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Formal (4+1)-Cyclization of Ammonium Ylides with Vinylogous *para*-Quinone Methides

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Abstract

The formal (4+1)-cyclization between in situ generated achiral carbonyl-stabilized ammonium ylides and vinylogous *p*-quinone methides can be carried out under operationally simple conditions, leading to two different double bond regioisomers depending on the used conditions. Besides these racemic approaches, also a first proof-of-concept for enantioselective versions of these reactions has been obtained.

Keywords

ammonium ylides; quinone methides; cyclization; regioisomers; stereoselectivity

The spirocyclopentyl *para*-dienone motif can be frequently found in a broad range of biologically active natural products¹. Accordingly, the (asymmetric) synthesis of this class of compounds has been of great interest to the synthetic community^{2,3}. Most of the previously reported synthesis procedures relied on the use of transition metal-based catalysts in combination with carefully chosen (more or less complex) ligands². Alternatively, two recent formal (4+1)-approaches^{3,4} making use of the vinylogous *para*-quinone methides **1** as C4 acceptor molecules for a tandem sequence consisting of a conjugate 1,6-addition/cyclization to give intermediates **4**, followed by immediate vinylcyclopropane rearrangement to the final spirocyclopentyl *para*-dienones **2** have been reported³. Two independent strategies have been developed, using either bromomalonates, **3a** or sulfur ylides (generated *in situ* from sulfonium salts **3**)^{3b} (see Scheme 1a) as C1 synthons for this formal (4+1)-cyclization reaction with the vinylogous *para*-quinone methides **1** in a racemic and highly diastereoselective fashion.

Ammonium ylides⁵ are commonly regarded as the little siblings of sulfur ylides⁶ when it comes to cyclization reactions. However, it was demonstrated rather impressively in the past that often ammonium ylides allow for high enantioselectivities in cyclization reactions where sulfur ylides fail.^{5,7,8} For example, to achieve the first highly enantioselective spirocyclopropanation reaction of *para*-quinone methides **5**, our group recently reported a very selective approach by using simple Cinchona-based ammonium salts **6** as ammonium ylide precursors (Scheme 1b)⁷. Ammonium ylides have also been successfully used for

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formal (4+1) cyclizations in the past⁸ and we have reported the first highly enantioselective ylide-mediated synthesis of 2,3-dihydrobenzofurans as well,⁹ demonstrating the usefulness of simple (a)chiral ammonium ylides to facilitate interesting cyclization reactions where other methods may fail. Based on our experience in using chiral as well as achiral ammonium ylides for different cyclization reactions,^{7,9,10} and inspired by the power of the recently reported (racemic) (4+1)-cyclization reactions of vinylogous *p*-quinone methides **13**, we therefore became interested in elucidating the potential of ammonium ylides to undergo analogous (4+1)-cyclizations with acceptors **1** (Scheme 1c). Besides investigating the outcome of this transformation with simple achiral ammonium ylides (i.e. with respect to diastereo- and regioselectivity), we were also wondering if we would be able to introduce an asymmetric version by using Cinchona alkaloid-based chiral ammonium salts **6** (with R₃N being a Cinchona derivative) for this reaction as well.

All the racemic experiments were carried out with trimethylammonium salts **6** (R₃N = Me₃N), as we found in the past that this amine group is by far the best-suited tertiary amine-based leaving group for ammonium ylide-mediated cyclization reactions.¹⁰ Our initial experiments with achiral amide-based ammonium salts **6** (compare with Scheme 1c, R = NEt₂) turned out to be rather slow, giving only traces of product **2** and traces of intermediate vinylcyclopropane **4.3b**. In contrast, ester-based ammonium salts **6** (R = OEt) reacted significantly faster. Very interestingly, literally our first experiments with the ester-based ammonium salt **6a** and the parent vinyl *p*-quinone methide **1a** in EtOAc with an excess of solid Cs₂CO₃ as a base showed that ammonium ylides behave different from sulfur ylides, as we observed the formation of the double bond regioisomer **8** as well (besides the known *cis*-**2a**; Table 1, entry 1). To the best of our knowledge, formation of this product was not observed when using sulfur ylides,^{3b} and we were therefore wondering whether we could find reaction conditions that either favor product **2a**, or the regioisomer **8a** instead (Table 1 gives an overview of the most significant results). We found that the formation of **8a** is completely suppressed when using only a slight excess of base (entry 2), while at slightly elevated temperature the amount of **8a** is increasing (entry 3). In the case of employing K₃PO₄ as a base, the reaction proceeded significantly slower and no product **8a** was formed (entry 4). When using CH₂Cl₂ as solvent instead of EtOAc (entries 5-8), the reaction was found to be a bit slower but we identified suitable and robust conditions to favor either of the two reaction products. Exclusive formation of product **2a** can be achieved when using between 1 - 2 eq. of solid Cs₂CO₃ (reaction times up to 3 days were necessary to achieve high yields as shown in entry 8). In contrast, increasing the amount of base (entries 6 and 7) favored formation of **8a**, with the highest isolated yield of 67% being obtained when using 10 eq. Cs₂CO₃ (entry 7). Other solvent/base combinations and reaction conditions were tested as well but turned out to be less satisfactory.

With reliable reaction conditions for the selective formation of products **2a** (Table 1, entries 2 or 8) and **8a** (Table 1, entry 7) at hand, we were wondering about the mechanistic pathways leading to these products. For the literature-known product **2a**, a similar tandem reaction mechanism (cyclopropanation to give intermediate **4** first, followed by vinylcyclopropane rearrangement¹¹) as reported by Fan's group when using sulfur ylides can be postulated,^{3b} but it has to be pointed out that we were not able to observe the

postulated spirocyclopropane **4** in any of our reactions. For product **8a**, the mechanistic pathway is not yet clear. A possible double bond migration of the double bond of product **2a** under the basic reaction conditions was clearly ruled out by stirring **2a** with an excess of base (as well as additional CsBr and Me₃N) for 48 h, which did not result in any formation of **8a** at all. This means that the double bond migration has to occur during the cyclization/rearrangement process. We tried to get further insights by using selectively deuterated starting materials **1** and **6** and following the fate of the deuterium in the product,¹² but unfortunately these experiments did not provide any further insights into the pathway towards product **8a**.

For the ammonium ylide-mediated spirocyclopropanation of *p*-quinone methides **5**, a highly asymmetric version of the reaction could be achieved by using rather simple Cinchona alkaloids as chiral amine leaving groups.⁷ Since the proposed mechanism towards cyclopentene **2a** also involves an initial 1,6-addition which is supposed to be the stereo-discriminating step, we were interested if it would be possible to render this reaction enantioselective with a similar approach. To test our hypothesis, we synthesized a library of chiral ammonium salts **6-QD** and tested them for this (4+1)-annulation.

Of the synthesized ylide-precursors, only those containing the 9-O-methylated (R' = Me) Cinchona alkaloids **QD2** and **QD3** were found to be reactive under the optimized reaction conditions (see Table 2), while all the other auxiliaries did not allow for any product formation under conditions A or B (details not given in the Table). For both target reactions (formation of product **2a** under cond. A and formation of **8a** using cond. B) the desired products could be obtained in low yields and moderate enantioselectivities only. While the d.r. of **2a** was in neither case affected by the chiral amine, resulting in predominant formation of the *cis*-isomer (> 90% as observed in the racemic experiments as well), we were never able to reach comparable yields as observed in the racemic approach. Under conditions A (entries 1 and 3) the maximum yield for **2a** was already observed after 24 h and no further improvement could be achieved by prolonging the reaction times (which is in sharp contrast to the racemic protocol). For the formation of **8a**, the reaction was in general even slower, but here a reaction time of 3 days was found to be slightly beneficial (entries 2 and 4), but again no satisfying yields were possible.

Unfortunately, we were not able to improve both, yield and enantioselectivity further by optimizing the reaction conditions or varying the chiral auxiliaries. The lower yields in these asymmetric reactions, compared to the racemic protocol, may most likely be rationalized by the poorer leaving group ability of the Cinchona alkaloids compared to Me₃N10c and we have also observed a similar limitation in a previous study aiming on ammonium ylide-mediated cyclopropanation reactions.^{10e}

Because of these rather disappointing yields and the relatively low enantioselectivities which make the asymmetric procedure synthetically less useful, we only evaluated the application scope for the racemic protocols towards products **2** and **8** as shown in Scheme 2. Products **2a-i** were all obtained with reasonable *cis*-diastereoselectivities under Cond. A, although some influence of the substituents on the acceptor side were observed (i.e. in the synthesis of the *p*-methoxy-substituted **2e**). Most products could be obtained in relatively high yields,

apart from the furan-based **2j**, where a lot of unidentified decomposition products were observed. When applying the more basic reaction conditions (Cond. B), again the formation of the double bond regioisomers **8** became favored, although the yields were again somewhat lower, compared to the formation of products **2**, which is very well in agreement with our initial observations made during the reaction conditions screening (Table 1). An interesting observation made herein was that products **8** containing an electron donating group in the para-position of the aryl substituent (i.e. **8e** but to some lesser extent also other electron rich derivatives like **8d** and **8h**) tend to undergo some decomposition upon prolonged storage in solution and during silica gel column chromatography (the analogous products **2** however were found to be stable). Unfortunately, the NMR spectra of the hereby formed product(s) are not unambiguous, but it can be assumed that opening of the cyclopentene ring accompanied by rearomatization of the quinoid ring occurs (in analogy to the similar behavior of push-pull substituted spirocyclopropanes **77**).

In conclusion, an operationally simple protocol for the direct formal (4+1)-annulation of vinylogous *p*-quinone methides with ammonium ylides to access spirocyclopentenyl *para*-dienones has been developed. By choice of the reaction conditions, the double bond location of the cyclopentene ring can be controlled in a so far unprecedented fashion, thus representing a novel alternative approach to the recently reported sulfur ylide-mediated variant of this reaction.^{3b} Furthermore, also the asymmetric version of the reaction was investigated by using Cinchona alkaloids as simple chiral amine leaving groups. A first proof-of-concept that this reaction can be rendered enantioselective (with enantiomeric ratios up to 91:9) was obtained, albeit these asymmetric reactions perform in relatively low yields only, thus requiring future optimization before resulting in synthetically satisfactory yields and selectivities.

¹H- and ¹³C-NMR spectra were recorded on a Bruker Avance III 300 MHz spectrometer with a broad band observe probe and a sample changer for 16 samples, on a Bruker Avance DRX 500 MHz spectrometer, and on a Bruker Avance III 700 MHz spectrometer with an Ascend magnet and TCI cryoprobe, which are both property of the Austro-Czech NMR-Research Center "RERI-uasb". All NMR spectra were referenced on the solvent peak. High resolution mass spectra were obtained using an Agilent 6520 Q-TOF mass spectrometer with an ESI source and an Agilent G1607A coaxial sprayer or a Thermo Fisher Scientific LTQ Orbitrap XL with an Ion Max API Source. Analyses were made in the positive ionization mode if not otherwise stated. Purine (exact mass for [*M*+H]⁺ = 121.050873) and 1,2,3,4,5,6-hexakis(2,2,3,3-tetrafluoropropoxy)-1,3,5,2,4,6-triazatriphosphinane (exact mass for [*M*+H]⁺ = 922.009798) were used for internal mass calibration.

IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer with ATR unit.

HPLC was performed using a Thermo Scientific Dionex Ultimate 3000 system with diode array detector with a CHIRAL ART Amylose-C (250 x 4.6 mm, 5 μm) chiral stationary phase.

The vinyl-*para*-quinone methides **4** and ammonium salts **5** were prepared as described previously.^{3,10,13}

All other chemicals were purchased from commercial suppliers and used without further purification unless otherwise stated. All reactions were carried out under Argon.

Procedures

General procedure for the syntheses of cyclopentene products 2 (Cond. A)

To a solution of vinyl para-quinone methides **4** (0.10 mmol, 1 eq.) and ammonium salts **5** (0.15 mmol, 1.5 eq.) in dry DCM (2 mL) was added Cs₂CO₃ (0.15 mmol, 1.5 eq.) and the resulting mixture was stirred at room temperature for 72 hours. The mixture was diluted with DCM, filtered over Na₂SO₄, and concentrated under reduced pressure. The resulting residue was purified by column chromatography (silica gel, heptanes:EtOAc = 10:1) giving the corresponding products **2a-2j** in the yields reported in Scheme 2. All products are literature known and ¹H-NMR spectra were in full accordance to those previous reports.^{3b}, 14

General procedure for the syntheses of cyclopentene products 8 (Cond. B)

To a solution of vinyl para-quinone methides **4** (0.10 mmol, 1 eq.) and ammonium salts **5** (0.15 mmol, 1.5 eq.) in dry DCM (2 mL) was added Cs₂CO₃ (1.0 mmol, 10 eq.) and the resulting mixture was stirred at room temperature for 72 hours. The mixture was diluted with DCM, filtered over Na₂SO₄ and concentrated under reduced pressure. The resulting residue was purified by column chromatography (silica gel, heptanes:EtOAc = 10:1) giving the corresponding products **8a-8j** in the yields reported in Scheme 2.

Compound 8a

Prepared according to the general procedure B by stirring vinylogous *para*-quinone methide **1a** (33.4 mg, 0.10 mmol, 1 eq.), ammonium salt **5a** (36.5 mg, 0.16 mmol, 1.5 eq.) and Cs₂CO₃ (328.2 mg, 1.0 mmol, 10 eq.) in dry DCM (2 mL) for 72 hours at room temperature. After work-up with DCM followed by column chromatography (silica gel, heptanes:EtOAc = 10:1) compound **8a** was obtained in 67% yield (27.2 mg, 0.067 mmol, pale-yellow oil).

¹H NMR (700 MHz, δ, CDCl₃, 298 K): 7.23-7.25 (m, 1H), 7.15-7.22 (m, 3H), 7.04 (d, *J* = 7.1 Hz, 2H), 6.58 (d, *J* = 2.8 Hz, 1H), 6.19 (d, *J* = 2.8 Hz, 1H), 3.99-4.11 (m, 1H), 3.76 (dd, *J* = 10.7, 8.2 Hz, 1H), 3.18 (ddd, *J* = 18.3, 10.8, 2.1 Hz, 1H), 2.94 (ddd, *J* = 18.3, 8.1, 3.1 Hz, 1H), 1.26 (s, 9H), 1.11 (t, *J* = 7.1 Hz, 3H), 0.91 (s, 9H) ppm.

¹³C NMR (176 MHz, δ, CDCl₃, 298 K): 186.4, 164.1, 147.5, 147.2, 145.9, 143.4, 139.5, 139.1, 137.3, 128.0, 128.0, 127.4, 60.5, 56.5, 56.3, 35.2, 34.9, 34.7, 29.6, 29.0, 14.1 ppm.
MS (??): *m/z* (%) = ?? (??) [??].

HRMS (ESI): *m/z* calcd for C₂₇H₃₄O₃: 407.2581[M+H]⁺; found: 407.2582.

Compound 8b

Prepared according to the general procedure B by stirring vinylogous *para*-quinone methide **1a** (32.3 mg, 0.10 mmol, 1 eq.), ammonium salt **5b** (33.5 mg, 0.15 mmol, 1.5 eq.) and Cs₂CO₃ (324.2 mg, 1.0 mmol, 10 eq.) in dry DCM (2 mL) for 72 hours at room temperature.

After work-up with DCM followed by column chromatography (silica gel, heptanes:EtOAc = 10:1) compound **8b** was obtained in 62% yield (24.5 mg, 0.062 mmol, pale-yellow oil).

¹H NMR (300 MHz, δ , CDCl₃, 298 K): 7.17-7.24 (m, 4H), 7.04 (d, J = 9.4 Hz, 2H), 6.57 (d, J = 2.4 Hz, 1H), 6.17 (d, J = 2.4 Hz, 1H), 3.70-3.83 (m, 1H), 3.60 (s, 3H), 3.19 (dd, J = 18.2, 10.5 Hz, 1H), 2.94 (ddd, J = 18.2, 8.1, 2.7 Hz, 1H), 1.26 (s, 9H), 0.91 (s, 9H) ppm.

¹³C NMR (176 MHz, δ , CDCl₃, 298 K): 186.3, 164.2, 147.7, 147.4, 145.9, 143.1, 139.1, 138.9, 137.3, 128.0, 127.9, 127.4, 56.4, 56.2, 51.4, 35.3, 34.9, 34.7, 29.6, 29.0 ppm.

HRMS (ESI): m/z calcd for C₂₆H₃₂O₃: 393.2424 [M+H]⁺; found: 393.2417.

Compound 8c

Prepared according to the general procedure B by stirring vinylogous *para*-quinone methide **1b** (39.8 mg, 0.10 mmol, 1 eq.), ammonium salt **5a** (34.5 mg, 0.15 mmol, 1.5 eq.) and Cs₂CO₃ (321.0 mg, 1.0 mmol, 10 eq.) in dry DCM (2 mL) for 72 hours at room temperature. After work-up with DCM followed by column chromatography (silica gel, heptanes:EtOAc = 10:1) compound **8c** was obtained in 52% yield (25.4 mg, 0.052 mmol, yellow oil).

¹H NMR (300 MHz, δ , CDCl₃, 298 K): 7.40 (d, J = 8.0 Hz, 1H), 7.15-7.22 (m, 3H), 6.93-7.01 (m, 1H), 6.60 (d, J = 2.2 Hz, 1H), 6.13 (d, J = 2.2 Hz, 1H), 4.36 (t, J = 8.3 Hz, 1H), 3.92-4.03 (m, 2H), 2.83-3.08 (m, 2H), 1.16 (s, 9H), 1.04 (t, J = 7.1 Hz, 3H), 0.92 (s, 9H) ppm.

¹³C NMR (75 MHz, δ , CDCl₃, 298 K): 184.9, 162.8, 145.9, 145.0, 144.5, 142.0, 138.6, 137.9, 137.4, 132.1, 128.4, 127.6, 125.9, 124.9, 59.4, 55.3, 52.9, 36.7, 33.7, 33.7, 28.1, 28.0, 13.0 ppm.

HRMS (ESI): m/z calcd for C₂₇H₃₃BrO₃: 485.1686 [M+H]⁺; found: 485.1688.

Compound 8d

Prepared according to the general procedure B by stirring vinylogous *para*-quinone methide **1c** (66.8 mg, 0.20 mmol, 1 eq.), ammonium salt **5a** (67.8 mg, 0.30 mmol, 1.5 eq.) and Cs₂CO₃ (650 mg, 2.0 mmol, 10 eq.) in dry DCM (4 mL) for 72 hours at room temperature. After work-up with DCM followed by column chromatography (silica gel, heptanes:EtOAc = 10:1) compound **8d** was obtained in 56% yield (47.2 mg, 0.11 mmol, pale-yellow oil). This product tends to undergo some slow decomposition during column chromatography and/or prolonged storage in solution, leading to the formation of some unidentified product which coelutes even when using preparative HPLC.

¹H NMR (300 MHz, δ , CDCl₃, 298 K): 7.25 (br s, 1H), 7.02 (d, J = 7.8 Hz, 2H), 6.94 (d, J = 7.8 Hz, 2H), 6.59 (d, J = 2.1 Hz, 1H), 6.20 (d, J = 2.1 Hz, 1H), 3.99-4.13 (m, 2H), 3.74 (t, J = 9.6 Hz, 1H), 3.12 (dd, J = 18.2, 10.6 Hz, 1H), 2.92 (ddd, J = 18.5, 8.2, 2.6 Hz, 1H), 2.26 (s, 3H), 1.27 (s, 9H), 1.13 (t, J = 7.1 Hz, 3H), 0.93 (s, 9H) ppm.

^{13}C NMR (75 MHz, δ , CDCl_3 , 298 K): 186.4, 164.2, 147.4, 147.1, 146.0, 143.5, 139.7, 139.4, 139.1, 137.0, 128.6, 127.8, 60.5, 56.3, 56.2, 35.3, 34.9, 34.7, 29.6, 29.0, 21.0, 14.1 ppm.

HRMS (ESI): m/z calcd for $\text{C}_{28}\text{H}_{36}\text{O}_4$: 437.2686 $[\text{M}+\text{H}]^+$; found: 437.2686.

Compound 8e

Prepared according to the general procedure B by stirring vinylogous *para*-quinone methide **1d** (34.8 mg, 0.10 mmol, 1 eq.), ammonium salt **5a** (33.3 mg, 0.15 mmol, 1.5 eq.) and Cs_2CO_3 (324.9 mg, 1.0 mmol, 10 eq.) in dry DCM (2 mL) for 72 hours at room temperature. After work-up with DCM followed by column chromatography (silica gel, heptanes:EtOAc = 10:1) compound **8e** was obtained in 51% yield (22.1 mg, 0.051 mmol, pale-yellow oil). Product **8e** undergoes significant decomposition during column chromatography, therefore no pure spectra were obtained.

^1H NMR (300 MHz, δ , CDCl_3 , 298 K): 7.22 (br s, 1H), 6.95 (d, J = 8.4 Hz, 1H), 6.72 (d, J = 8.3 Hz, 1H), 6.56 (d, J = 2.4 Hz, 1H), 6.18 (d, J = 2.0 Hz, 1H), 3.95-4.11 (m, 2H), 3.72-3.67 (m, 1H), 3.72 (s, 3H), 3.11 (dd, J = 18.3, 10.9 Hz, 1H), 2.90 (ddd, J = 18.3, 8.1, 2.7 Hz, 1H), 1.24 (s, 9H), 1.10 (t, J = 7.1 Hz, 3H), 0.93 (s, 9H) ppm.

^{13}C NMR (75 MHz, δ , CDCl_3 , 298 K): 185.2, 167.0, 157.7, 146.3, 146.1, 144.7, 142.3, 138.5, 138.8, 127.8, 112.2, 59.3, 55.2, 54.8, 54.3, 34.4, 33.6, 33.3, 29.4, 28.4, 27.9, 13.4 ppm.

HRMS (ESI): m/z calcd for $\text{C}_{28}\text{H}_{36}\text{O}_3$: 421.2737 $[\text{M}+\text{H}]^+$; found: 421.2737.

8f

Prepared according to the general procedure B by stirring vinylogous *para*-quinone methide **1a** (32.1 mg, 0.10 mmol, 1 eq.), ammonium salt **5c** (43.3 mg, 0.15 mmol, 1.5 eq.) and Cs_2CO_3 (331.1 mg, 1.0 mmol, 10 eq.) in dry DCM (2 mL) for 72 hours at room temperature. After work-up with DCM followed by column chromatography (silica gel, heptanes:EtOAc = 10:1) compound **8f** was obtained in 58% yield (27.0 mg, 0.058 mmol, pale-yellow oil).

^1H NMR (300 MHz, δ , CDCl_3 , 298 K): 7.29-7.35 (m, 2H), 7.17-7.24 (m, 5H), 7.01-7.06 (m, 2H), 6.60 (d, J = 2.3 Hz, 1H), 6.23 (d, J = 2.3 Hz, 1H), 5.17 (d, J = 12.5 Hz, 1H), 5.00 (d, J = 12.5 Hz, 1H), 3.77 (t, J = 9.2 Hz, 1H), 3.21 (dd, J = 18.4, 10.6 Hz, 1H), 2.95 (ddd, J = 18.2, 8.2, 2.9 Hz, 1H), 1.18 (s, 9H), 0.89 (s, 9H) ppm.

^{13}C NMR (75 MHz, δ , CDCl_3 , 298 K): 184.9, 162.8, 146.4, 146.3, 145.7, 142.0, 138.3, 137.9, 135.8, 134.4, 127.5, 127.1, 127.0, 126.8, 126.3, 65.3, 55.8, 55.1, 34.1, 33.7, 33.5, 28.3, 27.8 ppm.

HRMS (ESI): m/z calcd for $\text{C}_{32}\text{H}_{36}\text{O}_3$: 469.2737 $[\text{M}+\text{H}]^+$; found: 469.2740.

Compound 8g

Prepared according to the general procedure B by stirring vinylogous *para*-quinone methide **1a** (33.2 mg, 0.10 mmol, 1 eq.), ammonium salt **5d** (37.5 mg, 0.15 mmol, 1.5 eq.) and Cs₂CO₃ (328.4 mg, 1.0 mmol, 10 eq.) in dry DCM (2 mL) for 72 hours at room temperature. After work-up with DCM followed by column chromatography (silica gel, heptanes:EtOAc = 10:1) compound **8g** was obtained in 58% yield (24.8 mg, 0.057 mmol, pale-yellow oil).

¹H NMR (300 MHz, δ, CDCl₃, 298 K): 7.17-7.23 (m, 4H), 7.00-7.06 (m, 2H), 6.61 (d, *J* = 2.2 Hz, 1H), 6.25 (d, *J* = 2.2 Hz, 1H), 3.74 (t, *J* = 9.4 Hz, 1H), 3.16 (dd, *J* = 18.0, 11.0 Hz, 1H), 2.91 (ddd, *J* = 17.9, 8.1, 2.9 Hz, 1H), 1.34 (s, 9H), 1.28 (s, 9H), 0.93 (s, 9H) ppm.

¹³C NMR (75 MHz, δ, CDCl₃, 298 K): 186.1, 163.7, 147.0, 146.9, 144.8, 143.6, 140.6, 140.2, 137.1, 128.0, 127.8, 127.3, 81.0, 56.8, 56.3, 34.9, 34.8, 34.5, 29.6, 28.9, 28.0 ppm.

HRMS (ESI): *m/z* calcd for C₂₉H₃₈O₃: 435.2894 [M+H]⁺; found: 435.2895.

Compound 8h

Prepared according to the general procedure B by stirring vinylogous *para*-quinone methide **1e** (75.0 mg, 0.20 mmol, 1 eq.), ammonium salt **5a** (67.8 mg, 0.30 mmol, 1.5 eq.) and Cs₂CO₃ (650.1 mg, 2.0 mmol, 10 eq.) in dry DCM (4 mL) for 72 hours at room temperature. After work-up with DCM followed by column chromatography (silica gel, heptanes:EtOAc = 10:1) compound **8h** was obtained in 46% yield (42.1 mg, 0.09 mmol, pale-yellow oil). This product tends to undergo some slow decomposition during column chromatography and/or prolonged storage in solution, leading to the formation of some unidentified product which coelutes even when using preparative HPLC

¹H NMR (300 MHz, δ, CDCl₃, 298 K): 7.69-7.89 (m, 4H), 7.35-7.47 (m, 5H), 6.76 (d, *J* = 2.2 Hz, 1H), 6.08 (d, *J* = 2.2 Hz, 1H), 4.77 (t, *J* = 7.8 Hz, 1H), 4.05 (q, *J* = 7.1 Hz, 2H), 3.24-3.31 (m, 1H), 1.19 (s, 9H), 1.11 (t, *J* = 7.1 Hz, 3H), 0.68 (s, 9H) ppm.

¹³C NMR (75 MHz, δ, CDCl₃, 298 K): 185.7, 164.0, 146.2, 146.2, 146.1, 142.9, 140.9, 138.4, 135.9, 133.8, 132.4, 128.7, 127.7, 125.9, 125.5, 124.7, 124.0, 60.4, 56.2, 49.5, 37.8, 34.6, 34.3, 30.4, 29.2, 28.7, 14.0 ppm.

HRMS (ESI): *m/z* calcd for C₃₁H₃₆O₃: 457.2737 [M+H]⁺; found: 457.2743.

Compound 8i

Prepared according to the general procedure B by stirring vinylogous *para*-quinone methide **1f** (40.9 mg, 0.10 mmol, 1 eq.), ammonium salt **5a** (35.0 mg, 0.15 mmol, 1.5 eq.) and Cs₂CO₃ (331.7 mg, 1.0 mmol, 10 eq.) in dry DCM (2 mL) for 72 hours at room temperature. After work-up with DCM followed by column chromatography (silica gel, heptanes:EtOAc = 10:1) compound **8i** was obtained in 64% yield (31.3 mg, 0.064 mmol, pale-yellow oil).

¹H NMR (700 MHz, δ, CDCl₃, 298 K): 7.22 (t, *J* = 2.3 Hz, 1H), 7.00 (d, *J* = 7.9 Hz, 2H), 6.92 (d, *J* = 8.0 Hz, 1H), 6.57 (d, *J* = 2.8 Hz, 1H), 6.18 (d, *J* = 2.8 Hz, 1H), 4.00-4.09 (m,

2H), 3.72 (dd, $J = 10.8, 8.3$ Hz, 1H), 3.15 (ddd, $J = 18.3, 10.8, 2.1$ Hz, 1H), 2.91 (ddd, $J = 18.3, 8.1, 3.1$ Hz, 1H), 1.25 (s, 9H), 1.11 (t, $J = 7.1$ Hz, 3H), 0.91 (s, 9H) ppm.

^{13}C NMR (126 MHz, δ , CDCl_3 , 298 K): 14.1, 29.0, 29.5, 34.7, 34.9, 35.3, 56.2, 56.3, 60.5, 127.8, 128.6, 129.6, 134.2, 137.0, 139.1, 139.7, 143.5, 146.0, 147.1, 147.4, 164.2, 186.4 ppm.

HRMS (ESI): m/z calcd for $\text{C}_{27}\text{H}_{33}\text{BrO}_3$: 485.1686 $[\text{M}+\text{H}]^+$; found: 485.1686.

Compound 8j

Prepared according to the general procedure B by stirring vinylogous *para*-quinone methide **1g** (31.0 mg, 0.10 mmol, 1 eq.), ammonium salt **5a** (34.3 mg, 0.15 mmol, 1.5 eq.) and Cs_2CO_3 (324.5 mg, 1.0 mmol, 10 eq.) in dry DCM (2 mL) for 72 hours at room temperature. After work-up with DCM followed by column chromatography (silica gel, heptanes:EtOAc = 10:1) compound **8j** was obtained in 46% yield (18.4 mg, 0.046 mmol, pale-yellow solid).

^1H NMR (300 MHz, δ , CDCl_3 , 298 K): 7.22 (s, 1H), 7.16 (br s, 1H), 6.50 (d, $J = 2.2$ Hz, 1H), 6.28 (d, $J = 2.3$ Hz, 1H), 6.23 (s, 1H), 5.92 (d, $J = 3.0$ Hz, 1H), 3.97-4.13 (m, 2H), 3.77 (t, $J = 9.4$ Hz, 1H), 3.16 (dd, $J = 18.3, 10.3$ Hz, 1H), 2.92 (ddd, $J = 18.3, 8.4, 2.8$ Hz, 1H), 1.26 (s, 9H), 1.12 (t, $J = 7.1$ Hz, 3H), 1.02 (s, 9H) ppm.

^{13}C NMR (75 MHz, δ , CDCl_3 , 298 K): 186.4, 163.8, 151.9, 147.3, 147.2, 145.3, 142.7, 141.5, 138.9, 138.7, 110.2, 106.8, 60.4, 56.1, 49.7, 34.7, 34.6, 34.5, 29.5, 29.1, 14.0 ppm.

HRMS (ESI): m/z calcd for $\text{C}_{25}\text{H}_{32}\text{O}_4$: 397.2373 $[\text{M}+\text{H}]^+$; found: 397.2375.

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Biosketches

Lukas Roiser was born in Linz, Austria in 1988. He started studying chemical engineering at the Johannes Kepler University in Linz in 2009 and graduated in the group of Mario Waser in 2014. His master thesis focused on the enantio- and diastereoselectivity in ammonium ylide-mediated epoxide syntheses. He stayed in the group

for his doctoral studies where he investigated the use of (ammonium)enolates for cyclization reactions. He successfully defended his PhD in June 2018.

Katharina Zielke was born in Wels, Austria, in 1990. She started studying chemistry at the Johannes Kepler University Linz in 2010, where she graduated in 2015 in Mario Waser's group. During her master thesis she investigated enantioselective epoxidation reactions using chiral ammonium salts. Since December 2015, she is working on her PhD Thesis in the same group with the main focus on enantioselective reaction methods.

Mario Waser was born in Steyr, Austria in 1977 and studied chemistry at the Johannes Kepler University Linz, Austria where he obtained his Ph.D. in 2005 in the group of Prof. Heinz Falk. After a postdoctoral stay in the group of Prof. Alois Fürstner at the Max-Planck Institut für Kohlenforschung (Mülheim, Germany), he spent two years as an R&D chemist working for DSM Linz. In 2009 he started his independent career as an Assistant Professor at the JKU Linz. In 2014 he obtained his habilitation (*venia docendi*) and became Associate Professor. His main research interests are on the design and application of asymmetric organocatalysts like novel bifunctional phase-transfer catalysts and on ammonium enolate-mediated reactions.

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- (14). Further details can be found in the online supporting information.

a) Recent Work: [Ref. 3b] **b) Our Recent Work: [Ref. 7]** **c) This Work:** **Scheme 1.**

Recent ylide-mediated *p*-quinone methide-based cyclizations towards spirocompounds 2 and 7 and the herein targeted ammonium ylide mediated (4+1)-reaction towards compounds 2 and 8.

Scheme 2.

Substrate scope for the selective formation of either products **2** or **8** under optimized reaction conditions.

Table 1Optimization of the reaction conditions for the regioselective synthesis of either product **2a** or **8a**.

entry ^a	base (equiv)	solvent	t / h	2a:8a ^b	yield ^c / %	d.r. (2a) ^b
1	Cs ₂ CO ₃ (10)	EtOAc	24	37:63	n.d. (full conv.)	n.d.
2	Cs ₂ CO ₃ (1.5)	EtOAc	24	100:0	85	91:9
3	Cs ₂ CO ₃ (2)	EtOAc (40 °C)	24	54:46	n.d. (full conv.)	n.d.
4	K ₃ PO ₄ (2)	EtOAc	24	100:0	n.d. (33% conv.)	89:11
5	Cs ₂ CO ₃ (1)	CH ₂ Cl ₂	72	100:0	60	92:8
6	Cs ₂ CO ₃ (4)	CH ₂ Cl ₂	72	11:89	n.d. (70% conv.)	n.d.
7	Cs ₂ CO ₃ (10)	CH ₂ Cl ₂	72	0:100	67	n.d.
8	Cs ₂ CO ₃ (1.5)	CH ₂ Cl ₂	72	100:0	90	92:8

^aAll reactions were carried out using 0.1 mmol **1a** and 1.5 equiv of **6a** in the solvents stated (0.05 M) at rt.^bDetermined by ¹H NMR analysis of the crude product.^cIsolated yields.

Table 2

Identification of the best suited leaving group for the enantioselective synthesis of either product **2a** or **8a**.

<p>1a $\xrightarrow{6\text{-QD}}$ <i>cis</i>-2a 8a</p> <p>R₃N:</p> <p>QD1: R = OMe, R' = H QD2: R = OMe, R' = Me QD3: R = H, R' = Me QD4: R = H, R' = H QD5: R = OH, R' = H</p>					
entry ^a	amine ^b	cond. ^c	Yield (2a) ^d / %	Yield (8a) ^e / %	e.r. ^f
1	QD2	A	29	--	84:16
2	QD2	B	--	42	89:11
3	QD3	A	47	--	78:22
4	QD3	B	--	31	91:9

^a All reactions were carried out using 0.1 mmol **1a** and 1.5 equiv of **6** in DCM (0.05 M) at rt.

^b Only amine **QD2** and **QD3**-based ammonium salts allowed for product formation.

^c Cond. A: with 1.5 equiv. Cs₂CO₃ for 24 h; Cond. B: with 10 equiv. Cs₂CO₃ for 72 h.

^d Isolated yields.

^e Determined by ¹H NMR analysis of the crude product.

^f Determined by HPLC using a chiral stationary phase.