Ring Opening and Rearrangement Reactions of Tricyclo[4.2.1.0^{2,5}]nonan-9-one

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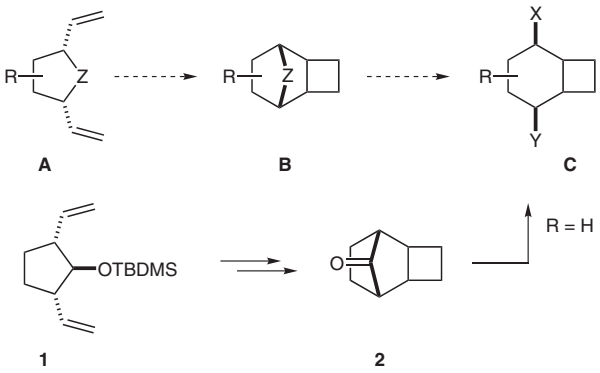
Abstract: A general concept is introduced to synthesize bicyclo[4.2.0]octanes by a sequence of intramolecular copper(I)-catalyzed [2+2] photocycloaddition and subsequent fragmentation reactions. The concept was tested by subjecting the photochemically accessible tricyclo[4.2.1.0^{2,5}]nonan-9-one to four different ring-opening or rearrangement reactions, which allowed for the formation of functionalized bicyclo[4.2.0]octanes by cleavage of the carbonyl bridge. All four methods investigated, Haller–Bauer cleavage, the Schmidt reaction, Baeyer–Villiger oxidation, and rhodium(II)-catalyzed rearrangement were applicable to tricyclo[4.2.1.0^{2,5}]nonan-9-one, but they differed with regard to enantioselectivity. Enzymatic Baeyer–Villiger oxidation was the most successful of these methods, also more successful than metal-catalyzed Baeyer–Villiger oxidation, providing access to enantiomerically enriched lactones, for example in 72% yield and 95% ee. The second-most successful method was with a commercially available rhodium catalyst, which effected ring enlargement of tricyclo[4.2.1.0^{2,5}]nonan-9-one to its homologue in good overall yield and modest enantioselectivity (up to 24% ee).

Key words: cycloadditions, ketones, lactones, photochemistry, ring opening, stereoselective synthesis

Bicyclo[4.2.0]octanes can be prepared by annulation of a four-membered ring to a six-membered ring, the annulation method of choice being a [2+2] cycloaddition. Most often, [2+2] cycloaddition is conducted photochemically, and requires an appropriate six-membered-ring enone as the starting material.[1] Thermal cycloaddition reactions have been reported less frequently, and among these, ketene cycloaddition has been shown to be the most reliable,[2] producing a cyclobutanone. Examples of intramolecular [2+2]-photocycloaddition reactions[3] as entry to the bicyclo[4.2.0]octane ring skeleton are scarce. In contrast, bicyclo[3.2.0]heptanes have often been prepared by the versatile intramolecular copper(I)-catalyzed [2+2] photocycloaddition of 1,6-dienes.[4] The latter reaction nicely complements intermolecular enone photocycloaddition, giving access to different substitution patterns and being compatible with several functional groups. Given these benefits, it is unfortunate that the copper(I)-catalyzed [2+2] photocycloaddition cannot be applied to 1,7-dienes and other 1,ω-dienes. Irradiation experiments with several 1,7-dienes did not result in the formation of bicyclo[4.2.0]octanes.[5] Apparently, copper association to these dienes is disfavored, and the catalytic effect of the metal, which is due to a long-wavelength ($\lambda \cong 250$ nm) charge-transfer excitation of the corresponding complex, does not operate. A possible detour to access bicyclo[4.2.0]octanes by an intramolecular copper(I)-catalyzed [2+2] photocycloaddition is depicted in Scheme 1. With a bridging substituent Z present in 1,7-diene **A**, intramolecular cycloaddition to provide **B** should be possible, and, upon cleavage of the bridge, products of type **C** could be obtained.



Scheme 1 General access to bicyclo[4.2.0]octanes **C** from 1,3-divinyl-substituted cyclopentanes or their heteroanalogues **A**, and more specific access via tricyclo[4.2.1.0^{2,5}]nonan-9-one (**2**), which is available from precursor **1**

In this paper, we describe our attempts to achieve the sequence depicted in Scheme 1 to produce a parent compound (R = H) of class **B**, i.e. tricyclo[4.2.1.0^{2,5}]nonan-9-one (**2**).[6] Compound **2** represents **B** in which a carbonyl group has been employed as the bridging group Z; the carbonyl bridge was incorporated in protected form from silyl ether **1** as starting material, and is accessible to various cleavage and rearrangement reactions. Since substrate **2** is a *meso* compound, any reaction leading to ring-opened products with X ≠ Y will offer the possibility of enantiotopos differentiation. There are fewer precedences for the ring-opening reactions of norbornan-7-ones[7] than for those of norbornan-2-ones. Examples will be discussed for the individual compounds below. On the basis of a literature survey, we decided to have a closer look at the Haller–Bauer cleavage, the Schmidt reaction, Baeyer–Villiger oxidation, and a rhodium-catalyzed ring-expansion reaction.

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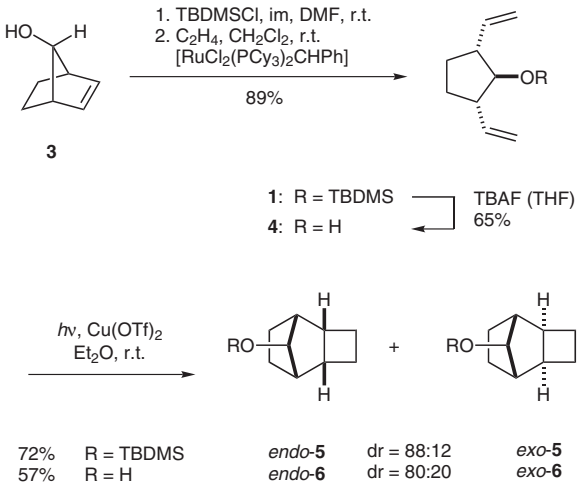
Firstly, tricyclo[4.2.1.0^{2,5}]nonan-9-one (**2**) had to be prepared. Mimicking a general access to compounds of type **B** (Scheme 1), we planned to synthesize the tricyclic substrate **2** by an intramolecular copper(I)-catalyzed [2+2] photocycloaddition. The synthesis commenced with the known alcohol **3** (Scheme 2), which was prepared in three steps from commercially available norbornadiene.[8] Ring-opening metathesis[9] was problematic because of the instability of the product under the reaction conditions. We therefore used the corresponding silyl ether, which was obtained by protection with *tert*-butyldimethylsilyl chloride and imidazole (im) in *N*,*N*-dimethylformamide (99% yield). The subsequent ring-opening metathesis was facile in the presence of the Grubbs first generation catalyst,[10] and proceeded quantitatively within 18 hours under an atmosphere of ethene (90% yield) (Scheme 2). The [2+2] photocycloaddition was attempted with silyl ether **1** and, after deprotection, with the volatile free alcohol **4**. The former reaction gave higher yields and selectivities than the latter, with the *endo*-product, *endo*-**5**, prevailing over *exo*-**5** with a diastereomeric ratio of 88:12 (Scheme 2). The selectivity decrease for the reaction of alcohol **4** is presumably due to coordination of copper to the hydroxy group. The coordination also explains the lower reaction rate for this reaction. While the conversion of **1** into **5** was complete within five hours, the reaction of alcohol **4** required 20 hours for full conversion of starting material.

Silyl ether **5** could be deprotected quantitatively (TBAF, THF) to yield the corresponding alcohol **6** in a diastereomeric ratio of 88:12. Separation of the diastereomers at either stage was impossible on a preparatively useful scale. We consequently continued to work with the *endo*/*exo*-mixture, which was oxidized to ketone **2** by use of *o*-iodoxybenzoic acid (IBX)[11] in dimethyl sulfoxide as oxidant (89% yield). The ketone was used in this form, i.e. as an *endo*/*exo*-mixture (dr = 88:12) for all subsequent reactions. It has been noted, however, that after most ring-opening or rearrangement reactions the purified product was exclusively derived from the *endo*-starting material.



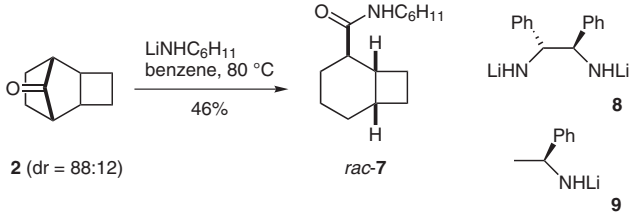
Scheme 2 Synthesis of silyl ethers **5** and alcohols **6** from known norbornenol **3**[8] by ring-opening metathesis and intramolecular copper(I)-catalyzed [2+2] photocycloaddition (im = imidazole)

Yields given in the subsequent schemes (see below) are not corrected for loss of *exo*-isomer, but were calculated on the basis of the mole equivalents of *endo*/*exo*-mixture, thus allowing for a theoretical maximum of 88% yield of *endo*-derived product. The configuration of the major *endo*-diastereomer was proved by characteristic NOE contacts (H-3/4, δ = 2.18 to H-7/8, δ = 1.85).

Haller–Bauer cleavage of compound **2** was investigated. Non-enolizable ketones can be cleaved into the corresponding acids or amides by treatment with hydroxide or amide as base (Haller–Bauer reaction or Haller–Bauer cleavage).[12] The cleavage of norbornan-7-ones was intensively studied and beautifully incorporated into several natural product syntheses by Mehta.[13] The regioselectivity of the Haller–Bauer cleavage has been extensively studied[14] and there are cases in which enantiomerically pure chiral ketones can lead to enantiomerically pure products via configurationally stable carbanions.[15] The reaction attracted our interest because Ishihara and Yano had reported in 2004 a kinetic resolution of 2-phenylcyclohexanone with chiral lithium bases.[16]

In a first set of experiments, we checked whether the title compound **2** underwent Haller–Bauer cleavage reactions under standard conditions. Indeed, reactions with potassium *tert*-butoxide (benzene, r.t., 62%)[17] and with sodium amide (benzene, reflux, 89%) proceeded cleanly and in good chemical yields. The application of a primary amide such as lithium hexylamide, as previously used by Ishihara and Yano, was successful, but resulted in lower yields (46%) than those obtained from the sodium amide reaction (Scheme 3). Best results were obtained when 2.2 equivalents of the amide were used in refluxing benzene. In refluxing tetrahydrofuran the yield amounted to only 14%. Attempts to use catalytic amounts (0.1 equiv) of lithium diisopropylamide to promote the cleavage in tetrahydrofuran at room temperature were not efficient (10% yield).

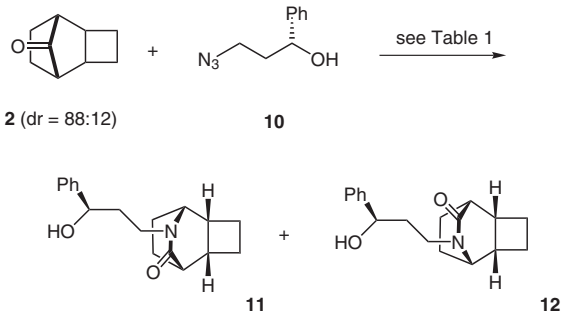
The secondary amide *rac*-**7** was isolated as a pure diastereomer with the relative configuration shown in Scheme 3. The yield decreased when RNH^- was used instead of NH_2^-; this indicates that the reaction, which likely proceeds by a rate-determining attack of the amide at the carbonyl carbon atom,[18] is highly sensitive towards the steric bulk of the base. In this respect, it did not come as a big surprise – but still was disappointing to note – that the chiral amine anions **8** and **9** (Scheme 3) were not suited to promote the desired cleavage under a variety of condi-



Scheme 3 Haller–Bauer cleavage of title compound **2** with lithium hexylamide to yield racemic bicyclo[4.2.0]octanone *rac*-**7**; structures of chiral amide bases **8** and **9**

tions. Starting material was recovered unchanged. Further experiments were not conducted.

The Schmidt reaction was investigated next. The classical Schmidt reaction[19] employs hydrogen azide as the reagent to convert a ketone into the corresponding secondary amide. The reaction has been previously applied to norbornan-7-ones, e.g. to nortricyclanone.[7e] Searching for a method which would possibly allow differentiation of the enantiotopic positions of ketone **2**, we found the use of chiral enantiomerically pure azides attractive. Aubé et al. have developed an elegant method, which relies on the use of chiral azido alcohols and which has been employed to desymmetrize prochiral ketones, e.g. 4-*tert*-butylcyclohexanone.[20] A typical chiral alcohol used by Aubé et al. in their studies is (*R*)-3-azido-1-phenylpropan-1-ol (**10**, Scheme 4). With this alcohol the desymmetrization of 4-*tert*-butylcyclohexanone was conducted in remarkable diastereoselectivity (dr = 95:5). It was also noted, however, that bicyclic *meso*-ketones were less susceptible to desymmetrization. Our plan was to employ alcohol **10** for a first screening, and if significant yields and diastereoselectivities were obtained, we would further test other azido alcohols.



Scheme 4 Schmidt reaction of title compound **2** with chiral alcohol **10** to give the diastereomeric tertiary amides **11** and **12**

The reaction of compound **2** with chiral alcohol **10** should lead to the two diastereomeric tertiary amides **11** and **12** (Scheme 4). The reaction is acid-catalyzed and proceeds via the *O*,*O*-hemiacetal of the ketone and the alcohol. After protonation and dehydration, the resulting onium ion is attacked intramolecularly by the azide nucleophile, which induces the dediazotation/migration sequence.[19] Gratifyingly, product formation was observed by gas–liquid chromatography (GLC) when the boron trifluoride–diethyl ether complex was used as the Lewis acid. The purification and product isolation was difficult and tedious, however. The reaction of ketone **2** in dichloromethane was much slower than the reaction described for cyclohexanones.[19,21] At –20 °C there was no conversion (Table 1, entry 1). The reaction started at room temperature but did not go to completion. It was necessary to heat the mixture to reflux to drive the reaction to completion. The high reaction temperature, in turn, was problematic, due to instability of the starting material under thermal conditions and required the tedious removal of byproducts in subsequent purification steps. The effect of stirring the reaction mixture at room temperature for different time periods prior to reflux was also examined (Table 1, entries 2 and 3). The latter reaction (Table 1, entry 3), in which the mixture was stirred for 12 hours, gave a low, but measurable diastereoselectivity. The key to complete reaction was the switch of the solvent to carbon tetrachloride (Table 1, entries 4 and 5). The reaction was completed at room temperature after 12 hours (Table 1, entry 4). In an optimized run (Table 1, entry 5), a yield of 83% could be achieved.

Table 1 Optimization of the Diastereoselective Schmidt Reaction of Compounds **2** and **10** To Yield Compounds **11** and **12**[a]

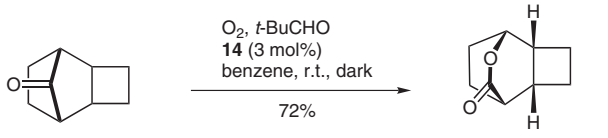
Entry	Lewis acid	Solvent	Reaction conditions	Yield[b] (%)	dr[c]
1	$BF_3{\cdot}OEt_2$	CH_2Cl_2	20 °C, 10 h	–	–
2	$BF_3{\cdot}OEt_2$	CH_2Cl_2	0 °C to r.t., 1 h, then reflux, 12 h	22	50:50
3	$BF_3{\cdot}OEt_2$	CH_2Cl_2	0 °C to r.t., 12 h, then reflux, 5 h	22	56:44
4	$BF_3{\cdot}OEt_2$	CCl_4	r.t., 12 h	64	–[d]
5	$BF_3{\cdot}OEt_2$	CCl_4	–20 °C to r.t., 36 h	83	58:42

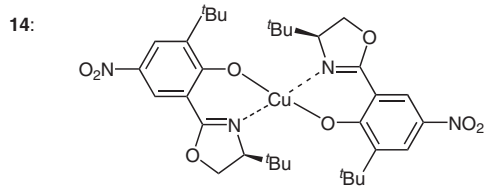
[a] See Scheme 4.
[b] Yield of isolated products (**11** and **12** combined).
[c] The dr of **11** and **12** was determined by NMR analysis of the product mixture.
[d] Appropriate signals could not be separated in the ^{1}H NMR spectrum, but the ^{13}C NMR spectrum showed signals of both diastereomers with equal height (i.e., dr = ~50:50).

It was disappointing that the diastereomeric ratio for the reaction of **2** with **10** to give **11** and **12** never exceeded 60:40 (Scheme 4, Table 1). Although the reaction can be used for the synthesis of pure amide enantiomers after separation of the diastereomers and cleavage of the auxiliary, the low selectivity made this route unattractive. An optimization beyond the variation of reaction conditions was not indicated, because the low selectivity achieved with the standard alcohol established that the tricyclic starting material **2** was not an optimal substrate for the diastereoselective Schmidt reaction.

Baeyer–Villiger oxidation, examined next, is generally applicable to ketones, and it was readily shown that ketone **2** could be oxidized to the corresponding lactone *rac*-**13** (Scheme 5) by *m*-chloroperbenzoic acid in dichloromethane (79% yield). There were two obvious alternatives for a possible enantioselective route to lactone **13** and its enantiomer *ent*-**13**: the use of a chiral transition-metal complex as catalyst[22] or the application of an enzymatic process.[23] Both options were checked in parallel. The success of the chiral copper(II) complex **14** (Scheme 5) in enantiotopos-differentiating Baeyer–Villiger oxidations of bicyclic and tricyclic ketones[24] made this catalyst our first choice for the transition-metal-catalyzed route. The use of benzene as the solvent and the exclusion of light to avoid any uncatalyzed background reactions were crucial for the success of the reaction. Un-

der these conditions, the *endo*-diastereomer of ketone **2** was converted into the enantioenriched (32% ee) lactone **13** (Scheme 5). The *exo*-diastereomer did not react and was recovered unchanged. Interestingly, the use of benzaldehyde instead of pivalaldehyde as oxygen carrier did result in oxidation of both *endo*- and *exo*-isomers of ketone **2**, but neither this, nor other modifications resulted in improved enantioselectivities.

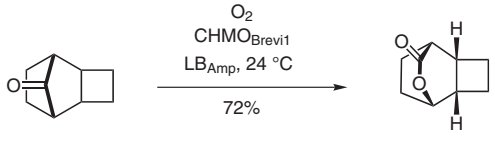




Scheme 5 Enantioselective Baeyer–Villiger oxidation, catalyzed by the chiral copper(II) complex **14**, of the ketone *endo*-**2** (*exo*-**2** did not react) to give lactone **13**

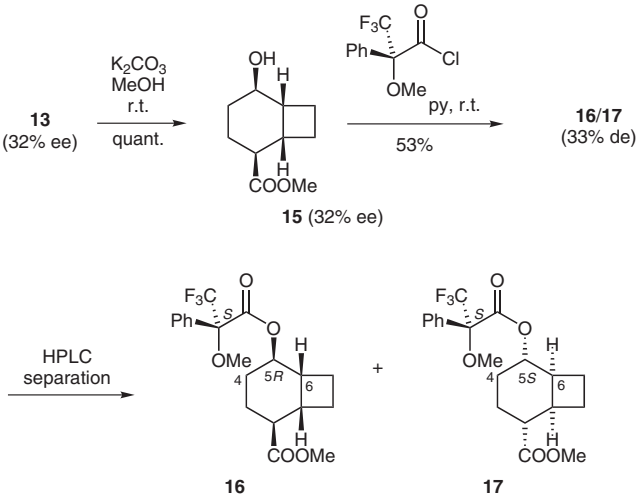
Enzymatic oxidation reactions were conducted with whole-cell systems. Previous work had shown that norbornan-7-ones[25] and norbornen-7-ones[26] can be oxidized enantioselectively. Our own experiments were conducted in a standardized setup, which allowed for rapid screening of recombinant *Escherichia coli* whole-cell-expression systems overexpressing Baeyer–Villiger monooxygenases (BVMO). In 12- or 24-well plates, 0.5 mg ketone per mL media was used, and the cultures were incubated for 24 hours at 24 °C. After that, the samples were extracted and analyzed by gas–liquid chromatography. Perhaps the most important result is that the flavin-dependent cyclohexanone monooxygenase, $CHMO_{Brevi2}$, and the cyclopentanone monooxygenase, $CPMO_{Coma}$, produced lactone **13** (75% and 86% ee, respectively), while $CHMO_{Brevi1}$ and $CHMO_{Brachy}$ gave predominantly the enantiomeric product *ent*-**13** (96% and 92% ee, respectively). As previously observed in the metal-catalyzed reaction, the *exo*-diastereomer of ketone **2** was not oxidized. The reaction of **2** to provide *ent*-**13**, catalyzed by $CHMO_{Brevi1}$, was conducted on preparative scale (0.1 g ketone) and yielded the product in 72% yield with an enantiomeric excess of 95% ee (Scheme 6).

The well-established Mosher method[27] was employed to prove the absolute configuration of lactones **13** and *ent*-**13** (Scheme 7). Lactone **13** was quantitatively ring-opened by treatment with potassium carbonate in methanol, and the resulting δ-hydroxy ester **15** was O-acylated with the corresponding (*R*)-(methoxy)(phenyl)(trifluoromethyl)acetyl chloride (Scheme 7). It was shown that the lactone opening proceeds without racemization. We intentionally worked with a mixture, which was only



Scheme 6 Enantioselective enzymatic Baeyer–Villiger oxidation of the ketone *endo*-**2** (*exo*-**2** did not react) to give lactone **13** (LB_{Amp} = Luria–Bertami medium supplemented with ampicillin)

enantiomerically enriched with lactone **13**, but also contained its enantiomer *ent*-**13**, so that we could obtain a diastereomeric mixture of acylation products **16** and **17**. As there is a change in priority according to the Cahn–Ingold–Prelog nomenclature, the stereogenic center of the (methoxy)(phenyl)(trifluoromethyl)acetyl group is formally (*S*)-configured. As expected, the diastereomeric excess corresponded to the enantiomeric excess of the starting lactone, and the major diastereomer was separated from the minor diastereomer by semiprepreparative HPLC (ZR-Carbon, MeCN–H_2O, 1:1) (Scheme 7). Because of the preferred conformation of the (methoxy)(phenyl)(trifluoromethyl)acetyl ester, in which its methoxy group is antiperiplanar to the carbonyl group, and the hydrogen atom at C-5 is synperiplanar to the O–CO bond, the phenyl group exerts a shielding effect at the protons adjacent to the stereogenic center C-5. Accordingly, a downfield shift at H-6 is expected for the (5*R*)-configuration, and a downfield shift at H-4 is expected for the (5*S*)-configuration. Indeed, in the major diastereomer **16**, to which the (5*R*)-configuration was assigned (Scheme 7), the proton H-6 resonated at δ = 2.62 and the H-4 protons at δ = 1.83 and 1.77. The ^1H–^1H COSY NMR spectrum revealed signals for the minor diastereomer **17** at δ = 2.50 for H-6 and at δ = 1.87 and 1.80 for the H-4 protons.



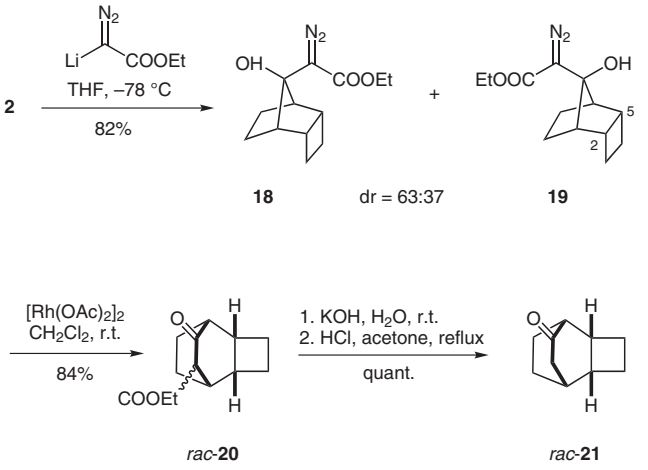
Scheme 7 Proof of absolute configuration of ketone **13** on the basis of the Mosher method

To the best of our knowledge, this is the first proof of the configuration of a product obtained by Baeyer–Villiger oxidation of a norbornan-7-one. Previous experiments for

norbornen-7-ones[26] conducted with cyclohexanone monooxygenase (E.C. 1.14.13.22) are difficult to compare.

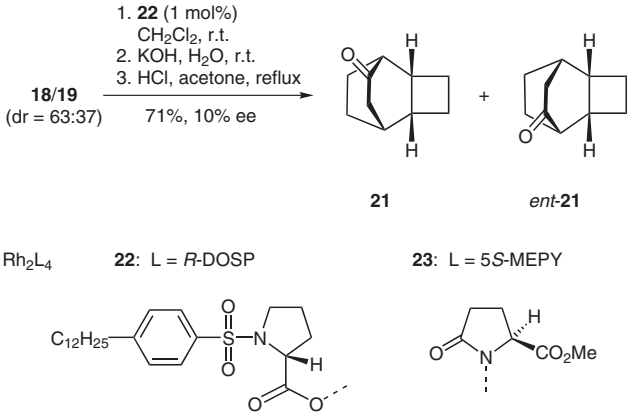
Rhodium(II)-catalyzed rearrangement was next examined. The rearrangement of β-diazo alcohols to the corresponding ketones[28] is an alternative to the long-established Tiffeneau–Demjanov rearrangement.[29] Like the latter, it can be used for the ring enlargement of cyclic ketones. Most frequently, the diazo group is introduced by addition of α-diazocarboxylates to ketones[30] and the rearrangement of the α-diazo-β-hydroxycarboxylates so obtained results primarily in β-oxocarboxylates, which are easily decarboxylated. In the presence of Lewis acids the two-step sequence of carbonyl addition/rearrangement can be conducted in one pot.[31] The rhodium-catalyzed dediazotization/rearrangement was studied by Pellicciari and Nagao.[32] In unsymmetrically substituted ketones the less substituted group usually migrates, while a phenyl group has a higher migration aptitude than an alkyl substituent. To the best of our knowledge, a rhodium-catalyzed rearrangement of α-diazo-β-hydroxycarboxylates has not yet been used for the differentiation of enantiotopic positions.

In preliminary experiments, we investigated the feasibility of the addition/rearrangement sequence in the racemic series. A smooth reaction between ketone **2** and lithiated ethyl α-diazoacetate resulted in a mixture of the two achiral, diastereomeric alcohols **18** and **19** (Scheme 8). The relative configuration was proved for the minor diastereomer **19** by a weak NOE signal between the hydroxy proton and H-2/5 of the ring. Treatment of the mixture **18/19** with catalytic amounts of the rhodium(II) acetate dimer (1 mol%) resulted in a smooth rearrangement to the racemic β-keto ester *rac*-**20** (Scheme 8). The decarboxylation of this product, to give the ketone *rac*-**21**, was induced by saponification and subsequent acidification of the resulting carboxylate (Scheme 8). Smooth decarboxylation to the ketone *rac*-**21** was also observed during GLC analysis of *rac*-**20**.



Scheme 8 Preparation of diazo alcohols **18** and **19** by carbonyl addition to ketone **2** and their consecutive reactions, i.e. rhodium-catalyzed rearrangement to β-keto ester *rac*-**20**, whose decarboxylation gave the ketone *rac*-**21**

Since the ring expansion of achiral ketone **2** to the chiral ketone **21** proceeded in an overall yield of 69%, and since the regioselective ring opening of ketone **21** is straightforward,[33] studies towards an enantioselective rearrangement were warranted. A matter of concern was that a complete separation of alcohols **18** and **19** could be achieved neither by column chromatography nor by HPLC. Provided that an enantiotopos-differentiating catalyst was found, it was clear that alcohols **18** and **19** should lead preferentially to different enantiomers with the very same catalyst. This disadvantage in mind we undertook experiments with the commercially available catalysts **22** and **23** (Scheme 9). With the mixture **18/19** (dr 63:37) as obtained from the addition reaction (Scheme 8) used on a preparative scale, catalyst **22** delivered ketone **21** in 71% yield and in a small but detectable 10% ee (Scheme 9).



Scheme 9 Enantioselective rhodium-catalyzed rearrangement of diazo alcohols **18/19** to ketones **21** and *ent*-**21**

The rhodium catalyst **23** (Scheme 9) showed no activity in the desired reaction (Table 2, entry 9). Further studies were undertaken to elucidate the influence of the diastereomeric composition of the substrate on the enantiomeric excess (Table 2). As anticipated (see above), one alcohol (**19**) was preferentially converted into one enantiomeric product **21** while – with the same catalyst **22** – its diastereomer **18** produced more of the isomer *ent*-**21** (cf. Table 2, entries 2 and 6).

Interestingly, minor diastereomer **19** seems to be more susceptible to an asymmetric induction by the catalyst. The use of a 15:85 mixture of **18/19** resulted in a **21**/*ent*-**21** enantiomeric ratio of 62:38 (23% ee, Table 2, entry 1), while the use of an 81:19 mixture of **18/19** gave product *ent*-**21** in only 10% ee (Table 2, entry 6). Even with almost pure diastereomer **18**, the enantiomeric ratio rose only to 58:42 (15% ee, Table 2, entry 8). Since the temperature could not be varied extensively (Table 2, entries 3–5) its influence remained low, although from this series it appears as if there was a slight increase of selectivity with a decrease in temperature. But when entries 6 and 7 of Table 2 are compared, no such effect is observed. It is unfortunate that compound **19** was not obtained diaste-

Table 2 Influence of Diastereomeric Composition and Conditions in the Reaction of **18/19** on the Enantiomeric Ratio of the Chiral Ketones **21**/*ent*-**21**[a]

Entry	dr (**18**/**19**)	Conditions[b]	er[c] (**21**/*ent*-**21**)	ee[d] (%)
1	15:85	cat. **22**, CH_2Cl_2, r.t., 6 h	62:38	23
2	22:78	cat. **22**, CH_2Cl_2, 5 °C, 12 h	56:44	12
3	63:37	cat. **22**, CH_2Cl_2, r.t., 8 h	45:55	10
4	63:37	cat. **22**, CH_2Cl_2, 0 °C, 12 h	46:54	8
5	63:37	cat. **22**, CH_2Cl_2, –20 °C, then 0 °C, 12 h	46:54	8
6	81:19	cat. **22**, CH_2Cl_2, r.t., 12 h	45:55	10
7	81:19	cat. **22**, CH_2Cl_2, 5 °C, 12 h	44:56	11
8	99:1	cat. **22**, CH_2Cl_2, 5 °C, 12 h	42:58	15
9	63:37	cat. **23**, CH_2Cl_2, r.t., 4 d	–	–

[a] Reaction depicted in Scheme 9.
[b] Decarboxylation occurred thermally on GLC injection. The er obtained by this method was identical to the er determined after saponification and decarboxylation (Scheme 9).
[c] The er was determined by GLC on a chiral stationary phase.
[d] The ee was calculated from the er.

reomerically pure, as with catalyst **22**, >30% ee would be predicted.

The configuration assignment of ketones **21** and *ent*-**21** was tentatively based on their CD spectra. The spectrum of ketone **21** shows a negative Cotton effect at 300 nm. The octant rule[34] for ketones predicts a negative Cotton effect for enantiomer **21**: six atoms lie on a nodal plane and have only low contributions to the optical rotation. For ketone **21**, three atoms (C-3, C-4, C-5) are located in a negative and one (C-10) in a positive octant, which should result in an overall negative Cotton effect.

In summary, four different ring-opening or ring-expansion reactions could be successfully applied to tricyclo[4.2.1.0^{2,5}]nonan-9-one (**2**). With regard to enantioselectivity, the enzymatic Baeyer–Villiger oxidation proved to be most successful, generating ketone **13** or its enantiomer *ent*-**13** in high enantiomeric excesses (86% ee and 96% ee). The second notable enantiotopos-differentiating reaction was achieved with the chiral commercially available rhodium catalyst **22**, which resulted in the homologation of **2** to provide **21** in up to 23% ee. While the stereospecific conversion of this homologation product into a ring-opened product (e.g., by Baeyer–Villiger oxidation)[32] is straightforward, the catalyst needs to be optimized. The Haller–Bauer cleavage and the Schmidt reaction were applicable to ketone **2**, but efficient enantiotopos differentiation could not be achieved. Further research will be devoted to optimizing the rhodium-catalyzed reaction and to applying this method and the enzymatic Baeyer–Villiger oxidation to other photochemically generated bicyclic ketones.

All reactions involving water-sensitive chemicals were carried out in flame-dried glassware with magnetic stirring under argon. Anhyd CH_2Cl_2 was distilled from CaH_2, and anhyd THF and Et_2O were distilled from Na prior to use. Anhyd EtOH and MeOH were distilled from Na. Anhyd Et_3N and DIPEA were distilled from CaH_2. Common solvents (Et_2O, pentane, EtOAc, CH_2Cl_2, MeOH) were distilled prior to use. All other solvents and reagents were used as received. TLC was performed on glass plates (silica gel 60, F_{254}, 0.25 mm) by coloration with ceric ammonium molybdate (CAM) or phosphomolybdic acid (PMA). Column chromatography was performed on silica gel 60 (230–400 mesh) (ca. 50 g per 1 g of material to be separated) with the eluent mixture indicated. ^{1}H and ^{13}C NMR spectra were recorded at 303 K on Bruker DMX-360 and AV-500 spectrometers. Chemical shifts are reported relative to TMS as internal standard. Apparent multiplets, which occur as a result of coincidental equality of coupling constants to those of magnetically nonequivalent protons, are marked as virtual (virt). The multiplicities of the ^{13}C NMR signals were determined by DEPT experiments and standard two-dimensional NMR experiments. *anti*-Bicyclo[2.2.1]hept-2-en-7-ol (**3**) was synthesized by a reported procedure.[8]

tert-Butyl(*anti*-2,5-divinylcyclopentyloxy)dimethylsilane (1) Protection of 3

anti-Bicyclo[2.2.1]-hept-2-en-7-ol (**3**; 1.10 g, 10.0 mmol) and imidazole (1.36 g, 20.0 mmol) were dissolved in anhyd DMF (25 mL). A soln of 50% TBDMSCl in toluene (5.20 mL, 4.52 g, 15 mmol) was added slowly to the mixture at r.t., and the soln was stirred overnight. H_2O (250 mL) was added, and the aqueous layer was extracted with Et_2O (3 × 150 mL). The combined organic layers were washed with brine (150 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was subjected to column chromatography (silica gel, pentane); this gave protected **3** as *anti*-(bicyclo[2.2.1]hept-2-en-7-yloxy)-*tert*-butyldimethylsilane.

Yield: 4.24 g (99%); colorless liquid; R_f = 0.60 (pentane).

IR (film): 2955 (s), 2857 (s), 1361 (m), 1256 (s), 1129 (s), 1112 (s), 897 (s), 836 (s) cm^{-1}.

^{1}H NMR (360 MHz, $CDCl_3$):δ = 5.94 (t, *J* = 2.2 Hz, 2 H), 3.44 (s, 1 H), 2.43–2.40 (m, 2 H), 1.83–1.78 (m, 2 H), 0.93–0.87 (m, 2 H), 0.87 (s, 9 H), 0.03 (s, 6 H).

^{13}C NMR (90.6 MHz, $CDCl_3$): δ = –4.7 (CH_3), 18.1 (C), 21.9 (CH_3), 25.9 (CH_2), 46.4 (CH), 82.9 (CH), 134.3 (CH).

MS (EI, 70 keV): *m*/*z* (%) = 224 (60) [M$^+$], 209 (5) [M$^+$ – CH_3], 167 (100) [M$^+$ – C_4H_9], 139 (30) [M$^+$ – C_6H_{13}], 75 (90) [$C_2H_7SiO^+$].

Anal. Calcd for $C_{13}H_{24}OSi$ (224.41): C, 69.58; H, 10.78. Found: C, 69.85; H, 10.79.

Ring-Opening Metathesis of Protected 3

anti-(Bicyclo[2.2.1]hept-2-en-7-yloxy)-*tert*-butyldimethylsilane (637 mg, 3.0 mmol) was dissolved in anhyd CH_2Cl_2 (30 mL) under an atmosphere of ethene (balloon). The Grubbs catalyst [Ru(=CHPh)Cl_2(PCy_3)$_2$] (74.0 mg, 90 μmol, 3 mol%) was added. The soln was stirred vigorously under an atmosphere of ethene at r.t. for 3 h. Silica gel (2 g) was added, the solvent was removed under reduced pressure, and the resulting brown powder was directly subjected to purification by column chromatography (silica gel, pentane); this gave **1**.

Yield: 703 mg (93%); colorless liquid; R_f = 0.28 (pentane).

IR (film): 2956–2857 (s, br, C-H), 1370 (m), 1256 (s), 1123 (s), 912 (s), 868 (s), 836 (s), 776 (s) cm^{-1}.

^{1}H NMR (360 MHz, $CDCl_3$): δ = 5.74 (ddd, *J* = 17.1, 10.2, 8.3 Hz, 2 H), 5.04 (ddd, *J* = 17.1, 2.0, 1.1 Hz, 2 H), 4.99 (ddd, *J* = 10.2, 2.0, 0.9 Hz, 2 H), 3.53 (t, *J* = 7.9 Hz, 1 H), 2.49–2.39 (m,

2 H), 1.94–1.84 (m, 2 H), 1.52–1.42 (m, 2 H), 0.88 (s, 9 H), 0.02 (s, 6 H).

^{13}C NMR (90.6 MHz, $CDCl_3$): δ = –3.6 (CH_3), 18.2 (C), 26.1 (CH_3), 27.8 (CH_2), 52.5 (CH), 83.9 (CH), 114.9 (CH_2), 141.4 (CH).

MS (EI, 70 keV): *m*/*z* (%) = 252 (10) [M^+], 237 (2) [$M^+ - CH_3$], 195 (100) [$M^+ - C_4H_9$], 119 (15) [$M^+ - C_6H_{17}OSi$], 91 (10), 75 [$C_2H_7SiO^+$] (50).

Anal. Calcd for $C_{15}H_{28}OSi$ (252.47): C, 71.36; H, 11.18. Found: C, 71.18; H, 11.18.

anti-2,5-Divinylcyclopentanol (4)

Compound **1** (314 mg, 1.20 mmol) was dissolved in anhyd THF (6 mL) and 1 M TBAF in THF (2.40 mL, 2.40 mmol) was added. After the mixture had stirred at r.t. for 1 h, silica gel (0.5 g) was added. The solvent was removed under reduced pressure, and the dry powder was placed on top of a chromatographic column for purification (silica gel, pentane–Et_2O, 1:1); this gave **4**.

Yield: 111 mg (65%); volatile, colorless liquid; R_f = 0.47 (pentane–Et_2O, 1:1).

IR (KBr): 3362 (s, br), 2955 (s), 2872 (s), 1640 (s), 1089 (s) cm^{-1}.

^{1}H NMR (360 MHz, $CDCl_3$): δ = 5.78 (ddd, *J* = 17.1, 10.2, 8.0 Hz, 2 H), 5.12 (ddd, *J* = 17.1, 1.8, 1.0 Hz, 2 H), 5.05 (ddd, *J* = 10.2, 1.8, 0.8 Hz, 2 H), 3.46 (t, *J* = 9.1 Hz, 1 H), 2.46–2.34 (m, 2 H), 1.98–1.87 (m, 2 H), 1.64 (br s, 1 H), 1.54–1.45 (m, 2 H).

^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 27.4 (CH_2), 51.6 (CH), 81.8 (CH), 115.5 (CH_2), 140.6 (CH).

MS (EI, 70 keV): *m*/*z* (%) = 138 (1) [M^+], 120 (5) [$M^+ - H_2O$], 94 (15) [$M^+ - C_2H_4O$], 91 [$M^+ - C_2H_7O$]; 83 (45) [$M^+ - C_3H_3O$], 79 (50) [$M^+ - C_4H_{11}$], 70 (85) [$C_4H_6O^+$], 67 (65) [$M^+ - C_4H_7O$], 55 (100) [$C_4H_7^+$].

Copper-Catalyzed [2+2] Photocycloaddition; General Procedure

A 15-mL quartz tube with a rubber seal was charged with $Cu(OTf)_2$ (10 mol%) under argon, and the copper salt was dissolved in anhyd, degassed Et_2O (10 mL). The appropriate substrate was added, and the tube was filled with additional Et_2O (final diene concentration ca. 50 mmol/L). The mixture was shaken or treated with ultrasound until the $Cu(OTf)_2$ was mostly dissolved. The tube was irradiated at r.t. (254 nm, Rayonet RPR-2537 Å) until conversion was complete (by GLC and TLC analysis). The Et_2O soln was then added to a mixture of 25% aq NH_3 (15 mL) and ice (15 g). After the ice had melted, the layers were separated. The aqueous layer was saturated with NaCl and extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), filtered, and concentrated.

tert-Butyldimethyl(tricyclo[4.2.1.0^{2,5}]non-9-yloxy)silane (5)

According to the general procedure, compound **1** (126 mg, 560 μmol) and $Cu(OTf)_2$ (18.0 mg, 50.0 μmol, 10 mol%) were dissolved in anhyd Et_2O (15 mL) and irradiated at 254 nm for 5 h. Workup and column chromatography (silica gel, pentane) gave **5**.

Yield: 91.0 mg (72%); *endo*/*exo* = 88:12; colorless oil.

endo-5

R_f = 0.55 (pentane).

IR (film): 2953 (s), 2856 (s), 1375 (m), 1256 (s), 1125 (s), 1060 (s), 907 (s), 863 (s), 835 (s) cm^{-1}.

^{1}H NMR (360 MHz, $CDCl_3$): δ = 3.76 (s, 1 H), 2.53–2.47 (m, 2 H), 1.99–1.95 (m, 4 H), 1.87–1.83 (m, 2 H), 1.83–1.78 (m, 4 H), 0.87 (s, 9 H), 0.03 (s, 6 H).

^{13}C NMR (90.6 MHz, $CDCl_3$): δ = –4.7 (CH_3), 18.2 (C), 19.9 (CH_2), 21.2 (CH_2), 25.9 (CH_3), 35.8 (CH), 44.9 (CH), 81.7 (CH).

MS (EI, 70 keV): *m*/*z* (%) = 252 (10) [M^+], 237 (2) [$M^+ - CH_3$], 224 (1) [$M^+ - C_2H_4$], 195 (100) [$M^+ - C_4H_9$], 119 (20) [$M^+ - C_6H_{16}OSi$], 91 (15) [$C_7H_7^+$], 75 (70) [$C_2H_7SiO^+$], 59 (10).

HRMS (EI): *m*/*z* calcd for $C_{15}H_{28}OSi$: 252.1909; found: 252.1906.

Anal. Calcd for $C_{15}H_{28}OSi$ (252.47): C, 71.36; H, 11.18; Si, 11.12. Found: C, 71.31; H, 11.30; Si, 11.13.

Tricyclo[4.2.1.0^{2,5}]nonan-9-ol (6)

*Method A (from **4**)*: According to the general procedure, alcohol **4** (28.0 mg, 200 μmol) and $Cu(OTf)_2$ (6 mg, 20.0 μmol, 10 mol%) were dissolved in anhyd Et_2O (15 mL) and irradiated at 254 nm for 20 h. Workup and column chromatography (silica gel, pentane–Et_2O, 1:1) gave alcohol **6**.

Yield: 16.0 mg (120 μmol, 57%); *endo*/*exo* = 80:20; colorless crystals.

*Method B (from **5**)*: Photoproduct **5** (1.24 g, 4.90 mmol) was dissolved in anhyd THF (10 mL) and 1 M TBAF in THF (ca. 5% H_2O content; 12.0 mL, 12.0 mmol) was added. After the mixture had stirred at r.t. for 12 h, most of the THF was removed under reduced pressure, H_2O (100 mL) was added, and the soln was extracted with Et_2O (2 × 100 mL). The aqueous layer was saturated with NaCl and again extracted with Et_2O (2 × 50 mL). The combined organic layers were washed with brine (80 mL), dried (Na_2SO_4), and filtered, and the solvent was removed under reduced pressure. Column chromatography (silica gel, pentane–Et_2O, 1:1) gave alcohol **6**.

Yield: 678 mg (100%); colorless crystals

endo-6

R_f = 0.33 (pentane–Et_2O, 1:1).

IR (KBr): 3362 (s, br), 2968 (s), 2939 (s), 2879 (s), 1110 (s), 1048 (s) cm^{-1}.

^{1}H NMR (360 MHz, $CDCl_3$): δ = 3.88 (s, 1 H), 2.55–2.52 (m, 2 H), 2.00–1.95 (m, 6 H), 1.94–1.91 (m, 2 H), 1.81–1.77 (m, 3 H).

^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 19.8 (CH_2), 20.9 (CH_2), 36.2 (CH), 44.5 (CH), 81.8 (CH).

MS (EI, 70 keV): *m*/*z* (%) = 138 (1) [M^+], 120 (10) [$M^+ - H_2O$], 110 (10) [$M^+ - C_2H_4$], 91 (90) [$C_7H_7^+$], 79 (100) [$C_6H_7^+$], 77 (50) [$C_6H_5^+$], 67 (45) [$C_4H_3O^+$], 55 (30) [$C_3H_3O^+$], 53 (30) [$C_4H_5^+$], 51 (30) [$C_4H_3^+$].

Anal. Calcd for $C_9H_{14}O$ (138.21): C, 78.21; H, 10.21. Found: C, 77.76; H, 10.23.

Tricyclo[4.2.1.0^{2,5}]nonan-9-one (2)

Alcohol **6** (566 mg, 4.09 mmol) was dissolved in DMSO (30 mL), and IBX (2.80 g, 10.2 mmol) was added. After stirring for 48 h at r.t., the reaction mixture was hydrolyzed by the addition of H_2O (250 mL), and the mixture was extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with brine (100 mL), dried (Na_2SO_4), and filtered, and the solvent was removed under reduced pressure. Purification of the residue by column chromatography (silica gel, pentane–Et_2O, 1:1) gave ketone **2**.

Yield: 495 mg (89%); easily melting and volatile solid; mp 32 °C; R_f = 0.34 (pentane–Et_2O, 1:1).

IR (KBr): 2959 (s), 1764 (vs), 1453 (m) cm^{-1}.

endo-2

^{1}H NMR (360 MHz, $CDCl_3$): δ = 2.85–2.78 (m, 2 H), 2.28–2.22 (m, 4 H), 2.20–2.14 (m, 2 H), 1.90–1.80 (m, 4 H).

^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 18.2 (CH_2), 20.6 (CH_2), 31.3 (CH), 42.0 (CH), 214.3 (C).

MS (EI, 70 keV): *m*/*z* (%) = 136 (20) [M$^+$], 108 (20) [M$^+$ – CO], 93 (20) [M$^+$ – C_3H_7], 91 (15) [$C_7H_7^+$], 79 (100) [$C_6H_7^+$], 77 (20) [$C_6H_5^+$], 67 (50) [$C_4H_3O^+$].

Anal. Calcd for $C_9H_{12}O$ (136.19): C, 79.37; H, 8.88. Found: C, 79.49; H, 8.60.

N-Hexylbicyclo[4.2.0]octane-2-carboxamide (7)

To a soln of *n*-hexylamine (108 μL, 82.0 μg, 808 mmol) in anhyd benzene (5 mL), 2.5 M *n*-BuLi in hexane (351 μL, 239 μg, 808 mmol) was added at 0 °C. After 15 min, ketone **2** (50.0 mg, 367 mmol) was added and the soln was refluxed for 12 h. After cooling to r.t., the soln was hydrolyzed by the addition of H_2O (5 mL) and extracted with Et_2O (5 × 10 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), and filtered, and the solvent was removed under reduced pressure. Purification by column chromatography (silica gel, pentane–Et_2O, 8:2) gave **7** as a single diastereomer.

Yield: 40.0 mg (46%); colorless crystals; R_f = 0.12 (pentane–Et_2O, 8:2).

IR (KBr): 3287 (m), 2960 (s), 2927 (s), 2858 (s), 1642 (s), 1549 (s), 1240 (m), 1207 (m) cm^{-1}.

^{1}H NMR (360 MHz, $CDCl_3$, 300 K): δ = 5.39 (br s, 1 H), 3.22 (dt, *J* = 7.1, 5.9 Hz, 2 H), 2.53–2.64 (m, 1 H), 2.30–2.40 (m, 1 H), 2.23 (ddd, *J* = 11.6, 9.3, 3.6 Hz, 1 H), 2.03–2.15 (m, 1 H), 1.93 (virt quin, *J* ≅ 9.3 Hz, 1 H), 1.72–1.87 (m, 2 H), 1.61–1.66 (m, 1 H), 1.38–1.57 (m, 6 H), 1.22–1.35 (m, 7 H), 0.88 (t, *J* = 6.8 Hz, 3 H).

^{13}C NMR (90.6 MHz, $CDCl_3$, 300 K): δ = 14.0 (CH_3), 21.2 (CH_2), 22.5 (CH_2), 23.6 (CH_2), 25.7 (CH_2), 26.3 (CH_2), 26.5 (CH_2), 26.7 (CH_2), 29.7 (CH_2), 31.5 (CH_2), 33.4 (CH), 36.6 (CH), 39.4 (CH), 47.5 (CH), 176.0 (C).

MS (EI, 70 eV): *m*/*z* (%) = 237 (49) [M$^+$], 222 (15) [M$^+$ – CH_3], 209 (85) [M$^+$ – C_2H_4], 194 (38) [M$^+$ – CONH], 180 (18) [M$^+$ – C_4H_9], 169 (100) [M$^+$ – C_5H_8], 67 (62) [$C_5H_5^+$], 55 (23) [$C_4H_7^+$].

HRMS (EI): *m*/*z* calcd for $C_{15}H_{27}NO$: 237.2093; found: 237.2092.

7-(3-Hydroxy-3-phenylpropyl)-7-azatricyclo[4.2.2.0^{2,5}]decan-8-one (11, 12)

Lactone **2** (50.0 mg, 367 μmol) and alcohol **10** (98.0 mg, 551 μmol) were dissolved in CCl_4 (3 mL) and the mixture was cooled to –20 °C. At that temperature, BF_3·OEt_2 (140 μL, 156 mg, 110 μmol) was added dropwise (gas evolution) and the same temperature was maintained for another 4 h. Afterwards the temperature was raised to –10 °C (12 h) and then to r.t. (24 h). The solvent was then removed under reduced pressure and the yellow residue was hydrolyzed by the addition of 15% aq KOH (2 mL). After 15 min, H_2O (5 mL) was added and the soln was extracted with CH_2Cl_2 (5 × 10 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), and filtered, and the solvent was removed under reduced pressure. Purification of the residue by column chromatography (silica gel, pentane–EtOAc, 1:1) gave an inseparable mixture of diastereomers **11** and **12**.

Yield: 87.0 mg (83%); colorless liquid; R_f = 0.15 (pentane–EtOAc, 1:1).

IR (film): 3364 (m, br), 2954 (s), 2930 (s), 2860 (s), 1640 (s), 1455 (s), 1284 (s), 1068 (m), 745 (m), 693 (m) cm^{-1}.

^{1}H NMR (360 MHz, $CDCl_3$, 300 K): δ = 7.20–7.39 (m, 5 H), 5.28 (s, 1 H), 4.49–4.62 (dd, *J* = 10.2, 3.2 Hz, 1 H), 4.03–4.16 (m, 1 H), 3.49–3.55 (m, 1 H), 3.02–3.14 (m, 1 H), 2.53–2.80 (m, 3 H), 1.62–2.41 (m, 10 H). [Note that the ^{1}H NMR signals of the two diastereomers **11** and **12** overlap, except for H-3′: δ = 4.56 (dd, *J* = 10.3, 3.3 Hz) and δ = 4.52 (dd, *J* = 10.1, 3.1 Hz), which were used for the determination of the dr. The other signals are therefore reported for the 50:50 mixture of **11** and **12**.]

^{13}C NMR (90.6 MHz, $CDCl_3$, 300 K): δ = 17.3 (CH_2), 18.5 (CH_2), 18.6 (CH_2), 18.8 (CH_2), 19.4 (CH_2), 21.8 (CH_2), 22.7 (CH_2), 33.0 (CH), 33.9 (CH), 36.4 (CH), 37.4 (CH), 38.6 (CH_2), 38.7 (CH_2), 41.4 (CH), 41.4 (CH), 41.9 (CH_2), 42.0 (CH_2), 57.5 (CH), 57.7 (CH), 69.8 (CH), 70.0 (CH), 125.5 (CH), 125.6 (CH), 127.0 (CH), 127.0 (CH), 128.2 (CH), 128.2 (CH), 144.1 (C), 144.1 (C), 176.7 (C). [Note that the ^{13}C NMR signals are separated for the two diastereomers **11** and **12**, except for CO (δ = 176.7) and C-2′ (δ = 17.3)].

MS (EI, 70 eV): *m*/*z* (%) = 285 (18) [M$^+$], 267 (11) [M$^+$ – H_2O], 238 (1) [M$^+$ – CH_3OH_2], 238 (1) [$C_{16}H_{16}NO^+$], 231 (1) [M$^+$ – C_4H_2], 212 (2) [M$^+$ – C_4H_9O], 207 (1) [M$^+$ – C_6H_6], 179 (77) [$C_{11}H_{17}NO_2^+$], 165 (100) [$C_{10}H_{15}NO_2^+$], 109 (18) [$C_8H_{13}^+$], 97 (8) [$C_6H_9O^+$], 91 (15) [$C_7H_7^+$], 79 (62) [$C_6H_7^+$], 67 (15) [$C_4H_3O^+$], 55 (15) [$C_3H_3O^+$], 50 (1) [$C_4H_2^+$].

HRMS (EI): *m*/*z* calcd for $C_{18}H_{24}NO_2$ [M + H$^+$]: 286.1807; found: 286.1799.

7-Oxatricyclo[4.2.2.0^{2,5}]decan-8-one (13/*ent*-13)

Method A (Cu-catalyzed): A mixture of (*S*)-2-*tert*-butyl-6-(4-*tert*-butyl-4,5-dihydrooxazol-2-yl)-4-nitrophenol[35] (9.0 mg, 27.0 mmol, 2.6 mol%) and $Cu(OAc)_2$·H_2O (2.40 mg, 12.0 mmol, 1.1 mol%) in H_2O-saturated benzene (5 mL) was stirred under an atmosphere of O_2 (balloon) for 15 min. The reaction flask was then covered with Al foil to exclude any light, and ketone **2** (145 mg, 1.07 mmol) and 98% *t*-BuCHO (120 μL, 92.0 mg, 1.07 mmol) were added. The soln was stirred vigorously under an atmosphere of O_2 (balloon). Every 24 h another 1 equiv *t*-BuCHO (120 μL, 92.0 mg, 1.07 mmol) was added until a total amount of 3 equiv had been added. After 4 d, Et_2O (10 mL) was added and the soln was washed with sat. aq $NaHCO_3$ (5 mL) and brine (5 mL). After drying (Na_2SO_4) and filtration of the mixture, the solvent was removed under reduced pressure. Purification by column chromatography (silica gel, pentane–H_2O, 8:2) gave lactone **13**.

Yield: 118 mg (72%); 32% ee; colorless crystals.

Method B (enzymatic): A baffled Erlenmeyer flask was charged with fresh LB_{Amp} media (250 mL), inoculated with a preculture of a recombinant *E. coli* strain ($CHMO_{Brevi1}$) (2.5 mL, 1%), and the culture was incubated at 37 °C and 120 rpm in an orbital shaker for 2 h. Afterwards an IPTG stock soln (50 μL) was added to a final concentration of 0.004 wt/v, and addition of ketone **2** (97 mg, 0.712 mmol) and β-cyclodextrin (808 mg, 0.712 mmol) followed. The culture was incubated for 24 h at 24 °C and 120 rpm in an orbital shaker. The biomass was removed by centrifugation (15 min, 4000 rpm) and the aqueous layer was extracted with Et_2O (3 × 250 mL). The combined organic layers were dried (Na_2SO_4) and filtered, and the solvent was removed under reduced pressure. After column chromatography (silica gel, pentane–Et_2O, 7:3) lactone *ent*-**13** was isolated.

Yield: 78 mg (72%); 95% ee; colorless crystals; $[\alpha]_D^{20}$ –41.5 (*c* 10.0 g·L^{-1}, CH_2Cl_2).

rac-13

Mp 107 °C; R_f = 0.10 (pentane–Et_2O, 7:3).

IR (KBr): 2959 (s), 1752 (s), 1006 (m, C–O) cm^{-1}.

^{1}H NMR (360 MHz, $CDCl_3$): δ = 4.65–4.61 (m, 1 H), 2.87–2.69 (m, 2 H), 2.59–2.53 (m, 1 H), 2.40 (dddd, *J* = 13.5, 10.7, 4.9, 2.3 Hz, 1 H), 2.28–2.09 (m, 4 H), 2.00–1.74 (m, 3 H).

^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 17.3 (CH_2), 17.9 (CH_2), 19.1 (CH_2), 21.3 (CH_2), 32.2 (CH), 34.5 (CH), 38.5 (CH), 78.9 (CH), 176.6 (C).

MS (EI, 70 keV): *m*/*z* (%) = 152 (10) [M$^+$], 123 (2) [M$^+$ – HCO], 97 (5) [M$^+$ – C_4H_7], 70 (10) [M$^+$ – C_5H_9O].

HRMS (EI): *m*/*z* calcd for $C_9H_{12}O_2$: 152.0837; found: 152.0835.

Anal. Calcd for $C_9H_{12}O_2$ (152.19): C, 71.03; H, 7.95. Found: C, 70.91; H, 8.00.

Methyl 5-Hydroxybicyclo[4.2.0]octane-2-carboxylate (15)

K_2CO_3 (118 mg, 854 mmol) was added to a soln of lactone **13** (33% ee; 52.0 mg, 342 mmol) in anhyd MeOH (2 mL). After stirring at r.t. for 1 h, the soln was neutralized by the addition of dilute AcOH and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), and filtered, and the solvent was removed under reduced pressure. After column chromatography (silica gel, pentane–Et_2O, 1:1), ester **15** was obtained.

Yield: 62.0 mg (99%); colorless liquid; R_f = 0.17 (pentane–Et_2O, 1:1).

IR (film): 3416 (s, br), 2949 (s), 2868 (s), 1773 (vs), 1435 (s), 1274 (s), 1196 (s), 1064 (m) cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$, 300 K): δ = 3.73–3.79 (m, 1 H), 3.68 (s, 3 H), 2.63 (dd virt q, $J \cong 7.4, 4.6, 2.6$ Hz, 1 H), 2.43–2.48 (m, 1 H), 2.34–2.41 (m, 1 H), 2.03–2.10 (m, 1 H), 1.95–2.03 (m, 1 H), 1.66–1.86 (m, 5 H), 1.57–1.66 (m, 1 H), 1.49 (br s, 1 H).

^{13}C NMR (90.6 MHz, $CDCl_3$, 300 K): δ = 21.3 (CH_2), 23.6 (CH_2), 25.4 (CH_2), 29.5 (CH_2), 35.2 (CH), 41.2 (CH), 43.7 (CH), 51.6 (q, CH_3), 69.4 (d, CH), 176.2 (s, CO).

MS (EI, 70 eV): *m/z* (%) = 184 (2) [M^+], 166 (3) [$M^+ - H_2O$], 155 (6) [$M^+ - C_2H_5$], 152 (31) [$M^+ - CH_3OH$], 124 (23) [$M^+ - C_2H_4O_2$], 107 (54) [$M^+ - C_6H_5$], 96 (77) [$M^+ - C_4H_8O_2$], 91 (31), 79 (100) [$C_6H_7^+$], 67 (62) [$C_4H_3O^+$], 59 (100) [$C_3H_7O^+$], 55 (69) [$C_4H_7^+$], 51 (23) [$C_4H_3^+$].

Anal. Calcd for $C_{10}H_{16}O_3$ (184.232): C, 65.19; H, 8.75%. Found: C, 65.58; H, 8.65%.

Methyl (2*R*,5*S*)- and (2*S*,5*R*)-5-{[(*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]oxy}bicyclo[4.2.0]octane-2-carboxylate (16 and 17)

Ester **15** (41.0 mg, 223 μmol) was dissolved in anhyd py (8.20 mL), and (*R*)-(–)-(methoxy)(phenyl)(trifluoromethyl)acetyl chloride (41.6 μL, 56.2 mg, 223 μmol) was added by syringe. After the mixture had stirred at r.t. for 2.5 h, the solvent was removed under reduced pressure and the residue was purified by column chromatography (silica gel, pentane–H_2O, 2:8); this gave the Mosher esters **16** (*RS*) and **17** (*SS*) as a mixture of diastereomers; yield: 47 mg (53%); dr = 2:1, 33% de. Separation of the diastereomers was possible by semi-preparative HPLC (Sigma-Aldrich ZR-Carbon, 150 × 4.6 mm, MeCN–H_2O, 1:1, 30 mL/min, 215 nm), which gave pure main diastereomer **16** (dr >95:5). HPLC: t_R = 18.40 min (**16**), 19.82 min (**17**). Where possible, chemical shifts in the NMR spectra are reported separately below.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.53–7.48 (m, 2 H), 7.41–7.38 (m, 3 H), 5.08 (virt q, $J \cong 3.5$ Hz, 1 H), 3.65 (s, 3 H), 3.54 (q, $^5J_{HF}$ = 1.0 Hz, 3H) (**16**), 3.53 (q, $^5J_{HF}$ = 1.0 Hz, 3 H) (**17**), 2.65–2.54 (m, 2 H) (**16**), 2.65–2.54 (m, 1 H) (**17**), 2.50 (ddd, J = 10.8, 8.1, 3.5 Hz, 1H) (**16**), 2.54–2.46 (m, 2 H) (**17**), 2.15–1.52 (m, 8 H).

^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 175.6 (CO), 165.9 (CO), 132.4 (C), 129.5 (CH), 128.4 (CH), 127.3 (CH), 124.9, 121.7 (CF_3), 74.3 (CH) (**16**), 74.2 (CH) (**17**), 55.3 (CH_3), 51.7 (CH_3), 43.8 (CH) (**16**), 43.7 (CH) (**17**), 37.4 (CH), 35.1 (CH), 26.6 (CH_2) (**17**), 26.4 (CH_2) (**16**), 25.5 (CH_2) (**16**), 25.4 (CH_2) (**17**), 23.2 (CH_2) (**17**), 23.2 (CH_2) (**16**), 21.3 (CH_2) (**17**), 21.2 (CH_2) (**16**).

^{19}F NMR (235.4 MHz, $CDCl_3$): δ = –72.12 (CF_3) (**16**), –72.15 (CF_3) (**17**).

MS (EI, 70 eV): *m/z* (%) = 369 (1) [$M^+ - CH_3O$], 189 (78) [$C_9H_8OF_3^+$], 167 (63) [$C_{10}H_{15}O_2^+$], 135 (50) [$C_9H_{11}O^+$], 107 (100) [$C_8H_8^+$], 79 (50) [$C_6H_7^+$], 59 (6) [$C_3H_7O^+$], 41 (6) [$C_3H_5^+$].

Ethyl Diazo(9-hydroxytricyclo[4.2.1.0^{2,5}]non-9-yl)acetate (18, 19)

A soln of LDA [441 mmol; prepared from *i*-Pr_2NH (62.0 μL, 45 μg, 441 μmol) and 2.6 M *n*-BuLi in hexane (192 μL, 130 μg, 441 μmol) in anhyd THF (1 mL)] was added dropwise over 15 min to a cooled soln (–78 °C) of **2** (50.0 mg, 367 μmol) and ethyl diazoacetate (39.0 μL, 42.0 mg, 367 μmol) in THF (5 mL). After stirring at –78 °C for 1.5 h, the reaction mixture was hydrolyzed by fast addition of sat. aq NH_4Cl (2 mL) and warmed to r.t. Then H_2O (10 mL) was added, and the mixture was extracted with Et_2O (3 × 15 mL). The combined organic layers were washed with sat. aq $NaHCO_3$ (10 mL) and brine (10 mL), dried (Na_2SO_4), and filtered, and the solvent was removed under reduced pressure. After column chromatography (silica gel, pentane–Et_2O, 8:2) diazo esters **18** and **19** were isolated as a mixture of diastereomers.

Yield: 75 mg (82%); dr 67:33; yellow liquid; R_f = 0.09 (pentane–Et_2O, 8:2).

IR (KBr): 3566–3325 (br), 2943 (s), 2361 (s), 2067 (s), 1691 (vs), 1301 (s), 1171 (s), 1038 (s) cm^{-1}.

^1H NMR (360 MHz, $CDCl_3$, 300 K): δ = 4.23 (q, J = 7.1 Hz, 2 H), 2.83–2.92 (m, 1 H), 2.50–2.64 (m, 2 H), 2.18–2.28 (m, 2 H), 1.88–2.13 (m, 6 H), 1.46–1.61 (m, 2 H) 1.29 (t, J = 7.1 Hz, 3 H).

^{13}C NMR (90.6 MHz, $CDCl_3$, 300 K): δ = 14.5 (CH_3), 19.1 (CH_2), 22.1 (CH_2), 36.9 (CH), 46.4 (CH), 60.8 (CH_2), 86.8 (C), 133.1 (C), 166.9 (C).

MS (EI, 70 eV): *m/z* (%) = 250 (3) [M^+], 222 (53) [$M^+ - N_2$], 204 (13) [$M^+ - C_2H_6O$], 176 (65) [$M^+ - C_3H_6O_2$], 169 (42) [$M^+ - C_6H_9$], 131 (22) [$M^+ - C_3H_6O_2$], 120 (60) [$C_7H_4O_2^+$], 115 (46) [$C_6H_{11}O_2^+$], 93 (43) [$C_6H_5O^+$], 80 (100) [$C_6H_8^+$], 67 (64) [$C_5H_7^+$], 55 (49) [$C_4H_7^+$], 41 (46) [$C_3H_5^+$].

HRMS (EI): *m/z* calcd for $C_{13}H_{18}N_2O_3$: 250.1317; found: 250.1318.

Ethyl 8-Oxotricyclo[4.2.2.0^{2,5}]decane-7-carboxylate (20)

A soln of **18** and **19** (dr 67:33; 72.0 mg, 288 mmol) in anhyd CH_2Cl_2 (1 mL) was added to a soln of $[Rh(OAc)_2]_2$ (1.27 mg, 2.87 μmol, 1 mol%) in anhyd CH_2Cl_2 (4 mL), and the soln was stirred for 12 h at r.t. The catalyst was then removed by filtration, and the solvent was removed under reduced pressure. After column chromatography (silica gel, pentane–Et_2O, 8:2), *rac*-**20** was obtained as a mixture of diastereomers.

Yield: 54.0 mg (84%); dr 67:33; colorless liquid; R_f = 0.26 (pentane–Et_2O, 8:2) (PMA).

IR (KBr): 2935 (s), 1743 (s), 1715 (s), 1257 (s), 1147 (s), 1031 (s) cm^{-1}.

^1H NMR (360 MHz, $CDCl_3$, 300 K): δ = 4.09–4.29 (m, 2 H), 3.22 (d, J = 2.4 Hz, 1 H) (minor diastereomer), 2.99 (virt t, $J \cong 2.1$ Hz, 1 H) (major diastereomer), 2.48–2.88 (m, 2 H), 2.10–2.44 (m, 8 H), 1.66–1.97 (m, 2 H), 1.17–1.34 (m, 3 H).

^{13}C NMR (90.6 MHz, $CDCl_3$, 300 K): δ = 14.1 (CH_3), 16.2 (CH_2), 17.7 (CH_2), 18.7 (CH_2), 20.6 (CH_2), 31.6 (CH), 35.2 (CH), 35.8 (CH), 45.0 (CH), 58.3 (CH), 61.1 (CH_2), 169.5 (C), 209.7 (C).

MS (EI, 70 eV): *m/z* (%) = 222 (100) [M^+], 194 (35) [$M^+ - CO$], 176 (80) [$M^+ - C_2H_5OH$], 168 (42) [$M^+ - C_4H_6$], 148 (38) [$M^+ - C_3H_6O_2$], 115 (60) [$C_6H_{11}O_2^+$], 91 (55) [$C_7H_7^+$], 80 (95) [$C_5H_5O^+$], 67 (65) [$C_5H_7^+$], 55 (30) [$C_4H_7^+$], 53 (28) [$C_4H_4^+$], 41 (42) [$C_3H_5^+$].

HRMS (EI): *m/z* calcd for $C_{13}H_{18}O_3$: 222.1256; found: 222.1251.

Screening of Catalysts and Conditions in the Reaction of Esters 18 and 19 To Give Ketones 21 and *ent*-21; General Procedure

To preform the catalyst, the ligand (4 equiv) and $[Rh(OAc)_2]_2$ were stirred for 5 min in CH_2Cl_2. Then the soln was brought to the appropriate temperature (cf. Table 2) and the diazo esters **18** and **19** were slowly added. After the appropriate time an aliquot was taken, and

filtered through a pad of silica gel (EtOAc), and the ee was determined by GC. Decarboxylation to ketones **21** was achieved thermally in the injection block heated at 230 °C. The ee determined this way was the same as that determined by previous decarboxylation.

Tricyclo[4.2.2.0^{2,5}]decan-7-one (21)

Ester **20** (31.0 mg, 139 mmol) was dissolved in dilute aq KOH (2 mL) and the soln was stirred at r.t. for 1 h. Then the soln was acidified with diluted HCl, and acetone (3 mL) was added. The soln was refluxed until no starting material was detectable (TLC, ca. 30 min). H_2O (3 mL) was added and the soln was extracted with Et_2O (3 × 15 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), and filtered, and the solvent was removed under reduced pressure. After column chromatography (silica gel, pentane–Et_2O, 9:1) ketone **21** was obtained.

Yield: 21 mg (100%); colorless liquid; R_f = 0.23 (pentane–Et_2O, 9:1).

IR (film): 2917 (s), 1713 (vs), 1482 (m), 1404 (m) cm^{-1}.

^{1}H NMR (360 MHz, $CDCl_3$, 300 K): δ = 2.43–2.70 (m, 2 H), 1.99–2.38 (m, 10 H), 1.51–1.77 (m, 2 H).

^{13}C NMR (90.6 MHz, $CDCl_3$, 300 K): δ = 18.3 (CH_2), 18.5 (CH_2), 20.0 (CH_2), 20.9 (CH_2), 31.6 (CH), 31.9 (CH), 35.0 (CH), 44.4 (CH_2), 45.5 (CH), 216.8 (C).

MS (EI, 70 eV): *m*/*z* (%) = 150 (98) [M$^+$], 122 (22) [M$^+$ – CO], 108 (63) [$C_8H_{14}^+$], 93 (75) [$C_6H_5O^+$], 79 (100) [$C_6H_7^+$], 67 (67) [$C_4H_3O^+$], 54 (31) [$C_4H_6^+$], 41 (31) [$C_3H_5^+$].

HRMS (EI): *m*/*z* calcd for $C_{10}H_{14}O$: 150.1045; found: 150.1045.

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