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# Enantioselective Cycloisomerization of 1,5-Enynes Promoted by Cyclometalated NHC–Pt$^{II}$–Monophos Catalysts

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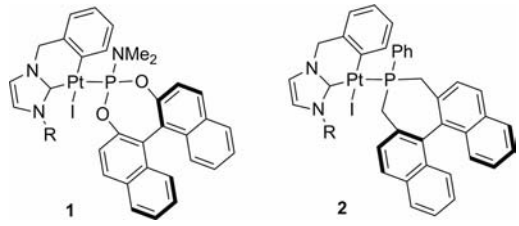
The enantioselective cycloisomerizations of 1,5-enynes bearing non-migrating oxygen functions at the propargylic carbon atom have been carried out by using Monophos–Pt$^{II}$ and Binepine–Pt$^{II}$ complexes as chiral precatalysts. They afforded the corresponding bicyclo[3.1.0]hexan-3-one in up to 63% enantiomeric excess. The stereochemical outcome of these reactions has been investigated in order to highlight possible matching–mismatching effects between the chiral catalyst and chiral substrates with opposite configurations at the stereogenic carbon. A substantial effect of the stereogenic carbon has been evidenced.

## Introduction

Extensive synthetic and mechanistic studies have been carried out on the transition-metal promoted cycloisomerizations of enynes, since these are key reactions that allow the easy preparation of synthetically important building blocks.[1] Notably, 1,5-enynes bearing an oxygenated function at the propargylic position have been widely used as suitable precursors for the bicyclic and polycyclic scaffolds of terpenoid derivatives. Relevant examples are the syntheses of sabinol,[2] sabina ketone,[3] cubebol,[4] carenes,[4b,5] cedrene,[6] and others,[7] by gold- or platinum-catalyzed rearrangements of enynes of this class. The highly desirable access to these and analogous bicyclic scaffolds in enantiomerically enriched form has been envisioned so far by either diastereoselective cyclizations or chirality transfer from enantiomerically enriched substrates.[2,4] Here, we disclose the first studies on the enantioselective cycloisomerizations of 1,5-enynes of this class, in the frame of our ongoing work on enantioselective platinum-promoted cycloisomerizations.[8] Especially, the preliminary studies reported here are intended to evidence the effects of the stereogenic carbon of the substrates on the stereochemical course of these reactions.

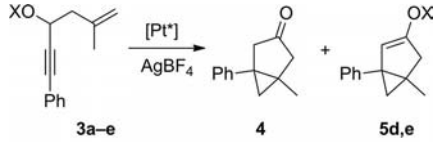
## Results and Discussion

Our previous work highlighted cyclometalated N-heterocyclic carbene complexes **1** and **2** (Scheme 1) as the first platinum-based catalysts allowing highly enantioselective cycloisomerizations of *N*-tethered enynes into the corresponding aza-bicyclo[4.1.0]heptenes.[8c,8d] The Ph-Binepine complexes **2** afforded very high levels of enantioselectivity (*ee*s of up to 97%), while the Monophos complexes **1** displayed higher catalytic activity but somewhat lower stereocontrol in these reactions (*ee*s of up to 84%).




Scheme 1. Platinacyclic catalysts for the enantioselective cycloisomerizations of [1,*n*]-enynes.

These previous studies demonstrated that precatalysts **1** and **2** are especially suited for reactions in which platinum behaves as a Lewis acid, i.e. for reactions involving an electrophilic activation of the alkyne moiety.[9] Therefore, as a logical extension of this work, we next considered the cycloisomerization of 3-hydroxylated 1,5-enynes[10] and their *O*-substituted analogues, typified by **3a**–**e** in Scheme 2.




[Pt*] = **1** or **2**
OX = OH, OMe, OBn, OTBS, OSiPh$_2$*t*Bu
(see Table 1)

Scheme 2. Cycloisomerization of 1,5-enynes with non-migrating oxygen functions at the propargylic position.

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The starting materials **3** display a stereogenic center at the propargylic position, which might affect the stereochemical course of the reaction. A priori, the presence of this stereogenic center does not rule out the possibility of setting enantioselective, catalyst-controlled reactions; nevertheless, the role of the stereogenic center should be established before entering into extensive studies on enantioselective variants of these processes.

For initial studies, 5-methyl-1-phenylhex-5-en-1-yn-3-ol (**3a**) served as the model substrate, then the corresponding ethers **3b**,**c** and the *O*-silylated derivatives **3d**,**e** were considered. On the basis of extensive literature reports,[2,3,11] these 1,5-enynes, which display non-migrating oxygen functions at the propargylic position, were anticipated to lead to the bicyclo[3.1.0]hexan-3-one **4** or to the corresponding enol ethers **5** as the cycloisomerization products (Scheme 2). The cycloisomerization experiments were carried out under standard conditions, by activating the platinum complexes **1** and **2** by addition of $AgBF_4$.[12] The main results are summarized in Table 1. Both the Monophos and Binepine complexes **1** and **2** proved to be suitable precatalysts for these reactions, which led to the expected bicyclic derivatives **4** or **5** in moderate to good yields. The silyl enol ethers **5d**,**e** were suitably converted into **4** by reaction with tetrabutylammonium fluoride (TBAF), and the enantiomeric excesses were measured on samples of **4**[13] by HPLC.

Table 1. Enantioselective cycloisomerizations of 1,5-enynes promoted by the $Pt^{II}$ complexes **1** and **2**.

| | Substrate OX | | [Pt*][a] | Yield[b] | 4/5[c] | *ee* (**4a**) [%][d] |
|---|---|---|---|---|---|---|
| 1 | **3a** | OH | **1a**, R = Me | 64 | – | 53 |
| 2 | **3a** | OH | **2a**, R = $CH_2Ph$ | 42 | – | 9 |
| 3 | **3b** | OMe | **1a**, R = Me | 40 | 100:0 | 29 |
| 4 | **3c** | $OCH_2Ph$ | **1a**, R = Me | 67 | 100:0 | 29 |
| 5 | **3d** | OTBS | **1a**, R = Me | 95 | 40:60 | 63 |
| 6 | **3d** | OTBS | **1b**, R = $CH_2Ph$ | 55 | 85:15 | 59 |
| 7 | **3d** | OTBS | **1c**, R = $CMe_3$ | 56 | 77:33 | 67 |
| 8 | **3d** | OTBS | **2a**, R = $CH_2Ph$ | 60 | 100:0 | 25 |
| 9 | **3d** | OTBS | **2b**, R = Me | 41 | 63:37 | 4 |
| 10 | **3e** | $OSiPh_2tBu$ | **1a**, R = Me | 77 | 50:50 | 65 |

[a] Conditions: 4 mol-% catalyst, 12 mol-% $AgBF_4$, toluene, 60 °C, 18 h. [b] Isolated yield of **4** + **5**. [c] The **4/5** ratios are given for reactions run in reagent grade, non-dried solvents. Ratios may vary with the amount of water in the reaction mixture. [d] By chiral HPLC.

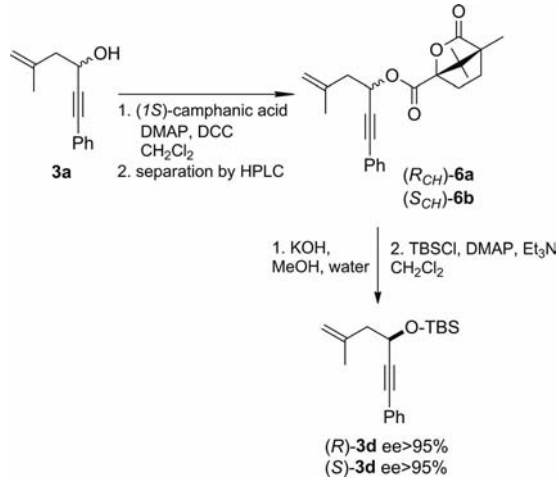
In contrast to the cycloisomerizations of the *N*-tethered enynes,[8c,8d] here the Monophos-$Pt^{II}$ complexes **1** proved to be better catalysts than the Binepine complexes **2**, in terms of both catalytic activity and enantioselectivity. Thus, for instance, the propargylic alcohol **3a** was converted into the bicyclo[3.1.0]hexan-3-one derivative **4** in 53% *ee* when using the (*R*)-Monophos complex **1a** as the precatalyst, while the (*S*)-Ph-Binepine complex **2a** afforded **4** in <10% *ee* (Entry 1 vs. 2). The same trend was observed for the *O*-silylated substrate **3d** (Entries 5–7 vs. 8,9).

From experiments on different substrates, it appears that simple modifications of the oxygen substituent are crucial with respect to the stereochemical outcome of the reaction: the O–Bn and O–Me substituted enynes **3b** and **3c**, respectively, afforded the corresponding ketones in <30% *ee* (Entries 3 and 4), while the bulky silyl ethers **3d** and **3e** allowed enantiomeric excesses of 63–65% to be obtained. The enantioselectivity levels could be slightly modulated by changing the N-substituent in the carbene moiety of the platinum catalysts **1** (Entries 5–7) – the bulky *t*Bu group gives the highest enantioselectivity.

These preliminary results demonstrate the feasibility of the enantioselective cycloisomerization of 1,5-enynes with non-migrating oxygen functions at the propargylic position, into bicyclic [3.1.0] scaffolds. An interesting issue that remains to be solved is the role of the stereogenic carbon center of the substrate in the stereochemical control of these cycloisomerization processes.

Literature data provide strong evidence for a degree of chirality transfer from chiral propargylic substrates to the final products in analogous reactions. Studies on this topic involve, however, either enyne substrates with migrating oxygen groups (OAc, OPiv)[4,16] at their propargylic positions or propargylic alcohols with additional stereogenic centers.[2] Therefore, the results of these studies cannot consistently be extrapolated to substrates **3** in Scheme 2. It is reasonably expected that the stereogenic center of **3** will modulate the enantioselectivity levels, although the degree of stereochemical control afforded by the stereogenic center and the chiral catalyst can hardly be anticipated. The following experiments allowed us to get reliable information on this crucial point.

At first, the reaction sequence in Scheme 3 provided us with samples of the enantiomerically enriched, silylated enynes **3d** with opposite carbon configurations. The procedure involves resolution of alcohol **3a** by SFC separation of the diastereomeric camphanic esters **6** and conversion of the enantiomerically enriched alcohols to the corresponding TBS ethers (*R*)- and (*S*)-**3d**.

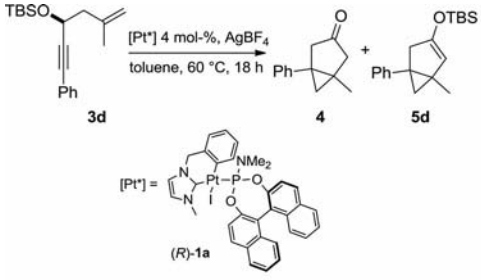



Scheme 3. Synthesis of (*R*)- and (*S*)-**3d**.

The configuration of the propargylic carbons of the diastereomeric esters **6** has been assigned by an X-ray diffraction study of (*S*)-**6b** (see Supporting Information).[15]

The enantiomerically enriched substrates **3d** were subjected to cycloisomerization in the presence of either $PtCl_2$ or the (*R*)-Monophos complex (*R*)-**1**. The results are reported in Scheme 4. From these experiments, it appears that: (a) a substantial but partial transfer of chirality from enantiomerically enriched **3d** (>95% *ee*) takes place when using $PtCl_2$ as the catalyst, which leads to the final product **4** in 54% enantiomeric excess (Entry 2); (b) when using the platinacyclic catalyst **1a**, the stereochemical control from the chiral catalyst overcomes the effect of the chiral substrate (Entries 2 and 3); (c) the (*R*)-configured substrate (*R*)-**3d** constitutes a matching pair with the (*R*)-Monophos complex (*R*)-**1a**, which allows the desired cycloisomerization product **4** to be obtained in 92% enantiomeric excess. The same catalyst converts the (*S*)-configured substrate into **4** with 35% *ee* (Entries 3 and 4). These results are fully consistent with the 63% *ee* obtained in the cycloisomerization of racemic **3d**.




| | Substrate | Catalyst | Yield [%] (4+5d)[b] | *ee* (4) |
|---|---|---|---|---|
| 1 | *Rac*-**3d** | (*R*)-**1a** | 95 | 63(-) |
| 2 | (*S*)-**3d**[a] | $PtCl_2$ | 48 | 54(+) |
| 3 | (*S*)-**3d** | (*R*)-**1a** | 86 | 35(-) |
| 4 | (*R*)-**3d** | (*R*)-**1a** | 88 | 92(-) |

[a] Samples of (*S*)- and (*R*)-**3d** with >95^% ee were used.
[b] Conditions: 4 mol-% catalyst, 12 mol-% $AgBF_4$, toluene, 60 °C, 18 h.

Scheme 4. Catalytic cycloisomerizations of the enantiomerically enriched substrates **3d**.

These results highlight a significant role of the stereogenic center of oxygen-functionalized 1,5-enynes in the stereochemical outcome of the targeted cycloisomerizations. They also show that the configuration of the stereogenic center does not simply translate into the stereochemistry of the product, and, therefore, chiral induction can be carried out by means of chiral catalysts. The above results also demonstrate that the platinacyclic Monophos complexes **1** display high catalytic activity and have the potential of inducing high stereocontrol in these cycloisomerizations.

## Experimental Section

### Typical Procedure for the Enantioselective Cycloisomerizations

Propargylic alcohol **3a**[16] was prepared by 2,3-Wittig rearrangement of the corresponding allyl propargyl ether.[17]

**5-methyl-1-phenylbicyclo[3.1.0]hexan-3-one (4):** $AgBF_4$ (4 mg, 0.02 mmol) and enyne **3a** (50 mg, 0.16 mmol, in 4.5 mL of toluene) were added sequentially to a solution of $Pt^{II}$ complex **1a**[8d] ($6.4 \times 10^{-3}$ mmol, 4 mol-%) in toluene (0.5 mL) under argon. The mixture was stirred at 60 °C for 18 h. The solvent was removed under reduced pressure, the crude mixture was monitored by NMR spectroscopy, and the final product, **4**, was purified by column chromatography with heptane/EtOAc (90:10) as the eluent. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 0.64 (d, $^2J$ = 6.0 Hz, 1 H, $CH_2$), 1.06 (s, 3 H, Me), 1.24 (m, 1 H, $CH_2$), 2.48 (d, $^2J$ = 19.0 Hz, 1 H, $CH_2$), 2.63 (d, $^2J$ = 19.0 Hz, 1 H, $CH_2$), 2.67 (dq, $^2J$ = 19.0, $^4J$ = 2.0 Hz, 1 H, $CH_2$), 2.92 (dq, $J$ = 19.0, $J$ = 2.0 Hz, 1 H, $CH_2$), 7.25–7.4 (5 H, Ph) ppm. $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ = 18.6 (Me), 23.8 ($CH_2$), 26.1 (C), 33.5 (C), 48.3 ($CH_2$), 50.3 ($CH_2$), 126.6, 128.5, 129.2, 140.1 (C), 216.4 (CO) ppm. ESI-MS: $m/z$ = 187 $[M + H]^+$. Enantiomeric excesses were measured by chiral HPLC: Chiracel AD-H, heptane/2-propanol 99:1, 1 mL/min, retention times 4.4 and 5.3 min. Racemic **4** was obtained by $PtCl_2$-promoted cycloisomerization.

**Supporting Information** (see footnote on the first page of this article): Further experimental procedures and characterization details of the compounds and an ORTEP diagram of the *S*-configuration of the propargylic carbon of ($S_{CH}$)-**6b** are presented.

## Acknowledgments

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[12] The reactions proceed with an $Ag^I$ to $Pt^{II}$ ratio of 1:1. However, for practical reasons, an excess of $AgBF_4$ (3:1 ratio) was rou-

  

tinely used to generate the catalytically active species. It has been ascertained that, under these conditions, $AgBF_4$ does not display any catalytic activity.
[13] The silylated enol ether **5d** displays the same enantiomeric excess as cyclopentanone **4**. Therefore, it is postulated that hydrolysis of **5d** takes place after the enantio-determining cyclization step. Formation of **4** might be promoted by the excess of $AgBF_4$.
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