Discussion Addendum for:

Facile Syntheses of Aminocyclopropanes: N,N-Dibenzyl-N-(2-ethenylcyclopropyl)amine [Benzenemethanamine, N-(2-ethenylcyclopropyl)-N-(phenylmethyl)]

Armin de Meijere*¹ and Sergei I. Kozhushkov¹

Institut für Organische und Biomolekulare Chemie der Georg-August-Universität, Tammannstr. 2, D-37077 Göttingen, Germany


Since the original report in 1996,² the transformations of N,N-dialkylcarboxamides with 1,2-dicarbanionic organometallics in situ generated from organomagnesium (Grignard) as well as organozinc reagents in the presence of stoichiometric or substoichiometric (semi-catalytic) quantities of a titanium alkoxide derivative of type XTi(OR)₃ with (X = OR, Cl, Me) has become a powerful tool in organic synthesis.³ According to the generally accepted mechanism, the key intermediate is a titanacyclopropane-type complex 3a, which can directly cycloadd to an amide carbonyl (Variant A) or undergo ligand exchange with alkenes to afford new titanacyclopropanes 3b (pathway B). Both variants work well, both in their inter- as well as intramolecular versions. (Scheme 1).³a,b,5

The simplicity of the experimental handling and relatively low cost of the reagents favor these so-called Kulinkovich-de Meijere cyclopropanations for an increasing range of applications in organic
The present Discussion Addendum is focused on the most remarkable new developments and synthetic employments of this reaction published since 2005.

**Scheme 1. Generally accepted mechanism of the Kulinkovich-de Meijere cyclopropanation**

**Attempted Further Extensions of the Reaction Scope**

Several studies on the extension of the reaction scope appeared in this period. Thus, in an enantioselective version of the title reaction, compound 2 was obtained with ee up to 80% in the presence of chirally modified Ti(TADDOL)$_2$. A number of new spirocyclic 5 and ring-fused aminocyclopropanes 6 were prepared using an intermolecular cyclopropanation of lactams or applying cycloalkyl-Grignard reagents (Scheme 2). Treatment of substituted 1H-benzo[e][1,4]diazepine-2,5-diones 7 with EtMgBr/MeTi(OiPr)$_3$ resulted in selective cyclopropanation of only the anilide carbonyl group and afforded derivatives of spirobenzodiazepinone 8. Generally speaking, in most cases MeTi(OiPr)$_3$ turned out to be more efficient. Indeed, with the employment of Ti(OiPr)$_4$, 7 underwent decomposition.
Bertus and Szymoniak extended the Kulinkovich-de Meijere cyclopropanation towards imides 9 and developed a straightforward synthesis of α-spirocyclopropanated lactams 10 in 48–78% yields using MeTi(OiPr)_3 as a titanium reagent and Et_2O•BF_3 as an activator for the second step of the transformation. Notably, only one carbonyl group was converted under these conditions, yet the isolated product 10 could be cyclopropanated to give the bis-spirocyclopropane derivative 11 with a larger excess of the EtMgBr/MeTi(OiPr)_3 reagent and without addition of Et_2O•BF_3. Employing the former protocol, but with cyclohexylmagnesium instead of ethylmagnesium bromide, N-alkenylimides were converted to tricyclic lactams 12 with a cyclopropylamine moiety in reasonable yields (Scheme 3).
Scheme 3. Kulinkovich-de Meijere cyclopropanation of imides

Formation of tricyclic cyclopropylamines of type 13 can be arrested when the nitrogen-assisted elimination of the titanium alkoxide moiety from the corresponding tricyclic intermediate would form an iminium ion with a bridgehead double bond that would violate Bredt’s rule. In these cases, hydrolysis of the intermediates with water without addition of Et₂O•BF₃ leads to carbocyclic amino ketones 14, which are useful building blocks for the synthesis of certain alkaloids (Scheme 4). Yet, with a large enough lactam ring in the starting material, i.e. an eight- (ₙ = 3) or nine-membered (ₙ = 4) allyllactame, quenching of the tricyclic N,O-acetal with water furnishes the corresponding tricyclic cyclopropylamines 13 (ₙ = 3) and 13 (ₙ = 4), respectively, as the sole products. In further studies of intramolecular cyclopropanations with ligand-exchanged titanacyclopropane intermediates, Six et al. have tested a range of amides 15 fitted with (E)- or (Z)-disubstituted alkene moieties, mostly containing a terminal oxygen functionality (Scheme 5). Their intramolecular Kulinkovich-de Meijere reactions afforded predominantly exo-configured products exo-16 from (Z)-15 and endo-16 from (E)-15, respectively.
Scheme 4. Intramolecular cyclopropanations of alkenyllactams towards tricyclic cyclopropylamines

Scheme 5. Intramolecular Kulinkovich-de Meijere reactions of amides bearing disubstituted alkene moieties

Under the typical conditions, simple thioamides 17 upon treatment with alkylmagnesium halides in the presence of Ti(OiPr)$_4$ underwent a drastically different reaction, namely a reductive alkylation affording tertiary amines 18, even in the presence of styrene as a favorable ligand-exchange candidate.
Scheme 6. Inter- and intramolecular transformations of thioamides upon treatment with alkylmagnesium halides and titanium tetraisopropoxide\textsuperscript{11}

However, with an $N$-alkenyl group in the thioamide, such as in \textbf{19}, the compound undergoes the intramolecular cyclopropanation, albeit by a mechanism which is slightly different from that of the corresponding $N$-alkyl-$N$-alkenylamides. Thus, 2-azabicyclo[3.1.0]hexanes \textbf{20} were prepared from $N$-(but-3-enyl)thioamides \textbf{19} in good to very good yields (Scheme 6).\textsuperscript{11}

With a few exceptions, the thioamides are as efficiently converted to this framework as amides, but less productive for larger 2-azabicyclo[4.1.0]heptanes and 2-azabicyclo[5.1.0]octanes.

Several attempts to facilitate the generation of titanacyclop propane intermediates gave mixed results. Although active organometallic species formed from Ti(OiPr)\textsubscript{4} and nBuLi possessed properties similar to those of a titanacyclopropane, it was surprisingly more stable as well as less reactive than the intermediate from Grignard reagents and Ti(OiPr)\textsubscript{4}. Thus, this protocol has only found rather limited synthetic applications.\textsuperscript{12}
Selected New Examples of Kulinkovich-de Meijere Cyclopropanations towards Practically Useful Compounds

The majority of reductive cyclopropanations of amides was performed with the intention to obtain biologically active or other practically useful compounds. Although a number of competition experiments have disclosed that the reactivities towards reductive cyclopropanation decrease in the order nitriles > amides > esters, both the amide and the ester moiety in the suberic acid derivative 21 could be transformed with a large enough excess of reagents to yield 22 with cyclopropanol and cyclopropylamine fragments (Scheme 7).\textsuperscript{13}

![Scheme 7. Twofold cyclopropanation of a suberic acid amide ester\textsuperscript{13}](image)

The titanium-mediated cyclopropanation of 3-benzyloxypropionic acid N,N-dibenzylamide (23)\textsuperscript{14} afforded N,N-dibenzyl-N-[1-(2-benzyloxyethyl)-2-ethenylcyclopropyl]amine (24) in 56% yield. The latter was further transformed into cyclopropyl analogues of β-homoornithine 26 and β-
homoglutamic acid 25 in nine and six simple steps, respectively, as building blocks for potentially biologically relevant small peptide analogues (Scheme 8).\textsuperscript{14} Cyclopropane-annelated amino-substituted pyrrolizidine derivatives 27\textsuperscript{15} as well as the key intermediate 28 for the synthesis of 3,4-(aminomethano)proline 29\textsuperscript{16} were obtained in good yields utilizing the titanium-mediated ligand exchange aminocyclopropanation methodology in its intra- and intermolecular version, respectively (Scheme 9).

\begin{center}
\textbf{Scheme 9. Preparation of aminosubstituted 3-azabicyclo[3.1.0]hexanes 27, 28}
\end{center}

\begin{center}
\textbf{Scheme 10. Synthesis of a precursor to conformationally locked versions of L-deoxythreosyl phosphonate nucleosides 31\textsuperscript{17}}
\end{center}

Conformationally restricted versions of L-deoxythreosyl phosphonate nucleosides were synthesized by Marquez et al.\textsuperscript{17} in order to investigate the
conformational preference of the HIV reverse transcriptase. The key intermediates 30 en route to the enantiomeric diaxially disposed 4-(6-amino-9H-purin-9-yl)bicyclo[3.1.0]hexan-2-ol carbocyclic nucleoside 31 were assembled employing an intramolecular Kulinkovich-de Meijere reductive cyclopropanation of the appropriately substituted hexenoic acid \( N,N \)-dibenzylamide (Scheme 10).

![Scheme 11. Reductive aminocyclopropanations in the preparation of building blocks for inhibitors of monoamine oxidase](image)

An intermolecular aminocyclopropanation employing ligand exchange with substituted styrenes or ethenylheteroarenes and \( \text{ClTi(OR)}_3 \) as a titanium source has been used by Joullié et al. to synthesize various 2-arylcyclopropylamines 32 as starting materials for conformationally constrained analogues of the neurotransmitters histamine and tryptamine as inhibitors of monoamine oxidase (Scheme 11). Several other interesting applications of the Kulinkovich-de Meijere cyclopropanation in the synthesis of potentially biologically active compounds are summarized in Table 1.
Table 1. Selected Examples of the Kulinkovich-de Meijere Cyclopropanation Applied in Medicinal Chemistry*

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction/Biological target</th>
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<tbody>
<tr>
<td>1</td>
<td>![Reaction 1 Image] 1) EtMgBr, MeTi(OiPr)_3 THF, 0–25 °C, 1.25 h 2) H_2O, rt 29% Compositions against stress granules (ref 19)</td>
</tr>
<tr>
<td>2</td>
<td>![Reaction 2 Image] 1) EtMgBr, MeTi(OiPr)_3 THF, –78 °C, 0.5 h 2) –78 to 25 °C, 1 h (yields not reported) R = H, Me, OMe Inhibitors of the bromodomain BRD9 proteins (ref 20)</td>
</tr>
<tr>
<td>3</td>
<td>![Reaction 3 Image] EtMgBr, Ti(OiPr)_4 THF/Et_2O, rt 22% Potent inhibitors of M-tropic (R5) HIV-1 replication (ref 21)</td>
</tr>
<tr>
<td>4</td>
<td>![Reaction 4 Image] 1) EtMgBr, Ti(OiPr)_4 THF/Et_2O, rt, 16 h 2) H_2O, rt, 0.5 h 33% Selective linear tachykinin NK2 receptor antagonists (ref 22)</td>
</tr>
<tr>
<td>Step</td>
<td>Reaction Details</td>
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<tr>
<td>------</td>
<td>-----------------</td>
</tr>
<tr>
<td>5.1</td>
<td>EtMgBr, Ti(OiPr)₄, THF, -78 to rt, 12 h</td>
</tr>
<tr>
<td>6.1</td>
<td>EtMgBr, Ti(OiPr)₄, THF/Et₂O, -78 °C, 0.5 h</td>
</tr>
<tr>
<td>7.1</td>
<td>EtMgBr, MeTi(OiPr)₃, THF/Et₂O, -78 °C, 7 min</td>
</tr>
<tr>
<td>8.1</td>
<td>EtMgBr, MeTi(OiPr)₃, THF/Et₂O, -78 °C, 10 min</td>
</tr>
<tr>
<td>9.1</td>
<td>EtMgBr, Ti(OiPr)₄, THF, -78 °C, 5 h</td>
</tr>
<tr>
<td>Step</td>
<td>Equation</td>
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<td>15</td>
<td><img src="image6" alt="Chemical Structure" /></td>
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DOI: 10.15227/orgsyn.095.0289
*Not in all cases were the reaction and work-up conditions optimized; therefore, moderate or low yields in several cases can be attributed to the non-optimized procedures; for details see ref [5].

**Synthetically Useful and Theoretically Interesting Transformations of Dialkylaminocyclopropanes**

The 2-azabicyclo[3.1.0]hexanes and 2-azabicyclo[4.1.0]heptanes prepared by the Kulinkovich-de Meijere reaction as described above, are susceptible to undergo cleavage of a vicinal (with respect to the nitrogen atom) C–C bond and thus enter [3+2] cycloaddition or intramolecular aromatic electrophilic substitution reactions to afford polycyclic systems with potential synthetic utility towards biologically active compounds (Scheme 12). For example, 2,3,3a,4-tetrahydro-6(5H)-indolones 33 were obtained upon heating of bicycles 16 with acetic anhydride.35 Aerobic electrochemical oxidation of this family of bicyclic aminocyclopropanes afforded bicyclic α-amino endoperoxides 34, which exhibited moderate antimalarial activity against the parasite *Plasmodium falciparum*.10a,36 The ruthenium-catalyzed [3+2] cycloadditions of aminocyclopropanes 20 onto styrenes are not only of theoretical interest, but constitute a new highly diastereoselective synthetic approach to octahydrocyclopenta[b]pyrrole derivatives 35.37 At last, an intramolecular aromatic electrophilic substitution furnished oligocyclic 1-methyl-1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinoline derivatives 36.38
Scheme 12. Transformations of 2-azabicyclo[3.1.0]alkanes with scission of a cyclopropyl C–C bond adjacent to nitrogen

On the other hand, the aminocyclopropyl moiety can play the role of a directing group in the formation of C(sp^3)–C(sp^2) bonds in palladium(0)-catalyzed C–H functionalizations of cyclopropanes with retention of the three-membered ring. This remarkable transformation was developed by Cramer et al. and applied towards the synthesis of the cyclopropane-annelated γ-lactams. Employment of the bulky TADDOL phosphonate ligand L in combination with adamantane-1-carboxylic acid as a cocatalyst afforded γ-lactams 38 in excellent yields and with high enantioselectivities from achiral precursors. Applying this protocol, azaspirooctane and -
nonane 5, after debenzylation and acylation with chloroacetyl chloride were converted into enantiomerically enriched tricyclic γ -lactams 12 (Scheme 13). This sequence complements the alternative approach to such tricyclic aminocyclopropanes involving direct cyclopropanation of imides (cf. Scheme 3).⁷

Scheme 13. Enantioselective palladium(0)-catalyzed cyclopropane C–H activations in aminocyclopropanes³⁹

Additional Syntheses of Various Cyclopropylamines

Some alternative synthetic approaches to aminocyclopropanes have been reported in the last 15 years; however, the utilizations of most of them (such as cyclopropanations of enamines⁴⁰ or aminations of cyclopropanes/methylenecyclopropanes⁴¹) appear to be rather limited. Yet, the high-yielding zinc-mediated diastereo- and enantioselective direct transformation of cyclopropanols 39 into N,N-dialkylated cyclopropylamines 4 (Scheme 14), as recently reported by Rousseaux et al.,⁴²
has a great potential, albeit its synthetic applications have not yet been fully
developed.

Scheme 14. Zinc-mediated direct transformation of cyclopropanols into
$N,N$-dialkylcyclopropylamines

As was discovered in 2002 by Szymoniak et al., carbonitriles can be
directly converted into primary cyclopropylamines $40$ by treatment with
appropriate Grignard reagents in the presence of Ti(OiPr)$_4$ and subsequent
addition of Et$_2$O·BF$_3$ (Scheme 15).$^{43}$ For 1-arylcyclopropylamines $41$, an
alternative protocol developed by de Meijere et al. turned out to be more
favorable (Scheme 15).$^{44}$ For primary cyclopropylamines, these latter
methods may be superior to the original Kulinkovich-de Meijere protocol,
as the debenzylation step is saved. By the number of publications, the
conversion of nitriles has surpassed that of $N,N$-dialkylicarboxamides ($347$ vs
282 according to SciFinder).

Scheme 15. Conversion of carbonitriles into primary cyclopropyl-
amines$^{43,44}$
However, since the N-alkylated aminocyclopropane derivatives have found growing employment in medicinal chemistry research (see Table 1), the Kulinkovich-de Meijere cyclopropanation remains as one of the most important methods for the preparation of aminocyclopropanes, while the Kulinkovich-Szymoniak reaction has found its own important applications.

References

1. Institut für Organische und Biomolekulare Chemie der Georg-August-Universität, Tammanstr. 2, D-37077 Göttingen, Germany. Email: Armin.deMeijere@chemie.uni-goettingen.de Email: skozhus@gwdg.de


30. (a) Xi, N. PCT Int. Appl. WO 002013148537 A1, October 03, 2013; (b) Xi, N. Pat. Appl. US 020100093727 A1, April 15, 2010.


Armin de Meijere, born 1939, studied chemistry in Freiburg and Göttingen, receiving a doctoral degree (Dr. rer. nat.) in 1966 in Göttingen, completing postdoctoral training at Yale University in 1967-1969, and receiving Habilitation in 1971 in Göttingen. He was appointed full Professor of Organic Chemistry in Hamburg, 1977-1989 and ever since has been in Göttingen. He was visiting professor at 16 research institutions around the world including the University of Wisconsin, the Technion in Haifa, Israel, and Princeton University. His awards and honors include member of the Norwegian Academy of Sciences, Alexander von Humboldt/Gay Lussac prize, Honorary Professor of St. Petersburg State University in Russia, Adolf von Baeyer Medal of the German Chemical Society, Dr. honoris causa of the Russian Academy of Sciences. He has been or still is Editor or member of the editorial board of a number of scientific publications including Houben-Weyl, Chemical Reviews, Science of Synthesis, and Chemistry - A European Journal. His scientific achievements have been published in over 720 original publications, review articles, and book chapters as well as 25 patents.

Sergei I. Kozhushkov was born in 1956 in Kharkov, USSR. He studied chemistry at Lomonosov Moscow State University, where he obtained his doctoral degree in 1983 under the supervision of Professor N. S. Zefirov and performed his Habilitation in 1998. From 1983 to 1991, he worked at Moscow State University and then at Zelinsky Institute of Organic Chemistry. In 1991, he joined the research group of Professor A. de Meijere (Georg-August-Universität Göttingen, Germany) as an Alexander von Humboldt Research Fellow; since 1993 he has worked as a Research Associate, since 1996 he has held a position of a Scientific Assistant and since 2001 a permanent position as a Senior Scientist at the University of Göttingen. His current research interests focus on the chemistry of highly strained small ring compounds. The results of his scientific activity have been published in over 200 original publications, review articles, book chapters and patents.