Organic Syntheses

Discussion Addendum for:

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

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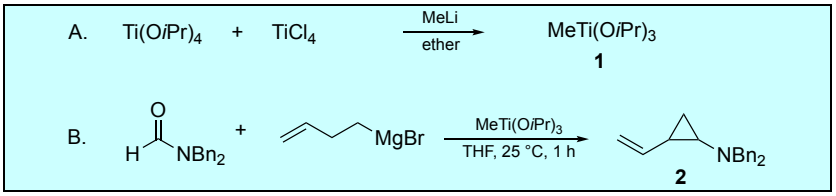

Since the original report in 1996,[2] the transformations of *N,N*-dialkylcarboxamides with 1,2-dicarbanionic organometallics *in situ* generated from organomagnesium (Grignard) as well as organozinc reagents in the presence of stoichiometric or substoichiometric (semi-catalytic) quantities of a titanium 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

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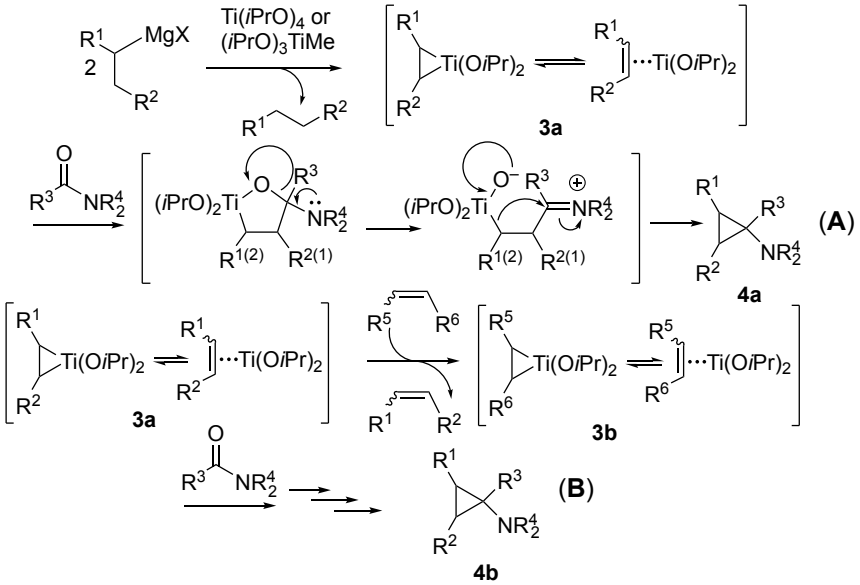
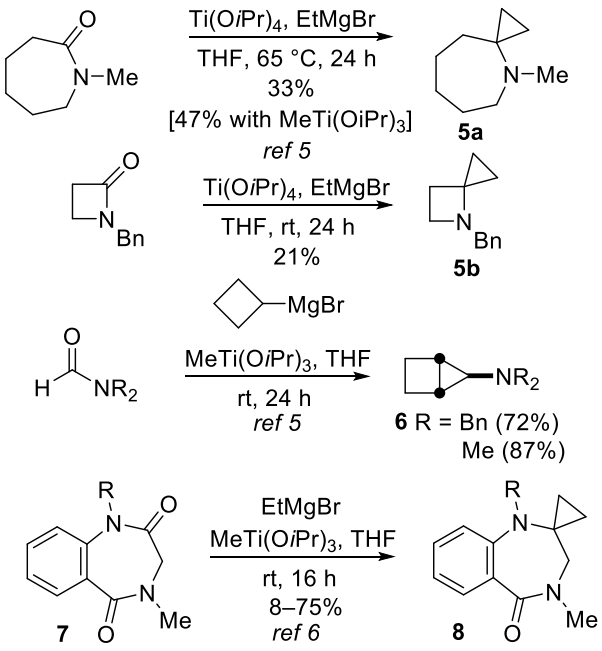
synthesis.[4] The present Discussion Addendum is focused on the most remarkable new developments and synthetic employments of this reaction published since 2005.



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

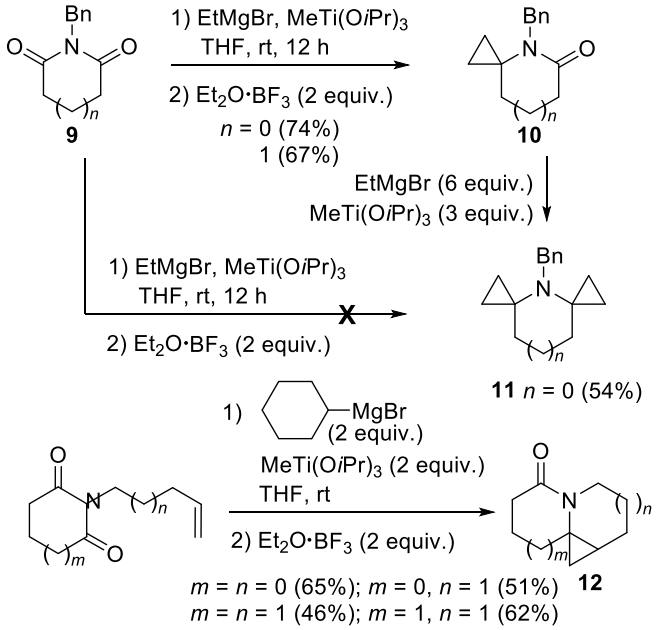
Attempted Further Extensions of the Reaction Scope

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*s up to 80% in the presence of chirally modified Ti(TADDOL)$_2$.[5] 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).[5] Treatment of substituted 1*H*-benzo[*e*][1,4]diazepine-2,5-diones **7** with EtMgBr/MeTi(O*i*Pr)$_3$ resulted in selective cyclopropanation of only the anilide carbonyl group and afforded derivatives of spirobenzodiazepinone **8**.[6] Generally speaking, in most cases MeTi(O*i*Pr)$_3$ turned out to be more efficient. Indeed, with the employment of Ti(O*i*Pr)$_4$, **7** underwent decomposition.



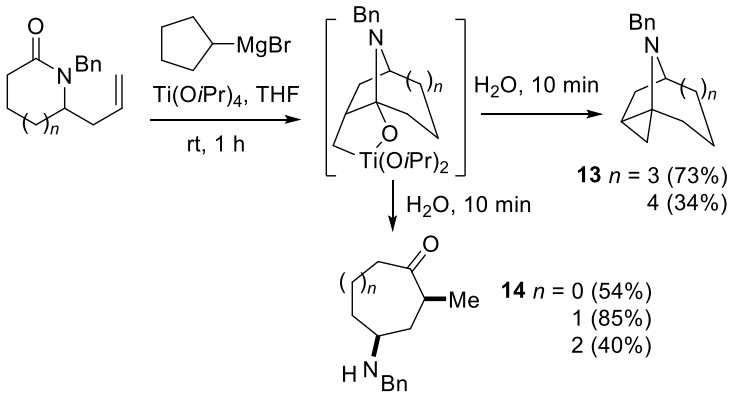
Scheme 2. Preparation of spirocyclic and ring-fused aminocyclopropanes

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(O*i*Pr)$_3$ as a titanium reagent and Et$_2$O•BF$_3$ as an activator for the second step of the transformation.[7] Notably, only one carbonyl group was converted under these conditions, yet the isolated product **10** could be cyclopropanated to give the bisspirocyclopropane derivative **11** with a larger excess of the EtMgBr/MeTi(O*i*Pr)$_3$ reagent and without addition of Et$_2$O•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).

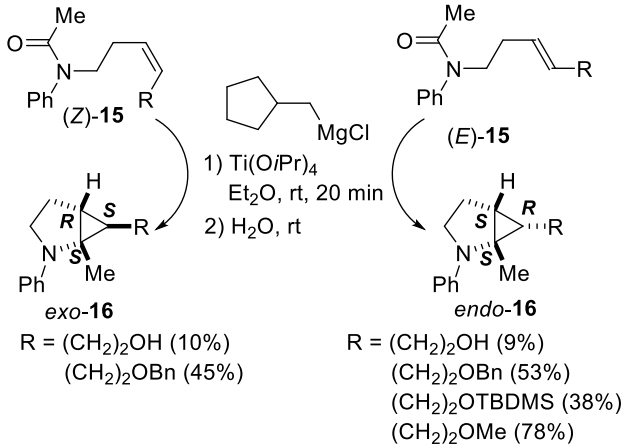


Scheme 3. Kulinkovich-de Meijere cyclopropanation of imides[7]

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.[8] In these cases, hydrolysis of the intermediates with water without addition of $Et_2O{\bullet}BF_3$ leads to carbocyclic amino ketones **14**, which are useful building blocks for the synthesis of certain alkaloids (Scheme 4).[9] Yet, with a large enough lactam ring in the starting material, i. e. an eight- (n = 3) or nine-membered (n = 3) 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.[9] 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).[10] Their intramolecular Kulinkovich-de Meijere reactions afforded predominantly *exo*-configured products *exo*-**16** from (*Z*)-**15** and *endo*-**16** from (*E*)-**15**, respectively.

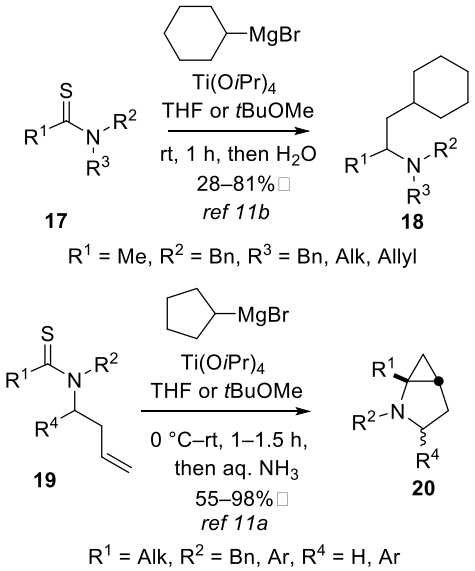


Scheme 4. Intramolecular cyclopropanations of alkenyllactams towards tricyclic cyclopropylamines[9]



Scheme 5. Intramolecular Kulinkovich-de Meijere reactions of amides bearing disubstituted alkene moieties[10]

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.



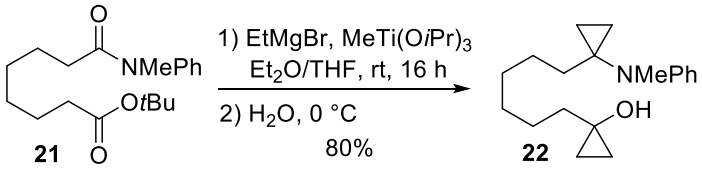
Scheme 6. Inter- and intramolecular transformations of thioamides upon treatment with alkylmagnesium halides and titanium tetraisopropoxide[11]

However, with an *N*-alkenyl group in the thioamide, such as in **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 **20** were prepared from *N*-(but-3-enyl)thioamides **19** in good to very good yields (Scheme 6).[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.

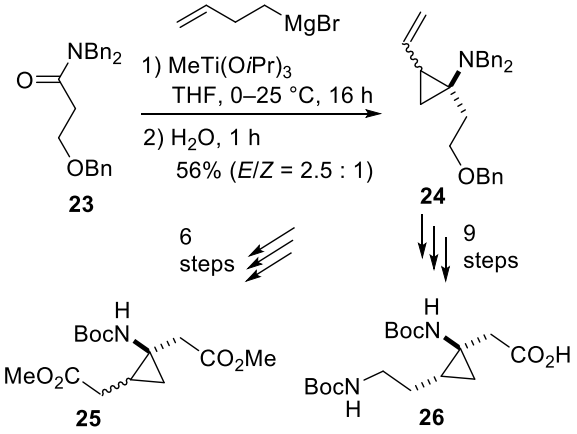
Several attempts to facilitate the generation of titanacyclopropane intermediates gave mixed results. Although active organometallic species formed from Ti(O*i*Pr)$_4$ and *n*BuLi possessed properties similar to those of a titanacyclopropane, it was surprisingly more stable as well as less reactive than the intermediate from Grignard reagents and Ti(O*i*Pr)$_4$. Thus, this protocol has only found rather limited synthetic applications.[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).[13]



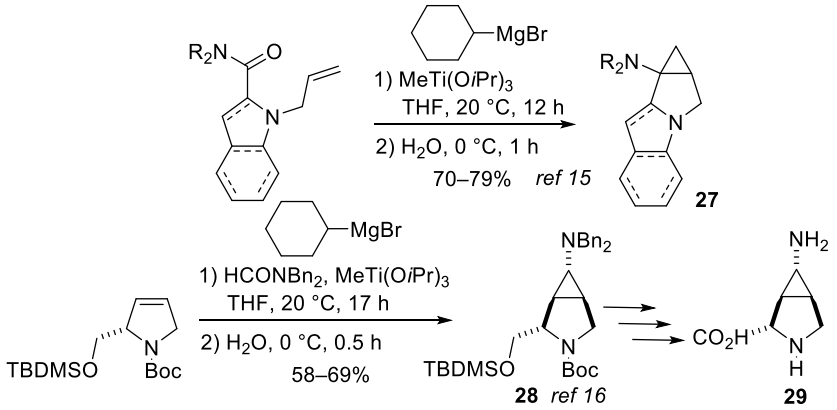
Scheme 7. Twofold cyclopropanation of a suberic acid amide ester[13]



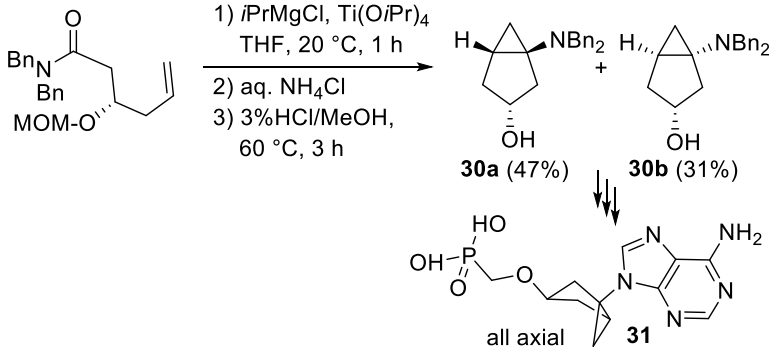
Scheme 8. Titanium-mediated cyclopropanation of 3-benzyloxypropionic acid *N,N*-dibenzylamide (23)[14]

The titanium-mediated cyclopropanation of 3-benzyloxypropionic acid *N,N*-dibenzylamide (**23**) 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).[14] Cyclopropane-annelated amino-substituted pyrrolizidine derivatives **27**[15] as well as the key intermediate **28** for the synthesis of 3,4-(aminomethano)proline **29**[16] were obtained in good yields utilizing the titanium-mediated ligand exchange aminocyclopropanation methodology in its intra- and intermolecular version, respectively (Scheme 9).



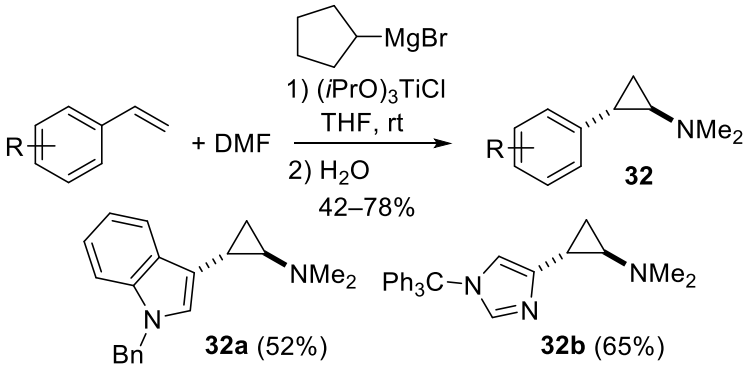
Scheme 9. Preparation of aminosubstituted 3-azabicyclo[3.1.0]hexanes 27, 28



Scheme 10. Synthesis of a precursor to conformationally locked versions of L-deoxythreosyl phosphonate nucleosides 31[17]

Conformationally restricted versions of L-deoxythreosyl phosphonate nucleosides were synthesized by Marquez et al.[17] in order to investigate the

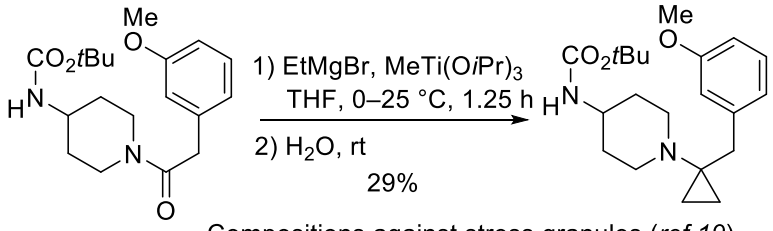
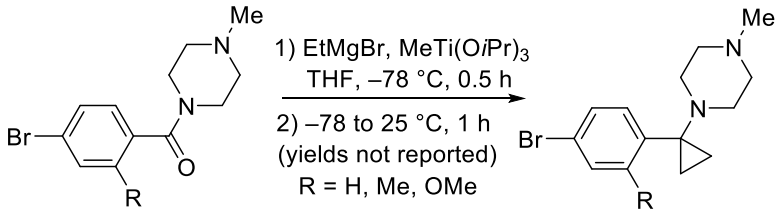
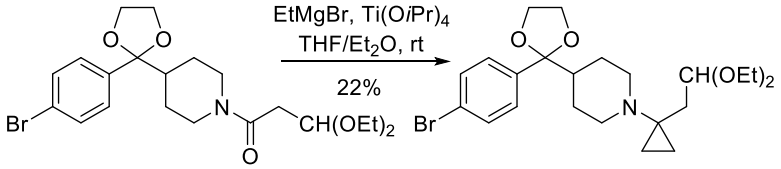
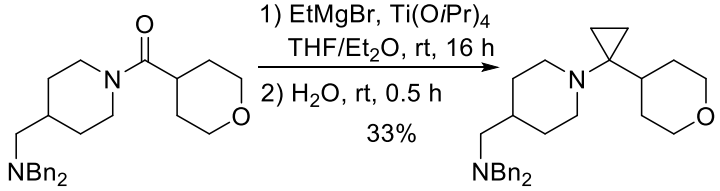
conformational preference of the HIV reverse transcriptase. The key intermediates **30** en route to the enantiomeric diaxially disposed 4-(6-amino-9*H*-purin-9-yl)bicyclo[3.1.0]hexan-2-ol carbocyclic nucleoside **31** were assembled employing an intramolecular Kulinkovich-de Meijere reductive cyclopropanation of the appropriately substituted hexenoic acid *N*,*N*-dibenzylamide (Scheme 10).

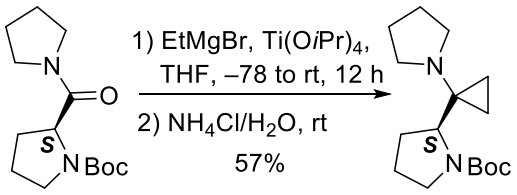
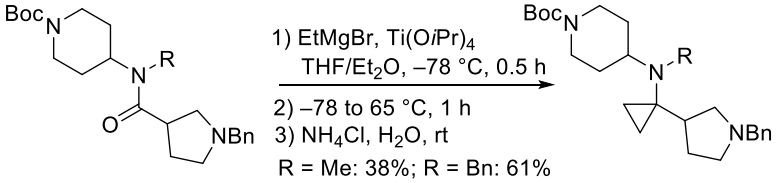
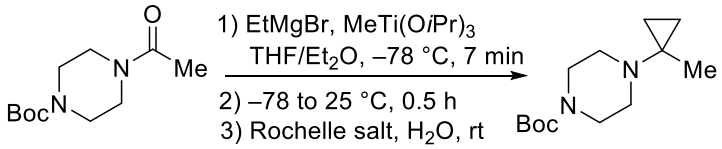
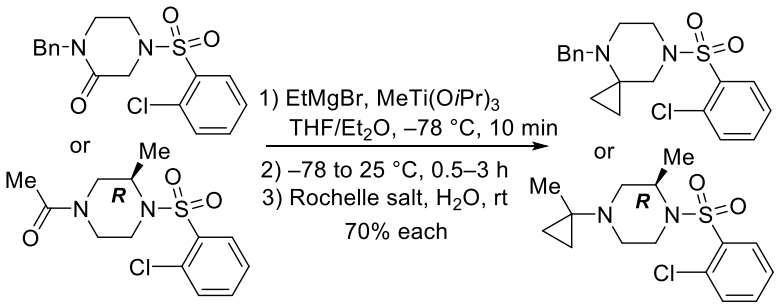
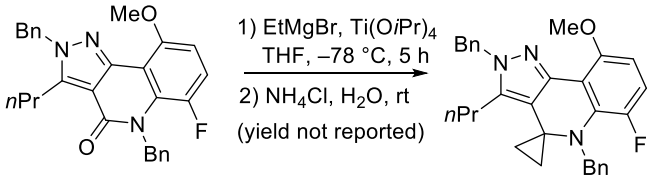


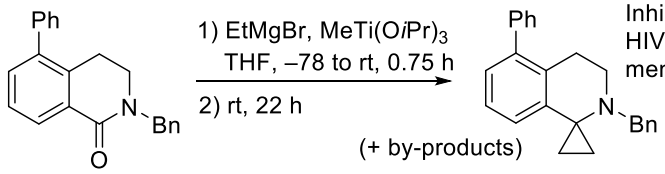
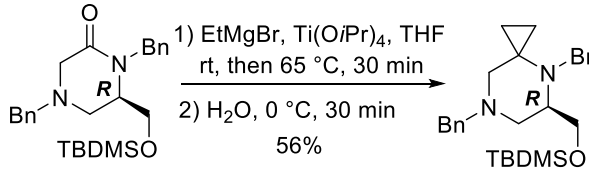
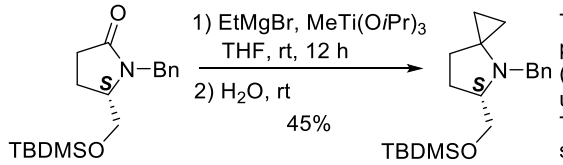
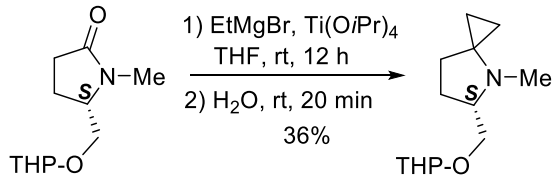
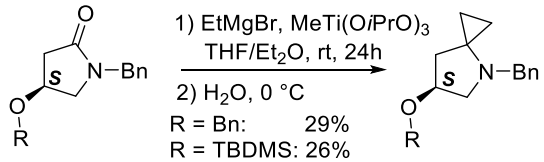
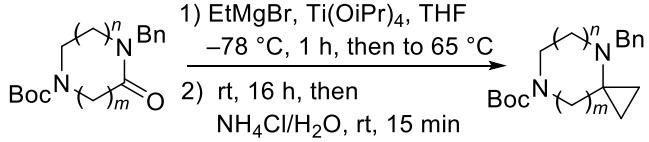
Scheme 11. Reductive aminocyclopropanations in the preparation of building blocks for inhibitors of monoamine oxidase[18]

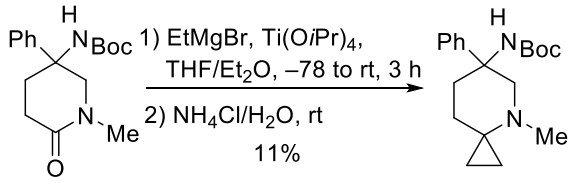
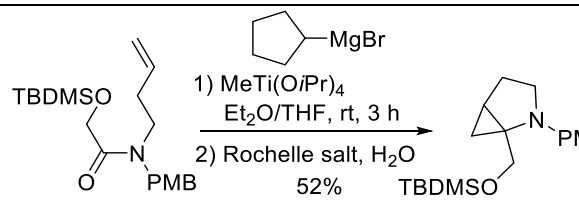
An intermolecular aminocyclopropanation employing ligand exchange with substituted styrenes or ethenylheteroarenes and $ClTi(OR)_3$ as a titanium source has been used by Joullié et al. to synthesize various 2-arylcyclopropylamines **32** as starting materials for conformationally constrained analogues of the neurotransmitters histamine and tryptamine as inhibitors of monoamine oxidase (Scheme 11).[18] 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*

Entry	Reaction/Biological target
1	 Compositions against stress granules (*ref 19*)
2	 Inhibitors of the bromodomain BRD9 proteins (*ref 20*)
3	 Potent inhibitors of M-tropic (R5) HIV-1 replication (*ref 21*)
4	 Selective linear tachykinin NK2 receptor antagonists (*ref 22*)

5	 Bacterial peptide deformylase inhibitors for the treatment of bacterial infections (*ref 23*)
6	 Pharmaceutical compositions against drug-resistant microbes (*ref 24*)
7	 *Hsp70* ATPase modulators as potential therapeutics for Alzheimer's and other neurodegenerative diseases (*ref 25*)
8	 Hydroxysteroid dehydrogenase inhibitors (*ref 25b*)
9	 Antitumor agents (*ref 26*)

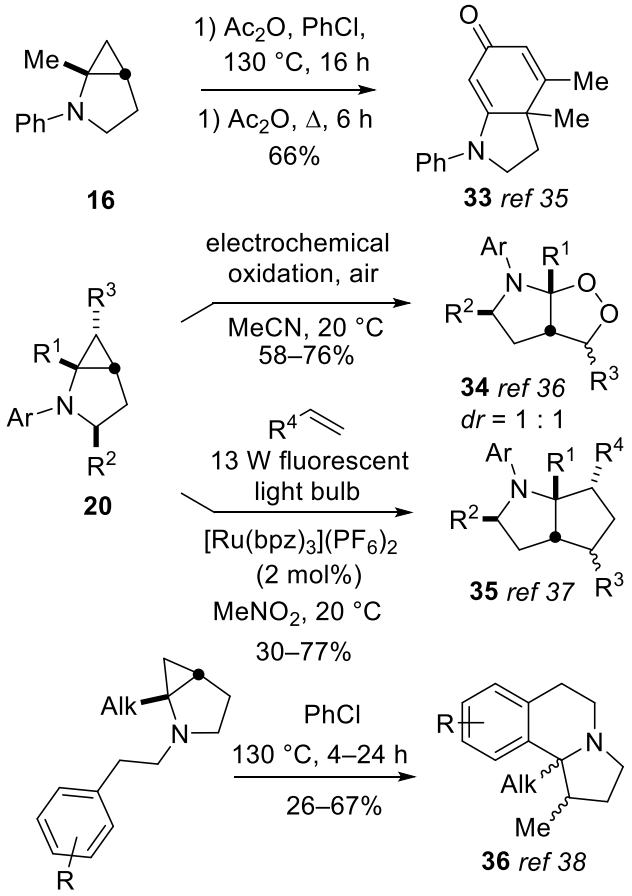
10		Inhibitors of HIV-1 attachment (*ref 27*)
11		HIV protease inhibitors (ref 28)
12		Transient receptor potential ankyrin 1 (TRPA1) antagonists useful in treatment of TRPA1-mediated diseases (*ref 29*)
13		Tyrosine kinase inhibitors for treatment of hyperproliferative disorders (*ref 30*)
14		Compounds having PGD2 receptor antagonist activity (*ref 31*)
15	 *n* = *m* = 1: 58%; *n* = 1, *m* = 2: 64%; *n* = 2, *m* = 1: 37%	Protein tyrosine kinase inhibitors (*ref 32*)

16		Glycine transporter 1 (GLYT-1) inhibitors (*ref 33*)
17		Interleukin-1 receptor associated kinase (IRAK4) modulators (*ref 34*)

*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

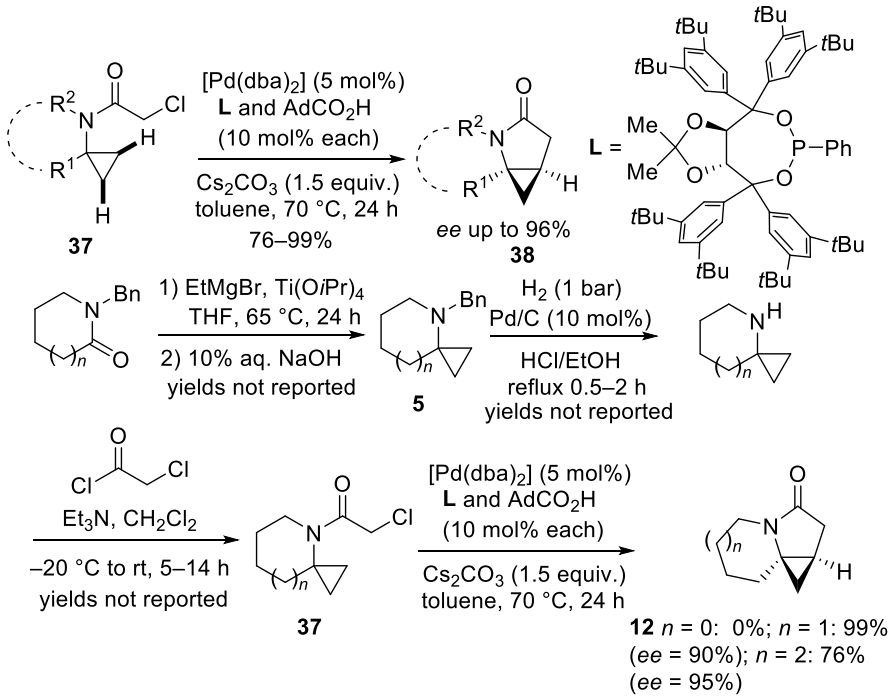
The 2-azabicyclo[3.1.0]hexanes and 2-azabicyclo[4.1.0]heptanes prepared by the Kulinkovich-de Meijere reaction as described above, are susceptible to undergo cleavage of a vicinal (with respect to the nitrogen atom) C–C bond and thus enter [3+2] cycloaddition or intramolecular aromatic electrophilic substitution reactions to afford polycyclic systems with potential synthetic utility towards biologically active compounds (Scheme 12). For example, 2,3,3*a*,4-tetrahydro-6(5*H*)-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-1,2,3,5,6,10*b*-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.[39] 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]

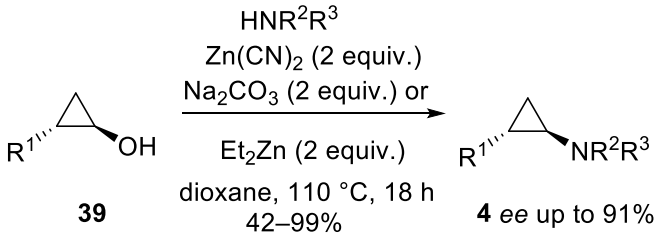


Scheme 13. Enantioselective palladium(0)-catalyzed cyclopropane C–H activations in aminocyclopropanes[39]

Additional Syntheses of Various Cyclopropylamines

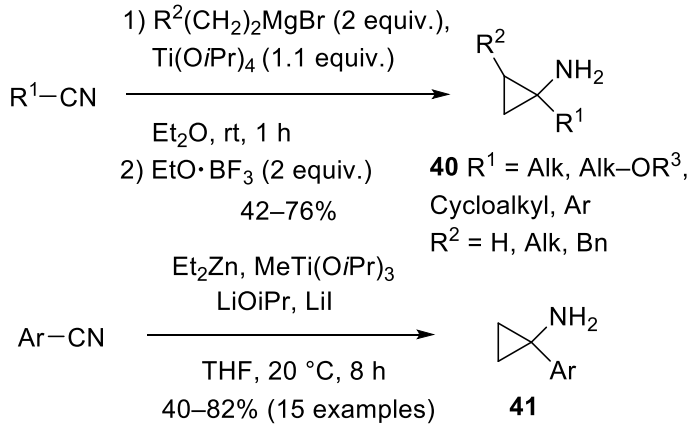
Some alternative synthetic approaches to aminocyclopropanes have been reported in the last 15 years; however, the utilizations of most of them (such as cyclopropanations of enamines[40] or aminations of cyclopropenes/methylenecyclopropanes[41]) appear to be rather limited. Yet, the high-yielding zinc-mediated 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[42]

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 $Et_2O{\cdot}BF_3$ (Scheme 15).[3,43] 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*-dialkylcarboxamides (347 *vs* 282 according to SciFinder).



Scheme 15. Conversion of carbonitriles into primary cyclopropylamines[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.

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