Synthetic Methods

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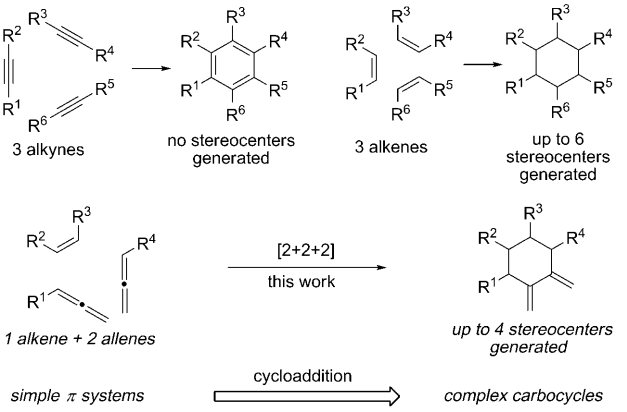
# Rhodium(I)-Catalyzed Ene–Allene–Allene [2+2+2] Cycloadditions: Stereoselective Synthesis of Complex *trans*-Fused Carbocycles**

*Andrew T. Brusoe and Erik J. Alexanian**

The development of new reactions that increase molecular complexity is a paramount goal of modern chemical synthesis.[1] Processes that enable the construction of multiple bonds and/or stereogenic centers in a single synthetic operation offer decisive advantages in developing step-economical[2] or greener[3] syntheses of complex synthetic targets. Three-component transition-metal-catalyzed cycloadditions of the general form $[m+n+o]$ have demonstrated the capability to rapidly generate complex molecules, as no less than three new σ bonds and a new ring system are formed from easily accessed π components.[4]

The metal-catalyzed [2+2+2] cycloaddition process is among the most useful of this group of transformations, and is applicable to the preparation of a variety of synthetically valuable carbo-[5] and heterocyclic[6] six-membered rings. Although all [2+2+2] cycloadditions forge three σ bonds in a single step, these reactions generate varying levels of stereochemical complexity, as dictated by the nature of the π systems involved.[7,8] In this regard, the alkyne π components commonly utilized in [2+2+2] cycloadditions limit the potential of these reactions to generate stereochemical complexity, as each alkyne reduces the maximum number of stereocenters created by two. For example, the alkyne cyclotrimerization reaction delivers benzenoid systems that possess no stereocenters, whereas an ideal [2+2+2] cycloaddition for increasing molecular complexity would use only alkenes and could theoretically provide access to cyclohexanes containing six contiguous stereogenic centers (Scheme 1). Herein, we report efforts towards this goal through the development of an alkyne-free rhodium(I)-catalyzed [2+2+2] cycloaddition by using simple alkenes and allenes as the π components. These reactions deliver synthetically valuable carbocycles and construct up to four contiguous stereogenic centers, including quaternary stereocenters, in a single synthetic step.

We began our studies of [2+2+2] cycloadditions of alkene and allene π systems using the readily synthesized ene–allene




***Scheme 1.*** Prototypical transition-metal-catalyzed [2+2+2] cycloadditions.

**1** as our model substrate. We initially employed a catalyst system comprised of rhodium(I) with bidentate phosphine ligands because of the demonstrated ability of these systems to facilitate $[m+n+o]$ cycloaddition processes.[4] Upon heating to 100 °C in toluene for 2 h in the presence of 2.5 mol % $[\{Rh(C_2H_4)_2Cl\}_2]$, 5 mol % AgOTf, and 6 mol % $H_8$-binap, the [2+2+2] cycloaddition between substrate **1** and 2.0 equivalents of allenoate **2** delivered *trans*-hydrindane **3** in 79 % yield, isolated as a single regioisomer and diastereomer (Table 1, entry 1).[9] We examined several other catalytic systems involving alternative rhodium(I) sources and bidentate phosphine ligands, each of which was less effective than our standard reaction conditions (Table 1, entries 2–6). In the absence of silver(I) salts the reaction was much less efficient (Table 1, entry 7), and AgOTf was superior to $AgBF_4$ (Table 1, entry 8). Performing the cycloaddition at a lower reaction temperature (Table 1, entry 9), or with polar solvents (Table 1, entries 10 and 11) proved suboptimal. Either a decrease (Table 1, entry 12) or an increase (Table 1, entry 13) in the amount of ethyl allenoate **2** added also lowered the reaction yields.

The structure of product **3** was determined by 2D NMR spectroscopy and subsequently confirmed by X-ray crystallography (Figure 1).[10] This cycloaddition generates two carbocyclic rings, three σ bonds, and four contiguous stereogenic centers. Furthermore, the *trans*-hydrindane framework, which is accessed in this highly convergent manner, constitutes the core of many classes of bioactive natural products and small molecules,[11] yet still presents a formidable synthetic challenge.[12]

Encouraged by this initial result, we sought to explore the generality of this process (Table 2). The rhodium(I)-catalyzed

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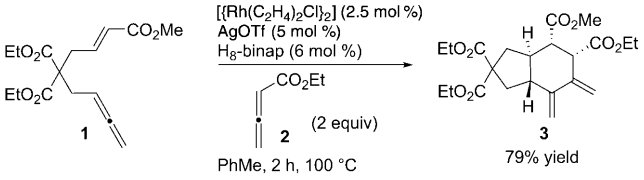
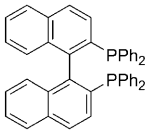
***Table 1:*** Influence of the reaction conditions on the [2+2+2] cycloaddition.

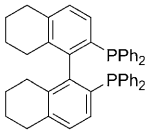



| Entry | Variation from standard conditions | Yield [%][b] |
|---|---|---|
| 1 | none | 79 |
| 2 | $[\{Rh(coe)_2Cl\}_2]$ instead of $[\{Rh(C_2H_4)_2Cl\}_2]$, 2 h | 76 |
| 3 | $[\{Rh(nbd)Cl\}_2]$ instead of $[\{Rh(C_2H_4)_2Cl\}_2]$, 7.5 h | 61 |
| 4 | $[Rh(PPh_3)_3Cl]$/AgOTf instead of $[\{Rh(C_2H_4)_2Cl\}_2]$/$H_8$-binap/AgOTf | < 2 |
| 5 | $[RhCl(PPh_3)_3]$ instead of $[\{Rh(C_2H_4)_2Cl\}_2]$/$H_8$-binap/AgOTf | < 2 |
| 6 | BINAP instead of $H_8$-binap, 3.5 h | 68 |
| 7 | No AgOTf | 59 |
| 8 | $AgBF_4$ instead of AgOTf, 1 h | 60 |
| 9 | 80 °C instead of 100 °C | 55 |
| 10 | dioxane, 80 °C instead of $PhCH_3$, 100 °C | 32 |
| 11 | $[\{Rh(coe)_2Cl\}_2]$/DCE instead of $[\{Rh(C_2H_4)_2Cl\}_2]$/$PhCH_3$ | 47 |
| 12 | 1.1 equiv allene instead of 2.0 equiv allene, 3 h | 54 |
| 13 | 5.0 equiv allene instead of 2.0 equiv allene | 58 |

[a] Reaction time was 24 h, or until full consumption of ene-allene substrate was observed as indicated. [b] All yields are of isolated products. coe = *cis*-cyclooctene, nbd = norbornadiene, OTf = trifluoromethanesulfonate.




binap




$H_8$-binap

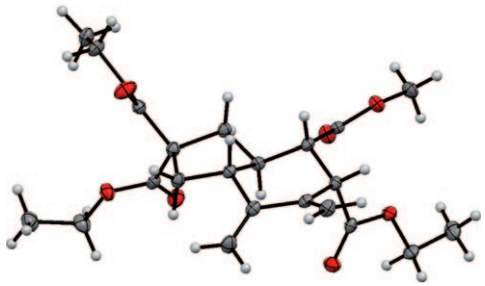
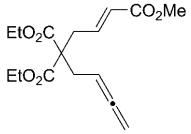
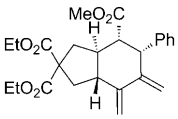
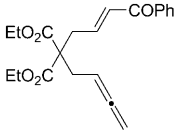
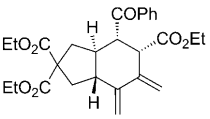
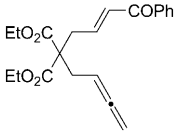
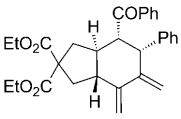
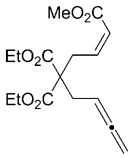
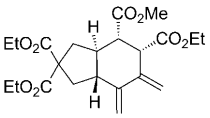
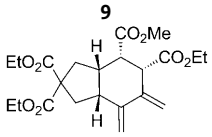
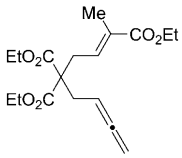
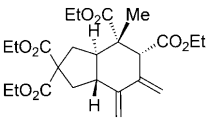
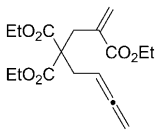
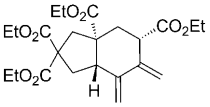


***Figure 1.*** ORTEP diagram of *trans*-hydrindane **3** (thermal ellipsoids set at 50 % probability).

***Table 2:*** Ene–allene–allene [2+2+2] cycloaddition.[a]

| Entry | Ene–allene substrate | Allene | Product | Yield [%][b] |
|---|---|---|---|---|
| 1 |  **1** |  |  **4** | 59[c] |
| 2 |  **5** |  |  **6** | 61 |
| 3 |  **5** |  |  **7** | 42 |
| 4 |  **8** |  |  **9**<br>  **10** | 76<br>1.2:1[d]<br>**9**:**10** |
| 5 |  **11** |  |  **12** | 72 |
| 6 |  **13** |  |  **14** | 62 |

[a] Reaction conditions: allene (2 equiv), $[\{Rh(C_2H_4)_2Cl\}_2]$ (2.5 mol%), AgOTf (5 mol%), $H_8$-binap (6 mol%), 100 °C, PhMe, 2–24 h. [b] Yields of the isolated product. [c] $AgBF_4$ (5 mol%) was used instead of AgOTf. [d] The diastereomeric ratio of **9**:**10** was determined by $^1H$ NMR spectroscopy of the crude reaction mixture.

cycloaddition of substrate **1** with phenyl allene efficiently provided the aryl-substituted *trans*-hydrindane product **4**, isolated as a single isomer (Table 2, entry 1), thus demonstrating that the reaction is not limited to the addition of electron-poor allenes. Reactions that utilized enones as the alkene π component were also successful, as demonstrated by the [2+2+2] cycloadditions of substrate **5** with ethyl allenoate and phenyl allene to provide products **6** and **7**, respectively (Table 2, entries 2 and 3). An ene–allene substrate that contains a *Z*-enoate π component, also underwent efficient [2+2+2] cycloaddition, however a 1.2:1 mixture of *trans*-hydrindane **9** and *cis*-fused product **10** was isolated (Table 1, entry 4). We next explored the versatility of the ene–allene–allene cycloaddition in the stereoselective construction of carbocycles that contain quaternary stereocenters. The cycloaddition of substrates **11** and **13** furnished *trans*-hydrindanes **12** and **14** containing quaternary stereocenters at positions both inside the ring system and at the ring junction, respectively, both isolated as single diastereomers in good yield.

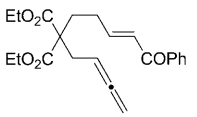
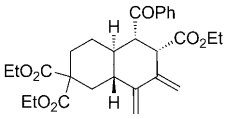
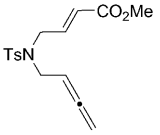
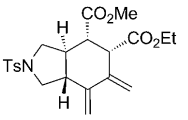
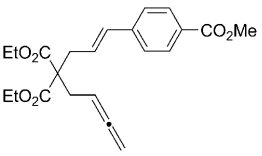
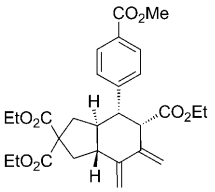
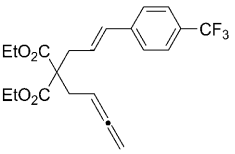
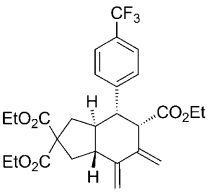
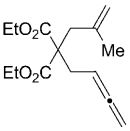
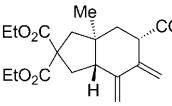
  

Further studies to survey the substrate scope of the ene–allene component of the [2+2+2] process are shown in Table 3. The cycloaddition is not limited to the synthesis of bicyclo[4.3.0] systems, as bicyclo[4.4.0] *trans* decalins are also accessible (Table 3, entry 1).[13] Substrates with tosylamide linkages could also be used, as demonstrated by the reaction of substrate **17** (Table 3, entry 2). Importantly, while enoates and enones are excellent alkene π components in the [2+2+2] process, they are not required for the cycloaddition to proceed. For example, styrenyl substrates **19** and **21** provided access to aryl-substituted *trans*-hydrindanes **20** and **22**, respectively (Table 3, entries 3 and 4). The alkyl-substituted ene–allene substrate **23** also afforded the [2+2+2] cycloadduct, however the product **24** was isolated in low yield (Table 3, entry 5).

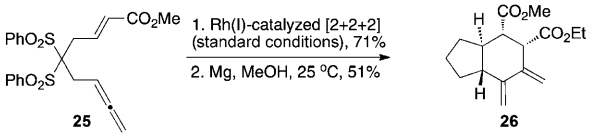
The ene–allene substrates that contain malonate-derived tethers are easily prepared by using standard alkylation procedures. Furthermore, simple substitution of the diester linkage for a bis(sulfone) facilitates the removal of the tether functionality after the [2+2+2] process. For example, after the catalytic cycloaddition of the bis(sulfone) ene–allene **25**, a mild reduction provides the *trans*-hydrindane product **26** [Eq. (1)].[14,15]

The exocyclic 1,3-diene furnished by the [2+2+2] cycloaddition facilitates a multitude of further synthetic manipulations of the initial reaction products.[16] Preparation of this useful functionality commonly requires multistep protocols.[17] We have found that the direct transformation of the initially formed 1,3-diene products is possible in a one-pot process. For instance, upon completion of the initial rhodium(I)-catalyzed cycloaddition, a simple substitution of the Ar atmosphere for $H_2$ results in the 1,4-hydrogenation

***Table 3:*** Additional studies of ene–allene substrate scope in the [2+2+2] cycloaddition.[a]

| Entry | Ene–allene substrate | Allene | Product | Yield [%][b] |
|---|---|---|---|---|
| 1 |  **15** |  |  **16** | 48 |
| 2 |  **17** |  |  **18** | 45 |
| 3 |  **19** |  |  **20** | 63 |
| 4 |  **21** |  |  **22** | 58 |
| 5 |  **23** |  |  **24** | 27 |

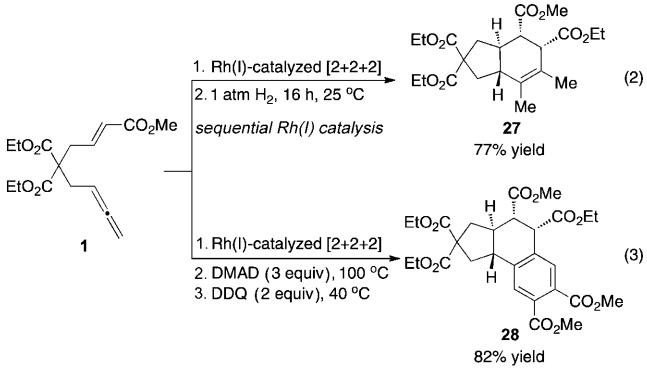
[a] Reaction conditions: allene (2 equiv), [{Rh($C_2H_4$)$_2$Cl}$_2$] (2.5 mol%), AgOTf (5 mol%), $H_8$-binap (6 mol%), 100 °C, PhMe, 2–24 h. [b] Yield of the isolated product.




(1)

of the diene, thus providing cyclohexene **27** using sequential rhodium(I) catalysis [Eq. (2)].[18] Elaboration of the initially formed *trans*-hydrindane to an aromatic 6-6-5 tricycle is easily achieved through a Diels–Alder/oxidation sequence. Subsequent to the [2+2+2] process, the direct addition of dimethylacetylenedicarboxylate (DMAD) to the reaction mixture followed by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) provides expedient access to product **28** in 82% overall yield [Eq. (3)].

Preliminary studies have demonstrated the potential of our current catalytic system in the development of an enantioselective variant of the ene–allene–allene cycloaddi-



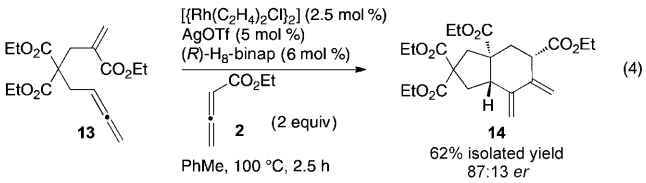

(2)

(3)

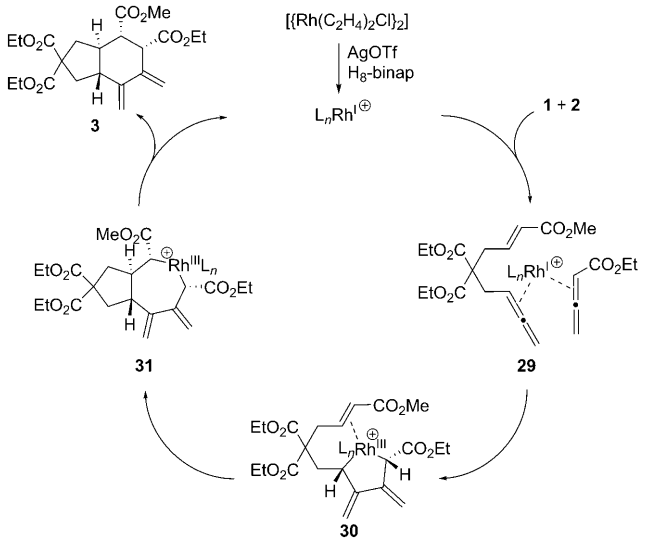
tion. The reaction of substrate **13** using 2.5 mol% of [{Rh($C_2H_4$)$_2$Cl}$_2$], 5 mol% of AgOTf, and 6 mol% of (*R*)-$H_8$-binap delivered the [2+2+2] cycloadduct **14** in 62% yield as a single diastereomer with an enantiomeric ratio of 87:13 [Eq. (4)].[19] The development of a general, highly enantiose-

lective variant of this cycloaddition will be a focus of future studies.




A preliminary mechanistic hypothesis for the catalytic ene–allene–allene [2+2+2] cycloaddition is shown in Scheme 2 using substrate **1** and ethyl allenoate **2**. Following




***Scheme 2.*** Plausible reaction pathway for the ene–allene–allene [2+2+2] cycloaddition.

the activation of the precatalyst with silver(I) and $H_8$-binap, a cationic rhodium(I) species coordinates to the substrate ene–allene and ethyl allenoate at the internal allenic π bonds. Oxidative coupling then generates bis(methylene)-substituted rhodacyclopentane **30**.[20] Although the *cis*-substituted metallacycle **30** may ultimately lead to the observed product, further studies are necessary to determine whether the initial oxidative-coupling step is highly stereoselective, or if equilibration between **30** and a *trans*-substituted metallacycle occurs. Formation of the rhodacyclopentane is followed by a stereoselective 1,2-insertion of the tethered alkene, thus providing metallacycle **31** and establishing the *trans* ring fusion of the bicyclic framework. Final carbon–carbon bond-forming reductive elimination then affords product **3** and regenerates the active catalyst.[21]

In conclusion, a rhodium(I)-catalyzed [2+2+2] cycloaddition has been developed that gives direct access to important classes of stereochemically rich carbocycles, including *trans*-fused hydrindanes and decalins, from simple π components. This process increases molecular complexity by generating three σ bonds and two carbocyclic rings, as well as up to four contiguous stereocenters, including quaternary centers, in a single step. Further studies will continue to develop $[m+n+o]$-type cycloaddition approaches to complex carbocycle synthesis, and develop general enantioselective variants of these processes.

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**Keywords:** alkenes · allenes · carbocycles · cycloaddition · rhodium

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