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Enantioselective Spirocyclopropanation of *para*-Quinone Methides Using Ammonium Ylides

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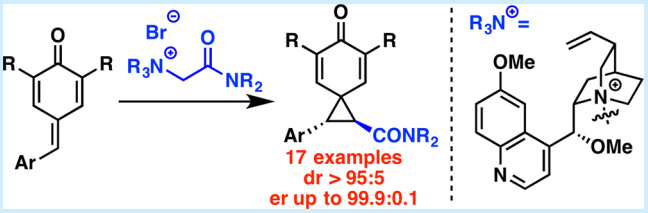
Supporting Information

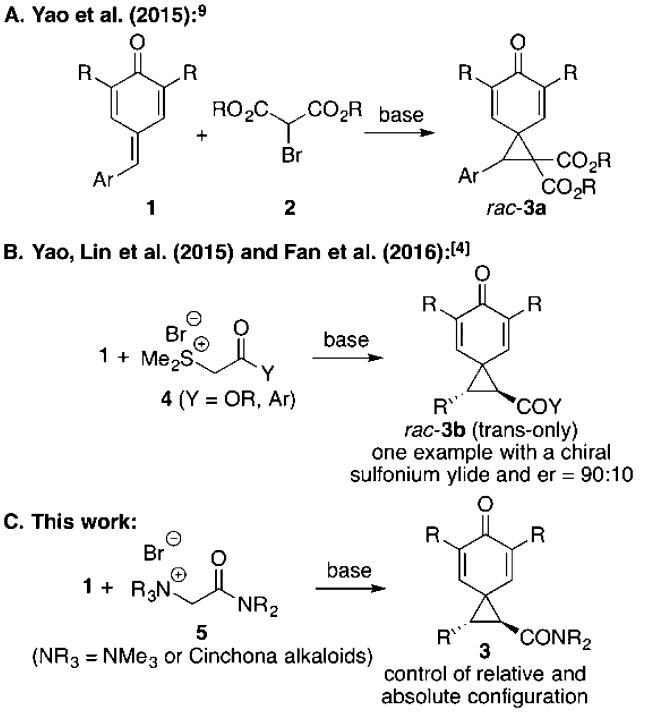
ABSTRACT: The use of Cinchona alkaloid-based chiral ammonium ylides allows for the first highly enantioselective and broadly applicable spirocyclopropanation reactions of *para*-quinone methides. This strategy provides a straightforward protocol toward the chiral spiro[2.5]octa-4,7-dien-6-one skeleton, which is a frequently found structural motif in important biologically active molecules.



The spirocyclopropane motif is a recurring important structural element in a variety of natural (biologically active) compounds.[1] Among the different possible variations, the spiro[2.5]octa-4,7-dien-6-one skeleton has become increasingly relevant because of its presence in biologically active natural products with, e.g., DNA-alkylating properties.[2] In addition to their interesting pharmacological properties, spirocyclopropanes may also serve as versatile key-intermediates in the synthesis of complex (pharmaceutically interesting) targets.[3] One potentially powerful approach to access the spiro[2.5]octa-4,7-dien-6-one motif is to start from quinoide-type structures.[4,5] Hereby two complementary strategies have been reported, either by making use of *para*-quinone methides as acceptors for cyclopropanation reactions[4] or by reacting quinone diazides with olefins.[5] Quinone methides have become a very privileged and unique class of acceptors for asymmetric transformations over the course of recent years.[6] While *ortho*-quinone methides were successfully used for a variety of (4 + *n*)-type cyclizations even with onium ylides,[7] *para*-quinone methides **1** have become increasingly important for vinylogous enantioselective 1,6-addition reactions.[8] In addition, very recently the first reports describing the use of these reactive substrates for Michael-initiated cyclopropanation reactions either with α-bromo malonates (Scheme 1A)[9] or sulfonium ylides (Scheme 1B)[4] have been reported, allowing for a straightforward construction of the spiro[2.5]octa-4,7-dien-6-one skeleton of compounds of general structure **3**.

Our group has a fundamental interest in the use of ammonium ylides for asymmetric three-membered ring-forming reactions like epoxidation and aziridination[10] as well as in the synthesis of chiral cyclopropanes.[11] Ammonium ylides have been very successfully used for asymmetric cyclopropanations over recent years.[12] Therefore, the reports by the groups of Yao and Lin[4a] and Fan[4b] (Scheme 1B) were particularly inspiring for us because they clearly proved the potential of sulfonium ylides for cyclopropanation reactions of *para*-quinone methides. Interestingly, both groups were able to achieve high yields and excellent diastereoselectivities using

Scheme 1. Recent Michael-Initiated Cyclopropanation Reports for the Synthesis of Spiro[2.5]octa-4,7-dien-6-ones 3 and the Herein Targeted Enantioselective Approach via Chiral Ammonium Ylides Starting from Ammonium Salts 5



dimethylsulfide-based ylides and with a broad substrate scope. However, while Yao and Lin et al.[4a] realized that Aggarwal's chiral limonene-based sulfur ylide[13] did not allow them to facilitate this cyclopropanation reaction, Fan et al.[4b] reported a single example using a chiral binaphthyl-derived sulfonium

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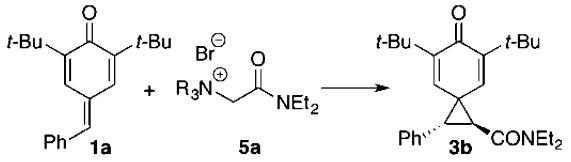
salt,[14] which gave up to 90:10 enantiomeric ratio (er) in one test reaction. Based on the high versatility of chiral ammonium ylides for asymmetric cyclopropanation reactions,[12] we became interested in addressing the spirocyclopropanation of quinone methides **1**, aiming at developing the first highly enantioselective and broadly applicable synthesis of the chiral targets **3** (Scheme 1C).

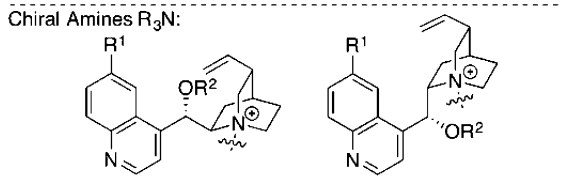
We decided to focus on amide-based ammonium ylide-precursors **5a** that would use trimethylamine as an achiral amine leaving group for initial optimization experiments (Table 1, entries 1−5). This amine was chosen because of its established superior leaving group ability for other cyclization reactions.[10]

We soon found that using Cs_2CO_3 as a solid base in combination with a slight excess of the acceptor **1a** allowed for a high yielding synthesis of the racemic spiro-target **3b** with a clear preference for the *trans* isomer (entry 5, Table 1). Focusing on the development of an asymmetric protocol next, we tested a series of rather simple Cinchona alkaloids. Very interestingly, while free −OH containing derivatives like **QD1** or **Q1** gave only very little product formation (entries 6, 10), the simple O-methylated analogues **QD2** and **Q2** turned out to be much higher yielding (entries 7, 11). The same trend was also observed when using the cinchonine and cinchonidine-based **Q3**, **Q4** and **QD3**, **QD4** (entries 8, 9, 12, 13). Very importantly, very high enantiomeric excesses for both enantiomers of **3b** could be achieved. However, we also observed that the use of these chiral auxiliaries required longer reaction times and a slightly larger excess of acceptor to achieve a full conversion compared to the achiral approach when using Me_3N (2.5 equiv of **1a** for 72 h at rt compared to 1.5 equiv of **1a** for 24 h at rt). In addition, the *trans*/*cis* ratio of around 2.5:1 was still not what we desired (it should be noted that *cis*-**3b** was obtained with the same very high enantiomeric excess as the *trans* isomer). As we initially realized that the use of a stronger base like *t*-BuOK allowed for very high diastereoselectivities in the achiral attempts (entry 3), we also explored other bases for the enantioselective reaction. However, the yields were not satisfying in those cases. Nevertheless, we reasoned that the higher *trans*-selectivity with stronger bases might be due to the base-mediated isomerization of the *cis*-cyclopropane. Importantly we found that enantiomerically pure *cis*-**3b** could be isomerized to *trans*-**3b** by treatment with either *t*-BuOK or Cs_2CO_3 at elevated temperature. This latter observation then inspired us to carry out the overall reaction at reflux, which finally resulted in a protocol that allowed us to obtain **3b** in very high yield (98%) and with literally complete control of the absolute (er > 99.8:0.2) and the relative configuration (dr > 40:1) (the chiral amine could also easily be recovered and reused after the reaction by Al_2O_3 column chromatography). It should be noted that attempts to carry out this reaction in a catalytic fashion starting from α-bromoacetamides in the presence of substoichiometric amounts of **Q2** resulted in almost the same high stereoselectivities but unfortunately were limited with respect to yield (20−30%) and catalyst turnover, as decomposition of the quinone methide **1a** turned out to be fast compared to the *in situ* formation of ammonium salt **5a** (details can be found in the Supporting Information).[15]

Having identified highly selective and high-yielding conditions for the formation of chiral spiro[2.5]octa-4,7-dien-6-ones **3**, we next evaluated the application scope of this reaction (Scheme 2). A variety of different acceptors and nucleophiles were well tolerated, and in all cases, more or less complete

Table 1. Identification of the Optimum Conditions and the Best-Suited Chiral Amine Leaving Group for the Ammonium Ylide-Mediated Synthesis of 3b





QD1: R^1 = OMe, R^2 = H
QD2: R^1 = OMe, R^2 = Me
QD3: R^1 = H, R^2 = Me
QD4: R^1 = H, R^2 = H

Q1: R^1 = OMe, R^2 = H
Q2: R^1 = OMe, R^2 = Me
Q3: R^1 = H, R^2 = Me
Q4: R^1 = H, R^2 = H

entry	amine	base (equiv)	cond.[a]	yield[b] (%)	dr[c] (*trans*/*cis*)	er (*trans*)[d]
1	Me_3N	K_2CO_3 (4×)	**A**	traces		
2	Me_3N	Cs_2CO_3 (4×)	**A**	69	3.3:1	
3	Me_3N	*t*-BuOK (2×)	**A**	76	13:1	
4	Me_3N	DBU (3×)	**A**	55	2.8:1	
5	Me_3N	Cs_2CO_3 (5×)	**B**	86	2.5:1	
6	**QD1**	Cs_2CO_3 (5×)	**C**	9	6:1	n.d.
7	**QD2**	Cs_2CO_3 (5×)	**C**	79	1.8:1	2:98
8	**QD3**	Cs_2CO_3 (5×)	**C**	59	3.3:1	2.5:97.5
9	**QD4**	Cs_2CO_3 (5×)	**C**	n.d.		
10	**Q1**	Cs_2CO_3 (5×)	**C**	3	3.1:1	n.d.
11	**Q2**	Cs_2CO_3 (5×)	**C**	85	2.5:1	>99.8:0.2
12	**Q3**	Cs_2CO_3 (5×)	**C**	57	2.7:1	99.5:0.5
13	**Q4**	Cs_2CO_3 (5×)	**C**	n.d.		
14	**Q2**	Cs_2CO_3 (6×)	**D**	98	>40:1	>99.8:0.2

[a]All reactions were carried out using 0.1 mmol **5a** in CH_2Cl_2 (A: with 1 equiv **1a**, rt, 24 h; B: with 1.5 equiv **1a**, rt, 24 h; C: with 2.5 equiv **1a**, rt, 72 h; D: with 2.5 equiv **1a**, reflux, 96 h. [b]Isolated yields. [c]Determined by NMR analysis of the crude product. [d]Determined by HPLC using a chiral stationary phase.

stereocontrol could be achieved. Gratefully, we were able to obtain crystals of the bromo-substituted **3l**, which were of sufficient quality to unambiguously determine the absolute configuration for that heavy atom-containing derivative by anomalous single crystal X-ray analysis.[15,16] By assuming a similar mode of face-differentiation for the reactions with the other test substrates, we therefore propose the same absolute configuration given in Scheme 2. An interesting observation was made when we attempted the synthesis of the dimethylamino-containing cyclopropane **3k**. This product was clearly identified in the crude reaction mixture. However, after silica gel column chromatography, we isolated the chiral alcohol

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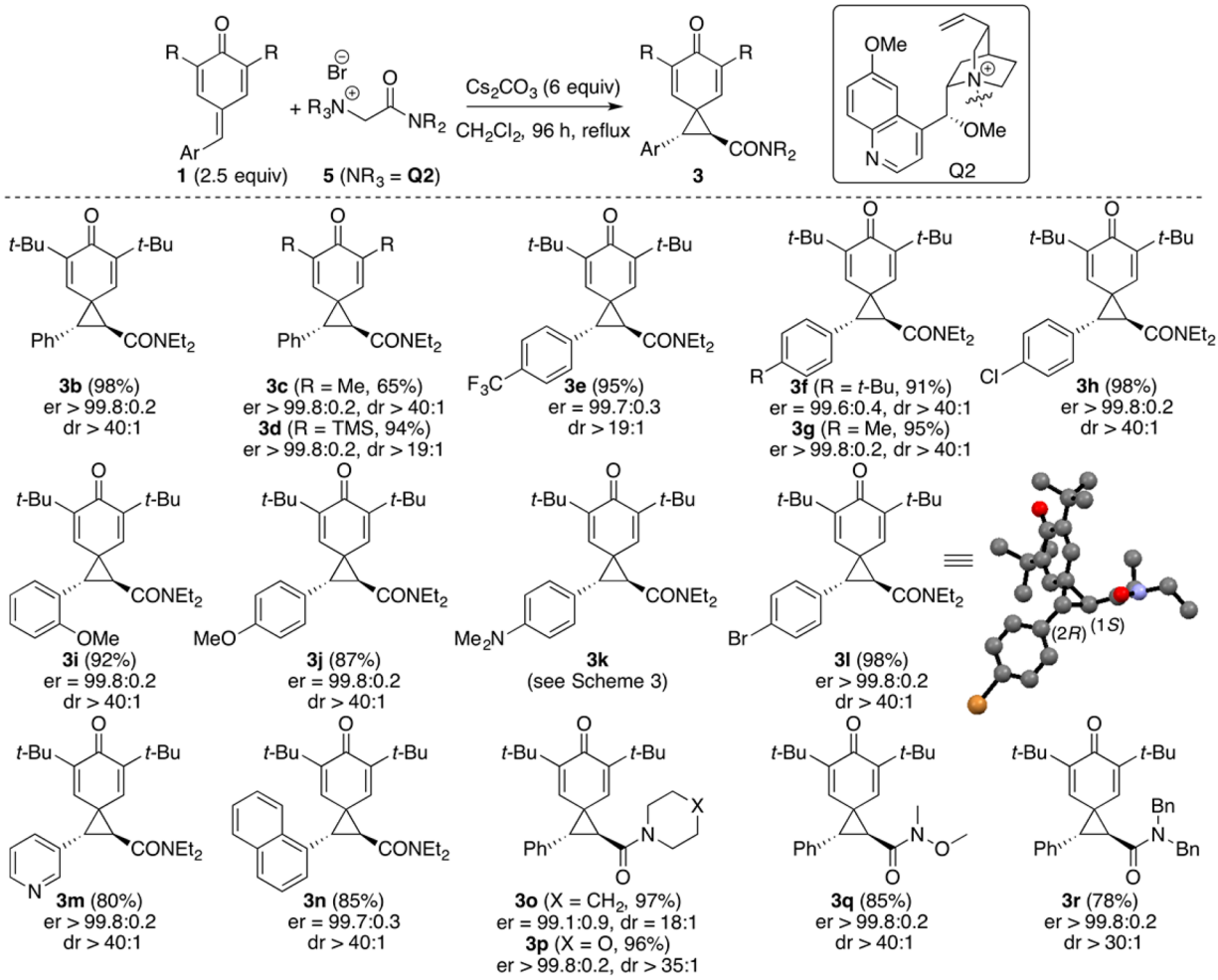
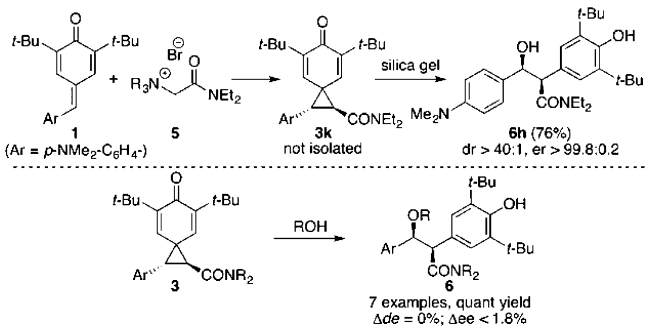
Scheme 2. Application Scope of the Asymmetric Ammonium Ylide-Mediated Synthesis of Spirocyclopropanes 3[a]



[a]Absolute configuration was determined by single crystal analysis of **3l**[15,16] and the other derivatives were proposed in analogy.

6h in reasonable yield and with a very high enantio- and diastereoselectivity (Scheme 3). Further investigations proved

Scheme 3. Stereospecific Nucleophilic Ring Opening Reactions of 3[15]



that products **3** can, in general, easily be employed in stereospecific cyclopropane ring-opening reactions with alcohols at room temperature (Scheme 3).[15]

Based on the proposed absolute configuration for *trans*-cyclopropanes **3**, addition of an alcohol should thus result in compounds **6** with the configuration given in Scheme 3. Only during the ring opening of one example did we observe a measurable but still a rather small erosion of the enantiopurity (Δ = 1.8%), but with all of the other investigated transformations with different cyclopropanes **3** and different alcohols, they proceeded without any noticeable decrease in er (see the Supporting Information).[15]

In conclusion we have developed a highly asymmetric and broadly applicable protocol for the straightforward synthesis of chiral spiro[2.5]octa-4,7-dien-6-ones. Key to success for this first ammonium ylide-based cyclopropanation of *para*-quinone methides was the use of a simple Cinchona alkaloid-based amine leaving group in combination with carefully fine-tuned reaction conditions, which resulted not only in high enantio- but also in very high diastereoselectivities. The hereby obtained products can be used for stereospecific ring-opening reactions as exemplified by the addition of simple alcohols.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00869.

Synthesis procedures, analytical details, and copies of NMR spectra and HPLC data of all the compounds (PDF)

Crystallographic data for **3l** (CIF)

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Notes

The authors declare no competing financial interest.

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(15) Further details can be found in the online Supporting Information.

(16) CCDC 1513618 (Cambrige Crystallographic Data Centre, www.ccdc.cam.ac.uk) contains the supplementary crystallographic data for **3l**.

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