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Transfer of Chirality in Rhodium-Catalyzed Intramolecular (5+2) Cycloaddition of 3-Acyloxy-1,4-enyne (ACE) and Alkyne: Enantioselective Synthesis of Bicyclo[5.3.0]decatrienes

Dr. Xing-zhong Shu,

School of Pharmacy, University of Wisconsin, Madison, WI 53705-2222, Fax: (+1) 608-262-5345

Casi M. Schienebeck,

School of Pharmacy, University of Wisconsin, Madison, WI 53705-2222, Fax: (+1) 608-262-5345

Wangze Song,

School of Pharmacy, University of Wisconsin, Madison, WI 53705-2222, Fax: (+1) 608-262-5345

Dr. Ilia A. Guzei, and

Department of Chemistry University of Wisconsin Madison, WI 53706-1322

Prof. Dr. Weiping Tang

School of Pharmacy, University of Wisconsin, Madison, WI 53705-2222, Fax: (+1) 608-262-5345.

Department of Chemistry University of Wisconsin Madison, WI 53706-1322

Weiping Tang: wtang@pharmacy.wisc.edu

Abstract

Chiral Bicyclic—Bicyclo[5.3.0]decatrienes were prepared enantioselectively for the first time from readily available chiral 3-acyloxy-1,4-enynes (ACEs). The chirality of the allylic/propargylic esters in ACEs could be transferred with high efficiency to the bicyclic products in most cases. The experimentally observed overall inversion of stereochemistry confirmed the prediction from previous computational studies.

Keywords

stereospecific; cycloaddition; rhodium; enyne; polycyclic; catalysis

The 5–7 fused bicyclo[5.3.0]decane skeletons are present in numerous bioactive natural products and pharmaceutical agents.^[1] The (4+3) cycloaddition^[2] and (5+2) cycloaddition^[3] are among the most efficient and general ways to access these bicyclic scaffolds.^[4] There are, however, very few examples of enantioselective versions of these cycloadditions.^[5] We recently developed a Rh-catalyzed (5+2) cycloaddition of 3-acyloxy-1,4-enyne (ACE) with a tethered alkyne for the synthesis of racemic bicyclo[5.3.0]-decatrienes [Eq. (1)].^[6]

Correspondence to: Weiping Tang, wtang@pharmacy.wisc.edu.

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Afterwards, the more challenging intermolecular version of this cycloaddition was also realized for the synthesis of achiral mono-cyclic seven-membered rings.^[7] Prior to our study, vinylcyclopropane has been the only 5-carbon building block developed for transition metal-catalyzed intramolecular^[8] and intermolecular^[9] (5+2) cycloadditions. Hetero-(5+2) cycloadditions using cyclopropylimine^[10] or vinyl epoxide^[11] were also reported.

(1)

There are three potential strategies for the preparation of optical pure bicyclic product **2**: 1) introduction of a stereogenic centre to the tether region of **1** for a stereo-convergent cycloaddition, 2) employment of a chiral ligand for a dynamic kinetic asymmetric transformation of **1** to **2**, and 3) transfer of chirality from the propargylic ester in **1** to product **2** in an enantiospecific cycloaddition. To achieve high stereoselectivity using the first two methods, fast inter-conversion of the two enantiomeric propargylic esters or conversion of both enantiomeric propargylic esters to an achiral intermediate is required. If the first two methods are feasible, the transfer of chirality is then less likely, and vice versa.

In 2005, Toste and co-workers demonstrated that the chirality transfer from ACEs to cyclopentenones, the Rautenstrauch rearrangement,^[12] could be realized efficiently using achiral cationic gold catalysts with only 2–9% erosion of *ees* [Eq. (2)].^[13] Computational study suggested that a centre-to-helix-to-centre chirality transfer mechanism was involved in this Au-catalyzed rearrangement.^[14] The successful synthesis of optical pure cyclopentenones from chiral ACEs encouraged us to investigate the enantioselective synthesis of more complex bicyclic compound **2** from enyne **1** by chirality transfer. However, we found that while Rh(I) catalysts were very effective in promoting the intramolecular (5+2) cycloaddition of ACEs with alkynes, gold and other transition metals did not provide any desired cycloaddition product.^[6,7] The centre-to-helix-to-centre chirality transfer mechanism proposed for Au-catalyst^[14] is not necessarily applicable to Rh^I-catalyzed (5+2) cycloadditions.

(2)

The ester group in ACE is an allylic and a propargylic ester. Evans has successfully transferred the chirality in allylic carbonates to various allylic alkylation products using Rh(I) catalysts.^[15] Propargylic or allenylic products could also be obtained in Rh-catalyzed alkylation of propargylic esters or carbonates.^[16] The transfer of chirality, however, could not be realized in these propargylic substitution reactions.^[16] The study of chirality transfer for the Rh-catalyzed (5+2) cycloaddition of ACEs with alkynes would not only yield valuable optical pure bicyclo[5.3.0]decane skeletons, but also provide more insights for the mechanism of the Rh-catalyzed cycloaddition and allylic or propargylic substitutions.

Substrate **1a** was prepared from the corresponding chiral secondary alcohol. The absolute stereochemistry of **1a** was determined by comparison with known intermediates.^[17] We were pleased to find that product **2a** could be obtained with 95% *ee* in the presence of cationic [Rh(COD)₂]BF₄ catalyst (entry 1, Table 1). We then further examined the ligand dependency of the chirality transfer for this reaction. Tris(pentafluorophenyl) phosphine ligand did not make any difference (entry 2). Slightly lower *ees* were observed for other phosphine ligands (entries 3 and 4). Phosphite ligands decreased the efficiency of the chirality transfer significantly (entries 5 and 6).

The scope of the chirality transfer was then examined for substrates with different substitution on the tether, 1,4-enyne, and alkyne regions (Table 2). Substrates **1b** and **1c** with a nitrogen tether or gem-dimethyl substituent also worked well. The type of ester (acetate, pivalate, or benzoate) does not appear to impact on the enantiospecificity. The absolute configuration of product **2b** was determined by x-ray analysis (CCDC 946578). The stereochemistry of other bicyclic products was then assigned accordingly. The efficiency of chirality transfer dropped with malonate tether (entry 4). Running the reaction at higher concentration (0.25 M) led to higher yield (72%) but lower *ee* value (73%) for product **2d**.

Propargylic esters with an internal alkyne tends to undergo 1,3-acyloxy migration.^[18] We have previously demonstrated that electron-withdrawing group could facilitate the 1,2-acyloxy migration in Rh-catalyzed intramolecular^[6] and intermolecular^[7] (5+2) cycloaddition of ACEs. The corresponding chiral alcohols for substrates **1e–1g** were prepared from dinuclear Zn-catalyzed asymmetric addition of ethyl propiolate to α,β -unsaturated aldehydes developed by Trost group.^[19] Substrates **1e** and **1f** with an electron-withdrawing ester substituent could undergo stereospecific cycloaddition with high optical purity (entries 5 and 6). Similar to entry 4, lower *ee* and yield were observed for substrate **1g** (entry 7). The yield of product **2g** could be further improved with the addition of phosphine ligand (entry 8). Racemic products, however, were obtained under this condition. This suggests that a dynamic kinetic asymmetric transformation of both enantiomers of substrate **1g** to product **2g** with high *ee* is 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 phosphite ligand was required for substrates bearing an internal alkyne as the 2-carbon component (e.g. **1i**).^[6] On the other hand, phosphite ligands are detrimental to the efficiency of the chirality transfer (entries 5 and 6, Table 1). We were pleased to find that 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 realized for substrate **1j** using just the cationic catalyst (entry 11). The addition of (PhO)₃P ligand improved the yield but the *ee* of product **2j** became much lower (entry 12).

Research groups of Houk and Yu have done extensive computational studies on transition metal-catalyzed (5+2) cycloadditions involving vinylcyclopropanes.^[20] Recent DFT calculations by Houk and his co-workers on the (5+2) cycloaddition involving ACEs suggested that coordination of Rh catalyst anti to the acyloxy group on ACE was preferred.^[21] This would then generate a chiral Rh-allyl intermediate **4a/4b** in its σ -form (**4a**) or π -form (**4b**) from allylic/propargylic ester **3** through the mechanism of Rh-promoted 1,2-acyloxy migration and cyclization (Scheme 1).^[21] Syn-insertion of the tethered alkyne to Rh-allyl **4a/4b** may afford eight-membered metallacycle **5**. Reductive elimination can then produce final bicyclic product **2a**. An overall inversion of stereochemistry will be expected through this sequence of anti-coordination of Rh to ACE and syn-insertion of alkyne to Rh-allyl complex. The stereochemical correlation between substrate **1b** and product **2b** confirmed the proposed mechanism.

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

To gain further insights for the reaction mechanism, we prepared substrate (S)-**7** with a cis-alkene (Scheme 3). The cycloaddition occurred smoothly at room temperature in a rate that is similar to substrate **1a**. The isomerization of cis-alkene **7** to trans-alkene **1a** was not observed when the reaction was monitored by ¹H NMR. Coordination of the Rh catalyst to enyne **7** from the opposite face of the acetate would generate intermediate **3'**. The Rh-promoted 1,2-acyloxy migration and cyclization may first afford Rh-allyls **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 product (R)-**2a**. Indeed, (R)-**2a** was obtained as the major enantiomer.

More *ee* erosion was observed for substrate **7** with a cis-alkene than substrate **1a** with a trans-alkene. In the case of enyne **1a**, intermediates **4a/4b** could undergo a direct syn-carbometallation to yield metallacycle **5**. For enyne **7**, intermediates **4a'/4b'** had to undergo isomerization to their diastereomers **ent-4a/4b** for a syn-carbometallation to form **ent-5**. More carbene intermediates **6/6'** and **ent-6/6'** may be formed during the conversion of **4a'/4b'** to **ent-4a/4b**.

To evaluate the stereospecificity of the Rh-catalyzed (5+2) cycloaddition in more complex systems, we prepared substrates **8a** and **8b** with two stereogenic centres (Scheme 4). We expect a match-mismatched scenario for these two substrates. Indeed, the cycloaddition for substrate **8a** was completed in 18h. A 84% yield of the desired product was isolated without noticeable erosion of the diastereomeric ratio. On the other hand, the reaction for substrate **8b** was somewhat sluggish and a 52% yield of product **9b** was isolated after 72h. The diastereomeric ratio for product **9b** also dropped to 5:1. These results are consistent with the anti-coordination of Rh(I) complex to ACE. In metal complex **10a**, the Rh-catalyst is on the bottom face of the enyne and far away from the *i*-Bu group. The *i*-Bu group in intermediate **10b**, on the other hand, may have unfavorable steric interactions with the Rh-L complex on the top face of the enyne during the cycloaddition.

In summary, we have demonstrated that the chirality in ACE, which is readily available in optical pure form, can be efficiently transferred to the much more complex bicyclic (5+2) cycloaddition products. An overall inversion of stereochemistry was observed, which confirmed the prediction by computational studies. Various chiral bicyclo[5.3.0]decatrienes were prepared in high *ees* for the first time. Further elucidation of the mechanism of this Rh-catalyzed intramolecular (5+2) cycloaddition of ACE and alkyne including ligand effect on the erosion of *ees* by means of computational studies is ongoing and will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Scheme 1.
Proposed Mechanism for the Rh-catalyzed Stereospecific Intramolecular (5+2)
Cycloaddition of ACEs and Alkynes

Scheme 2.
Proposed Mechanism for the Erosion of *ees*

Scheme 3.
Transfer of Chirality for ACE 7

Scheme 4.

Rh-Catalyzed (5+2) Cycloaddition of ACEs with Multiple Stereogenic Centres

Conditions: a) $[\text{Rh}(\text{COD})_2]\text{BF}_4$ (5 mol%), $[\text{3,5-(CF}_3)_2\text{C}_6\text{H}_3]\text{P}$ (10 mol%), CH_2Cl_2 , 50 °C.

Table 1Screening of Catalysts and Conditions for the Transfer of Chirality from ACE **1a** to Bicyclic Product **2a**

entry	ligands	yield ^[a]	ee ^[b]
1	no ligand	97%	95%
2	(C ₆ F ₅) ₃ P	97%	95%
3	PPh ₃	47%	91%
4	[3,5-(CF ₃) ₂ C ₆ H ₃] ₃ P	98%	85%
5	(CF ₃ CH ₂ O) ₃ P	48%	59%
6	(PhO) ₃ P	87%	63%

^[a] Yields were calculated based on ¹H NMR using internal standard.

^[b] All ees were determined by HPLC analysis.

Table 2Scope of the Rh^I-catalyzed Chirality Transfer from **1** to **2**^[a]

entry	Substrate and its <i>ee</i>	Product and its <i>ee</i>	yields ^[b]
1	(S)- 1a (96% <i>ee</i>)	(S)- 2a (95% <i>ee</i>)	88%
2	(R)- 1b (92% <i>ee</i>)	(R)- 2b (92% <i>ee</i>)	70%
3	(S)- 1c (86% <i>ee</i>)	(S)- 2c (85% <i>ee</i>)	81%
4 ^[c]	(R)- 1d (99% <i>ee</i>)	(R)- 2d (90% <i>ee</i>)	61%
5	(R)- 1e (90% <i>ee</i>)	(R)- 2e (90% <i>ee</i>)	67%
6	(R)- 1f (93% <i>ee</i>)	(R)- 2f (92% <i>ee</i>)	85%
7 ^[c]	(R)- 1g (93% <i>ee</i>)	(R)- 2g (59% <i>ee</i>)	46%
8 ^[d]	(R)- 1g (93% <i>ee</i>)	(R)- 2g (0% <i>ee</i>)	60%
9	(R)- 1h (98% <i>ee</i>)	(R)- 2h (93% <i>ee</i>)	60%
10 ^[e]	(R)- 1i (99% <i>ee</i>)	(R)- 2i (84% <i>ee</i>)	80%

entry	Substrate and its <i>ee</i>	Product and its <i>ee</i>	yields ^[b]

11 ^[c]	(R)- 1j (95% <i>ee</i>)	(R)- 2j (91% <i>ee</i>)	52%
12 ^[f]	(R)- 1j (95% <i>ee</i>)	(R)- 2j (41% <i>ee</i>)	74%

^[a] Conditions unless otherwise noted, Rh(COD)₂BF₄ (7 mol %), CH₂Cl₂ (0.1M), rt to 40 °C, 12–36 h.

^[b] Isolated yields.

^[c] Rh(COD)₂BF₄ (10 mol %).

^[d] Rh(COD)₂BF₄ (10 mol %), (*p*-CF₃C₆H₄)₃P (20 mol%).

^[e] Rh(COD)₂BF₄ (7 mol %), (CF₃CH₂O)₃P (14 mol%).

^[f] Rh(COD)₂BF₄ (10 mol %), (PhO)₃P (20 mol%).