Desymmetrizations of *meso-tert*-norbornenols by rhodium(I)-catalyzed enantioselective retro-allylations[†][‡]

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Rhodium-catalyzed desymmetrizations of *meso-tert*-norbornenols by retro-allylations generate allyl-rhodium species that allow for a rich and diverse downstream reactivity.

The allylation of carbonyl groups is a reaction of fundamental importance to organic chemistry.¹ On the other hand, the reverse reaction pathway—retro-allylation from tertiary homoallylic alcohols—is a process observed with a range of main group and transition-metals.² Yorimitsu and Oshima disclosed in seminal contributions that the released late transition-metal allyl species can be used in coupled allylation processes.³ Contrasting carbonyl allylation reactions,⁴ catalytic enantioselective variants of retro-allylations are limited to two examples. Hayashi and co-workers demonstrated kinetic resolutions of racemic tertiary alcohols with a chiral rhodium catalyst.⁵ We have recently reported one example of an enantioselective palladium(0)-catalyzed arylative retro-allylation allowing the preparation of a highly substituted cyclohexene using a taddol-based phosphoramidite ligand.⁶

Herein, we report the complementary reaction profile of allyl rhodium species **3s/3p** generated by desymmetrization of bicyclic *meso-tert*-norbornenols **1** and illustrate their synthetic potential and variable reactivity (Scheme 1).

A simultaneous coordination of the alkoxide and the olefin moiety⁷ of **4** to a chiral Rh(1)-complex induces an enantioselective retro-allylative C–C bond cleavage leading to allyl rhodium species either as their σ - (**5**s) or a π -bound (**5**p) complex (Scheme 2).⁸ β -Hydride elimination forms regioisomeric dienes **6**⁹ and a rhodium hydride species, which in turn, is prone to re-addition to the formed diene.¹⁰ Re-additions in a 1,2- or 1,4-fashion could lead to enolate **7** and subsequent metal or base promoted isomerization yields more stable enone **8** as the terminal product. In view of the facile



Scheme 1 Desymmetrization of *meso-tert*-norbornenols 1 by metal promoted retro-allylation.



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Scheme 2 Proposed pathway for the formation of enone 8.

reversibility and the small differences in activation barriers of such additions/eliminations of rhodium hydrides to 6, we sought to explore conditions to address the selective formation of specific product branches.

Refluxing a solution of **4a** in the presence of 2.5 mol% $[Rh(cod)(OH)]_2$, 6 mol% (*R*)-Binap and caesium carbonate¹¹ in toluene gave ring opened enone **8a** in 79% yield, albeit in a moderate enantiomeric ratio of 75 : 25 (Table 1, entry 1). Screening of a range of chiral diphosphines (Scheme 3) led to the identification of Josiphos **L6** as a promising ligand giving **8a** with an er of 91 : 9 (entry 9). Performing the reaction at 115 °C and replacing toluene with chlorobenzene increased the yield from initially 36% to 74% (entry 10).

 Table 1 Optimization of the desymmetrization^a



^{*a*} Conditions: 0.05 mmol **4a**, 2.5 mol% [Rh(OH)(cod)]₂, 6.0 mol% L*, 1.0 equiv. Cs₂CO₃, toluene (0.15 M), 110 °C, 12 h. ^{*b*} Isolated product **8a**. ^{*c*} By HPLC with a CSP (sign of the optical rotation). ^{*d*} At 120 °C. ^{*e*} PhCl instead of toluene. ^{*f*} At 115 °C.

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Scheme 3 Utilized ligands L* (DTBM = $3,5-tBu-4-MeO-C_6H_2$).

With the optimized conditions, we then explored the influence of substituent R on the tertiary alcohol (Table 2). Aromatic groups with different steric and electronic properties are well tolerated and have little impact on the reactivity and selectivity of the process (entries 1–5). Although substituent R is oriented away from the reaction site, small alkyl groups cause diminished enantioselectivities (entries 6 and 7).

Noteworthy, when the base was omitted in the retro-allylation reaction of 4a, regio-isomeric β-hydride elimination of 5 became the dominant pathway and led to presumed diene 9 (Scheme 4). Subsequent 1,4-addition might form allylrhodium species 10, which again undergoes H elimination accounting for the observed diene 11, formed in 77% yield and an er of 78 : 22. On the other hand, when vinyl substituted tert-alcohol 4h was submitted to the reaction conditions. formation of diene 13 as well as aromatic product 14 was observed (Scheme 5). This suggests a preferential re-addition of the rhodium hydride species to the terminal, activated olefin instead of the cyclohexadiene moiety of 6h.¹² Enolate 12 might subsequently isomerize to the more stable enone 13 or aromatize to arene 14. Fine-tuning of the reaction condition by the addition of ten equivalents of cyclohexene mitigated the undesired oxidation to arene 14.

Modifications of the bicyclic framework 1, for example 15 lacking the tetrahydrofuran reveal that subtle differences of the substrate have a significant impact on the reactivity profile of the allyl rhodium species (Scheme 6). In addition, slight modifications of the reaction conditions impact the fate of the putative organometallic species 16 as well.

Table 2 Formation of enon	es 8 ^a
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^{*a*} Conditions: 0.05 mmol **4**, 2.5 mol% [Rh(OH)(cod)]₂, 6.0 mol% **L6**, 1.0 equiv. Cs₂CO₃, PhCl (0.15 M), 115 °C, 12 h. ^{*b*} Isolated product **8**. ^{*c*} By HPLC with a CSP (sign of the optical rotation). ^{*d*} ent-**L6** was used.



Scheme 4 Proposed reaction pathways for the formation of diene 11.



Scheme 5 Pathways for the formation of diene 13.

For example, performing the retro-allylation of **15** with $[Rh(OH)(cod)]_2$, **L6** and caesium carbonate (conditions A), presumably forms regio-isomeric diene **17**. The concomitantly formed rhodium hydride species then selectively reduces the carbonyl group of **17** yielding **18** over the previously dominant 1,4-reduction of the diene moiety. In contrast, $[Rh(OAc)(C_2H_4)_2]_2$, **L6** and 4 Å molecular sieves instead of caesium carbonate (conditions B) selectively provide diene **20** with an *exo*-methylene group by the following mechanistic scenario: a 1,4-hydrorhodation of **17** leads to alkyl rhodium species **19**, which in turn undergoes β -alkoxide elimination to



Scheme 6 Proposed reaction pathways for the formation of 18 or 20.

 Table 3
 Formation of alcohols 18 and dienes 20^a



^{*a*} Conditions A: 0.05 mmol **15**, 5 mol% $[Rh(OH)(cod)]_2$, 12.0 mol% *ent*-**L6**, 1.0 equiv. Cs₂CO₃, PhCl (0.15 M), 120 °C, 12 h; Conditions B: 0.05 mmol **15**, 5 mol% $[Rh(OAc)(C_2H_4)_2]_2$, 12.0 mol% *ent*-**L6**, 20 mg 4 Å MS, PhCl (0.15 M), 120 °C, 12 h. ^{*b*} Isolated product **18** or **20**. ^{*c*} Determined by HPLC with a CSP (sign of the optical rotation). ^{*d*} With **L6**.

yield **20**.¹³ A range of secondary alcohols **18** and methylene cyclohexenes **20** can be accessed from norbornenols **15** using these complementary conditions (Table 3). The observed enantioselectivities for the formation of **20** (entries 2, 4, 6, 8) are excellent and generally significantly higher than those for the formation of **18** (entries 1, 3, 5, 7), demonstrating a pronounced effect of the added base on the selectivity.¹¹ The relative configuration of the secondary alcohol function of **18** was assigned by X-ray crystal structure analysis of the Diels–Alder adduct **21** obtained from **18a** and 4-phenyl-3*H*-1,2,4-triazoline-3,5-dione (PTAD) (Scheme 7).§¹⁴ This selectivity suggests a facial reduction of the carbonyl group as depicted for **17** (Scheme 5).

In summary we showed that bicyclic *meso-tert*-norbornenols can be desymmetrized by retro-allylation mechanisms with chiral rhodium(1) catalysts. Subtle differences of the substrate structure and more importantly of the reaction conditions lead to diverging reaction pathways and hold the promise of a further rich downstream chemistry. Ongoing research is directed towards a deeper understanding and control of the individual steps as well as the development of synthetic applications.



Scheme 7 Determination of the relative configuration of 18 as its Diels-Alder adduct 21.

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Notes and references

§ Crystallographic data for **21**: $C_{25}H_{27}N_3O_5$, M = 449.51, triclinic, space group *P*1, a = 7.9939 (5) Å, b = 11.9064 (9) Å, c = 13.8485 (12) Å, $\alpha = 68.816$ (3)°, $\beta = 77.480$ (4)°, $\gamma = 72.174$ (3)°, V = 1161.6 (2) Å³, Z = 2, $D_{calc} = 1.285$ Mg m⁻³, T = 100 K, reflections collected: 6601, independent reflections: 4009 ($R_{int} = 0.062$), R(all) = 0.0818, wR(gt) = 0.1508. CCDC 779921.

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