Enol Activation

DOI: 10.1002/anie.201409591

Design and Enantioselective Synthesis of Cashmeran Odorants by Using "Enol Catalysis"**

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Dedicated to Roger L. Snowden on the occasion of his 65th birthday

Abstract: *Novel Cashmeran odorants were designed by molecular modeling. Their short syntheses involve a novel asymmetric Brønsted acid catalyzed Michael addition of unactivated α-substituted ketones. This key transformation was realized by utilizing a new type of enol activation catalysis and affords different cyclic ketones bearing α-quaternary stereocenters in good to excellent yields and with high enantioselectivity. Subsequent McMurry coupling and Saegusa–Ito oxidation furnished the enantiopure target odorants, one enantiomer of which indeed possesses the typical olfactory aspects of Cashmeran.*

Cashmeran (**1**)[1] is a unique synthetic odorant which combines floral-fruity musky with conifer-type woody aspects in perfect balance. High proportions of around 25% of Cashmeran were used by Maurice Roucel in "Dans Tes Bras" (Frederic Malle, 2008), and by Alessandro Gualtieri in "Duro" (Nasomatto, 2007). Since Cashmeran is also a key ingredient of trendy oud/agarwood accords, it has recently become an increasingly popular ingredient in the perfumer's palette. Although this odor profile is highly desirable in perfumery, almost no other odorants are known with the typical odor profile of Cashmeran.[2] The enantiomers of **1** possess similar odors and the same odor thresholds (*th*), within the standard deviation (see the Supporting Information). Herein, we present the successful design and enantioselective preparation of a new class of bicyclic Cashmeran odorants. Our synthetic efforts towards these targets inspired the development of a novel Brønsted acid catalyzed asymmetric Michael addition and of "enol catalysis" as a new and potentially widely useful organocatalytic activation mode.

Very recently, a *tert*-butyl-substituted 5,5-dimethylcyclopentenyl butanone (**2**) was discovered that displays a typical Cashmeran odor with pronounced musk facets in the direction of Moxalone but with a rather high odor threshold of 25.0 ng L^{-1} air compared to that of Cashmeran (**1**, 0.89 ng L^{-1} air, Figure 1).[4] The importance of the γ,δ-double bond for the musk character was proven by comparison of hydrogenated and dehydrogenated analogues of **2**;[4] however, the central parameters are the relative distances of the bulky quaternary C atoms to the osmophoric carbonyl function (H-bond acceptor) in the flexible butanone side chain of **2**. Fixing this in the hydroindenone ring systems **3** and **4** leads to an overlay,[3] in which the *tert*-butyl group of **2** matches one *gem*-dimethyl group of Cashmeran (**1**), while the other bulky quaternary C atom of **2** mimics the α-methylene unit of the cyclohexenone ring of **1** (Figure 1). In the target structures **3** and **4**, the quaternary carbon atom C-7a becomes a stereocenter, and being close to the carbonyl osmophore, it can be expected to have a differentiating influence on the

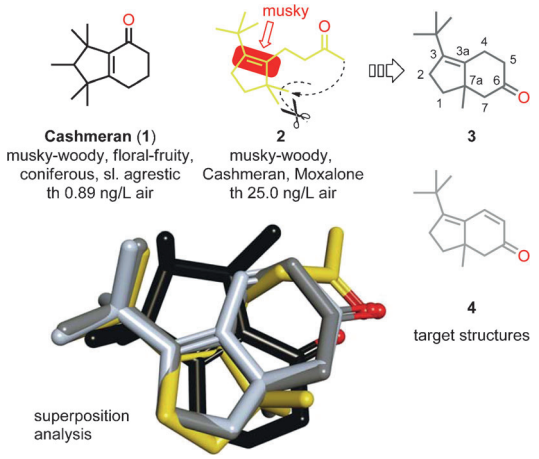

Figure 1. Design of new potential Cashmeran odorants **3** and **4** (shaded greys) by molecular modeling with the MOE software package on Cashmeran (**1**, black) and a recently discovered dimethylcyclopentenyl butanone lead **2** (gold) with related odor.[3] The feature overlap (*F*), which describes the configurational similarity as a negative value of the probability density overlap function, has a value of −102.4. The grand alignment score of the probability-density overlap is −78.6.

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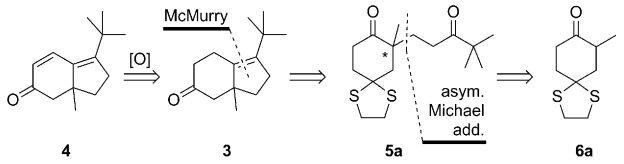
[**] We gratefully thank Alain E. Alchenberger and Dominique Lelievre for the olfactory evaluations, Katarina Grman for the odor threshold and *ee* determinations, Dr. Gerhard Brunner and Dr. Veronika Zelenay for NMR experiments and IR spectra, and Dr. Fabian Kuhn and Dr. Susanne Kern for mass-spectroscopic data. We are grateful for the generous support from the Max Planck Society, the Fonds der Chemischen Industrie (fellowship to G.P.), as well as to the X-ray, GC, and HPLC departments of the MPI für Kohlenforschung, to Hendrik van Thienen and Dr. Sébastien Prevost for the large scale synthesis of (*S*)-TRIP, and to Prof. Dr. Nuno Maulide and Dr. Marco Luparia for helpful discussions.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201409591.

olfactory properties. Structures **3** and **4** both superimpose well on the leads **1** and **2**, and these compounds thus constitute Cashmeran odorants bearing quaternary stereocenters.

As shown in the retrosynthetic analysis (Scheme 1), our strategy for the construction of **3** and **4** involves a regioselective and enantioselective Michael addition of *tert*-butyl vinyl ketone (**7a**) to the monoprotected 2-methylcyclohexan-1,4-

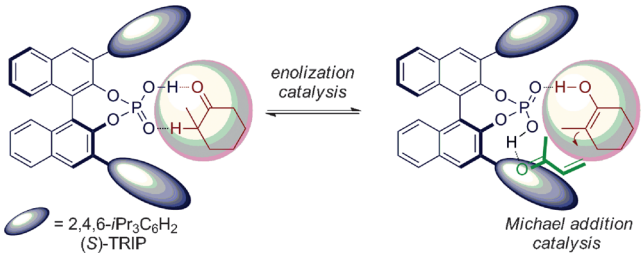


Scheme 1. Retrosynthetic analysis of the targets **3** and **4**.

dione **6a** as the key step, followed by an intramolecular McMurry coupling to install the double bond. The flattened dienone structure **4**, which corresponds better to the planar ring system of Cashmeran (**1**), should then be accessible through a Saegusa–Ito reaction or a related oxidation.

The key transformation is challenging and requires selective modification at the more hindered position of α-substituted ketone **6a**. This problem has previously been addressed by Pfau and d'Angelo, who reported the use of preformed imines derived from (+)-α-methylbenzylamine.[5] Recently, Carter and coworkers[6] disclosed a thiourea-based primary amine catalyzed formation of α-quaternary stereocenters from α-alkyl-substituted cycloalkanones and electron-deficient alkenes, excluding vinyl ketones. In both reports, tautomerization to the thermodynamically favored enamine was observed. However, despite our efforts, the latter methodology gave very poor conversions, whereas the former afforded products with good e.r. values (91:9) but required stoichiometric amounts of enantiopure amine and two additional steps (imine formation/imine cleavage, see the Supporting Information). The limited success of both methods with the challenging substrate combination of the O,O-acetal analogue of **6a** and the bulky vinyl ketone **7a** prompted us to develop a novel strategy.

Despite the versatility of enantiopure all-carbon α,α-disubstituted cyclohexanones as building blocks in organic synthesis, only a limited number of catalytic systems for their synthesis have been reported. In most cases, they involve allylation reactions via π-allyl palladium intermediates[7] or Michael reactions on activated substrates, for example, β-ketoesters or diketones.[8] The formation of isomeric enolates on α-branched ketones is still a major challenge and some allylation protocols have circumvented it with preformed enolates[9] or decarboxylative allylic alkylation[10] under Pd^0 catalysis.[11] Organocatalytic approaches to these stereogenic centers mainly rely on phase transfer[12] or enamine catalysis, and they have almost exclusively been applied to dicarbonyl compounds,[13] and only very recently to α-branched aldehydes.[14] The limited applicability to other substrates, such as simple α-substituted ketones, can be attributed to the difficult formation of the sterically constrained enamine intermediate. Furthermore, when the β-ester functionality is removed, the lack of selectivity in the formation of the most substituted enamine has to be considered. To overcome this limitation, and inspired by the concerted acid–base mechanism found in enzymatic enolization,[15] we envisioned a shift from enamine to enol catalysis through a Brønsted acid catalyzed Michael reaction between **6a** and **7a** (Scheme 2). Acid-catalyzed enolizations are well documented[16] and we hypothesized that

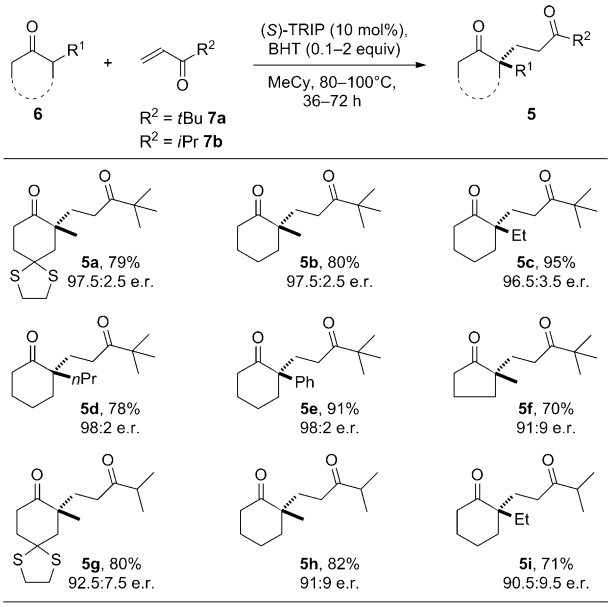


Scheme 2. Design of an asymmetric Brønsted acid catalyzed Michael addition.

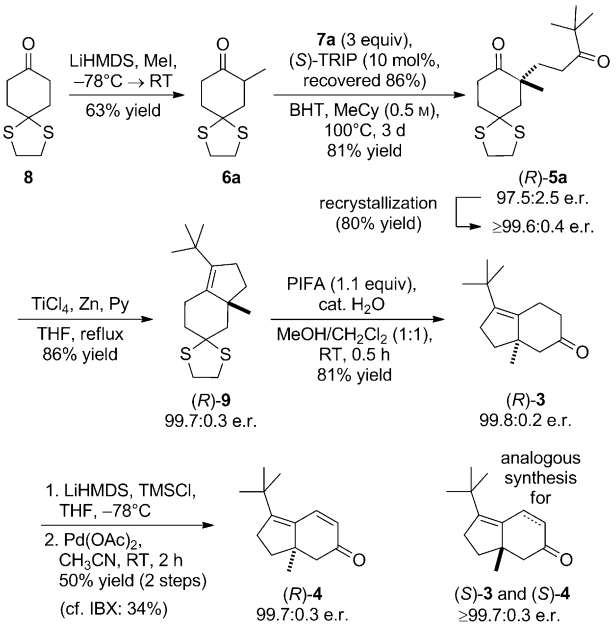
chiral phosphoric acids,[17] for example, (*S*)-TRIP,[18] could accelerate both the enolization and the activation of the electrophile and the nucleophile through their Brønsted acidic P–OH and Brønsted basic P=O moieties, respectively. Chiral Brønsted acids have indeed recently been used in the Robinson annulation of β-ketoester derivatives of 1-indanone with methyl vinyl ketone.[19] Furthermore, simple unsubstituted ketones have been activated by chiral phosphoric acids in aldol reactions with glyoxylate, and in one example a quaternary stereocenter is formed albeit with limited enantioselectivity.[20] However, we are unaware of any successful direct methods that can be used to regio- and enantioselectively form an all-carbon quaternary α-stereocenter on ketones.

We started our investigation by treating ketone **6a** with an excess of enone **7a** in the presence of 10 mol% of different chiral BINOL-derived phosphoric acids or disulfonimides[21] bearing different substituents in the 3 and 3′ positions of the backbone (see the Supporting Information). Thioacetal **6a** was preferred over the corresponding O,O-acetal, which proved unstable under the acidic reaction conditions. When the reaction mixture was heated above 70 °C, most of the phosphoric acids afforded the desired products in moderate yields and with good to excellent enantioselectivity. (*S*)-TRIP, which bears 2,4,6-iPr$_3$C$_6$H$_2$ groups, was found to be superior and interestingly, the enantioselectivity proved to be little influenced by reaction conditions, which allowed the reaction to be run at 100 °C with methylcyclohexane as the solvent. Radical polymerization of the enone was found to be an undesired side reaction, but upon employing 3 equiv of the electrophile and adding of 0.1 equiv of BHT as a radical scavenger, the desired product **5a** could be isolated in 79% yield with 97.5:2.5 e.r. after 3 days. Gratifyingly, diketone **5a** gave crystals suitable for X-ray analysis,[22] which were used to determine the absolute configuration of the products (see the Supporting Information).

We carried out a preliminary investigation into the substrate scope of our new reaction (Scheme 3). Six-membered rings bearing different alkyl chains in the α-position



Scheme 3. Substrate scope of the enantioselective Michael reaction.



Scheme 4. Synthesis of the target odorants **3** and **4** in both enantiomeric forms with high enantiomeric purity (≥99.7:0.3 e.r.). LiHMDS = lithium bis(trimethylsilyl)amide, py = pyridine, PIFA = phenyliodine bis(trifluoroacetate).

reacted smoothly, even at 80 °C, and afforded products **5b**–**5d** in good to excellent yields (78 % to 95 %) and with excellent enantioselectivity (≥96.5:3.5 e.r.) after 36 h. Even α-phenyl-substituted ketones are compatible with the method, and product **5e** could be isolated after 36 h in 91 % yield with 98:2 e.r. Furthermore, five-membered ring substrates could also be employed with only a slight decrease in enantioselectivity (**5f**, 70 % yield, 91:9 e.r.). When the electrophile was switched to isopropyl vinyl ketone (**7b**), conversions were lower owing to faster radical polymerization of the enone. However, upon increasing the amount of electrophile **7b** to 5 equiv and the amount of BHT to 2 equiv and stirring the reaction mixture at 100 °C for 36 h, products **5g**–**5i** could be isolated in good yields (71–82 %) and with good enantioselectivities (91:9 to 92.5:7.5 e.r.).

As depicted in Scheme 4, this novel type of enol activation was then employed for the synthesis of the target structures **3** and **4**. The required substrate **6a** was prepared in 63 % yield through standard enolate alkylation of the commercially available thioacetal **8** with methyl iodide and LiHMDS as the base. The reaction of ketone **6a** under the optimized conditions for the asymmetric Michael reaction furnished the corresponding adduct (*R*)-**5a** in 81 % yield with an e.r. of 97.5:2.5. A single recrystallization from pentane afforded the product with essentially perfect enantiopurity (≥99.6:0.4), and the catalyst could be recovered in 86 % yield and reused without any loss of activity or selectivity. Intramolecular McMurry coupling[23] of the diketone (*R*)-**5a** by using the method developed by Lenoir,[24] and subsequent oxidative deprotection of the thioketal group of (*R*)-**9**[22] with PIFA[25] provided the first target compound (*R*)-**3** as a colorless odoriferous liquid in 70 % overall yield with retained enantioselectivity (99.8:0.2 e.r.). From several methods for the introduction of the α,β-double bond,[26] the Saegusa–Ito oxidation protocol[27] turned out to be the most efficient. Accordingly, (*R*)-**3** was converted via the corresponding trimethylsilyl enol ether (obtained as a 1:1 mixture of regioisomers) into the conjugated target compound (*R*)-**4** (50 % yield over 2 steps, 99.7:0.3 e.r.). Both enantiomers (*S*)-**3** and (*S*)-**4** were prepared with high optical purity in an analogous manner by simply employing (*R*)-TRIP in the key step.

The olfactory properties and odor thresholds of the enantiomeric hydroindenones **3** and **4** are summarized in Figure 2. While (*R*)-**3** possesses some of the fruity aspects of Cashmeran and its enantiomer (*S*)-**3** surprisingly shares the dark woody facet of Cashmeran (**1**), only (*R*)-**4** displays a typical woody-musky Cashmeran odor, but with a higher threshold (15.1 ng L^{-1} air versus 0.89 ng L^{-1} air for **1**). However, compared to the lead structure **2** (25.0 ng L^{-1} air), the activity is increased by 40 % and the character of (*R*)-**4** is closer to that of Cashmeran. Based on these results, an (*R*)-configuration of the methyl group on C-7a seems to be crucial for a Cashmeran odor, and the flattened structure of (*R*)-**4** as compared to (*R*)-**3** increases the affinity towards the corresponding receptors. Furthermore, from the different Cashmeran facets of the enantiomers of hydroindenone **3**, we may

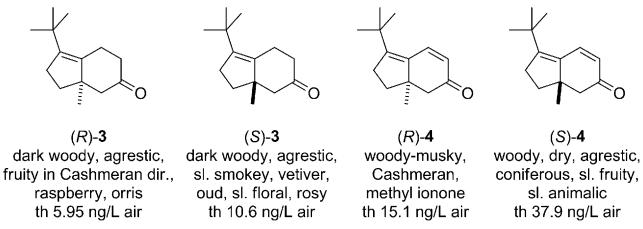


Figure 2. Olfactory properties of the enantiopure target compounds **3** and **4**.

conclude that the perception of Cashmeran-type odorants involves at least two olfactory receptors, and probably more.

In conclusion, we designed novel Cashmeran odorants through molecular modeling and developed a concise synthesis. The key step of the sequence involves a novel Michael addition involving enol activation catalysis, which proved to be rather general. Both enantiomers of the target products **3** and **4** were obtained in an overall yield of 28% and 14%, respectively. (*R*)-**4** proved to be fully complementary to the olfactory receptors for Cashmeran odorants and accordingly, an *R*-configured quaternary carbon in the β-position to the carbonyl osmophore and a flat geometry are required. These first insights into the geometry of the receptors will facilitate the future generation of olfactophore models. Furthermore, the newly developed enol catalysis opens new exciting prospects in asymmetric catalysis.

Experimental Section

General procedure for the Brønsted acid catalyzed Michael reaction: In a screw-cap vial, the α-substituted ketone **6** (0.2 mmol, 1 equiv), 2,6-di-*tert*-butyl-4-methylphenol (0.02 mmol, 0.1 equiv), and (*S*)-TRIP (0.02 mmol, 0.1 equiv) were dissolved in methylcyclohexane (0.2 mL). To this solution, a second solution of the corresponding enone **7** (0.6 mmol, 3 equiv) in methylcyclohexane (0.2 mL) was added. The reaction mixture was stirred at 80–100 °C for 36–72 h. The crude mixture was then allowed to cool to room temperature and directly purified by flash chromatography.

(*R*)-**3** (99.8:0.2 e.r.): $[\alpha]_D^{23} = -29.8$ ($c = 1.10$, EtOH). Odor description: dark woody agrestic odor with fruity aspects in the direction of Cashmeran and nuances of raspberry and orris, and slightly rooty oud and vetiver facets, somewhat recalling epoxy cedrene. The odor is sweeter and fattier than that of the *S*-enantiomer. Odor threshold: 5.95 ng L^{-1} air.

(*S*)-**3** (99.7:0.3 e.r.): $[\alpha]_D^{23} = +30.0$ ($c = 1.04$, EtOH). Odor description: dark woody (woody facet of Cashmeran), agrestic odor with slightly smoky aspects, nuances of vetiver and oud, and slightly floral facets (rosy in Mefrosol direction). The odor is more floral and woody than that of the *R*-enantiomer. Odor threshold: 10.6 ng L^{-1} air.

(*R*)-**4** (99.7:0.3 e.r.): $[\alpha]_D^{23} = +307.4$ ($c = 1.01$, EtOH). Odor description: woody-musky odor reminiscent of Cashmeran with aspects of methyl ionone. The odor is less sweet, musky, and fruity than that of Cashmeran, but more raspberry-like than apple-like in its fruity character and drier in its woody note, containing slightly rooty facets. Odor threshold: 15.1 ng L^{-1} air.

(*S*)-**4** (99.8:0.2 e.r.): $[\alpha]_D^{23} = -311.6$ ($c = 0.96$, EtOH). Odor description: woody, dry, agrestic odor with coniferous aspects and a slightly fruity, animalic, and powdery tonality. Odor threshold: 37.9 ng L^{-1} air.

Received: September 29, 2014
Published online: ■■ ■■, ■■■■

Keywords: Brønsted acid catalysis · enol catalysis · fragrances · Michael addition · structure–activity relationships

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Communications

Enol Activation

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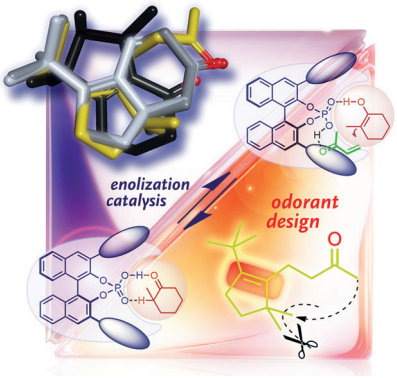
Design and Enantioselective Synthesis of Cashmeran Odorants by Using "Enol Catalysis"



Cashmere Wood is the term perfumers use for the typical odor of Cashmeran. Novel representatives of this family were designed and stereoselectively synthesized through enol activation. The key transformation is a chiral phosphoric acid catalyzed Michael addition of enones to α-substituted ketones to afford all-carbon quaternary stereocenters. Olfactory analysis of the target odorants granted insight into the structural requirements for Cashmeran odorants.