Cycloaddition

DOI: 10.1002/anie.201306919

Transfer of Chirality in the Rhodium-Catalyzed Intramolecular [5+2] Cycloaddition of 3-Acyloxy-1,4-enynes (ACEs) and Alkynes: Synthesis of Enantioenriched Bicyclo[5.3.0]decatrienes**

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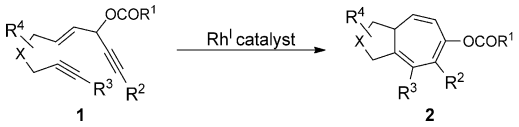
Fused bicyclo[5.3.0]decane skeletons are present in numerous bioactive natural products and pharmaceutical agents.[1] The [4+3][2] and [5+2][3] cycloadditions are among the most efficient and general reactions to access these bicyclic scaffolds.[4] However, there are only very few examples of enantioselective versions of these cycloadditions.[5] We recently developed a Rh-catalyzed [5+2] cycloaddition of 3-acyloxy-1,4-enynes (ACEs) with a tethered alkyne for the synthesis of racemic bicyclo[5.3.0]decatrienes [Eq. (1)].[6]

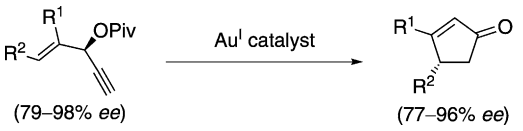


1 2 (1)

Afterwards, the more challenging intermolecular version of this cycloaddition for the synthesis of achiral monocyclic seven-membered ring systems was also achieved.[7] Prior to our study, vinylcyclopropane had been the only five-carbon building block that could be employed in transition-metal-catalyzed intramolecular[8] or intermolecular[9] [5+2] cycloadditions. Hetero-[5+2] cycloadditions of cyclopropylimines[10] or vinylepoxides[11] have also been reported.

There are three potential strategies for the preparation of optically pure bicyclic products **2**: 1) the introduction of a stereogenic center to the tether moiety of **1** for a stereoconvergent cycloaddition, 2) the employment of a chiral ligand for a dynamic kinetic resolution of **1**, and 3) a transfer of chirality from the propargylic ester of **1** to product **2** in an enantiospecific cycloaddition. To achieve high stereoselectivity with the first two methods, fast interconversion of the two enantiomeric propargylic esters or conversion of both enantiomeric propargylic esters into an achiral intermediate is required. If the first two methods were feasible, a transfer-of-chirality reaction would then be more difficult to realize, and vice versa.

In 2005, Toste and co-workers demonstrated that chirality transfer from ACEs to cyclopentenones in a Rautenstrauch rearrangement[12] could be efficiently carried out using achiral cationic gold catalysts, with an erosion in *ee* of only 2–9% [Eq. (2); Piv = pivaloyl].[13] Computational studies suggested



(79–98% *ee*) (77–96% *ee*) (2)

that a center-to-helix-to-center chirality transfer mechanism was involved in this Au-catalyzed rearrangement.[14] The successful synthesis of optically pure cyclopentenones from chiral ACEs encouraged us to investigate the enantioselective synthesis of more complex bicyclic compounds **2** from enynes **1** by a transfer of chirality. However, we found that whereas rhodium(I) catalysts were very effective in promoting the intramolecular [5+2] cycloaddition of ACEs with alkynes, gold and other transition metals did not provide the desired cycloaddition product.[6,7] The center-to-helix-to-center chirality transfer mechanism proposed for a gold catalyst[14] is not necessarily applicable to Rh^I-catalyzed [5+2] cycloadditions.

The ester functional group in ACEs is both an allylic and a propargylic ester. Evans and co-workers successfully transferred the chirality of allylic carbonates to various products of allylic alkylation by rhodium(I) catalysis.[15] Propargylic or allenylic products could also be obtained by the Rh-catalyzed alkylation of propargylic esters or carbonates.[16] A transfer of chirality, however, could not be realized for these propargylic substitution reactions.[16] The development of rhodium-catalyzed [5+2] cycloadditions of ACEs with alkynes that entail a transfer of chirality would not only yield valuable optically pure bicyclo[5.3.0]decane skeletons, but would also provide more insights into the mechanism of rhodium-catalyzed cycloaddition and allylic or propargylic substitution reactions.

Substrate **1a** was prepared from the corresponding chiral secondary alcohol; its absolute stereochemistry was determined by comparison with known intermediates.[17] We were pleased to find that product **2a** could be obtained in 95% *ee* in the presence of the cationic $[Rh(cod)_2]BF_4$ catalyst (cod = 1,5-cyclooctadiene; Table 1, entry 1). We then examined the ligand dependency of this reaction. Addition of tris(pentafluorophenyl)phosphine did not lead to a change in reaction outcome (entry 2). Slightly lower *ee* values were observed for other phosphine ligands (entries 3 and 4). Employing phos-

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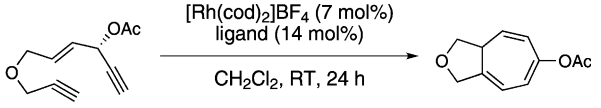
[**] We thank the NIH (R01GM088285) and the University of Wisconsin for funding.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201306919.

Table 1: Optimization of the reaction conditions for the [5+2] cycloaddition.



(*S*)-**1a** (96% *ee*) (–)-**2a**

Entry	Ligand	Yield[a] [%]	*ee*[b] [%]
1	–	97	95
2	$(C_6F_5)_3P$	97	95
3	PPh_3	47	91
4	$[3,5\text{-}(CF_3)_2C_6H_3]_3P$	98	85
5	$(CF_3CH_2O)_3P$	48	59
6	$(PhO)_3P$	87	63

[a] Yields were determined by ^1H NMR spectroscopy of the crude reaction mixture using an internal standard. [b] All *ee* values were determined by HPLC analysis on a chiral stationary phase.

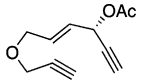
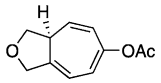
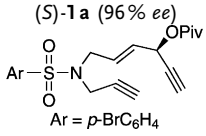
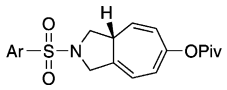
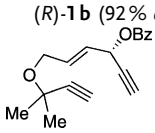
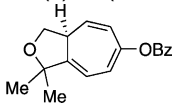
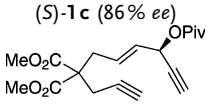
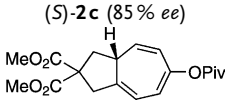
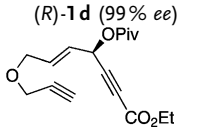
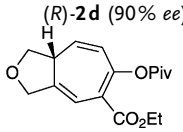
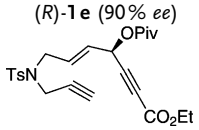
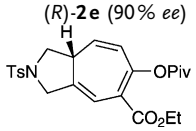
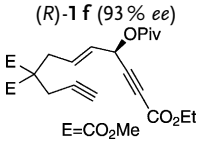
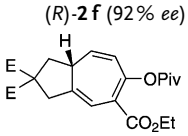
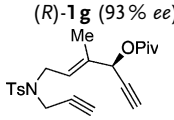
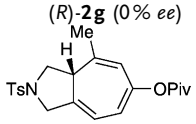
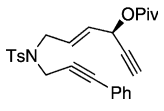
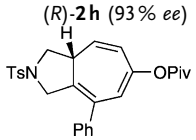
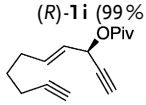
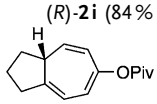
phite ligands significantly decreased the efficiency of the chirality transfer (entries 5 and 6).

The scope of the intramolecular [5+2] cycloaddition was then examined for substrates with different substitution patterns on the tether, the 1,4-enyne, and the alkyne moieties (Table 2). Substrates **1b** and **1c,** which include a nitrogen tether or a *gem*-dimethyl substituent, were efficiently converted into the corresponding products. The ester substituent (acetate, pivalate, or benzoate) does not have an impact on the enantiospecificity. The absolute configuration of product **2b** was determined by X-ray analysis.[18] The stereochemistry of the other bicyclic products was then assigned accordingly. The efficiency of the chirality transfer was found to be lower with a malonate tether (entry 4). Running the reaction at a higher concentration (0.25 M) led to a higher yield (72%), but a lower *ee* (73%) for product **2d**.

Propargylic esters with an internal alkyne tend to undergo 1,3-acyloxy migration.[19] We have previously demonstrated that electron-withdrawing groups could facilitate the 1,2-acyloxy migration in Rh-catalyzed intramolecular[6] or intermolecular[7] [5+2] cycloadditions of ACEs. The corresponding chiral alcohols of substrates **1e**–**1g** were prepared by a dinuclear Zn-catalyzed asymmetric addition of ethyl propiolate to α,β-unsaturated aldehydes, which had been developed by the Trost group.[20] Substrates **1e** and **1f** with electron-withdrawing ester substituents could undergo stereospecific cycloaddition (entries 5 and 6). As for entry 4, substrate **1g**, which also bears a malonate tether, was converted into **2g** in a diminished yield and with a lower *ee* value (entry 7). The yield of product **2g** could be improved by the addition of a phosphine ligand (entry 8). However, under these reaction conditions, racemic products were obtained. This suggests that a dynamic kinetic resolution of racemic **1g** into highly enantioenriched **2g** should be possible with an appropriate chiral ligand. We also found that high selectivity could be achieved for ACEs with a trisubstituted alkene (entry 9).

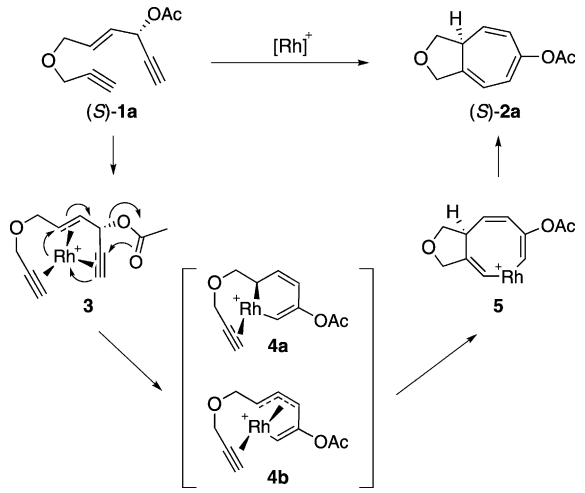
The addition of a phosphite ligand was required for substrates that bear an internal alkyne as the two-carbon component (**1i**).[6] On the other hand, phosphite ligands are detrimental to the efficiency of the chirality transfer (Table 1, entries 5 and 6). A synthetically useful 84% *ee* could be obtained for product **2i** (entry 10). A moderate 52% yield and high efficiency of chirality transfer could be achieved for substrate **1j** by using only the cationic catalyst (entry 11). The addition of $(PhO)_3P$ improved the yield, but the *ee* of product **2j** decreased significantly (entry 12).

Table 2: Scope of the Rh^I-catalyzed [5+2] cycloaddition.[a]

Entry	Substrate	Product	Yield[b] [%]
			
1	(*S*)-**1a** (96% *ee*)  Ar = *p*-BrC_6H_4	(*S*)-**2a** (95% *ee*) 	88
2	(*R*)-**1b** (92% *ee*) 	(*R*)-**2b** (92% *ee*) 	70
3	(*S*)-**1c** (86% *ee*) 	(*S*)-**2c** (85% *ee*) 	81
4[c]	(*R*)-**1d** (99% *ee*) 	(*R*)-**2d** (90% *ee*) 	61
5	(*R*)-**1e** (90% *ee*) 	(*R*)-**2e** (90% *ee*) 	67
6	(*R*)-**1f** (93% *ee*)  E=CO_2Me	(*R*)-**2f** (92% *ee*) 	85
7[c]	(*R*)-**1g** (93% *ee*)	(*R*)-**2g** (59% *ee*)	46
8[d]	(*R*)-**1g** (93% *ee*) 	(*R*)-**2g** (0% *ee*) 	60
9	(*R*)-**1h** (98% *ee*) 	(*R*)-**2h** (93% *ee*) 	60
10[e]	(*R*)-**1i** (99% *ee*) 	(*R*)-**2i** (84% *ee*) 	80
11[c]	(*R*)-**1j** (95% *ee*)	(*R*)-**2j** (91% *ee*)	52
12[f]	(*R*)-**1j** (95% *ee*)	(*R*)-**2j** (41% *ee*)	74

[a] Reaction conditions, unless otherwise noted: $[Rh(cod)_2]BF_4$ (7 mol%), CH_2Cl_2 (0.1 M), RT–40°C, 12–36 h. [b] Yields of isolated products are given. [c] $[Rh(cod)_2]BF_4$ (10 mol%). [d] $[Rh(cod)_2]BF_4$ (10 mol%), $(p\text{-}CF_3C_6H_4)_3P$ (20 mol%). [e] $[Rh(cod)_2]BF_4$ (7 mol%), $(CF_3CH_2O)_3P$ (14 mol%). [f] $[Rh(cod)_2]BF_4$ (10 mol%), $(PhO)_3P$ (20 mol%). Bz = benzoyl, Piv = pivaloyl, Ts = toluene-4-sulfonyl.

The research groups of Houk and Yu have carried out extensive computational studies on transition-metal-catalyzed [5+2] cycloadditions that involve vinylcyclopropanes.[21] Recent DFT calculations by Houk and co-workers on the intermolecular [5+2] cycloaddition of ACEs and alkynes suggested that coordination of the Rh catalyst to the acyloxy group of the ACE in an *anti* orientation was preferred (Scheme 1).[22] This would then generate a chiral Rh–allyl

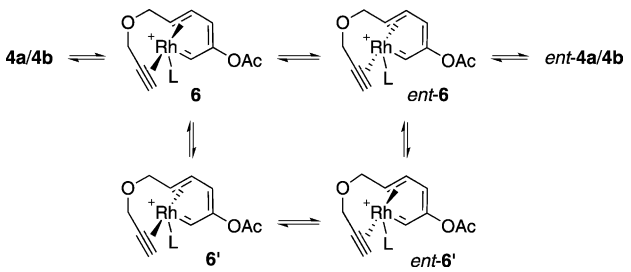


Scheme 1. Proposed mechanism for the Rh-catalyzed stereospecific intramolecular [5+2] cycloaddition of ACEs and alkynes.

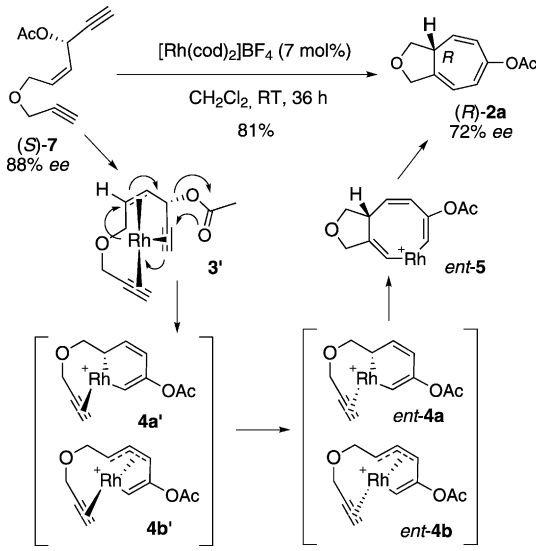
intermediate in its σ form (**4a**) or π form (**4b**) from the allylic and propargylic ester **3** through Rh-promoted 1,2-acyloxy migration and cyclization.[22] *Syn* insertion of the tethered alkyne into the Rh–allyl species **4a**/**4b** would afford the eight-membered metallacycle **5**. Reductive elimination then leads to the final bicyclic product **2a**. An overall inversion of configuration is expected, because of *anti* coordination of the rhodium complex to ACE and *syn* insertion of the alkyne into Rh–allyl complex. Stereochemical correlation between substrate **1b** and product **2b** confirmed this proposed mechanism.

When we resubmitted the bicyclic products to the reaction conditions, we did not observe a noticeable change in *ee*. This result suggests that the erosion of the *ee* for substrates in Table 2 occurred before formation of the final cycloaddition product. We have previously shown that carbene intermediates could be generated and trapped by an excess of external alkenes to form cyclopropanes.[6,7] We thus speculate that the formation of the carbene intermediates **6**/**6′** and *ent*-**6**/**6′** (Scheme 2) may account for the erosion of the *ee* that was observed for some substrates (Table 2). Phosphine or phosphite ligands (Table 1) may decrease the efficiency of the chirality transfer by promoting the formation of carbene intermediates and facilitating the equilibration between the enantiomers **4a**/**4b** and *ent*-**4a**/**4b**.

To gain further insights into the reaction mechanism, we prepared substrate (*S*)-**7** with a *cis* alkene moiety (Scheme 3). Cycloaddition occurred smoothly at room temperature with a rate that is similar to that for substrate **1a**. The isomer-



Scheme 2. Proposed pathway for the erosion in *ee*.

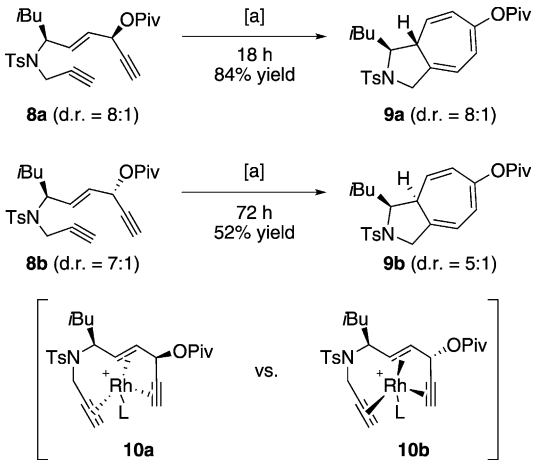


Scheme 3. Transfer of chirality for ACE **7**.

ization of the *cis* alkene **7** into the *trans* configured alkene **1a** was not observed by ^{1}H NMR spectroscopy. Coordination of the rhodium catalyst to enyne **7** from the opposite face of the acetate would generate intermediate **3′**. Rh-promoted 1,2-acyloxy migration and cyclization may first afford the Rh–allyl species **4a′** and **4b′**. Dissociation followed by re-coordination of the tethered alkyne is required for the formation of their diastereomeric metal complexes *ent*-**4a** and *ent*-**4b**, which could undergo syn-carbometallation to form metallacycle *ent*-**5**. Reductive elimination of *ent*-**5** would yield (*R*)-**2a**. Indeed, (*R*)-**2a** was obtained as the major enantiomer.

The erosion of the ee was more pronounced for *cis* alkene **7** than for the *trans* alkene **1a**. In the case of enyne **1a**, the intermediates **4a**/**4b** could undergo a direct *syn* carbometallation to yield metallacycle **5**. For enyne **7**, the intermediates **4a′**/**4b′** have to isomerize to their diastereomers *ent*-**4a**/**4b** before a *syn* carbometallation to form *ent*-**5** can take place. Carbene intermediates **6**/**6′** and *ent*-**6**/**6′** may also be formed during the conversion of **4a′**/**4b′** into *ent*-**4a**/**4b**.

To evaluate the stereospecificity of the Rh-catalyzed [5+2] cycloaddition in more complex systems, we prepared substrates **8a** and **8b**, which bear two stereogenic centers (Scheme 4). We expected a match/mismatch scenario for these two substrates. Indeed, the cycloaddition of substrate **8a** was completed in 18 h. The desired product was isolated in



Scheme 4. Rh-catalyzed [5+2] cycloaddition of ACEs with multiple stereogenic centers. [a] $[Rh(cod)_2]BF_4$ (5 mol%), $[3,5\text{-}(CF_3)_2C_6H_3]_3P$ (10 mol%), CH_2Cl_2, 50°C.

84% yield without noticeable erosion of the diastereomeric ratio. On the other hand, the reaction of **8b** was somewhat sluggish, and the product **9b** was isolated in 52% yield after 72 h. Furthermore, the diastereomeric ratio for product **9b** had dropped to 5:1. These results are consistent with *anti* coordination of the Rh^I complex to the ACE. In metal complex **10a**, the rhodium catalyst is coordinated to the bottom face of the enyne and thus placed far away from the *i*Bu group. In intermediate **10b**, however, the rhodium complex resides on the top face of the enyne during the cycloaddition process and may experience unfavorable steric interactions with the *i*Bu substituent.

In summary, we have demonstrated that the chirality of ACEs, which are readily available in an optically pure form, can be efficiently transferred to the significantly more complex bicyclic products of a [5+2] cycloaddition. Inversion of the configuration was observed, which confirmed predictions from computational studies. Various chiral bicyclo-[5.3.0]decatrienes were prepared with high *ee* for the first time. Further elucidation of the mechanism of this Rh-catalyzed intramolecular [5+2] cycloaddition of ACEs and alkynes, including a study of the ligand effect on the erosion of *ee* by computational means, is ongoing and will be reported in due course.

Received: August 6, 2013
Published online: October 21, 2013

Keywords: catalysis · enynes · polycyclic compounds · rhodium · stereospecific reactions

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