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(3+3)-Annulation of Donor-Acceptor Cyclopropanes with Diaziridines

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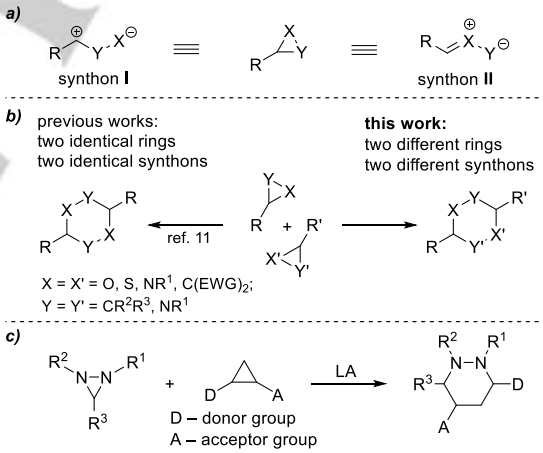
Abstract: The first example of (3+3)-annulation of two different three-membered rings is reported herein. Donor-acceptor cyclopropanes in reaction with diaziridines were found to afford perhydropyridazine derivatives in high yields and diastereoselectivity under mild Lewis acid catalysis. The disclosed reaction is applicable for the broad substrate scope and exhibits an excellent functional group tolerance.

One-step construction of cyclic molecules from simple building blocks with a considerable increase in a structure complexity is one of the most important challenges of contemporary organic chemistry. The essential processes for this purpose are various cycloadditions, annulations and domino reactions with diverse unsaturated compounds being typical building blocks.[1,2] In contrast to alkenes, imines, alkynes, *etc*., three-membered rings remain significantly underexplored as starting compounds for the synthesis of larger rings except for their involvement into (3+2)-cycloadditions. Meanwhile, three-membered heterocycles have a high potential for organic synthesis; the high strain energy and facile cleavage of the polarized carbon-heteroatom bond ensure their efficient use as synthetic equivalents of 1,3-zwitter-ionic synthon **I** (Scheme 1*a*).[3]

Cyclopropanes were for a long time considered as rather kinetically inert species due to the absence of highly polarized bonds in the all-carbon ring. However, the intensive study of donor-acceptor (D–A) cyclopropanes[4-6] during last decades has disproved this belief. Donor and acceptor substituents at the vicinal carbon atoms polarize C–C bond between, allowing D–A cyclopropanes to react efficiently as equivalents of synthon **I** (Scheme 1a).[7]

On the other hand, three-membered heterocycles can exhibit a reactivity of synthetic equivalents of common 1,3-dipoles (azomethine ylides for aziridines,[8] carbonyl ylides for oxiranes,[9] synthon **II** in Scheme 1*a*) producing cycloadducts in reactions with the appropriate unsaturated compounds. This kind of reactivity is predominant for most three-membered rings with two heteroatoms. Thus, in reactions involving small ring opening diaziridines act as synthetic equivalents of azomethine imines (synthon **II**, X = Y = NR).[10]

Three-membered rings due to their dipolar nature are able to undergo (3+3)-cyclodimerization affording the corresponding six-membered rings (Scheme 1*b*).[11] However, (3+3)-annulation of two different saturated three-membered rings has not been reported thus far owing to the difficulties in the selective activation of this reactivity mode.[12] The reported reactions of D–A cyclopropanes with aziridines,[13] oxiranes,[14] oxaziridines[15] led to various products different from (3+3)-cycloadducts. Herein, we report the first successful (3+3)-annulation of two different saturated three-membered rings exemplified by Lewis acid-induced coupling of D–A cyclopropanes with diaziridines (Scheme 1*c*).



Scheme 1. General concept of this work.

We started our research by determining the optimal conditions for the title annulation using 2-phenylcyclopropane-1,1-diester **1a** and readily available bicyclic diaziridine **2a** as model compounds. The screening of Lewis acids, which were previously reported as efficient initiators of D–A cyclopropane reactions with diverse nitrogen nucleophiles,[16] the variation of the reaction duration and temperature as well as ratio and concentration of starting compounds (Table 1) revealed that the best yields of the desired hexahydropyridazine **3a** were obtained under catalysis with $Sc(OTf)_3$ (Table 1, entry 4) or $Ni(ClO_4)_2 \cdot 6H_2O$ (Table 1, entries 6, 7) in dichloromethane. It is noteworthy that milder Lewis acids failed to initiate this annulation, while more activating Lewis acids as well as heating of the reaction mixture above 60 °C promoted the

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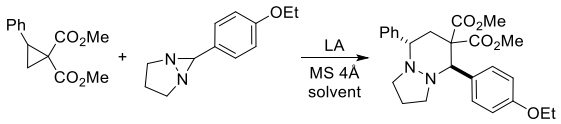
decomposition of diaziridine resulting in low conversion of D–A cyclopropane.

Table 1. Variation of reaction conditions for (3+3)-annulation of **1a** and **2a**.[a]



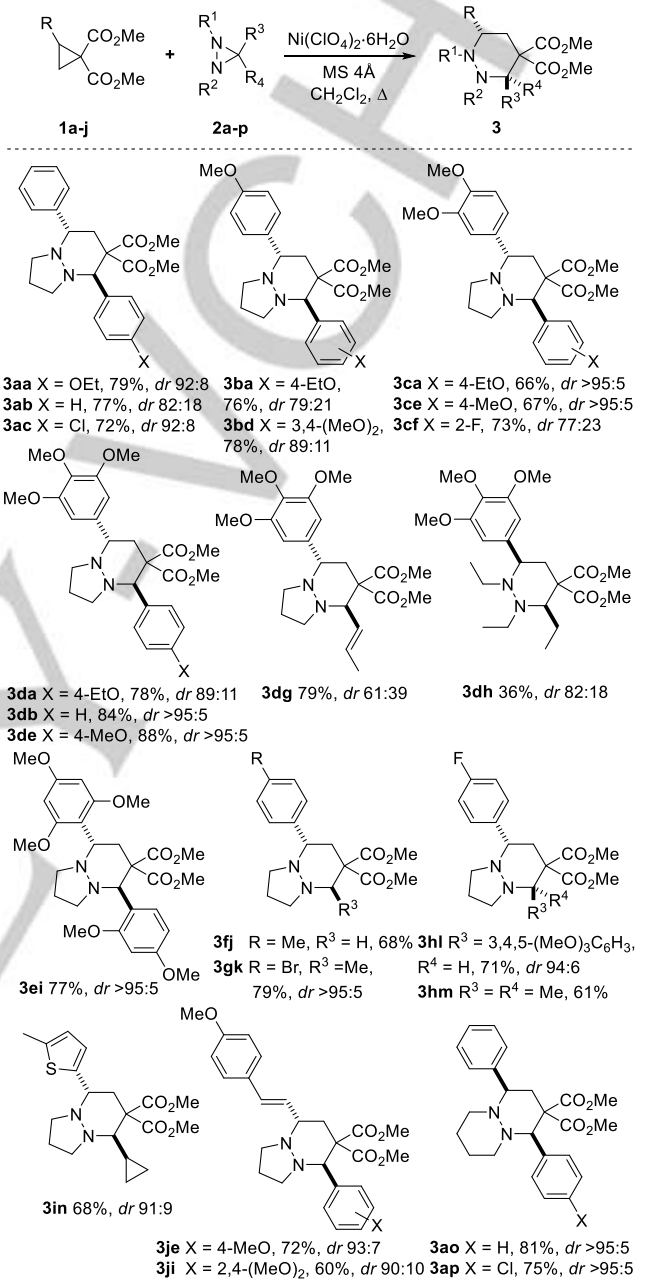
1a **2a** **3aa**

Entry	LA (mol%)	Solvent	T [°C]	t [h]	Yield [%][b] (*trans*:*cis*)[c]
1	$SnCl_4$ (110)	CH_2Cl_2	rt	1	-
2	$Sn(OTf)_2$ (10)	CH_2Cl_2	rt	4	Traces
3	$Sn(OTf)_2$ (10)	CH_2Cl_2	40	4	25[d]
4	**$Sc(OTf)_3$ (10)**	**CH_2Cl_2**	**40**	**4**	**78 (69:31)**
5	$Ni(OTf)_2$ (20)	CH_2Cl_2	40	4	10[d]
6	**$Ni(ClO_4)_2{\cdot}6H_2O$ (20)**	**CH_2Cl_2**	**40**	**4**	**73 (89:11)[e]**
7	**$Ni(ClO_4)_2{\cdot}6H_2O$ (20)**	**CH_2Cl_2**	**40**	**4**	**79 (92:8)[f]**
8	$Ni(ClO_4)_2{\cdot}6H_2O$ (20)	$(CH_2Cl)_2$	83	4	- [g]
9	$Ni(ClO_4)_2{\cdot}6H_2O$ (20)	CH_3NO_2	80	2	- [g]

[a] Reaction conditions: 0.05 M solution of **1a**, 1.5 equiv. of **2a**. [b] Isolated yields. [c] Diastereomeric ratio (*dr*) was determined by NMR analysis of crude product. [d] Low conversion of **1**; *dr* was not determined. [e] Addition of **2a** in a single portion. [f] Portionwise addition of **2a**. [g] Decomposition of **2a** prevailed.

With the optimized reaction conditions in hand, we investigated the scope of the disclosed (3+3)-annulation by varying substituents in both reactants (Scheme 2). The reaction was found to proceed efficiently for a broad series of cyclopropanes bearing electron-enriched (**1b-g,i**) and electroneutral (**1a,f-h**) (hetero)aromatic group as a donor. Moreover, alkenyl-substituted D–A cyclopropane **1j** was found to be equipotent to (het)aryl-substituted analogs. On the other hand, a large variety of bicyclic diaziridines, both with aryl, alkyl, alkenyl, cyclopropyl groups at the carbon atom of three-membered ring and unsubstituted at this atom (**2j**) participated efficiently in the annulation.

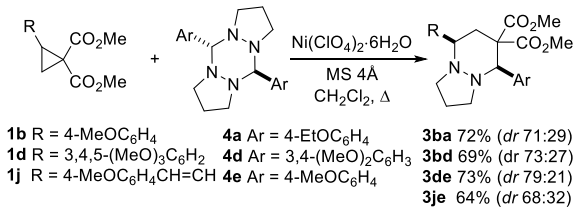
However, electron-withdrawing substituents in both aromatic group of D–A cyclopropane **1** and diaziridine **2** significantly decelerated the reported reaction. All attempts to involve 2-(2-nitrophenyl)cyclopropane-1,1-dicarboxylate into this annulation were unsuccessful. Similarly, 4-pyridyl analog of **2a** was found to be inert against cyclopropanes **1** under the used conditions. Monocyclic triethyldiaziridine **2h** demonstrated the intermediate behavior. Its reaction with D–A cyclopropane **1d** afforded (3+3)-annulation product only in 36% yield due to the low conversion (*ca*. 50%) of cyclopropane. In other words, yield based on the consumed cyclopropane equals to *ca.* 72%. Presumably, *trans*-arrangement of ethyl substituents at two nitrogen atoms[17] hinders the nucleophilic attack of diaziridine on the cyclopropane resulting in the higher proportion of decomposed diaziridine.



Scheme 2. Scope of (3+3)-annulation of cyclopropanes **1** with diaziridines **2**. General reaction conditions: 0.05 M solution of **1**, portionwise addition of **2** (1.25–3 equiv.), molecular sieves 4Å, CH_2Cl_2, reflux. Yields of isolated products are given; *dr* was determined by NMR analysis of crude product.

In the presence of Lewis acids diaziridines can undergo (3+3)-cyclodimerization; and the dimers, in reactions with unsaturated compounds, were reported to demonstrate similar reactivity as parent diaziridines affording the same products.[18] The possible explanation is the intermediacy of the same 1,3-dipole in reactions of both diaziridines and the corresponding cyclodimers

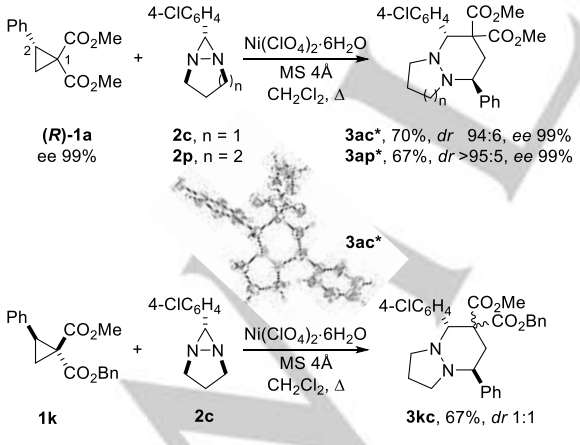
4. To check the validity of this hypothesis, we studied the reaction of cyclopropanes **1** with compounds **4** and disclosed that pyrazolo[1,2-*a*]pyridazine derivatives **3** were formed as well. However, a surprising reversal of the reaction diastereoselectivity was observed. When substrates **2** were used as starting compounds, *trans*-**3** were formed as major or single products, while in reactions of dimers **4** the predominant formation of *cis*-**3** was noted (Scheme 3). Moreover, $Sc(OTf)_3$ failed to promote the reaction of D–A cyclopropanes **1** with dimers **4** in contrast to the reaction between **1** and **2**.



Scheme 3. Reaction of D–A cyclopropanes **1** with diaziridine dimers **4**.

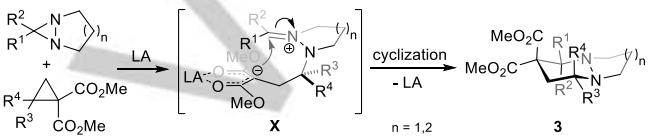
These results are in conflict with both the intermediacy of the same species in two processes and the thermodynamic control of this annulation. Indeed, according to DFT calculations at the B3LYP/6-311G** level, *cis*-**3ab** is slightly (1.34 kJ mol^{-1}) more stable than *trans*-**3ab**,[19] however, any attempts to induce *cis*-*trans* epimerization of both isomers of **3** were unsuccessful.[20]

To shed more light on the mechanism of reaction, we studied its stereochemical features (Scheme 4). The reaction of the optically pure cyclopropane (*R*)-**1a** with diaziridines **2c**,**p** proceeded with a full inversion at the reacting C(2) atom. On the other hand, the reaction of diastereomerically pure D–A cyclopropane **1k** bearing two different acceptor groups with diaziridine **2c** resulted in an equimolar mixture of epimers at the malonate carbon atom (Scheme 4).[21]



Scheme 4. Stereochemical features of (3+3)-annulation between D–A cyclopropanes **1** and diaziridines **2**.

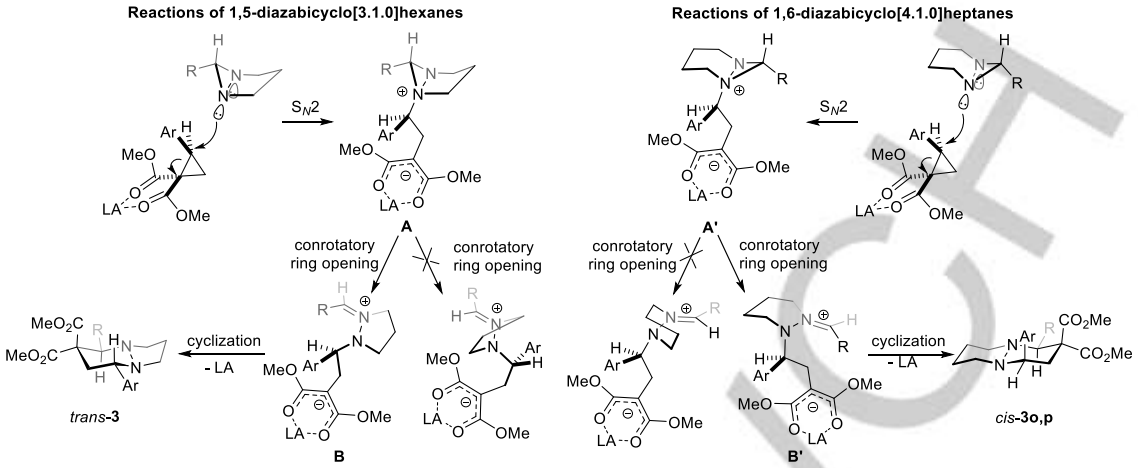
From the investigations presented in Scheme 4 it is possible to conclude that: a) the studied annulation includes the cyclopropane ring opening *via* S_N2-like mechanism; b) the final step of the adducts **3** formation is cyclization of 1,6-zwitter-ion **X** **(**Scheme 5). Herewith, the reaction diastereoselectivity is governed by: 1) the relative arrangement of the fragment of former cyclopropane against the iminium moiety and 2) *E*-/*Z*-configuration of this moiety. These features are similar for all **X** formed from 1,5-diazabicyclo[3.1.0]hexanes (**2a-g**,**i**,**k**,**l**) but one of two parameters is opposite in reactions of dimers **4** and 1,6-diazabicyclo[3.1.0]hexanes **2o,p**. The diastereoselectivity data show also that **X** is transient species the cyclization of which is faster than *Z*-/*E*-isomerization and sp^3 nitrogen inversion (otherwise compounds **2** and **4** should produce the same reaction mixture).[22]



Scheme 5. The intermediate **X** determining diastereoselectivity of **3** formation.

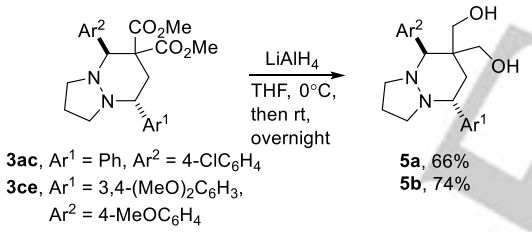
In turn, **X** is formed by the nucleophilic attack of a diaziridine on D–A cyclopropane followed by a conrotatory ring opening of the nitrogen heterocycle isoelectronic to a cyclopropane anion.[23] Due to the steric restrictions induced by a small size of the linker between two nitrogen atoms, this opening can proceed in one direction only affording the intermediate **X** with *Z*-configuration of the iminium moiety. Therefore, the reaction diastereoselectivity is primarily determined by a relative arrangement of malonate and iminium fragments in **X** that is resulted from the different approaches of various diaziridines to D–A cyclopropanes in S_N2 step.

As 1,5-diazabicyclo[3.1.0]hexanes has the *pseudo*-boat conformation,[24] steric repulsions during its approach to **1** would be minimal when the methine hydrogen at the cyclopropane C(2) atom is directed to the C(6) atom of diaziridine. Oppositely, this direction of the approach of two reactants is unfavorable due to the boat conformation of the six-membered ring in diaziridines **2o,p**.[19,24b] Therefore, these diaziridines approach to D–A cyclopropane in a such way that the methine hydrogen at the cyclopropane C(2) atom is directed to the C(3)–C(4) bond of diaziridine. This is why intermediates **A** and **A'** are formed with different diastereoselectivity. Further diaziridine ring opening and cyclization of the produced intermediates **B** (**B'**) proceed in a stereoselective manner affording *trans*-**3** and *cis*-**3** respectively. The results of this analysis are summarized in Scheme 6. Nevertheless, further study of mechanism is desirable for the better understanding factors influencing the reaction efficiency and stereoselectivity.



Scheme 6. Proposed mechanism of (3+3)-annulation.

The malonate fragment is usually considered as inappropriate functionality for screening of bioactivity. So, we studied the possibility to reduce products **3** affording the corresponding diol derivatives. Indeed, the reduction of **3ac** and **3ce** with $LiAlH_4$ proceeded smoothly furnishing compounds **5a,b** in reasonable yields (Scheme 7).



Scheme 7. Reduction of **3** to the corresponding diols **5**.

To conclude, we disclosed that the Lewis acid-catalyzed reaction of donor-acceptor cyclopropanes with diaziridines affords perhydropyridazine derivatives in high yield and diastereoselectivity. This finding provides the way to a new engaging valley of small rings reactivity: (3+3)-annulations of two different three-membered rings. The presented here and related transformations would be an efficient tool for the synthesis of diverse non-symmetrically substituted six-membered rings.

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Keywords: annulation • small ring systems • donor-acceptor cyclopropanes • diaziridines • nitrogen heterocycles

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[19] For details, see Supporting Information.

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[21] The structure of compound **3ac*** as well as structures of compounds **3ca**, **3hl**, **3ao**, **2p** and **4b** were unambiguously proved by X-ray data. CCDC1582038 (**2p**), 1582039 (**4d**·$CHCl_3$), 1585886 ((5*R*,8*S*)-**3ac***), 1581835 ((5*RS*,8*SR*)-**3ca**), 1581838 ((5*RS*,8*SR*)-**3hl**), and 1581841 ((5*RS*,8*RS*)-**3ao**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

[22] Nevertheless, partial isomerization in intermediate **X** can be responsible for the formation of diastereomeric mixtures in the most studied reactions. For related results in (3+2)-cycloaddition of some diaziridines with 2,3-dicyanobut-2-enedioates, see: A. F. Khlebnikov, A. S. Konev, A. A. Virtsev, D. S. Yufit, G. Mloston, H. Heimgartner, *Helv. Chim. Acta* **2014**, *97*, 453-470.

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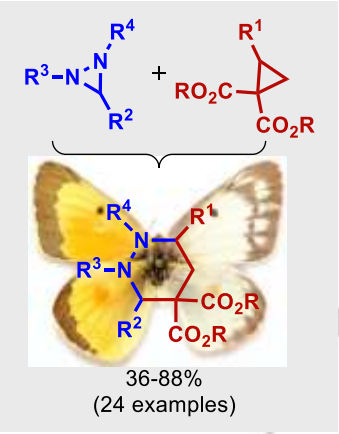
Beautiful dissymmetry: Reported here is the first example of (3+3)-annulation of two different saturated three-membered rings. Namely, coupling of diaziridines with donor-acceptor cyclopropanes is shown to afford hexahydropyridazine derivatives. This approach can be an efficient tool for the synthesis of diverse non-symmetric polysubstituted six-membered rings.



A. O. Chagarovskiy, V. S. Vasin, V. V. Kuznetsov, O. A. Ivanova, V. B. Rybakov, A. N. Shumsky, N. N. Makhova, I. V. Trushkov**

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(3+3)-Annulation of Donor-Acceptor Cyclopropanes with Diaziridines

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