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Unexpected transfer hydrogenation of C–C-double bonds during Tandem-RCM-isomerization reactions

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Abstract

Unexpected hydrogen transfer from 2-propanol to C–C-double bonds has been observed in the course of a Tandem RCM-isomerization reaction leading to sterically congested spirocycles.

Keywords: Ruthenium; Metathesis; Isomerization; Hydrogenation; Transferhydrogenation; Tandem sequence

Catalytic reaction sequences have been recognized as extraordinarily valuable tools in organic synthesis over the past few years [1,2]. In the olefin metathesis field [3,4], a considerable number of publications describe Domino-type sequences, such as ROM-RCM-CM sequences [5–7]. Reaction sequences combining metathesis and non-metathesis steps, often described as Tandem reactions, have been less thorougly explored [2,8]. Examples include the combination of olefin metathesis with hydrogenation [9], dehydrogenative oxidation [10], atom transfer radical cyclization [11–13], dihydroxylation [14], and coupling of diazo compounds [15]. A common feature of these Tandem sequences is, that formerly independent catalytic cycles are connected by an organometallic transformation in situ. Recently, a Tandem RCM-isomerization sequence has been developed by us [16–18] and by Snapper et al. [19]. This novel synthetic method has been designed for the synthesis of cyclic enol ethers starting from metathesis precursors bearing an allyl ether group. It relies on the conversion of the propagating species of olefin metathesis, a ruthenium carbene complex, to a ruthenium hydride which is believed to be the active catalyst for the isomerization step [20,21]. In our work, four different additives or additive combinations (protocols A–D) have been discovered to achieve this crucial organometallic transformation (Scheme 1).

In search for applications of our synthetic method we started to investigate its utility for the synthesis of enantiopure spirocyclic 2,3-dihydropyrans. This work was inspired by work recently published by Dixon et al., who introduced a camphor-derived δ-lactol auxiliary for asymmetric α-alkylation of glycine amide [22]. Dixon's δ-lactol auxiliary was synthesized by hydroformylation of homoallylic alcohol **2**, which is in turn available by highly diastereoselective Grignard-addition to camphor (**1**). We thought that the hitherto unknown dihydropyran **6** might serve as a chiral auxiliary that can be attached to a substrate via an OH-group and allow for the stereoselective manipulation of other functional groups in the proximity, either by diastereoselective addition or by diastereoselective α-functionalization (Scheme 2).

Our synthesis of **6** starts from homoallylic alcohol **2**, which is then allylated to yield metathesis precursor **3**. Ring closing metathesis of **3** with first generation Grubbs' catalyst (**A**) to give dihydropyran **4** has previously been described by Marco et al. [23]. In accord with this report, we found that RCM of **3** proceeds rapidly and in quantitative yield in dichloromethane in the presence of just 2 mol% of **A**. However, our RCM-isomerization protocols require toluene as a solvent. When conducting the ring closing

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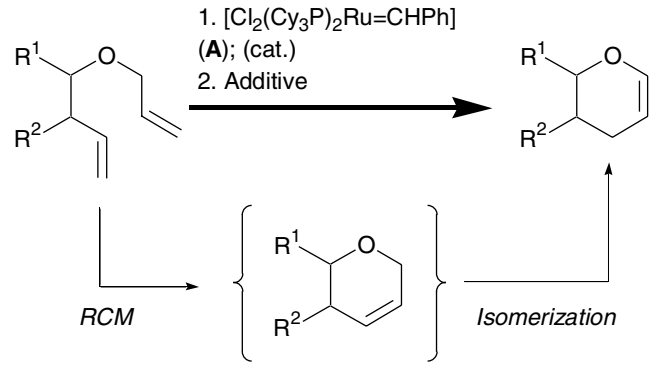
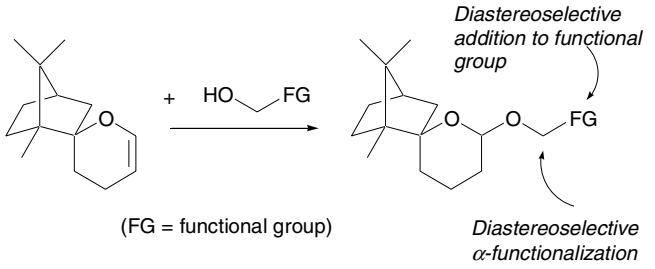


Additives:
Protocol A: H_2C=CHOEt
Protocol B: $NaBH_4$ or NaH
Protocol C: 2-propanol; NaOH
Protocol D: Et_3SiH

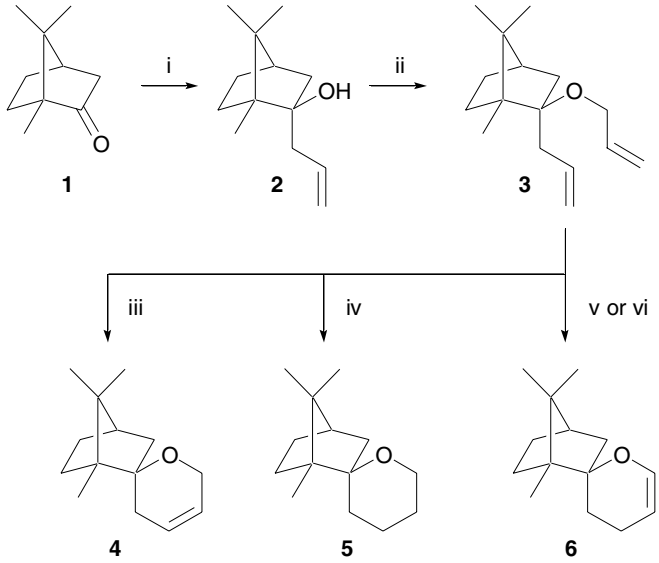
Scheme 1. Concept of Tandem RCM-isomerization sequence.



Scheme 2. Proposed use of camphor-derived **6** as a chiral inductor.

metathesis reaction in this solvent, it was found that the reaction becomes rather slow at ambient temperature, while previous studies revealed that RCM reactions in refluxing toluene often lead to undesired side reactions [24], presumably due to decomposition of the active ruthenium species [25]. Heating the reaction mixture to 40–50 °C leads to a significant rate enhancement of the metathesis step, resulting in complete conversion of **3** to the intermediate RCM product **4**. From our previous experience with the various additives required to induce the isomerization step we knew that 2-propanol in combination with 30 mol% NaOH gives the best results with respect to isolated yield and reaction time. Thus, we decided to test these conditions first. Surprisingly, after 3.5 h in refluxing toluene none of the desired enolether **6** could be detected, but spirocyclic tetrahydropyran **5** was isolated in good yield (Scheme 3). A related observation has recently been made by Dalko et al., who describes the formation of hydrogenated products after exposure of RCM reactions to large excesses of silanes at elevated temperatures over prolonged periods of time [26].

Obviously, a transfer hydrogenation of a C–C-double bond with an alcohol occurs; these processes are – compared to the well-known transfer hydrogenation of ketones with secondary alcohols – rare. In most cases, described in the literature a simple terminal alkene is used as a hydrogen scavenger in the metal catalyzed dehydrogenation of secondary alcohols to ketones [27,28]. In other examples,



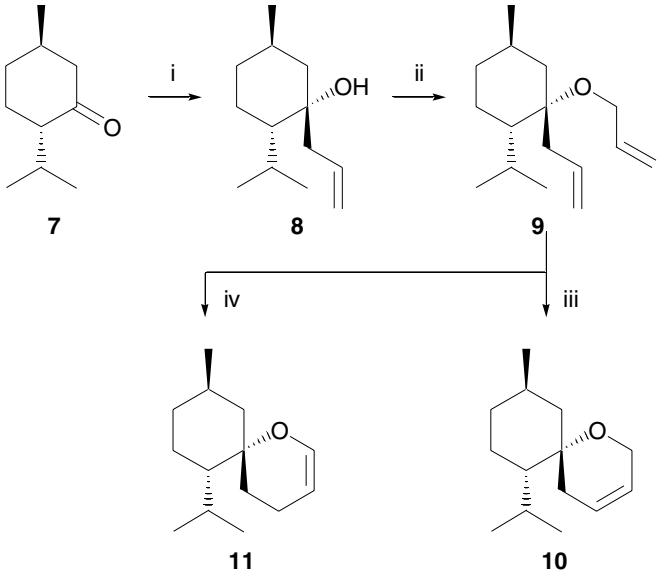
Scheme 3. *Reagents and conditions*: (i) H_2C=$CHCH_2MgBr$, Et_2O, −20 °C (96%); (ii) NaH, allyl bromide, THF, 65 °C (96%); (iii) **A** (2 mol%), CH_2Cl_2, 20 °C (98%, cf. Ref. [23]); (iv) **A** (5 mol%), toluene, 40 °C, then add 2-propanol and NaOH (25 mol%), 110 °C for 3.5 h (71% of **5**); (v) **A** (5 mol%), toluene, 40 °C, then add 2-propanol and NaOH (25 mol%), 80 °C for 2.5 h (61% of **6** with incomplete conversion); (vi) **A** (10 mol%), toluene, 40 °C, then NaH (40 mol%), 110 °C for 12 h (98% of **6**).

aldol condensation products are hydrogenated with alcohols as a source of hydrogen [29–31]. We had previously observed the formation of tetrahydropyran byproducts when using our the so-called protocol C, however, this was exclusively the case when an unprotected alcohol was in the proximity of the reacting double bond [18], leading to the assumption that a catalyst directing or activating effect was required to induce hydrogenation activity. Thus, the selective formation of **5** was fully unexpected and had to be investigated in more detail. Monitoring the reaction by TLC revealed that in the first instance the desired enolether **6** is formed, which is then hydrogenated. We have no indication that hydrogen transfer occurs directly from 2-propanol to dihydropyran **4**. In an attempt to optimize the reaction conditions for the formation of **6**, we first reduced the reaction time. This turned out to be ineffective, because very short reaction times resulted in incomplete conversion, while longer reaction times resulted in the formation of larger quantities of hydrogenated product **5**. We then lowered the temperature to 95 °C, which gave a 2:1 ratio of **6** and **5** after 1 h. The highest yield of **6** using this protocol was obtained after 2.5 h at 80 °C. However, conversion remained incomplete which led to the consideration of another RCM-isomerization protocol, the so-called protocol B. After some optimization it was discovered that using 10 mol% of A and a reaction time of 12 h results in a quantitative conversion and a 98% isolated yield of **6**. With these results in hand, we started to investigate an analogous synthesis of an alternative enantiopure chiral auxiliary which is derived from (−)-menthone (**7**). Addition of allyl magnesium bromide to menthone had been described previously. This reaction gave homoallylic

alcohol **8** with slightly lower diastereoselectivity (de 94%) compared to camphor. *O*-allylation of **8** to yield allyl ether **9** turned out to be surprisingly difficult: even with eight equivalents of NaH and three equivalents of allyl bromide in refluxing THF only a mediocre yield of **9** was obtained after 12 h. This is probably caused by strong steric hindrance due to the *cis*-arrangement of isopropyl and hydroxy group in alcohol **8**. A remarkable difference is also observed in the reactivity in the RCM step. RCM of **9** was directly conducted under the conditions required for the Tandem sequence and resulted in a yield of 48%, whereas the camphor analogue **4** was obtained in quantitative yield. The reduced yield probably also reflects the strong steric hindrance involved in the formation of spirocycle **10**. With respect to the experiences made in the camphor series we were surprised to see that **9** under the conditions of protocol C is converted to enol ether **11** without formation of any tetrahydropyran byproduct, even if the reaction is conducted at 110 °C (Scheme 4).

Having established the routes to enantiopure spirocyclic dihydropyrans **6** and **11**,[1] we undertook first attempts to evaluate the concept outlined in Scheme 2. To this end, methyl glycolate was bound to **6** in the presence of a Brønsted acid. In initial experiments, a catalytic amount of *para*-toluene sulfonic acid was used. NMR-spectroscopic analysis of the reaction mixture revealed the presence of an aldehydic byproduct, which obviously did not contain any glycolate. An additional signal in the olefinic region suggests that structure **12** is assigned to this product. The required acetal **13** was eventually obtained by using the milder acid pyridinium *para*-tosylate (PPTS). No rearrangement product **12** could be detected in this case, the mediocre yield of 57% might be attributed to decomposition of the acetal during column chromatography. We were furthermore pleased to see that exclusively the equatorially substituted product is formed during acetal formation. This structural assignment is based on the observation of a large coupling constant of 9.6 Hz for the acetal proton. The methylene protons of the –OC$\underline{H_2}$CO$_2$Me-group, which are now diastereotopic, are separated by more than 0.1 ppm, indicating that the chemical surrounding is obviously quite different. In an attempt to stereoselectively functionalize this compound, it was lithiated with LiHMDS and subsequently treated with MeI. NMR-analysis of the reaction mixture shows that there is a moderate face differentiating effect of the camphor-derived auxiliary, with two diastereomeric lactates **14** being formed in a 2:1 ratio. The two quartets observed for the –C*H*Me– proton are baseline separated in the 400 MHz-^{1}H NMR-spectrum (chemical shift difference 0.16 ppm), which might suggest future use of **6** as a covalently bound shift reagent for alcohols (Scheme 5).

In conclusion, we describe the synthesis of two potential chiral auxiliaries or reagents derived from camphor or menthone, respectively. Key step is the Tandem RCM-



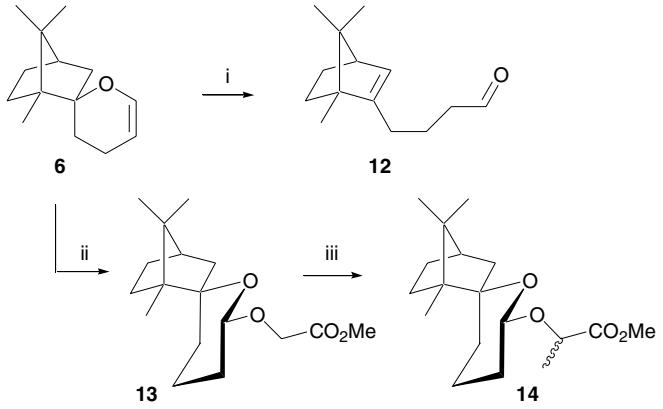
Scheme 4. *Reagents and conditions*: (i) $H_2C{=}CHCH_2MgBr$, Et_2O, −20 °C (94%); (ii) NaH, allyl bromide, THF, 65 °C, 12 h (41%); (iii) **A** (5 mol%), toluene, 40 °C (48%); (iv) **A** (5 mol%), toluene, 40 °C, then add 2-propanol and NaOH (25 mol%), 110 °C for 10 h (57%).

[1] †*Representative procedures and analytical data.*

Tetrahydropyran **5**. To a solution of diene **3** (0.40 g, 1.7 mmol) in toluene (20 mL) was added catalyst **A** (70 mg, 5 mol%). The solution was heated to 40 °C until the starting material was fully consumed (TLC), then 2-propanol (1.7 mL) and NaOH (17 mg, 0.4 mmol) were added. The mixture was heated to reflux for 3.5 h. The organic layer was diluted with MTBE, washed with water, dried with $MgSO_4$, filtered and evaporated. The solvent was removed in vacuo, and the residue was purified by flash chromatography to give **5** (251 mg, 71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.55 (dm, 11.8 Hz, 1H), 3.46 (ddd, 11.6 Hz, 11.3 Hz, 11.3 Hz, 1H), 2.07 (ddd, 12.8 Hz, 7.3 Hz, 3.8 Hz, 1H), 1.76–1.61 (3H), 1.57–1.24 (7H), 1.15 (d, 12.8 Hz, 1H), 1.02 (s, 3H), 0.92 (ddd, 12.0 Hz, 9.0 Hz, 5.5 Hz, 1H), 0.82 (s, 3H), 0.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 82.7 (0), 60.3 (2), 52.6 (0), 48.9 (0), 45.4 (1), 39.4 (2), 31.8 (2), 30.0 (2), 27.0 (2), 25.7 (2), 21.4 (3), 21.2 (2), 20.9 (3), 10.5 (3); $[\alpha]_D^{20}$ −64.3 (*c* 0.90, CH_2Cl_2); HRMS (EI) calculated for $C_{14}H_{24}O$ (M^+) 208.1827, found: 208.1811; IR (film, KBr) ν 2933 (s), 2856 (m) cm^{-1}.

Dihydropyran **6**: To a solution of **3** (500 mg, 2.1 mmol) in toluene (20 mL) was added catalyst **A** (175 mg, 10 mol%) and the solution was heated to 50 °C until the starting material was fully consumed (TLC). Subsequently, NaH (43 mg, 60% dispersion in mineral oil, 1.1 mmol) is added and the mixture is heated to reflux for 12 h. Workup was done as described above for **5**. Compound **6** was obtained as a colourless liquid (430 mg, 98%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.23 (dm, 6.0 Hz, 1H), 4.62 (m, 1H), 2.16–1.98 (3 H), 1.75–1.60 (4H), 1.51–1.35 (2H), 1.25 (d, 13.3 Hz, 1H), 1.09 (s, 3 H), 0.98 (m, 1H), 0.88 (s, 3H), 0.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.0 (1), 99.6 (1), 84.1 (0), 52.2 (0), 49.5 (0), 45.0 (1), 44.7 (2), 30.1 (2), 27.5 (2), 27.1 (2), 21.5 (3), 21.2 (3), 18.4 (2), 10.8 (3); $[\alpha]_D^{20}$ −40 (*c* 1.15, CH_2Cl_2); HRMS (EI) calculated for $C_{14}H_{22}O$ (M^+) 206.1671, found 206.1648; IR (film, KBr) n 3058 (m), 2930 (s), 2846 (s), 1654 (s) cm^{-1}.

Dihydropyran **11**. Following the procedure given above for **5**, diene **9** (0.40 g, 1.7 mmol) was converted to **11** (199 mg, 57%). ^{1}H NMR (400 MHz, C_6D_6) δ 6.35 (dm, 6.1 Hz, 1H), 4.52 (ddm, 6.0 Hz, 5.9 Hz, 1H), 2.18 (dm, 13.4 Hz, 1H), 2.11 (dseptett, 6.9 Hz, 2.2 Hz, 1H), 2.05–1.92 (2H), 1.86–1.69 (4H), 1.51–1.44 (m, 1H), 1.03 (d, 6.9 Hz, 3H), 1.02–0.92 (2H), 0.91 (d, 7.0 Hz, 3H), 0.84 (d, 6.4 Hz, 3H), 0.85 (m, 1H); ^{13}C NMR (100 MHz, C_6D_6) δ 142.6 (1), 98.9 (1), 76.9 (0), 50.6 (1), 40.9 (2), 35.6 (2), 29.3 (2), 27.8 (1), 26.0 (1), 23.8 (3), 22.7 (3), 20.7 (2), 18.1 (3), 17.6 (2); $[\alpha]_D^{20}$ −5.1 (*c* 1.00, CH_2Cl_2); HRMS (EI) calculated for $C_{14}H_{24}O$ 208.1827 (M^+), found: 208.1820; IR (film, KBr) ν 3058 (m), 2958 (s), 2857 (s), 1649 (s) cm^{-1}.



Scheme 5. *Reagents and conditions*: (i) $HOCH_2CO_2Me$, PTSA (10 mol%), DCM, 20 °C; (ii) $HOCH_2CO_2Me$, PPTS (10 mol%), DCM, 20 °C (57%); (iii) LiHMDS, MeI, THF, −78 °C (70% combined yield).

isomerization sequence recently developed in our laboratories. In the case of camphor-derived **6**, the isomerization step was accompanied by an unexpected transfer hydrogenation, which takes place for this substrate remarkably easy. Preliminary investigations into the use of **6** as a chiral auxiliary are also presented. Future studies will further elucidate which factors enhance the tendency of enol ethers to undergo subsequent transfer hydrogenation, and whether such a process might become a general and useful synthetic method for the formation of saturated hetero- and carbacycles via Tandem RCM-transfer hydrogenation. Another aspect of this ongoing project will be the use of **6** and **11** as removable chiral groups, with a view towards stereoselective synthesis and NMR-based analysis of enantiomeric ratios.

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