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Enantioselective Intermolecular [2 + 2 + 2] Cycloadditions of Ene–Allenes with Allenoates

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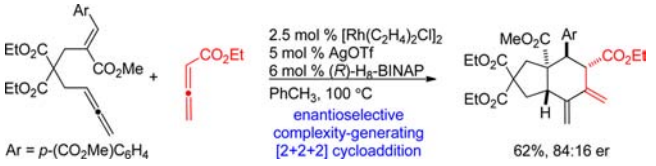
ABSTRACT



An enantioselective [2 + 2 + 2] cycloaddition of ene–allenes with allenoates is described, which transforms simple π-components into stereochemically complex carbocycles in a single step. The rhodium(I)-catalyzed cycloaddition proceeds with good levels of enantioselectivity, and with high levels of regio-, chemo-, and diastereoselectivity. Our results are consistent with a mechanism involving an enantioselective intermolecular allene–allene oxidative coupling.

An important goal of chemical synthesis is the rapid construction of valuable complex molecular architectures from simple building blocks.[1] Transition-metal-catalyzed cycloadditions have proven to be remarkably useful in accomplishing these goals.[2] These processes provide efficient access to a diverse set of carbocyclic and heterocyclic compounds from simple π-systems in a single step with perfect atom economy. The prototype for such a process is the [2 + 2 + 2] cycloaddition,[3] which constitutes a powerful approach to carbocyclic,[4] heterocyclic,[5] aromatic,[6] and heteroaromatic[7] systems.

Alkynes are commonly used as π-components in multicomponent cycloadditions. Despite the efficiency with which they react in metal-catalyzed cycloadditions, alkynes intrinsically limit the stereochemical complexity of the carbocyclic product (Scheme 1). For example, a cycloaddition employing three alkynes affords a product containing no stereocenters, whereas a cycloaddition involving three alkenes could generate a cyclohexane possessing up to six stereocenters in a single step. We demonstrated the potential of alkene and allene π-systems to deliver complex *trans*-fused hydrindanes with high levels of diastereoselectivity.[8] Herein, we report the development of an enantioselective variant of this ene–allene–allene [2 + 2 + 2] cycloaddition. This reaction represents a rare enantioselective intermolecular [2 + 2 + 2] cycloaddition capable

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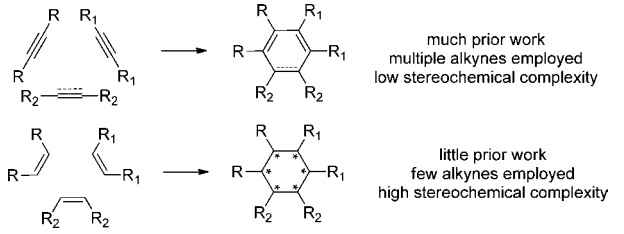
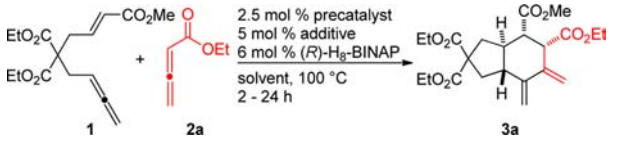
of generating multiple stereocenters.[9] In addition, our studies have revealed a number of interesting mechanistic details of this multicomponent cycloaddition process.

Scheme 1. Prototypical [2 + 2 + 2] Cycloadditions Constructing Six-Membered Carbocycles



Our prior studies demonstrated the ability of $[Rh(C_2H_4)_2Cl]_2$, H_8-BINAP, and AgOTf to facilitate highly diastereoselective ene−allene−allene [2 + 2 + 2] cycloadditions. The development of an asymmetric variant of the cycloaddition began by using (*R*)-H_8-BINAP as a ligand, which led to an efficient [2 + 2 + 2] cycloaddition between ene−allene **1** and commercially available ethyl allenoate **2a** delivering product **3a** in 79% yield with a promising 81:19 er (Table 1, entry 1), which could be recrystallized to 95:5 er. We screened a variety of different reaction conditions to increase the enantioselectivity of the transformation. Representative results are summarized in Table 1. Solvents and precatalysts did not significantly impact enantioselectivity (entries 2−6). Surprisingly, the enantioselectivity of the reaction is constant with temperature changes (45 to 120 °C, entries 1, 7, and 8). Silver(I) ions do not inhibit the reaction (entry 9), but the use of noncationic complexes gives poor results (entry 10). Other silver(I) salts (entries 11−13) can increase enantioselectivity substantially (up to 92:8 er). The conditions in entry 1 were chosen as our standard conditions because they provide the best combination of yield and enantioselectivity and are general toward all substrates investigated.

Table 1. Optimization Studies of the [2 + 2 + 2] Cycloaddition



1 2a 3a

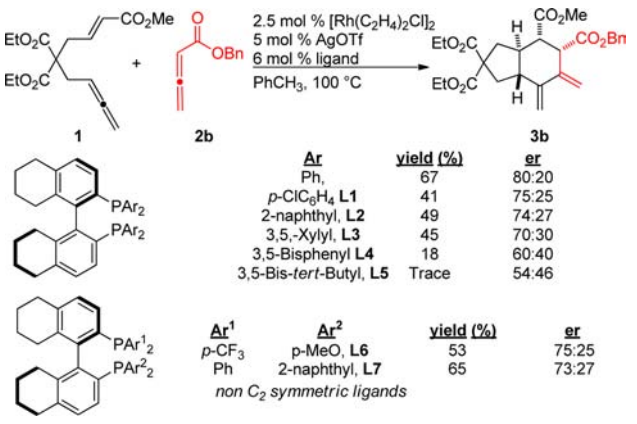
entry	precatalyst	additive	solvent	yield[a]	er
1	$[Rh(C_2H_4)_2Cl]_2$	AgOTf	toluene	79% (55%)[b]	81:19 (95:5)[b]
		standard conditions			
2	$[Rh(C_2H_4)_2Cl]_2$	AgOTf	mesitylene	75%	84:16
3	$[Rh(C_2H_4)_2Cl]_2$	AgOTf	benzene	66%	81.19
4	$[Rh(C_2H_4)_2Cl]_2$	AgOTf	$ClCH_2CH_2Cl$	32%	71:29
5	$[Rh(C_2H_4)_2Cl]_2$	AgOTf	dioxane	52%	81:19
6	$[Rh(COD)Cl]_2$	AgOTf	toluene	70%	81:19
7[c]	$[Rh(C_2H_4)_2Cl]_2$	AgOTf	toluene	67%	81:19
8[d]	$[Rh(C_2H_4)_2Cl]_2$	AgOTf	toluene	35%	81:19
9	$[Rh(COD)_2][OTf]$	–	toluene	59%	81:19
10	$[Rh(C_2H_4)_2Cl]_2$	–	toluene	26%	79:21
11	$[Rh(C_2H_4)_2Cl]_2$	$AgPF_6$	toluene	49%	80:20
12	$[Rh(C_2H_4)_2Cl]_2$	$AgBF_4$	toluene	53%	88:12
13	**$[Rh(C_2H_4)_2Cl]_2$**	**AgOMs**	toluene	51%	**92:8**

[a] Isolated yield. [b] After single recrystallization. [c] Reaction at 120 °C. [d] Reaction at 45 °C.

A number of addition reaction parameters were evaluated. These include reactant stoichiometry, concentration, rate of addition, metal to ligand ratios, and the presence of Lewis acidic and basic additives (e.g., pyridines). These changes were found to have no major impact on the enantioselectivity, and several modifications resulted in decreased reaction efficiency. A screen of 39 ligands confirmed the H_8-BINAP family as the optimal choice for our studies (see the Supporting Information).

As no alternative ligand to (*R*)-H_8-BINAP proved capable of increasing reaction enantioselectivity, we systematically studied the effects of H_8-BINAP structure modification on the reaction (Scheme 2, using benzyl allenoate **2b**).[10]

Scheme 2. Ligand Structure Studies on Enantioselectivity



1 2b 3b

Ar	yield (%)	er
Ph,	67	80:20
p-ClC_6H_4 **L1**	41	75:25
2-naphthyl, **L2**	49	74:27
3,5,-Xylyl, **L3**	45	70:30
3,5-Bisphenyl **L4**	18	60:40
3,5-Bis-*tert*-Butyl, **L5**	Trace	54:46

Ar^1	Ar^2	yield (%)	er
p-CF_3	p-MeO, **L6**	53	75:25
Ph	2-naphthyl, **L7**	65	73:27

non C_2 symmetric ligands

Specifically, we sought to understand the influence of steric and electronic modifications of the biaryl phosphine groups on reaction enantioselectivity, which required the preparation of four new (*R*)-H_8-BINAP derivatives.[11] The use of moderately electron-withdrawing[12] (*R*)-*p*-Cl-H_8-BINAP **L1** decreased the yield and enantioselectivity. Substituting the phenyl rings for larger aromatic systems gave lower enantioselectivities. We also prepared two new H_8-BINAP derivatives lacking C_2 symmetry to determine the effects of an unsymmetrical catalyst structure.[13] However, electronic and steric modification in this manner was unable to increase reaction enantioselectivities.

We next explored the substrate scope of the enantioselective [2 + 2 + 2] cycloaddition (Table 2). Overall, the

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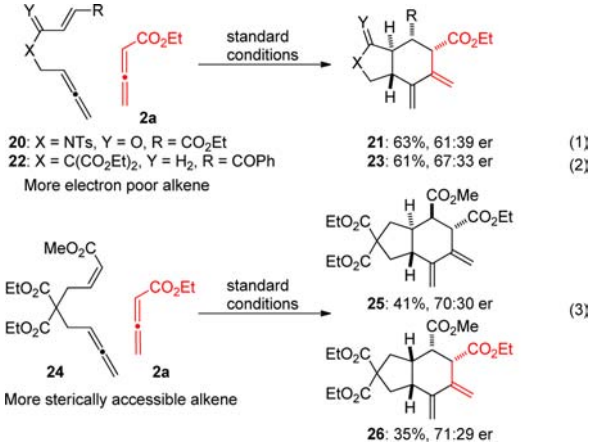
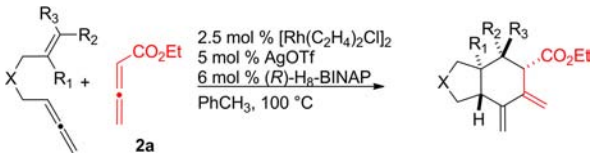
reaction proceeded with moderate to good levels of enantioselectivity across a range of substrates. Steric or electronic modification of the ester had little effect on the reaction (entries 1–3). Styrenyl ene–allene substrate **8** delivers **9** with similar yields and selectivities to those obtained using enoate substrates. Notably, the cycloaddition is also capable of the enantioselective construction of quaternary stereocenters. Reactions involving 1,1-disubstituted alkenes deliver products possessing quaternary stereocenters at the ring junction (entries 5–6). The use of trisubstituted alkene π-components also produces cycloadducts containing quaternary stereocenters with good yields and enantioselectivities (entries 7–8). In addition to malonates, sulfonamide and 1,2-disubstituted aryl tethers were tolerated in this reaction. The sulfonamide derived product **17** can be easily recrystallized to excellent levels of enantiopurity (98:2 er). The final reaction parameter we evaluated was the use of alternative allenoates. In general, the reaction enantioselectivity was not sensitive to modifications of the ester of **2**, which allows postreaction differentiation of the adjacent esters. Using other allenes gave either low yields or poor enantioselectivities (e.g., phenylallene, not shown). In contrast to reactions with ene–allene **1** as the substrate, the use of other silver salts and solvents to increase the enantioselectivity of these reactions further was not successful.

Further studies of substrate scope demonstrated that alkenes capable of more strongly coordinating to the metal gave lower enantioselectivity.[14] We present additional substrates to show the inverse correlation between coordinating ability and enantioselectivity. Substituting the enoate with a fumarate (eq 1, compare with Table 2, entry 9) or an aryl enone (eq 2, compare with Table 2, entries 1–3) results in lower enantioselectivities. In addition, changing the geometry of the alkene (eq 3, compare with Table 2, entry 1) also has a deleterious effect on reaction enantio- and diastereoselectivity. The catalyst is expected to coordinate more strongly with these substrates, and these results suggest that this increase significantly lowers enantioselectivity. With the exception of (*Z*)-alkene **24**, all substrates gave excellent diastereoselectivity.



We present two plausible mechanisms in Figure 1. In catalytic cycle A, initial oxidative coupling of the allenes[15] yields **27**. Insertion of the alkene then gives metallacycloheptane **28**, which undergoes reductive elimination to afford

Table 2. Substrate Scope of the [2 + 2 + 2] Cycloaddition



entry	substrate	yield[a], er
1	**1**: R = Me,	**3a**: 79%, 81:19 er
2	**4**: R = *t*Bu,	**5**: 80%, 83:17 er
3[b]	**6**: R = CH_2CF_3,	**7**: 82%, 77:23 er
4	**8**	**9**: 63%, 84:16 er
5	**10a**: R = CO_2Et,	**11a**: 62%, 86:14 er
6	**10b**: R = CO_2Bn,	**11b**: 65%, 87:13 er
7	**12**	**13**: 72%, 78:22 er
8	**14**: Ar = *p*-$(CO_2Me)C_6H_4$	**15**: 62%, 84:16 er
9	**16**	**17**: 46%, 81:19 er (98:2 er)[c]
10	**18**	**19**: 58%, 81:19 er
11	**2b**: R = Bn	**3b**: 67%, 80:20
12	**2c**: R = Ph	**3c**: 51%, 76:24
13	**2d**: R = p-OMePh	**3d**: 66%, 76:24
14	**2e**: R = Cy	**3e**: 56%, 74:26
15	**2f**: R = *t*Bu	**3f**: 50%, 82:18

[a] Isolated yield. [b] Reaction with benzyl allenoate, **2b**. [c] After single recrystallization.

the cycloadduct. In catalytic cycle B, oxidative coupling of the ene−allene would generate *trans*-metallacycle **29**.[16] Insertion of allenoate **2a** could then occur, followed by reductive elimination. Typically, intramolecular oxidative coupling of 1,5-ene−allenes form *cis*-metallacycles,[17] likely because they are less strained (the strain energy for *trans*-bicyclo-[3.3.0]octane is 6.4 kcal/mol higher than that of the *cis* isomer).[18] Should our reaction operate by path B, one would expect a preference for the formation of a *cis* ring junction. Based on the stereochemical outcome of our system, we propose catalytic cycle A to be operative.

Additional insight into the operative pathway in the [2 + 2 + 2] cycloaddition was provided by a reaction involving ene−allene substrate **31** containing an unsaturated lactone (Figure 2). Instead of undergoing the [2 + 2 + 2] cycloaddition, it participates in a formal [4 + 2] cycloaddition involving the allene and allenoate π-components to deliver **34**. A plausible mechanism for the formation of this product is shown in Figure 2. Initial allene−allenoate oxidative coupling forms metallacycle **32**, which contains a carbon-bound rhodium enolate.[19] Isomerization of this metallacycle to an oxygen-bound rhodium enolate (**33**) allows C−O reductive elimination to provide a benzyl-enol ether; loss of the benzyl group gives lactone **34**. Importantly, this [4 + 2] product is formed during the time frame for our standard cycloadditions. Furthermore, such unsaturated lactones have been identified as minor byproducts (< 5%) in our standard cycloadditions (e.g., **1** to **3b**). This suggests that allene−allenoate coupling is a kinetically viable process and can occur on the same time scale as the cycloaddition. Moreover, lactone **34**, which likely does not coordinate as strongly to the metal center as our standard substrates, is formed with somewhat higher enantioselectivity than any [2 + 2 + 2] cycloaddition studied, which is consistent with the inverse relationship between the coordinating ability of the alkene and enantioselectivity (*vide supra*). The formation of product **34** is consistent with catalytic cycle A, involving an intermolecular allene−allenoate coupling. Notably, such an enantioselective allene−allene coupling is unprecedented.[20]

In conclusion, we have developed an intermolecular enantioselective [2 + 2 + 2] cycloaddition of ene−allenes and allenoates for the synthesis of enantioenriched carbocycles possessing multiple stereocenters. This reaction represents a rare example of an intermolecular cycloaddition affording carbocyclic products containing multiple stereogenic centers. This reaction generates three σ-bonds, two

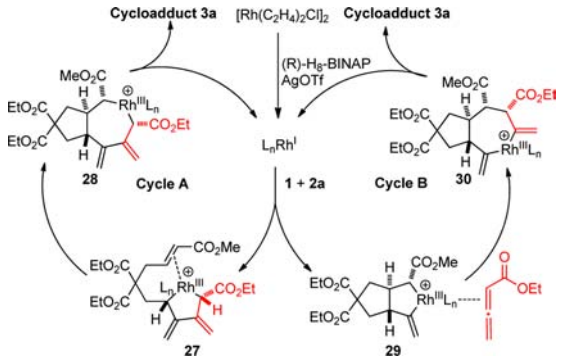


Figure 1. Plausible mechanisms for the [2 + 2 + 2] cycloaddition.

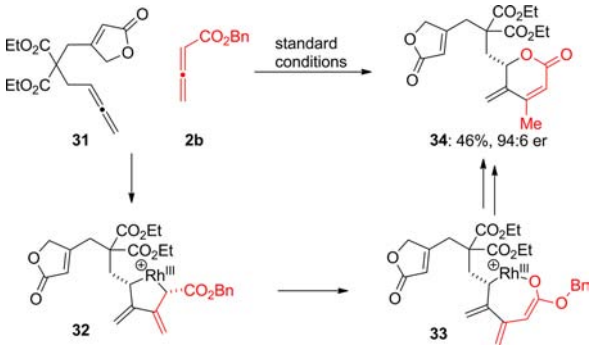


Figure 2. Unexpected [4 + 2] cycloadduct demonstrates allene−allenoate coupling as a kinetically viable process.

carbocyclic rings, and up to four contiguous stereocenters in a single step with excellent levels of reaction regio-, chemo-, and diastereoselectivity. A catalyst system comprised of a rhodium(I) precatalyst, a silver(I) salt, and a bidentate phosphine, delivers the carbocyclic products with good levels of enantioselectivity. Our studies are consistent with a mechanism involving an enantioselective allene−allenoate oxidative coupling, followed by insertion of the alkene. We have also discovered an enantioselective formal allene−allenoate [4 + 2] cycloaddition as an alternative reaction pathway.

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Supporting Information Available. Experimental details and spectroscopic data is available for all new products. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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