Carbocycles

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Stereoselective Nickel-Catalyzed [2+2] Cycloadditions of Ene-Allenes**

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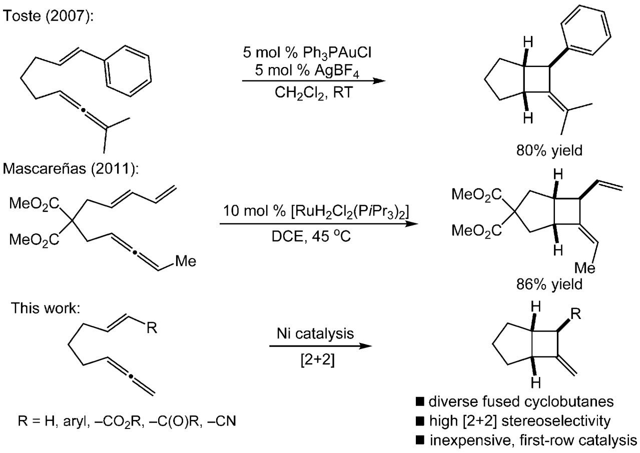
Abstract: *A stereoselective nickel-catalyzed [2+2] cycloaddition of ene-allenes is reported. This transformation encompasses a broad range of ene-allene substrates, thus providing efficient access to fused cyclobutanes from easily accessed π-components. A simple and inexpensive first-row catalytic system comprised of [Ni(cod)$_2$] and dppf was used in this process, thus constituting an attractive approach to synthetically challenging cyclobutane frameworks under mild reaction conditions.*

Transition-metal-catalyzed [m+n]-type cycloadditions are invaluable tools for the rapid construction of stereochemically complex carbocycles.[1] Catalytic, intramolecular [2+2] cycloadditions constructing synthetically valuable fused cyclobutanes[2] from simple π-components such as alkenes would be highly enabling in this regard. Recent work has demonstrated the utility of intramolecular, stereoselective ene-allene [2+2] cycloadditions to achieve this goal (Scheme 1). However, these reactions currently require styrene[3] or diene[4] π-components and substituted allenes as reaction partners, thus limiting potential applications in complex synthesis.[5]

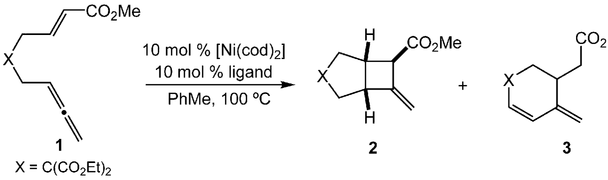
A catalytic ene-allene [2+2] transformation with broad substrate scope, ideally using inexpensive first-row metals as catalysts, would constitute a highly attractive transformation for the stereoselective synthesis of complex cyclobutanes. In the course of previous work in our laboratory targeting nickel-catalyzed, complexity-generating [2+2+2] cycloadditions of alkenes and allenes, we observed the production of a [2+2] ene-allene cycloadduct as a minor byproduct with one of our substrates.[6] Intrigued by this unexpected reactivity, we became interested in a nickel-catalyzed ene-allene cycloaddition for providing access to diverse fused cyclobutanes from easily accessed π-components. Herein, we report the successful development of a general, metal-catalyzed ene-allene [2+2] using an inexpensive first-row metal (Scheme 1).



Scheme 1. Metal-catalyzed ene-allene [2+2] cycloadditions. DCE = 1,2-dichloroethane.

Initial efforts targeted the [2+2] cycloaddition of the ene-allene **1** using [Ni(cod)$_2$] and various mono- and bidentate phosphine ligands (Table 1). Reactions using a number of monodentate phosphines delivered the cycloadduct **2** in poor yield (entries 1–3). Higher reaction yields were achieved using bidentate phosphine ligands (entries 4–8). In particular,

Table 1: Nickel-catalyzed [2+2] cycloaddition of the ene-allene **1**.



Entry	Ligand	Yield **2** (**3**) [%][a]
1	PPh$_3$	16
2	P(p-F-Ph)$_3$	20
3	P(o-tol)$_3$	< 2
4	binap	< 2 (21)[b]
5	xantphos	48
6	dppb	65
7	dppe	< 2 (51)[b]
8	dppf	83 (11)[b]
9[c]	dppf	54 (23)[b]
10	no ligand	< 2

Reactions were performed in PhMe under Ar atmosphere with the ene-allene added over 45 min. [a] Yield of isolated product. [b] Yield of **3**. [c] Reaction temperature 60 °C. dppb = 1,4-bis(diphenylphosphino)-butane.

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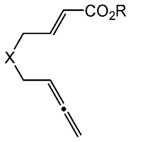
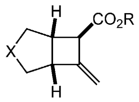
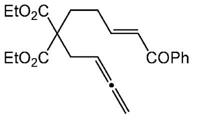
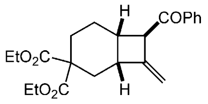
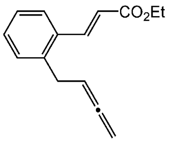
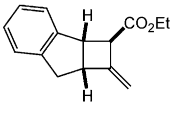
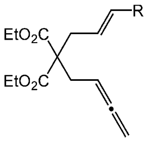
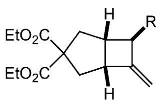
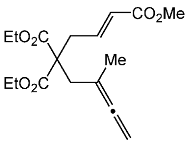
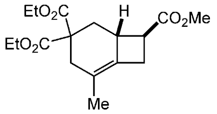
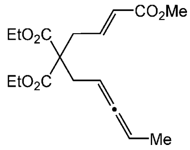
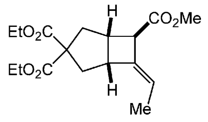
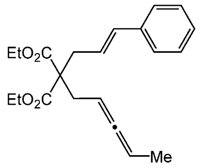
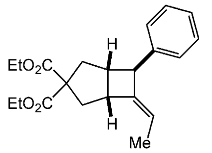
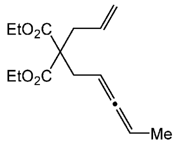
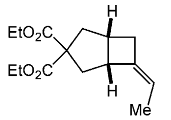
dppf [1,1′-bis(diphenylphosphino)ferrocene] provided superior results, leading to an 83% yield of the isolated [2+2] cycloadduct as a single diastereomer (entry 8). These reactions indicate that phosphines with a large bite angle are instrumental in controlling the reaction selectivity. Interestingly, the use of dppe [1,2-bis(diphenylphosphino)ethane] as the ligand selectively produced the *endo*-1,3-carbocyclic diene **3**, the product of an ene-allene cycloisomerization (51%; entry 7).[7] In these reactions, the ene-allene was added slowly (ca. 45 min) to minimize competing intermolecular processes.[5,8] Lowering the reaction temperature decreased reaction efficiency (entry 9), and control experiments demonstrated that the phosphine ligand is required for efficient reactivity (entry 10). No reaction occurred in the absence of the nickel catalyst.

Next, we surveyed the reactions of a broad range of ene-allene substrates (Table 2). Ene-allenes containing heteroatom tethers provided [2+2] cycloadducts with similar yield to the malonate-tethered substrate **1**, thus delivering the products **5** and **7** in 79 and 71% yield, respectively (entries 1–3). Though this reaction benefits from the Thorpe–Ingold effect,[9] it is not essential to the cycloaddition (entry 4). Simply extending the tether unit in the 1,7-ene-allene substrate **10** enabled access to the bicyclo[4.2.0]octane **11** in 64% yield (entry 5). The reaction of the cinnamate derivative **12** successfully produced cyclobutane **13**, demonstrating the capability of this cycloaddition in polycycle synthesis. Notably, terminal allenes, which are traditionally difficult substrates in this [2+2] manifold,[3,4] reacted efficiently under these catalytic conditions.

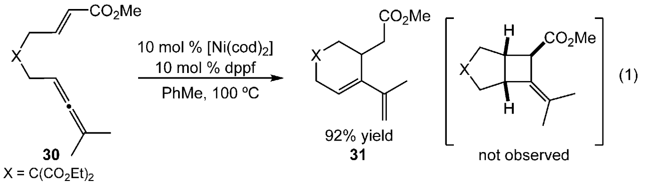
Table 2: Nickel-catalyzed [2+2] cycloadditions of ene-allenes.

Entry	Ene-allene	Product	Yield [%][a]
			
1	**1**: $X=C(CO_2Et)_2$, $R=Me$	**2**: $X=C(CO_2Et)_2$, $R=Me$	83
2	**4**: $X=NTs$, $R=Me$	**5**: $X=NTs$, $R=Me$	79
3	**6**: $X=O$, $R=Et$	**7**: $X=O$, $R=Et$	71
4	**8**: $X=CH_2$, $R=Et$	**9**: $X=CH_2$, $R=Et$	47
5	 **10**	 **11**	64
6	 **12**	 **13**	45
			
7	**14**: $R=CO_2t\text{Bu}$	**15**: $R=CO_2t\text{Bu}$	61
8	**16**: $R=CN$	**17**: $R=CN$	73
9	**18**: $R=COMe$	**19**: $R=COMe$	70
10	**20**: $R=COPh$	**21**: $R=COPh$	93
11	 **22**	 **23**	49
12	 **24**	 **25**	95
13[b]	 **26**	 **27**	57
14[b]	 **28**	 **29**	48

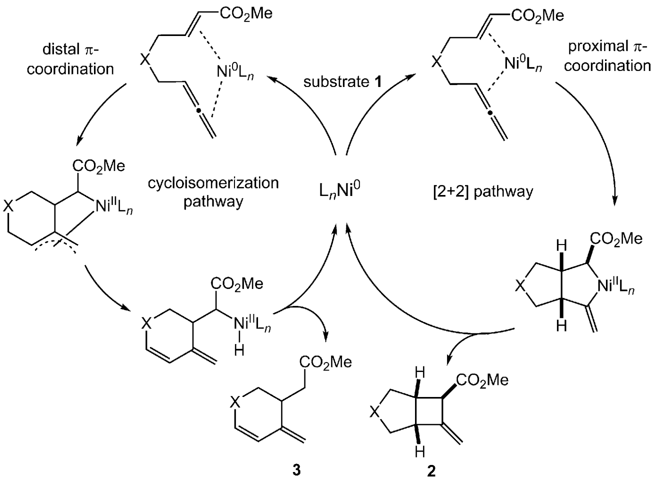
All reactions were performed in PhMe under Ar using 10 mol% [$Ni(cod)_2$] and 10 mol% dppf at 100 °C. The ene-allenes were added over about 45 min; see the Supporting Information for details. [a] Yield of isolated product. [b] Xantphos (10 mol%) substituted for dppf as ligand. Ts = 4-toluenesulfonyl.

We continued by evaluating a range of electronically and sterically diverse 1,6-ene-allene substrates. An array of electron-poor alkenes are applicable to the [2+2], including acrylates, acrylonitriles, and enones (Table 2, entries 7–10). Allene substitution was permitted in the cycloaddition, as demonstrated by the cases shown in entries 11–14. Interestingly, substrate **22** containing a 1,1-disubstituted allene reacted exclusively at the distal π-bond of the allene to deliver the product **23** exclusively (entry 11). Alternatively, the 1,3-disubstituted allene substrate **24** reacted at the proximal π-bond of the allene, producing **25** in high yield (95%; entry 12). Importantly, the [2+2] process is also successful with styrene and unactivated alkene π-components as demonstrated by the reactions of substrates **26** and **28**, respectively (entries 13 and 14). In these two reactions, Xantphos proved superior to dppf as ligand.

An attempted [2+2] cycloaddition of the trisubstituted allene **30** uncovered an alternative catalytic pathway [Eq. (1)]. Under the standard reaction conditions, the Alder-ene product **31** was produced in high yield instead of the expected [2+2] cycloadduct. One possible explanation for this reactivity is that disubstitution of the allene terminus effectively blocks both π-faces of the internal allene π-bond, and directs the oxidative coupling of the alkene to the distal π-bond exclusively.[10] Analogous pathways have been previously observed with rhodium (yne-allenes)[11] and ruthenium (ene-sulfonylallenes)[12] catalysis.

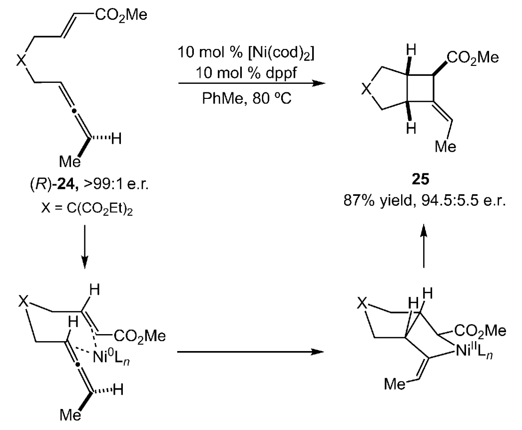


Our current mechanistic hypotheses for the catalytic [2+2] cycloaddition and ene-allene cycloisomerization are presented in Scheme 2. The [2+2] pathway commences with coordination of the nickel center to the alkene and proximal π-bond of the allene. Stereoselective oxidative coupling of the ene-allene deliver a *cis*-fused bicyclic nickelacycle, which undergoes reductive elimination to deliver [2+2] product **2**. Alternatively, ene-allene coordination of the nickel center involving the distal π-bond favors cycloisomerization of the substrate. Initial oxidative coupling provides an allyl nickel(II) metallacycle, which is capable of β-hydride elimination to deliver a nickel hydride species. C−H bond-forming reductive elimination then delivers the cycloisomerization product **3**.



Scheme 2. Plausible catalytic cycle for the nickel-catalyzed [2+2] cycloaddition.

As 1,3-disubstituted allenes introduce axial chirality in the ene-allene substrate, we were also interested in determining the potential for chirality transfer in the [2+2] cycloaddition. We prepared the enantioenriched substrate (*R*)-**24**, which underwent the cycloaddition to deliver **25** with a good level of chirality transfer (94.5:5.5 e.r.; Scheme 3). We propose that the reaction proceeds by oxidative coupling of the allene opposite the methyl group, followed by reductive elimination to provide **25**.[13] The slight erosion in the product e.r. value can be rationalized by minor racemization of the substrate allene prior to cycloaddition.[14,15]



Scheme 3. Catalytic [2+2] cycloaddition of an enantioenriched ene-allene.

In conclusion, we have developed a nickel-catalyzed ene-allene [2+2] cycloaddition for the synthesis of fused cyclobutanes. This transformation uses a readily available first-row catalyst, and is applicable to a diverse range of alkenes and allenes. These cycloadditions proceed with excellent stereoselectivity, and preliminary studies have demonstrated the potential for chirality transfer in the [2+2] process. This mild nickel-catalyzed cycloaddition provides an attractive approach to the stereoselective synthesis of bicyclo[3.2.0]heptanes and related carbocyclic frameworks from easily accessed π-components in a highly atom-economical fashion.

Keywords: alkenes · allenes · carbocycles · cycloaddition · nickel

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[15] We were unable to determine the enantiomeric ratio of any unreacted starting material because of its absence in solution using our slow addition protocol. Although we cannot rule out the formation of minor diastereomers in this reaction (e.g, involving the facial selectivity of the ene-allene coupling), none were produced at levels high enough to permit detection and characterization of such products.

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