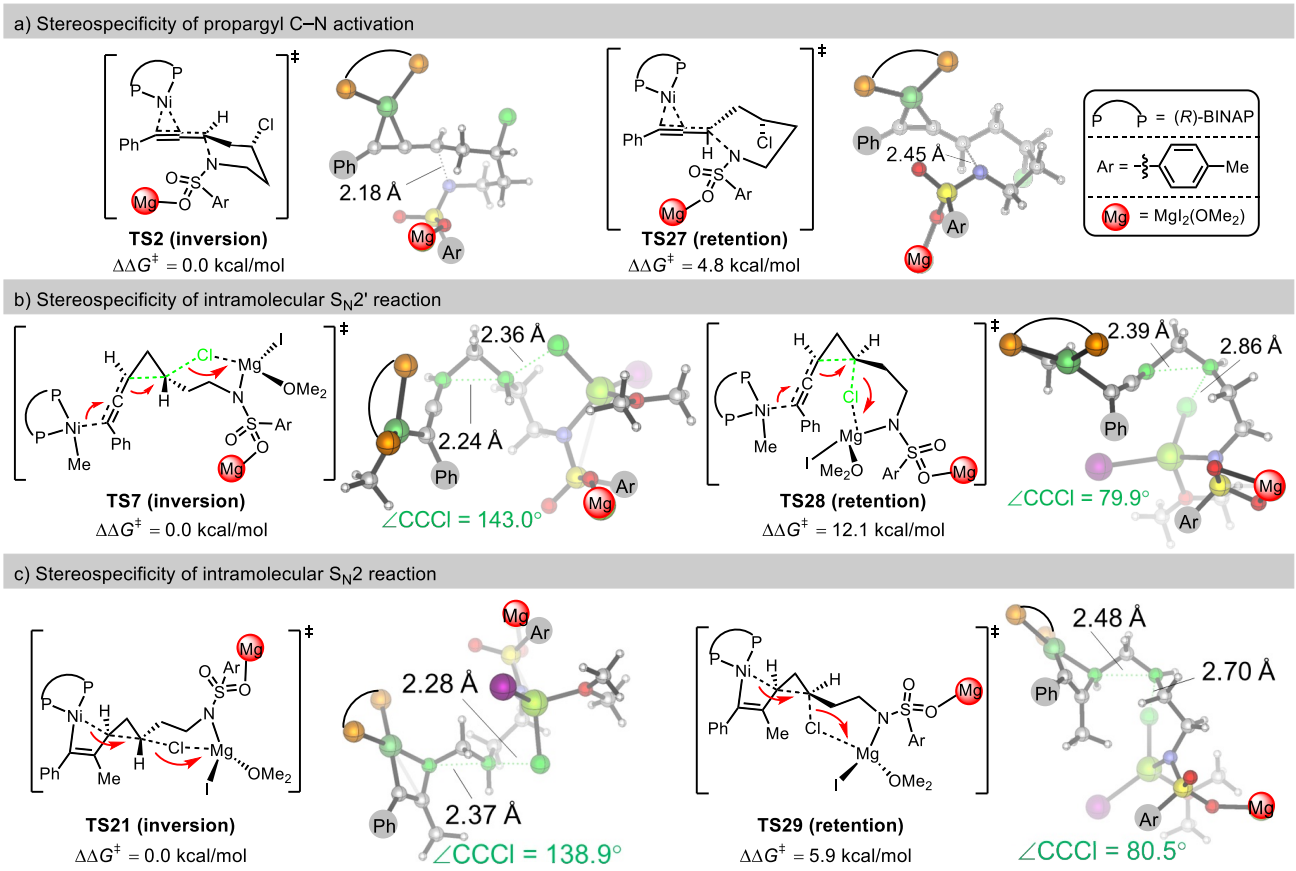


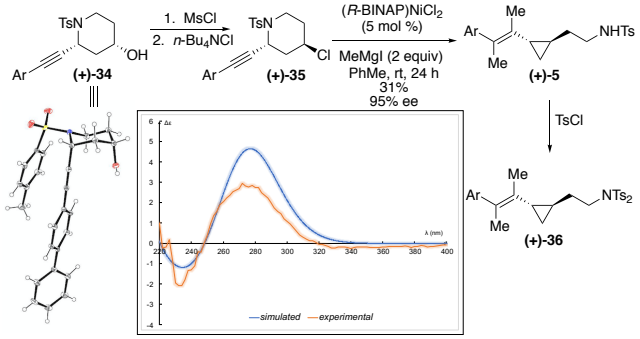
Figure 6. a) DFT-optimized structures and relative free energies of stereospecific propargyl C−N oxidative addition transition states. b) DFT-optimized structures and relative free energies of stereospecific intramolecular S_N2'-type reaction transition states in (*Z*)-vinylcyclopropane formation. c) DFT-optimized structures and relative free energies of stereospecific intramolecular S_N2-type reaction transition states in (*E*)-vinylcyclopropane formation.

Based on the operative mechanistic pathway, we next examined the origins of stereoselectivity in formation of the cyclopropane moiety (Figure 6). The overall stereochemical outcome is determined by the oxidative addition of the propargylic C−N bond and the intramolecular S_N2-type reaction for the formation of the cyclopropane. Oxidative addition can produce either stereoinversion or stereoretention, generating diastereomeric allenylnickel complexes.[43, 44, 45] Our IRC calculations determined that oxidative addition is stereospecific and proceeds with inversion (Figure S7). The stereoinvertive transition state **TS2** is 4.8 kcal/mol more favorable than the stereoretentive transition state **TS27**, indicating an exclusively stereoinvertive propargylic oxidative addition. The intramolecular S_N2-type reaction that generates the cyclopropane moiety also contributes to the stereochemical outcome of the reaction. This process exists in both the (*Z*)- and (*E*)-vinylcyclopropane formations, although the nature of the nucleophilic organonickel moiety differs. Both of the intramolecular S_N2-type reactions proceed exclusively with inversion at the alkylnickel and alkylchloride positions and are strikingly similar despite the change of the alkylmetal moiety (**TS7** vs. **TS28**, **TS21** vs. **TS29**, Figure 6b, 6c). These exclusive stereoinvertive cyclopropanations follow the classic back-side S_N2 attack.[9] The retentive cyclopropanation places the attacking nucleophile and the dissociating electrophile at the same face, which results in poor orbital overlap and is intrinsically disfavored.[46]

Consistent with these computational results, we have confirmed experimentally that the cyclopropane ring formation is enantiospecific and occurs with retention (double inversion) at the sulfonamide-bearing carbon, and inversion at the alkyl chloride (Scheme 7). Enantioenriched alkynylpiperidine **34** was prepared by lipase-catalyzed kinetic resolution.[47] Absolute configuration of the starting material was assigned based on X-ray crystallographic analysis of alcohol **34**, a precursor of piperidine **35**. The absolute configuration of vinylcyclopropane

5 was determined by comparing the experimental circular dichroism spectrum to the simulated spectrum of imide **36**.[48]

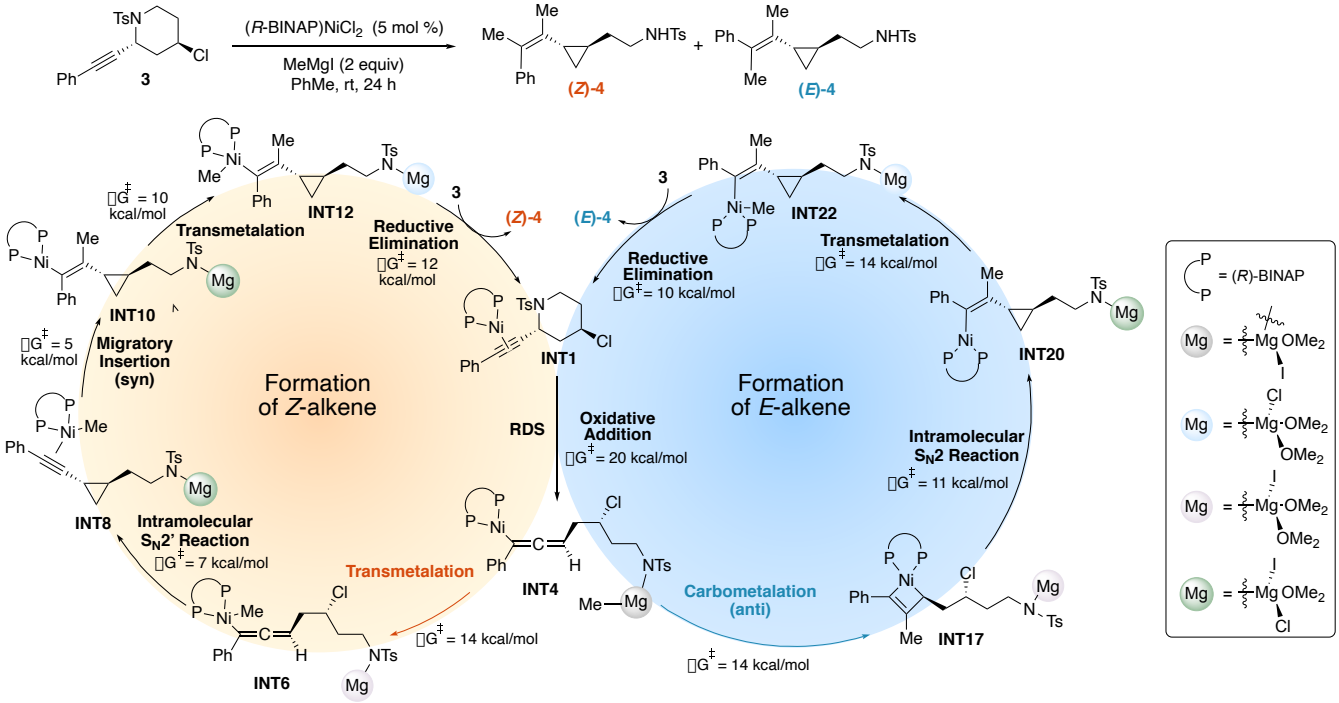
Scheme 7. Stereochemical Outcome of Domino Reaction.[a,b,c]



[a] MsCl (1.5 equiv), DMAP (0.1 equiv), Et_3N (1.5 equiv) DCM, rt, 2 h. [b] *n*-Bu_4NCl (2.0 equiv), THF, reflux 48 h. [c] TsCl (1.5 equiv), NaH (2 equiv), DMF, rt, 24 h.

Based on the experimental and computational mechanistic experiments, we propose the following domino mechanism (simplified version depicted in Scheme 8).[9] Initiation of the catalytic cycle occurs with oxidative addition of the progargylic sulfonamide. The key allenylnickel intermediate **INT4** can react via two pathways. Carbometallation by nucleophilic attack of the pendant organomagnesium complex affords metallacyclobutene **INT17**, and eventually leads to formation of the major diastereomer, (*E*)-**4**. Alternatively, allenylnickel complex **INT4** can undergo transmetallation and subsequently attack the pendant electrophilic alkyl chloride, leading to formation of the minor diastereomer, (*Z*)-**4**. The pathways that diverge from allenylnickel intermediate **INT4** have transition states that are similar in energy, consistent with the observed modest levels of diastereoselectivity. Each elementary step is stereospecific, with *anti*-carbometallation and *syn*-reductive elimination providing (*E*)-**4** and *syn*-migratory insertion and *syn*-reductive elimination generating (*Z*)-**4**.

Scheme 8. Proposed Mechanism of the Domino Reaction



In conclusion, we report a nickel-catalyzed domino reaction, to the best of our knowledge, the first example that includes separate XEC and dicarbofunctionalization reactions. The net transformation consists of ring-contraction of the piperidine and dicarbomethylation of the alkyne, generating highly substituted cyclopropanes bearing tetrasubstituted olefins and aminoethyl substituents. The reaction products are structurally related to histone demethylase inhibitors and we report the synthesis of derivatives that demonstrate selective inhibition of colon and non-small cell lung cancer cell lines. In addition, to accomplish rapid synthesis of the requisite starting materials, we report the first aza-Prins reaction of simple ynals to afford alkynyl piperidines, the starting materials for this domino reaction. Experimental and computational analysis of the reaction mechanism support a bifurcated reaction mechanism that accounts for product distributions. After oxidative addition, a key allenylnickel intermediate partitions into two different pathways, each with similar barrier heights, that lead to the observed reaction products. Future studies will include the development of related domino reactions and transformations that employ ambiphilic allenylnickel complexes.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. Experimental details, NMR spectra, experimental and calculated circular dichroism spectra, computational details, energies, and Cartesian coordinates of calculated structures (link PDF)

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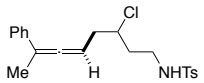

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