Ni(NHC)-Catalyzed Cycloaddition of Diynes and Tropone: Apparent Enone Cycloaddition Involving an 8π Insertion

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ABSTRACT: A Ni/N-heterocyclic carbene catalyst couples diynes to the C(α)−C(β) double bond of tropone, a type of reaction that is unprecedented for metal-catalyzed cycloadditions with aromatic tropone. Many different diynes were efficiently coupled to afford [5−6−7] fused tricyclic products, while [5−7−6] fused tricyclic compounds were obtained as minor byproducts in a few cases. The reaction has broad substrate scope and tolerates a wide range of functional groups, and excellent regioselectivity is found with unsymmetrical diynes. Theoretical calculations show that the apparent enone cycloaddition occurs through a distinctive 8π insertion of tropone. The initial intramolecular oxidative cyclization of diyne produces the nickelacyclopentadiene intermediate. This intermediate undergoes an 8π insertion of tropone, and subsequent reductive elimination generates the [5−6−7] fused tricyclic product. This initial product undergoes two competing isomerizations, leading to the observed [5−6−7] and [5−7−6] fused tricyclic products.

Tropone is a readily available seven-membered nonbenzenoid aromatic compound that can undergo cycloadditions to afford complex bridged motifs of a variety of natural products and medicinally important compounds (Figure 1a).1−4 The tropone cycloaddition reactivity can be generally understood by its resonance contributor, tropylium oxide (Figure 1b). This resonance structure explains the dipolar nature of tropone3a and the large LUMO coefficients at the alpha-positions (Figure 1c).5 Therefore, tropone cycloaddition reactions usually lead to bond formations at the α-positions as in (6 + 2),6 (6 + 3),7 and (6 + 4)8 cycloaddition reactions or in one α-position and the oxygen atom as in (8 + 2)9 and (8 + 3)10 cycloaddition reactions (Figure 1a).11 Reactions involving tropone as an enone moiety are rare. The exception involves disrupting the conjugation of tropone by precomplexation with iron−carbonyl (eq 1).12 Although this approach affords the desired nonbridged bicyclic products, such reactions require stoichiometric amounts of metal complexes as a protecting group for the other two double bonds. This inability to utilize tropones as enones is unfortunate, since selective activation of a single C−C π-bond in cycloaddition would greatly expand the synthetic utility of tropones, given the frequent occurrence of nonbridged seven-membered ring systems in biologically relevant compounds.4 We describe a solution to the long-standing problem of utilizing tropone as an enone through the use of a highly effective nickel catalyst that couples diynes with a single double bond of a tropone selectively to form fused tricyclic frameworks (vs bridged frameworks) without the need for precomplexation.

RESULTS AND DISCUSSION

Simple enones are known to undergo Ni-catalyzed cycloaddition with diynes (eq 2).13 However, these conditions fail to provide any cycloadduct product with tropone as shown in
Thus, we focused our investigation on discovering an alternative Ni-catalyzed cycloaddition protocol. Diyne and tropone were used as model substrates and were subjected to a catalytic amount of Ni(0) and a variety of phosphine and N-heterocyclic carbene (NHC) ligands (eq 4). Reactions run with monodentate and bidentate phosphines mostly afforded dimerization of diyne along with traces or low amounts of the desired cycloadduct (Table 1, entry 1−10). However, reactions run with NHCs resulted in good to excellent yields of cycloadduct 1a, which couples the diyne with a single C−C double bond of the tropone selectively (entries 11−15). Ultimately, SIPr proved to be the best ligand. Further optimization led to our final reaction conditions: diyne (1 equiv), tropone (1.1 equiv), 3 mol % of Ni(cod)2, 6 mol % of SIPr, THF, 60 °C, and 5 h. The model substrates afforded the desired product 1a along with another isomer 1a′ in excellent yield and >90% selectivity for 1a (eq 5). Similarly, cycloaddition of sulfonamide diyne 2

**Table 1. Ni-Catalyzed Cycloaddition of Diyne with Tropone**

<table>
<thead>
<tr>
<th>entry</th>
<th>L₃</th>
<th>Ni:Ln % conv of 1b</th>
<th>% yield of 1a</th>
<th>% yield of 1a²</th>
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<tbody>
<tr>
<td>1</td>
<td>PPh₃</td>
<td>1:2</td>
<td>&gt;99</td>
<td>14</td>
</tr>
<tr>
<td>2</td>
<td>PCy₃</td>
<td>1:2</td>
<td>&gt;99</td>
<td>29</td>
</tr>
<tr>
<td>3</td>
<td>P(ΟPr)₃</td>
<td>1:2</td>
<td>&gt;99</td>
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</tr>
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<td>4</td>
<td>PPh₂Me</td>
<td>1:2</td>
<td>&gt;99</td>
<td>9</td>
</tr>
<tr>
<td>5</td>
<td>P(ο-tolyl)₃</td>
<td>1:2</td>
<td>&gt;99</td>
<td>3</td>
</tr>
<tr>
<td>6</td>
<td>DPPF</td>
<td>1:1</td>
<td>&gt;99</td>
<td>4</td>
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<tr>
<td>7</td>
<td>BINAP</td>
<td>1:1</td>
<td>85</td>
<td>6</td>
</tr>
<tr>
<td>8</td>
<td>DPPB</td>
<td>1:1</td>
<td>&gt;99</td>
<td>6</td>
</tr>
<tr>
<td>9</td>
<td>Xantphos</td>
<td>1:1</td>
<td>&gt;99</td>
<td>–</td>
</tr>
<tr>
<td>10</td>
<td>ıtBu•Xantphos</td>
<td>1:1</td>
<td>&gt;99</td>
<td>–</td>
</tr>
<tr>
<td>11</td>
<td>IMes</td>
<td>1:2</td>
<td>96</td>
<td>79</td>
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<tr>
<td>12</td>
<td>lBu</td>
<td>1:2</td>
<td>98</td>
<td>71</td>
</tr>
<tr>
<td>13</td>
<td>lPr</td>
<td>1:2</td>
<td>&gt;99</td>
<td>&gt;99 (92)</td>
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<tr>
<td>14</td>
<td>SIPr</td>
<td>1:2</td>
<td>&gt;99</td>
<td>&gt;99 (95)</td>
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<tr>
<td>15</td>
<td>SIPr</td>
<td>1:2</td>
<td>&gt;99</td>
<td>&gt;99 (95)</td>
</tr>
</tbody>
</table>

"Reaction conditions: 10 mol % of Ni(cod)₂, 20 mol % of L₃, diyne (1 equiv, 0.1 M), tropone (1.1 equiv), toluene, 60 °C, 5 h. Determined by GC using naphthalene as an internal standard. %Isolated yield. THF was used instead of toluene.

**Table 2. Ni-Catalyzed Cycloaddition of Diynes (3–19) and Tropone (a)b**

<table>
<thead>
<tr>
<th>entry</th>
<th>L₃</th>
<th>Ni:Ln % conv of 1b</th>
<th>% yield of 1a</th>
<th>% yield of 1a²</th>
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<td>4</td>
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<td>1:2</td>
<td>&gt;99</td>
<td>9</td>
</tr>
<tr>
<td>5</td>
<td>P(ο-tolyl)₃</td>
<td>1:2</td>
<td>&gt;99</td>
<td>3</td>
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<td>6</td>
<td>DPPF</td>
<td>1:1</td>
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<tr>
<td>7</td>
<td>BINAP</td>
<td>1:1</td>
<td>85</td>
<td>6</td>
</tr>
<tr>
<td>8</td>
<td>DPPB</td>
<td>1:1</td>
<td>&gt;99</td>
<td>6</td>
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<td>Xantphos</td>
<td>1:1</td>
<td>&gt;99</td>
<td>–</td>
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<tr>
<td>10</td>
<td>ıtBu•Xantphos</td>
<td>1:1</td>
<td>&gt;99</td>
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<tr>
<td>11</td>
<td>IMes</td>
<td>1:2</td>
<td>96</td>
<td>79</td>
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<td>13</td>
<td>lPr</td>
<td>1:2</td>
<td>&gt;99</td>
<td>&gt;99 (92)</td>
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<tr>
<td>14</td>
<td>SIPr</td>
<td>1:2</td>
<td>&gt;99</td>
<td>&gt;99 (95)</td>
</tr>
<tr>
<td>15</td>
<td>SIPr</td>
<td>1:2</td>
<td>&gt;99</td>
<td>&gt;99 (95)</td>
</tr>
</tbody>
</table>

"Reaction conditions: diyne (1 equiv, 0.1 M), tropone (1.2 equiv), 3 mol % of Ni(cod)₂, 6 mol % of SIPr, THF, 60 °C, 5 h. Isolated yields (in black), ratio of major and minor cycloadducts (in blue), ratio of major and minor regioisomers (in red). The ratios were determined by 1H NMR of crude reaction mixture. The reaction was performed with 10 mol % catalyst loading at room temperature.
afforded a mixture of major and minor isomers 2a and 2a', respectively, which on subsequent treatment with p-bromobenzoyl chloride/NEt3/DMAP afforded major isomer 2a in 74% yield and p-bromobenzoyl derivative of minor isomer (2b) in 13% yield (eq 6) as crystalline solids (Figure 2). Surprisingly, 2b (and, therefore, 2a' as well) has [5-7-6] ring fusion compared to [5-6-7] in the case of the major isomer, 2a.15

With optimized reaction conditions in hand, the substrate scope was explored (Table 2). The cycloaddition occurred smoothly with the diyne bearing a sulfone backbone to form 3a along with minor isomer 3a'. Notably, this diyne is completely unreactive in several reported Ni-catalyzed cycloadditions.16 Although Ni catalysts have been reported to catalyze the cycloaddition of nitriles and diynes to form pyridines,16b,d diyne 4, which has a nitrile group in the backbone, selectively reacted with tropone to afford the desired cycloadducts (4a and 4a') in excellent yield. Inspired by Carreira’s work, we performed the cycloaddition reaction with 5, a diyne with a metabolically

Figure 3. The homocoupling pathway A of [Ni(IPr)]-catalyzed cycloaddition between nona-2,7-diyne 1 and tropone. Free energies (298 K) with respect to 21 are shown in kcal/mol.

Figure 4. The heterocoupling pathway B of [Ni(IPr)]-catalyzed cycloaddition between nona-2,7-diyne 1 and tropone. Free energies (298 K) with respect to 21 are shown in kcal/mol.
stable backbone,17 to give cycloadduct 5a in good yield along with minor isomer 5a′. Aryl substituted internal diynes are one of the most challenging substrates in Ni/NHC-catalyzed cycloaddition reactions.16e,18 Nevertheless, the reaction of aryl substituted symmetrical diynes with tropone afforded 6a and 7a in good yields. Interestingly, no minor cycloadduct (6a′ or 7a′) was obtained in these cases. To investigate the effect of electronics on the regioselectivity, we subjected unsymmetrical diynes 8 and 9 to standard reaction conditions; remarkably, exclusive formation of one regioisomer was detected (8a and 9a).

The use of different aryl groups (i.e., 3,4-dimethoxyphenyl and naphthyl) on alkyne terminals is also possible (10a and 11a). Due to recent interest in indole bearing novel compounds,19 diynes 12 and 13 were investigated. Biaryl cycloadducts (12a, 13a) were formed in very good yield and high regioselectivity. Interestingly, the regioselectivity was higher in the case of 3-substituted indole diyne than 5-substituted indole diyne (13a vs 12a). Cycloaddition of phenyl–ethyl diyne 14 and phenyl–silyloxyethyl 15 afforded regioisomers 14a and 15a, where the carbonyl resides next to the phenyl ring, exclusively, while a diyne with covalently bound δ-tocopherol can also be easily clicked together with tropone to afford regioselective cycloadduct 16a. An unsymmetrical diyne bearing an internal gem-dimethyl group reacted with tropone to afford an exclusive regioisomer 17a, which suggests that regioselectivity is highly dependent on the substituents on the alkyne units of a diyne rather than backbone.20 The cycloaddition of unsymmetrical isopropyl–methyl diyne (18) afforded products 18a and 18a′, where the bulkier group is next to the carbonyl of tropone. Cycloaddition of phenyl–isopropyl diyne 19 afforded a product where the isopropyl group is away from the carbonyl group (19a), suggesting that electronic factors override the steric factors (19a). Unfortunately, terminal diynes did not afford any cycloaddition product with tropone due to their high propensity to oligomerize under our reaction conditions.21,22

The lack of general methods to access troponoids prompted our investigation on the ability to convert the cycloadduct to a fully aromatized product. We found that compound 2a

Figure 5. Optimized structures, Gibbs free energies, and distortion and interaction energies of transition states of 8π insertion (TS25) and 2π insertion (TS37) of tropone. The Gibbs free energy changes (298 K) with respect to 24 are shown in kcal/mol.

Figure 6. Transition states for the intermolecular insertion of tropone into Ni(1Pr)–unsymmetrical diyne complexes.

can be consistently converted to tropone 20a by a three-step protocol.\textsuperscript{23} The hydrogenation of alkene 2a led to a saturated cycloheptanone, which was then subjected to dibromination. Finally, didehydrobromination afforded the desired tropone, 20a (eq 7).

\[\text{eq 7}\]

\[\text{Figure 7. Proposed mechanism for the Ni-catalyzed cycloaddition of diynes and tropone.}\]

\[\text{COMPUTATIONAL MECHANISTIC ANALYSIS}\]

We also undertook a mechanistic investigation of this reaction. Specifically, we studied the catalytic cycles for [Ni(IPr)]\textsubscript{2}-catalyzed cycloaddition of nona-2,7-diyne and tropone with DFT calculations.\textsuperscript{24} Homocoupling,\textsuperscript{25} where two alkynes undergo initial oxidative coupling, and heterocoupling,\textsuperscript{26} where an alkyne and the tropone undergo initial oxidative coupling, were both investigated.

The free energy changes for the homocoupling pathway are shown in Figure 3. From [Ni(IPr)]\textsubscript{2} complex 21, the coordination of diyne to form intermediate 22 is endergonic by 7.0 kcal/mol. Subsequent intramolecular oxidative cyclization via TS23 requires a 13.4 kcal/mol barrier with respect to 22, generating the metallacyclopentaladiene intermediate 24. This intermediate undergoes a facile 8π insertion (instead of 2π insertion, vide infra) of tropone via TS25, with a barrier of only 9.8 kcal/mol. The 8π insertion produces the eight-membered ring intermediate 26 with the tropone oxygen coordinated to nickel. The tropone piece of complex 26 can coordinate to nickel in four different fashions, generating the complexes 26 to 29.\textsuperscript{27} The four isomers have similar stabilities, and complex 29 undergoes reductive elimination via TS30 to give the product-coordinated complex 31. Product extrusion from 31 is exergonic by 2.8 kcal/mol to release the product and regenerate the nickel-diyne complex 22. The tautomerization of intermediate complex 29 to 29-enol\textsuperscript{27} is endergonic by 5.8 kcal/mol, and subsequent reductive elimination from 29-enol will form the 5−7−6 tricyclic product; however, the irreversible reductive elimination via TS30 suggests that the 5−7−6 tricyclic product arises from Ni-free tautomerization.

The calculations indicate that the resting state of pathway A is [Ni(IPr)]\textsubscript{2} complex 21, and oxidative cyclization through TS23 is the rate-limiting step of the catalytic cycle. The overall reaction barrier is 20.4 kcal/mol, which is consistent with the experimental conditions (60 °C, 5 h). In contrast, the heterocoupling pathway of [Ni(IPr)]-catalyzed cycloaddition between nona-2,7-diyne and tropone displays higher free energies (Figure 4). Specifically, from nickel−diyne complex 22, the intermolecular oxidative cyclization between alkylene and tropone can occur via TS34, with the carbonyl group of tropone distal to the forming C−C bond. This step requires a barrier of 42.5 kcal/mol with respect to the [Ni(IPr)]\textsubscript{2} complex 21, which is much less favorable as compared to the homocoupling pathway discussed above (Figure 4). Alternatively, the intermolecular cyclization can occur with the tropone carbonyl group proximal to the forming C−C bond, as in TS36. TS36 is 31.6 kcal/mol higher in free energy than the resting state 21, which is also less favorable than the productive homocoupling pathway. Therefore, unlike other
Ni-catalyzed couplings between alkynes and carboxylates
towards methylene groups. A heterocatalytic mechanism is not operative in the [Ni(Im)]-
catalyzed cycloaddition between diyne and tropone.

Next, insertion of the tropone was investigated, and two
probable pathways emerged: a traditional 2π insertion and a
distinctive 8π insertion. The transition states of 8π (TS25) and 2π insertion (TS37) of tropone were both located, and their free
energies and structures are shown in Figure 5.29 Interestingly, the
8π insertion is found to be more favorable by 12.3 kcal/mol.

We studied the origins of this preference by employing the
distortion/interaction model on TS25 and TS37. The
distortion energy reflects the structural changes from an complex 24 or tropone to the correponding geometries in the
transition states, and the interaction energy is the energy of
interactions between the distorted fragments, computed as the
difference between the activation energy and the total distortion
energy. The difference between the distortion energies of TS25
and TS37 is the major reason for the preference of 8π insertion.
The distortion energy is 17.8 kcal/mol energy for 24 and
13.7 kcal/mol energy for tropone to achieve the distorted geo-
metries in TS25, while it requires much larger distortions
(24.3 kcal/mol for 24 and 16.6 kcal/mol for tropone) in TS37.
Stronger steric repulsions are generated between the nickel-
acyclopentadiene moiety and tropone in TS37 as compared to
those in TS25. This difference between the steric repulsions eventually leads to the preference of the unconventional 8π insertion,
and this is the highest order of poly-π insertion so far.31

Regioselectivity. The transition states for the 8π insertion
of tropone with unsymmetrical diynes were also studied. For
the isopropyl–methyl diyne (Figure 6), the transition state
TS38-C1 that contains the bulky isopropyl group on the diyne
next to tropone is more stable than TS38-C2 by 0.7 kcal/mol
avoiding steric repulsions between the isopropyl group and Im
ligand. For phenyl–methyl diyne, the transition state TS39-C1
is 4.7 kcal/mol more stable than TS39-C2 mainly due to the
steric repulsions between the phenyl group and the bulky
NHC ligand in TS39-C1. Also, for phenyl–isopropyl diyne, the phenyl group is more sterically demanding, and a 4.0
kcal/mol preference to the TS40-C1 is found.

Overall, our data suggest that Ni-catalyzed cycloaddition
occurs via the mechanism shown in Figure 7. The homo-oxidative
coupling of diyne on Ni(0) forms Ni(II)–acyclopentadiene
intermediate I that undergoes 8π insertion of tropone to afford seven-
membered ring complex II. Intermediate II isomerizes from
oxygen coordination to η3-coordination resulting in intermediate
III, which can subsequently isomerize to an η3-coordinated-
Ni(II) complex V through intermediates IV. Finally intermediate
V reductively eliminates to give VI, which releases the tricyclic
product VII, and regenerates the Ni(0) catalyst. At this point,
compound VII can preferentially aromatize via sigmatropic shifts
to afford major product VIII. However, a minor pathway involves
tautomerization of VII to cycloheptatrienol IX, which undergoes
further 6π electrocyclization to afford an interesting bis(divinyl)–
cyclopropane intermediate, X. Intermediate X can either revert to
IX or irreversibly rearrange to [5–7–6] fused intermediate XI,
which undergoes further sigmatropic shifts to yield the observed
minor product, XII. This sigmatropic shift could be catalyzed by
a trace amount of water through the bridge of one or multiple
molecules of water.32 Due to the uncertainty of the catalyst,
we did not perform computational studies on the isomerization of
the tricyclic product VII.

In conclusion, we have discovered a nickel catalyst that can
effectively and selectively incorporate a single C–C π-bond of
tropane in the cycloaddition with diynes. We have also
successfully converted these cycloadducts to useful troponoids.
The mechanism of this novel cycloaddition reaction has been
investigated using DFT calculations. It involves a unique 8π
insertion of tropone to form the observed major and minor
products. The mechanistic studies to further understand this
unique reactivity of tropone and application of this chemistry are
underway in our laboratories.

**ASSOCIATED CONTENT**

Supporting Information

General experimental information, synthesis of diynes, spec-
trosopic characterizations, crystallographic analyses (CIF), and
computational data. This material is available free of charge via
the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(22) 2-Substituted tropones (shown below) were also unreactive in our cycloaddition with dyines.