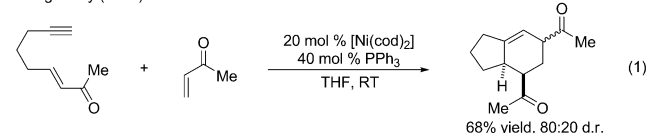


Stereoselective Nickel-Catalyzed [2+2+2] Cycloadditions and Alkenylative Cyclizations of Ene-Allenes and Alkenes**

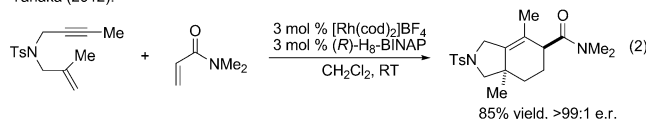
Njamkou N. Noucti and Erik J. Alexanian*

Transformations that facilitate the rapid generation of molecular complexity in the form of carbocyclic and heterocyclic structures are invaluable in organic synthesis.^[1] Such reactions enable highly step-economical^[2] or “greener”^[3] synthetic approaches to complex molecules from simple substrates. Transition-metal-catalyzed multicomponent [m+n+o]-type cycloadditions are prototypical examples of this type of process.^[4] Variants using multiple alkynes have been particularly successful, exemplified by the alkyne cyclo-trimerization reaction for constructing benzenoid systems.^[5] There are few intermolecular multicomponent cycloadditions reported using multiple alkenes, however. In 1999, Montgomery disclosed a nickel-catalyzed intermolecular [2+2+2] cycloaddition of two enones and one alkyne for the synthesis of substituted hydrindanes [Eq. (1); cod = cyclooctadiene-nyl].^[6a] Very recently, Tanaka has reported the first enantioselective [2+2+2] cycloaddition involving two alkenes and one alkyne using cationic rhodium catalysis, although this reaction is strictly limited to monosubstituted or 1,1-disubstituted alkenes and uses acrylamides as the sole added π -component [Eq. (2)].^[7]

Montgomery (1999):



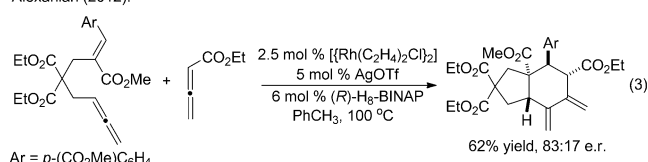
Tanaka (2012):



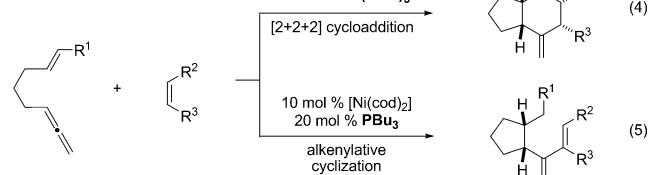
A notable aspect of these metal-catalyzed [2+2+2] cycloadditions with multiple alkenes is the high degree of stereochemical complexity generated in a single step. Our previous work involving multicomponent [2+2+2] cyclo-

additions incorporated two allenes and one alkene to furnish complex *trans*-fused carbocycles in a diastereo- and enantioselective manner [Eq. (3)].^[8] In the present study, we targeted the development of a general [2+2+2] cycloaddition applicable to multiple alkene components. Herein we report such a process for the highly stereoselective synthesis of *cis*-fused carbocycles [Eq. (4)]. These reactions utilize an inexpensive nickel catalyst, are applicable to diverse alkene components, and furnish carbocycles with high levels of diastereoselectivity and up to five contiguous stereocenters in a single step. Furthermore, by exchanging the phosphine ligands of the catalytic system, we have also developed an alkenylative carbocyclization applicable to diverse alkenes [Eq. (5)].

Alexanian (2012):



This work:



We initially targeted the [2+2+2] cycloaddition of ene-allene substrate **1** with *tert*-butyl acrylate for reaction development (Table 1). Our initial investigations using the cationic Rh^I system which we previously developed for [2+2+2] cycloadditions of **1** with added allenes^[8] provided no product (entry 2). We next considered using more π -basic Ni⁰ catalysts, as these have successfully catalyzed other [2+2+2] processes. However, attempted cycloaddition of **1** with *tert*-butyl acrylate using previously developed [2+2+2] catalytic systems involving [Ni(cod)₂] and PPh₃^[6a] or PCy₃^[6b] were unsuccessful (entries 3, 4).^[9] We ultimately identified P(*o*-tol)₃ as being ideally suited for the cycloaddition process, providing cycloadduct **2** as a single diastereomer in 71 % isolated yield (entry 1). Other ligands with either smaller (entries 5, 6), or larger cone angles (entries 7, 8) proved suboptimal.^[10] Slowing the addition rate of the ene-allene further increased reaction efficiency, producing the desired [2+2+2] cycloadduct in 90 % isolated yield (entry 9). Control experiments indicated a slow background reaction in the absence of

[*] N. N. Noucti, Prof. E. J. Alexanian
Department of Chemistry
The University of North Carolina at Chapel Hill
Chapel Hill, NC 27599 (USA)
E-mail: eja@email.unc.edu

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Table 1: Optimization of Ni-catalyzed [2+2+2] cycloaddition.^[a]

Entry	Variations from standard conditions	Yield [%] ^[b]
1	none	71
2	cationic Rh system [Eq. (3)] instead of Ni system	0
3	PPh ₃ as ligand instead of P(o-tol) ₃	0
4	PCyp ₃ as ligand instead of P(o-tol) ₃	trace
5	P(tBu) ₃ as ligand instead of P(o-tol) ₃	38
6	P(C ₆ F ₅) ₃ as ligand instead of P(o-tol) ₃	23
7	PMes ₃ as ligand instead of P(o-tol) ₃	64
8	Cy-JohnPhos as ligand instead of P(o-tol) ₃	34
9	ene-allene added over 1.25 h instead of 0.75 h	90
10	no ligand added (ene-allene addition rate of 8 μL min ⁻¹)	36
11	no nickel added	0

[a] Ene-allene substrate added over 0.75 h. [b] Yield of isolated product.

phosphine ligand (entry 10), and no cycloaddition in the absence of catalyst (entry 11).

With an optimized catalytic system in hand, we next surveyed the substrate scope with respect to the ene-allene substrates and alkene π -components in the [2+2+2] process (Table 2). A diverse set of ene-allenes participated in the cycloaddition with *tert*-butyl acrylate as the added alkene to deliver the *cis*-fused hydrindane products in moderate to excellent yields as single diastereomers. A variety of enoate π -components on the ene-allene substrate reacted efficiently (entries 1–3). Notably, the reaction was not limited to malonate-tethered ene-allene substrates. An ether-tethered ene-allene (entry 4) as well as an ene-allene with an unsubstituted tether (entry 5) delivered the corresponding hydrindanes in 41% and 52% yield, respectively, although a higher catalyst loading (30 mol%) was required with substrate **9**. Cycloadditions with electronically diverse ene-allene substrates containing either styrenyl or terminal aliphatic alkenes also performed well in the cycloaddition (entries 6, 7), however the reaction of ene-allene **13** involving a monosubstituted alkene yielded cycloadduct **14** as a mixture of diastereomers. A survey of added alkenes demonstrated that the reaction was also not limited to *tert*-butyl acrylate, as other electron-poor alkenes such as methyl acrylate and phenyl vinyl sulfone provided cycloadducts in good yields (entries 8, 9).

In order to probe the capability of the [2+2+2] process to construct polycyclic systems, we studied the cycloaddition of ene-allene **17** and indene (Table 2, entry 10). While our standard conditions using P(o-tol)₃ as ligand were ineffective in this case, substituting PBu₃ as ligand and increasing the catalyst loading to 25 mol% delivered the tetracyclic cycloadduct **18** and alkenylative cyclization product **19** in 70% combined yield. Notably, this cycloaddition delivers a tetracyclic product containing five contiguous stereogenic centers as a single diastereomer. The structure of *cis*-disubstituted *N*-tosyl pyrrolidine **19** was confirmed by X-ray crystallography (Figure 1).^[11]

Table 2: Nickel-catalyzed, stereoselective multicomponent [2+2+2] cycloaddition of ene-allenes and alkenes.^[a]

Entry	Ene-allene	Alkene	Product	Yield [%] ^[b]
1				90
2				60
3				65
4				41
5 ^[c]				52
6				51
7				72
8				81
9				74
10 ^[d]				70 18:19 1:1.1

[a] All reactions run with 10 mol % [Ni(cod)₂] and 20 mol % P(o-tol)₃ and 5 equiv alkene at 45 °C in PhH with ene-allene added over 1.25 h. [b] Yield of isolated product. [c] Run with 30 mol % [Ni(cod)₂] and 30 mol % P(o-tol)₃. [d] Run with 25 mol % [Ni(cod)₂] and 50 mol % PBu₃.

Interestingly, exchanging P(o-tol)₃ for PBu₃ in the reaction of ene-allene **1** with *tert*-butyl acrylate led to an alternative catalytic pathway—instead of [2+2+2] cycloaddition [Eq. (6)], the product of an alkenylative carbocyclization formed in high yield as a single diastereomer [Eq. (7)].

While an alkenylative cyclization has been previously reported involving enynes and ethylene (Ru catalysis),^[12] this represents a new pathway for ene-allene reactivity.^[13] The substrate scope of this process is illustrated in Table 3. Ether

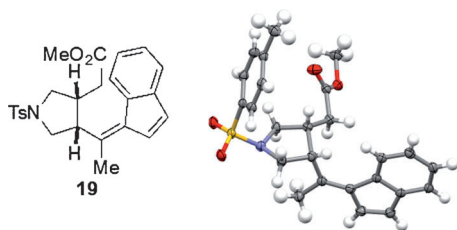
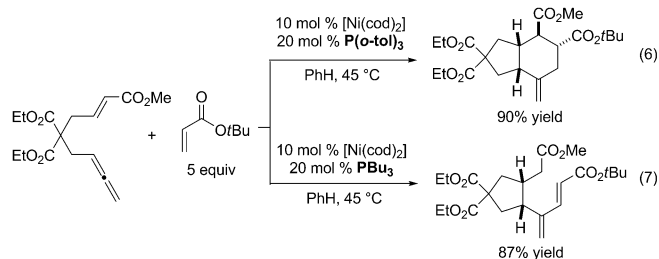


Figure 1. Structure and ORTEP diagram of **19** (thermal ellipsoids set at 50% probability).



and tosylamide-linked ene-allenes reacted with similar efficiencies to the malonate substrate (entries 2, 3). Other electron-poor alkenes, including acrylonitrile and ethyl crotonate are both viable partners, and provided the respective products in moderate yield (entries 4, 5). Styrenes are also useful reaction partners (entry 6) as carbocyclization of ene-allene **1** yielded diene **25** in 66% yield. Furthermore, simple unactivated alkenes are capable of reacting in this system. Both cyclic alkenes such as cyclopentene, and linear unactivated alkenes such as 1-hexene gave the corresponding products in moderate yield (entries 7, 8). Interestingly, the alkenylative cyclization involving 1-hexene proceeded through regioselective coupling at the internal position of the alkene, rather than at the terminal carbon as observed with the polarized alkenes studied.

In the course of our studies of ligand effects on the cycloaddition and alkenylative cyclization reactions, we discovered that with the use of the bidentate phosphine ligand Xantphos, no [2+2+2] cycloadduct was observed in the reaction of **1** with *tert*-butyl acrylate. Instead, ene-allene [2+2] cycloadduct **28** was isolated in 25% yield as a single diastereomer [Eq. (8)]. Removing the *tert*-butyl acrylate increased the yield to 48%. Notably, there are few examples of metal-catalyzed ene-allene [2+2] cycloadditions, and none with first-row transition metals.^[14]

A mechanistic hypothesis consistent with the observed reactivity is shown in Scheme 1. The initial oxidative coupling of the ene-allene substrate provides a *cis*-fused bicyclic nickelacycle **30**. With a monodentate phosphine as ligand,

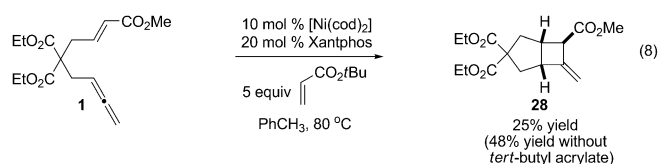
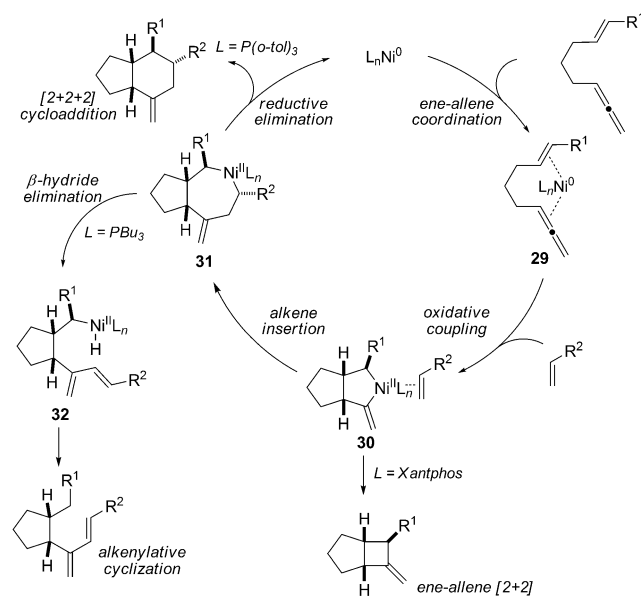


Table 3: Nickel-catalyzed, stereoselective alkenylative cyclization of ene-allenes and alkenes.^[a]

Entry	Ene-allene	Alkene	Product	Yield [%] ^[b]
1				86
2				82
3				90
4				61
5 ^[c]				41
6				66
7				49
8				60

[a] All reactions run with 10 mol % [Ni(cod)₂] and 20 mol % PBu₃ with 5 equiv alkene at 45 °C in PhH. [b] Yield of isolated product. [c] Run with 30 mol % [Ni(cod)₂] and 60 mol % PBu₃.



Scheme 1. Plausible mechanism for ligand-controlled reactivity of ene-allene-alkene cycloadditions and alkenylative cyclizations.

insertion of the alkene component occurs at this stage, to form nickelacycle **31**. With P(*o*-tol)₃ as ligand, reductive elimination occurs to provide the [2+2+2] cycloadduct. Alternatively, use of the less bulky and electron-rich PBu₃ as ligand preferentially leads to β -hydride elimination to give the nickel hydride **32**. Reductive elimination then provides the alkenylative cyclization product. Furthermore, with a large bite-angle bidentate ligand, reductive elimination of nickelacycle **30** takes place to deliver the ene-allene [2+2] cycloadduct.

In conclusion, we have developed highly stereoselective, nickel-catalyzed reactions for the multicomponent [2+2+2] cycloadditions and alkenylative cyclizations of ene-allenes with alkenes. A wide variety of simple alkenes are tolerated in this process, with cycloadditions generating up to five contiguous stereogenic centers in a single step. We have also demonstrated the capability of a Ni⁰-bidentate phosphine system to facilitate the ene-allene [2+2] cycloaddition. Through the judicious choice of ligand, any of these three pathways can be exclusively selected. These complexity-generating reactions harness inexpensive metal catalysts and common phosphine ligands to deliver a diverse set of valuable carbocycles for organic synthesis.

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