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Title: Intramolekulare Aza-Diels-Alder-Reaktionen von ortho-Chinonmethidiminen - ein schneller, katalytischer und enantioselektiver Aufbau benzoanellierter Chinolizidine

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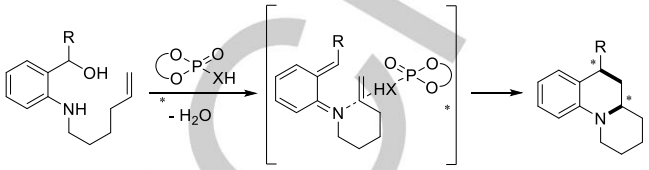
Intramolecular Aza-Diels-Alder-Reactions of *ortho*-Quinone Methide Imines – Rapid, Catalytic, and Enantioselective Assembly of Benzannulated Quinolizidines

Martin Kretzschmar,[a] Fabian Hofmann,[a] Daniel Moock[a] and Christoph Schneider*[a]

Abstract: Aza-Diels-Alder reactions (ADAR) constitute powerful processes that furnish *N*-heterocycles in a highly straightforward fashion. Intramolecular variants offer the additional potential to generate bi- and polycyclic systems with high stereoselectivity. We report herein a novel Brønsted acid-catalyzed process in which *ortho*-quinone methide imines tethered to the dienophile via the *N*-substituent react in an intramolecular ADAR form complex quinolizidines and oxazinoquinolines in one step. The reactions proceed under very mild conditions, with very good yields and good to very good diastereo- and enantioselectivities. Furthermore, it is possible to expand the process to a domino reaction which combines substrate synthesis, *ortho*-quinone methide imine formation and ADAR efficiently.

Aza-Diels-Alder-reactions (ADAR) are among the most important, straightforward, and stereoselective processes to form six-membered *N*-heterocycles.[1] They can be distinguished into two conceptionally different variants: electron-rich dienes undergoing a normal-type electron demand ADAR with imines as dienophiles and on the other hand electron-deficient azabutadienes undergoing an inverse electron demand ADAR with electron-rich dienophiles. A special class of strongly polarized azabutadienes comprise *ortho*-quinone methide imines which easily undergo conjugate and cycloaddition addition reactions with reconstitution of aromaticity.[2] Due to their transient nature *ortho*-quinone methide imines (also called *ortho*-azaxylylenes) are typically generated *in situ* directly from suitable precursors in the presence of their reaction partners.

In recent years, we and other groups have developed numerous Brønsted acid-catalyzed reactions of *ortho*-quinone methides[3] as well as *ortho*-quinone methide imines[4] and applied these processes toward the enantioselective synthesis of benzoannulated *O*- and *N*-heterocycles as well.[5,6] This strategy is based upon the acid-catalyzed dehydration of *ortho*-hydroxy- or *ortho*-amino benzyl alcohols to form hydrogen-bonded *ortho*-quinone methides and *ortho*-quinone methide imines, respectively. In this sceanario the chiral phosphate anion[7] is closely bound to the quinone methide and therefore able to catalyze the reaction with enol- and enamine-based nucleophiles with high enantiocontrol. Pursuing this strategy, we have recently established formal cycloadditions of enamides and *β*-ketoesters with *ortho*-quinone methide imines providing direct access to tetrahydroacridines and tetrahydroquinolines in good yields and enantioselectivities.[4a,b]



Scheme 1. Conceptualization of the Brønsted acid catalyzed, intramolecular ADAR of *ortho*-quinone methide imines.

The trivalency of nitrogen now opens the possibility to tether the dienophile directly into the substrate via *N*-substitution of the imine setting the stage for an intramolecular [4+2]-cycloaddition (Scheme 1). This general strategy was first formulated by Steinhagen and Corey in 1999 who described a racemic ADAR of *ortho*-quinone methide imines generated under basic conditions.[8] Since then this concept has not been followed up and there is currently no enantioselective process available to our knowledge.

We report herein the first Brønsted acid-catalyzed, intramolecular ADAR of *ortho*-quinone methide imines providing a rapid synthetic access to benzannulated quinolizidines and oxazinoquinolines with typically very good yields and good to very good diastereo- and enantioselectivities. First experiments were carried out with amino alcohol **1a** which was obtained in a convergent manner by reductive amination from the respective aniline (Table 1). Using chiral BINOL-based phosphoric acids only low conversion was observed. However, in the presence of the more reactive *N*-triflyl phosphoric amide **3a** as catalyst (10 mol%), the desired benzannulated quinolizidine **2a** was obtained with moderate yield but without any enantioselectivity (entry 1).

We then tested various *N*-triflyl phosphoric amides **3b-f** for the cycloaddition carrying different 3,3'-aryl substituents. *N*-Triflyl phosphoric amide **3f** with 9-anthracenyl groups in the 3,3'-position of the BINOL backbone was identified as the optimal catalyst delivering product **2a** as a single diastereomer and with an enantiomeric ratio of 88:12 e.r. (entry 6). Performing the reaction without the addition of 4 Å molecular sieves led to a significant acceleration of the reaction and delivered quinolizidine **2a** within one day in a very good yield (entry 7). By lowering the reaction temperature to 10 °C the enantioselectivity was further improved to 90:10 e.r. (entry 8).[9]

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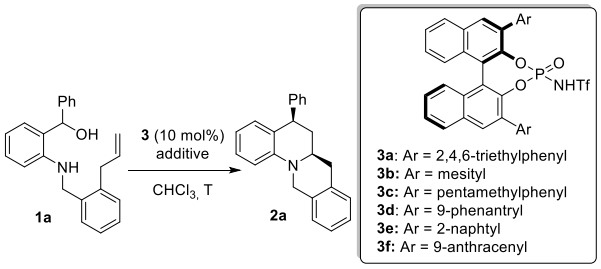
Table 1. Optimization of the phosphoric amide-catalyzed ADAR of **1a**.[a]

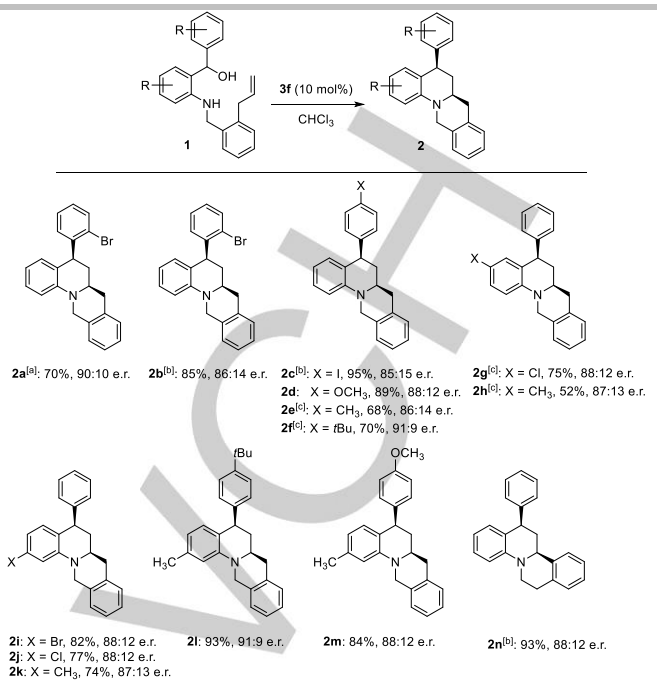


Entry	Cat.	Additive	Time	Yield [%][b]	e.r.[c]
1	**3a**	4Å MS	10d	53	50:50
2	**3b**	4Å MS	7d	27	56:44
3	**3c**	4Å MS	7d	26	60:40
4	**3d**	4Å MS	10d	63	66:34
5	**3e**	4Å MS	10d	23	69:31
6	**3f**	4Å MS	4d	68	88:12
7	**3f**	---	1d	93	88:12
8[d]	**3f**	---	5d	70	90:10

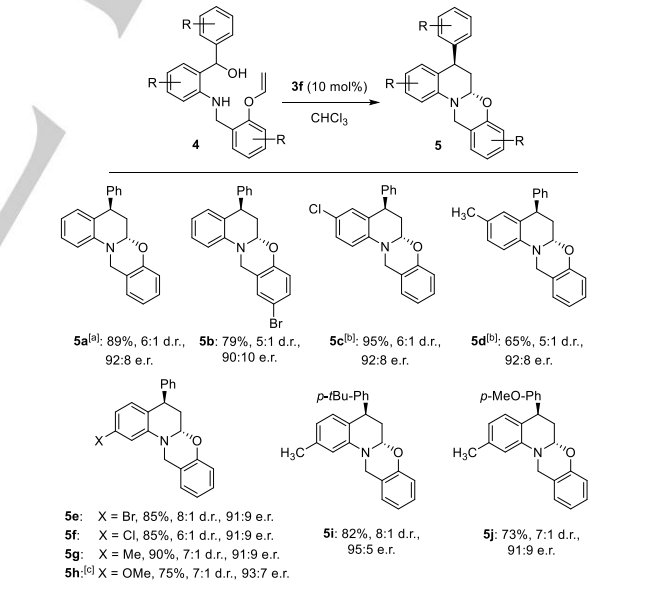
[a] Reaction conditions: 0.10 mmol *ortho*-aminobenzhydryl alcohol **1a**, catalyst **3** (10 mol%), 4 Å molecular sieves as additive (powdered, 25 mg), solvent (1 mL), rt, diastereomeric ratio was determined by NMR and was >20:1 in all cases. [b] Yield of isolated product after purification by flash column chromatography. [c] Enantiomeric ratio determined by HPLC on a chiral stationary phase (see the Supporting Information) [d] Reaction temperature: 10 °C.

The substrate scope of the reaction was investigated in reactions of differently substituted *ortho*-amino alcohols **1** (Scheme 2). It was possible to introduce different aryl groups as β-substituents of the *ortho*-quinone methide imine to obtain products **2a-f** in good yields, up to 91:9 e.r. and complete diastereoselectivity. Substrates containing halogen substituents generally required higher reaction temperatures to ensure complete conversion while still delivering products in comparable yields and enantioselectivities. Likewise, amino alcohols with various substituents in the *ortho*-quinone methide backbone were successfully transformed to furnish products **2g-m** in high yields and up to 91:9 e.r. Moving the benzannulation within the dienophile backbone was also tolerated and gave rise to product **2n** with excellent yield and good enantioselectivity. We assume that cycloadditions of substrates **1** proceed in a concerted and highly diastereoselective manner through an *endo*-transition state.

Subsequently, we expanded the substrate scope to reactions of amino alcohols **4** with an electronically activated enol ether as dienophile. As expected, this modification led to a significant rate acceleration. Substrate **4a** was fully consumed within 4 hours at room temperature whereupon oxazinoquinoline **5a** was obtained in 89% yield, 92:8 e.r. and as a mixture of two diastereomers with a ratio of 6:1 d.r. (Scheme 3). Contrary to quinolizidines **2** the major diastereomer of **5a** contained a 2,4-*trans* configuration, and the diastereoselectivity remained constant over the course of the reaction.



Scheme 2. Substrate scope of the phosphoric amide-catalyzed synthesis of benzannulated quinolizidines **2**. Reaction conditions: 0.10 mmol *ortho*-amino benzhydryl alcohol **1**, catalyst **3f** (10 mol%), $CHCl_3$ (1 mL), rt, 1d, diastereomeric ratio was determined via NMR and is >20:1 in all cases.; Enantiomeric ratio determined by HPLC on a chiral stationary phase (see the Supporting Information). [a] Reaction temperature: 10 °C, reaction time: 5d. [b] Reaction temperature: 50 °C. [c] Reaction time: 7d.



Scheme 3. Expansion of the substrate scope towards amino alcohols **4** tethered to an enol ether as dienophile. Reaction conditions: 0.10 mmol *ortho*-amino benzhydryl alcohol **4**, catalyst **3f** (10 mol%), $CHCl_3$ (1 mL), rt, 1d; [a] Reaction time: 4h, [b] Reaction time: 7d, [c] Reaction time: 1h.

Following this procedure, additional oxazinoquinolines **5b-j** were obtained in typically good yields, with up to 8:1 d.r. and with enantiomeric ratios of 90:10 e.r. or higher (Scheme 3). Alkyl-, alkoxy- and halogen groups were all tolerated as substituents. As expected, substrates carrying electron-releasing substituents reacted particularly fast. Thus, the reaction to form cycloadduct **5h** was completed within 1 hour at room temperature and the product

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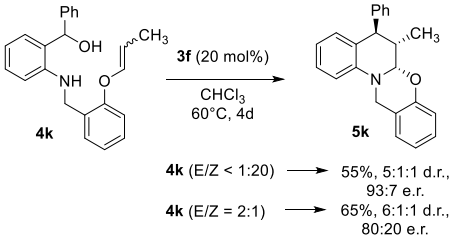
was obtained in 75% yield, 7:1 d.r. and 93:7 e.r. This result is consistent with the assumption that *ortho*-quinone methide imine formation is the rate-determining step of the reaction as we had observed in similar reactions recently.[4a-b] Products **5i** and **5j** with multiple substituents were also formed with enantioselectivities of up to 95:5 e.r. and in good yields.

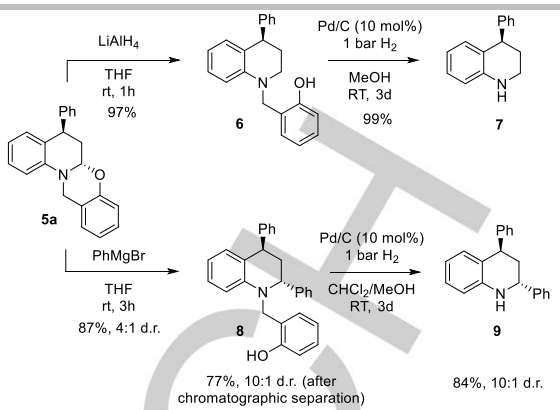


Scheme 4. Intramolecular ADAR of substituted enol ether **4k**.

Using substituted enol ethers more highly substituted cycloadducts were available. To showcase this scenario we subjected the methyl-substituted enol ether **4k** to the ADAR (Scheme 4). Starting from a stereochemically pure *Z*-enol ether we obtained cycloadduct **5k** in 55% yield, 93:7 e.r. and moderate diastereoselectivity under slightly modified reaction conditions. Interestingly, predominantly *E*-configured enol ether **4k** delivered the same major diastereomer **5k**, however with lower enantioselectivity. Thus, the ADAR of more polarized enol ether substrates is obviously not a concerted reaction and delivers the 2,3-*cis*-diastereomer in a stereoconvergent manner irrespective of the dienophile configuration.

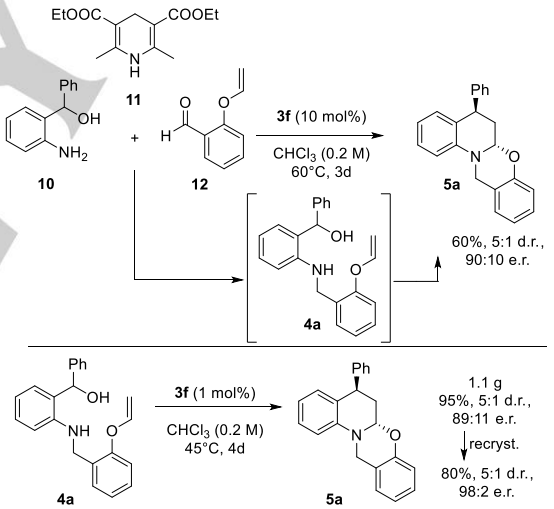
The cycloadducts **5** contain a newly formed and highly reactive *N,O*-acetal moiety which can be easily modified.[10] Accordingly, we transformed **5a** to the *N*-benzyl protected tetrahydroquinoline **6** by treatment with $LiAlH_4$ and subsequently to tetrahydroquinoline **7** by hydrogenation on palladium on charcoal both in very good yields (Scheme 5). Comparison of the specific rotation of **7** with the literature value[11] establishes its absolute configuration which was assigned to all further cycloadducts by analogy. The relative configuration was unambiguously assigned by ^{1}H-NMR spectroscopy.

Furthermore, we converted **5a** into the 2,4-disubstituted tetrahydroquinoline **8** by Grignard addition of phenyl magnesium bromide in good yield and moderate diastereoselectivity (Scheme 5). Column chromatography led to further purification and tetrahydroquinoline **8** was obtaind in 77% yield and 10:1 d.r. Upon debenzylation the free tetrahydroquinoline **9** was obtained likewise in good yield. In doing so we were able to expand the pool of synthetic strategies toward the stereoselective assembly of tetrahydroquinolines by a new, flexible and enantioselective process.[12]



Scheme 5. Transformation of **5a** into tetrahydroquinolines **7** and **9.**

To further simplify this process, we successfully developed a domino reaction that combines substrate synthesis and cycloaddition. We were able to start with free amino alcohol **10** and aldehyde **12** which were converted to **4a** in situ by reductive amination in the presence of *N*-triflyl phosphoric amide **3f** and Hantzsch ester **11**. Intermediate **4a** now served as substrate for the ADAR and delivered cycloadduct **5a** *in situ* in 60% overall yield and with good diastereo- and enantioselectivity (Scheme 6, top).



Scheme 6. Domino 3-component reaction (top) and large-scale experiment with only 1 mol% catalyst loading (bottom).

To demonstrate the applicability of our process, a large-scale synthesis of cycloadduct **5a** was conducted. In doing so we were able to further lower the catalyst loading to only 1 mol% (Scheme 6, bottom). We obtained 1.1 g of oxazinoquinoline **5a** in excellent yield and 89:11 e.r. which was further optically enriched to enantiomerically almost pure material by one recrystallization.

In conclusion, we have developed a new Brønsted acid-catalyzed and enantioselective process which furnishes benzannulated quinolizidines and oxazinoquinolines in a one-step process from simple substrates. The products that contain up to 3 new stereogenic centers were generated under mild reaction conditions in good to very good yields and stereoselectivities. Furthermore, it was possible to expand the process to a domino reaction which combined substrate synthesis, *ortho*-quinone methide

imine formation and ADAR efficiently while delivering the products with comparable results. Beyond that, the obtained oxazinoquinolines opened up the possibility of further functionalization toward highly substituted tetrahydroquinolines.

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Keywords: asymmetric synthesis • Brønsted acid catalysis • *ortho*-quinone methide imines • nitrogen heterocycles • organocatalysis

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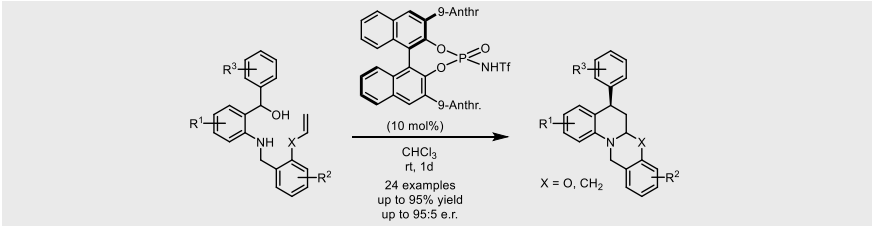

Chiral *N*-triflyl phosphoric amides are effective catalysts for the first enantioselective, intramolecular aza-Diels-Alder-reaction of *in situ* generated *ortho*-quinone methide imines. Benzannulated quinolizidines and oxazinoquinolines are readily accessible in good yields and enantioselectivities in this one-pot process.

*Martin Kretzschmar, Fabian Hofmann, Daniel Moock und Christoph Schneider**

Page No. – Page No.

Intramolecular Aza-Diels-Alder-Reactions of *ortho*-Quinone Methide Imines – Rapid, Catalytic and Enantioselective Assembly of Benzannulated Quinolizidines