St. Petersburg State University
Institute of Chemistry

Donor-Acceptor Cyclopropanes in the Synthesis of Carbo- and Heterocycles

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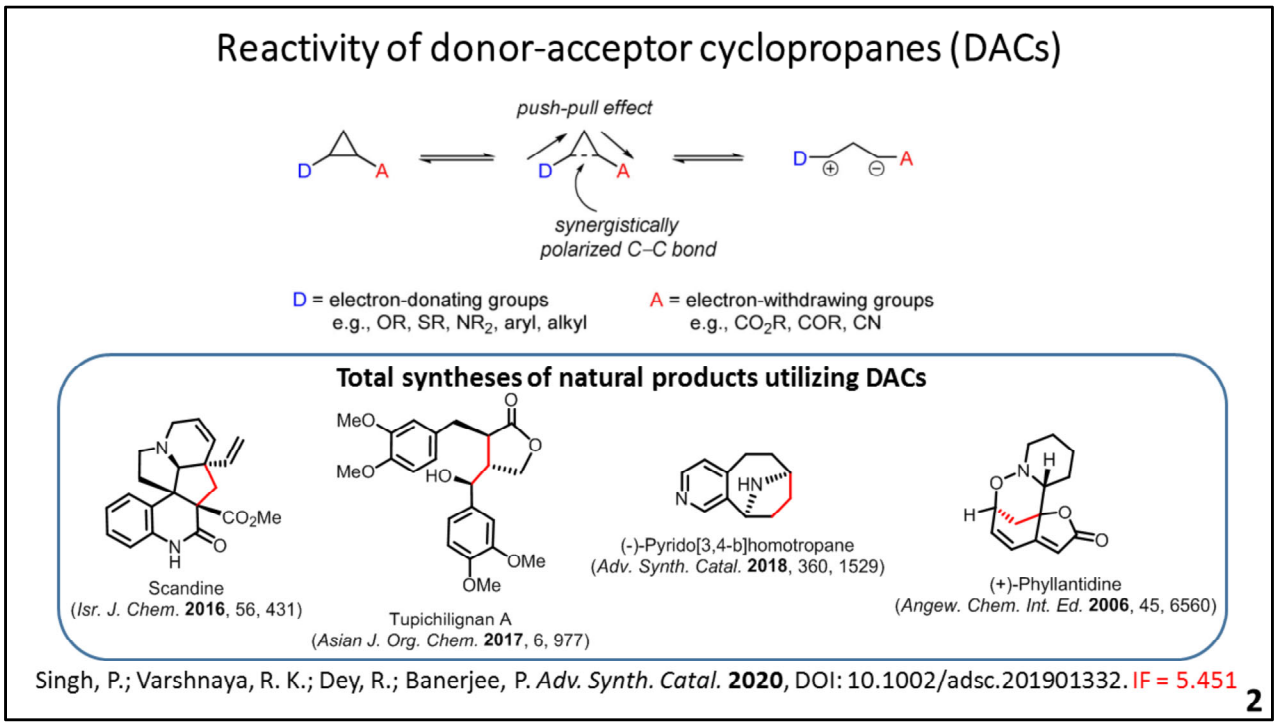
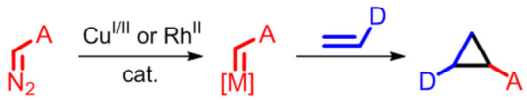
Hello, dear colleagues! Our team is pleased to present a talk titled “Donor-Acceptor Cyclopropanes in the Synthesis of Carbo- and Heterocycles”.



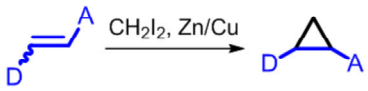
Donor-acceptor cyclopropanes (DACs) are currently experiencing a resurgence of interest. Despite the high strain energy of 28 kcal/mol, the unsubstituted cyclopropane ring is kinetically inert. The introduction of donor and acceptor substituents into the vicinal positions of the cyclopropane ring enhances the efficiency of the C–C bond cleavage. Typically employed donor substituents include aryl, alkyl, alkoxy, thioalkoxy, and amino groups. Alkoxycarbonyl, carbonyl, and cyano groups are often used as acceptor substituents. Under Lewis-acid catalysis, a 1,3-zwitterionic species is formed, for which a multitude of further transformations is possible. The synthetic utility of DACs is highlighted by their use in the total syntheses of a number of natural products. In this talk, we will focus on the cycloaddition reactions of DACs that result in the formation of carbo- and heterocycles.

Synthesis of DACs

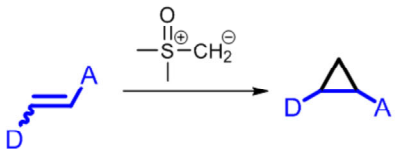
1. Reaction of diazo compounds with alkenes



2. The Simmons-Smith reaction



3. The Corey-Chaykovsky reaction



Menchikov, L. G.; Novikov R. A.; Tomilov, Yu.V. *Donor-Acceptor Cyclopropanes. Synthesis and Dimerization Reactions.* IOC RAS: Moscow, **2016**, 160 pp.

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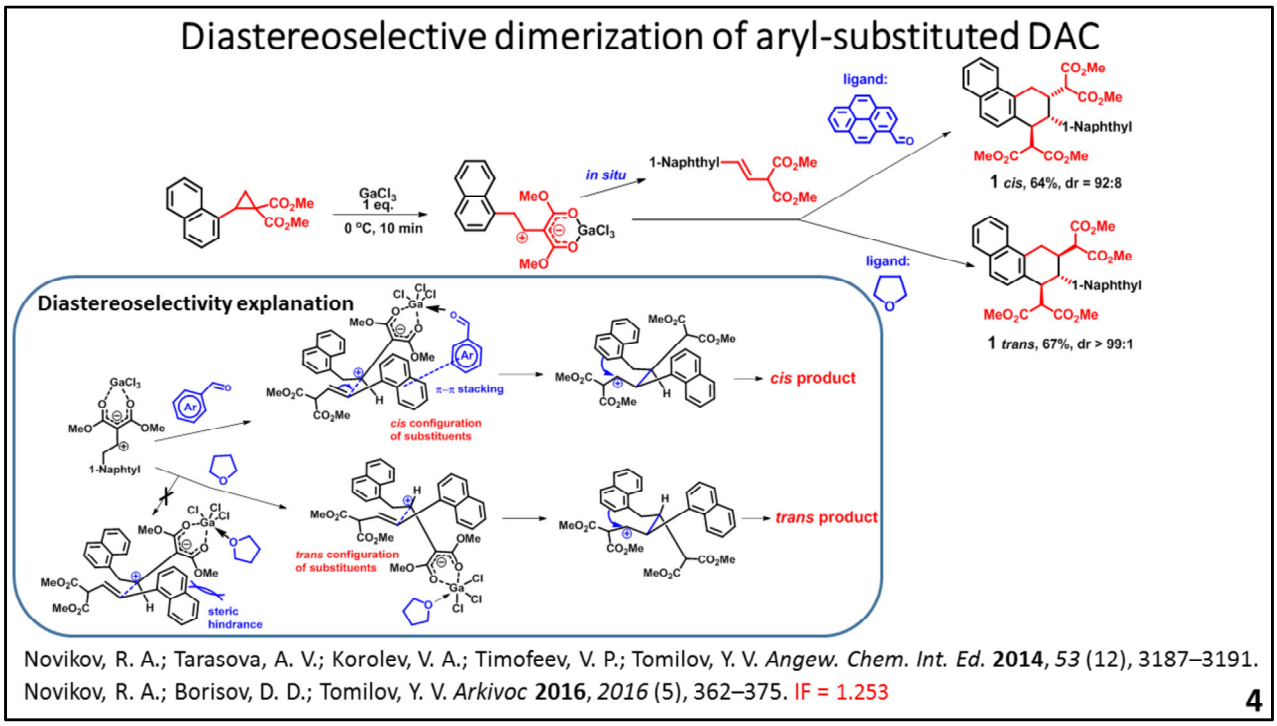
Let us first consider the principal synthetic routes for the preparation of DACs. A general synthetic method comprises the reaction of a donor-substituted alkene with diazo compound containing an electron-withdrawing group, typically in the presence of a metal catalyst. Alkyldiazo acetates and alkyldiazo malonates are particularly well-suited for this method. The reaction of diiodomethane and an alkene in the presence of activated zinc dust, usually zinc-copper couple, is known as the Simmons-Smith reaction. This is one of the most widely employed laboratory methods for the direct cyclopropanation of alkenes. The active methylenating species is thought to be iodomethylzinc iodide. The Corey-Chaykovsky reaction uses sulfur ylides based on dimethylsulfoxide or dimethylsulfide. This reaction is characterized by a high degree of regio- and diastereoselectivity.



Novikov, R. A.; Tarasova, A. V.; Korolev, V. A.; Timofeev, V. P.; Tomilov, Y. V. *Angew. Chem. Int. Ed.* **2014**, *53* (12), 3187–3191.
Novikov, R. A.; Borisov, D. D.; Tomilov, Y. V. *Arkivoc* **2016**, *2016* (5), 362–375. IF = 1.253

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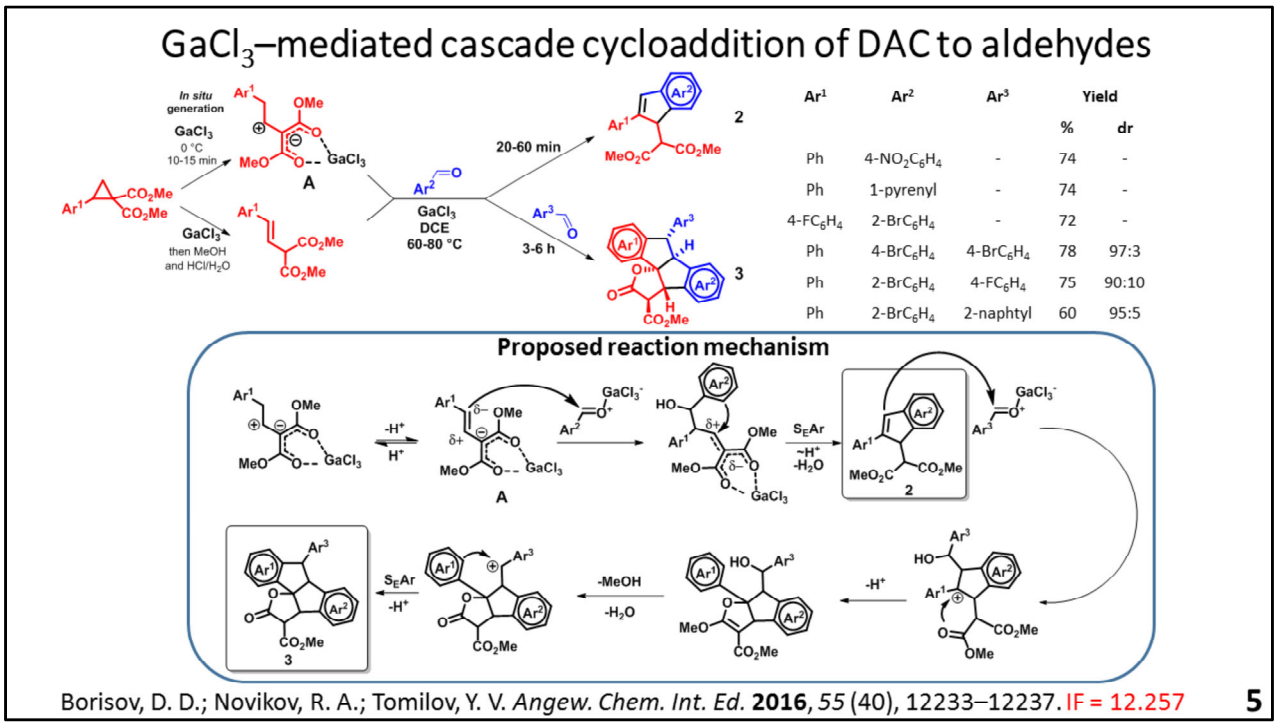
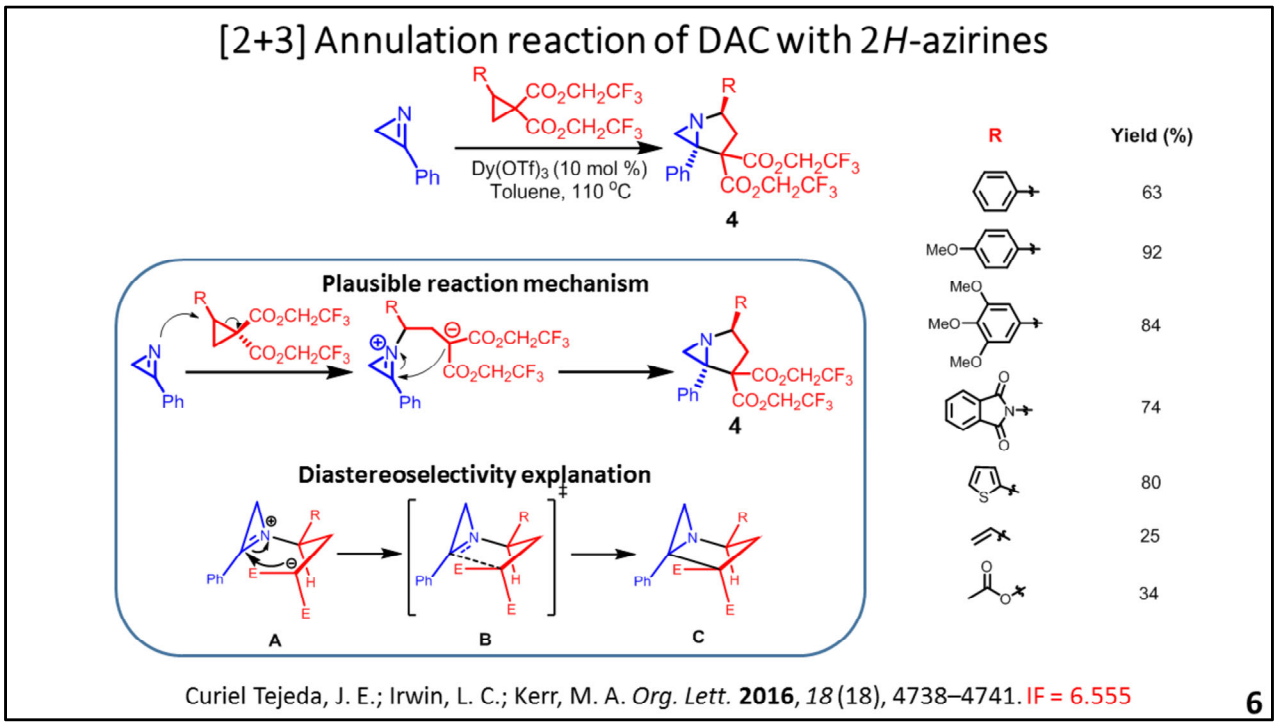
Dimerization reactions of DACs are an important class of transformations that lead to the formation of carbocycles. Tomilov and coworkers investigated the influence of ligand for the Lewis acid catalyst on the diastereoselectivity of the dimerization reaction of a 2-naphthyl-substituted DAC. Performing the reaction with tetrahydrofuran as a ligand leads to the formation of the *trans* product (**1** ***trans***) with high stereoselectivity (diastereomeric ratio (dr) > 99:1), whereas the use of 1-pyrenecarboxaldehyde affords the *cis* product (**1** ***cis***) in a 92:8 dr. The following explanation for the observed diastereoselectivity is proposed. In the case of 1-pyrenecarboxaldehyde, the aromatic ligand participates in the π–π stacking with the naphthalene moiety of the DAC fragment, which stabilizes the transition state leading to the *cis* product. In the case of tetrahydrofuran, however, this transition state is sterically hindered, and the more stable transition state furnishes the *trans* product.



Borisov, D. D.; Novikov, R. A.; Tomilov, Y. V. *Angew. Chem. Int. Ed.* **2016**, *55* (40), 12233–12237. IF = 12.257 **5**

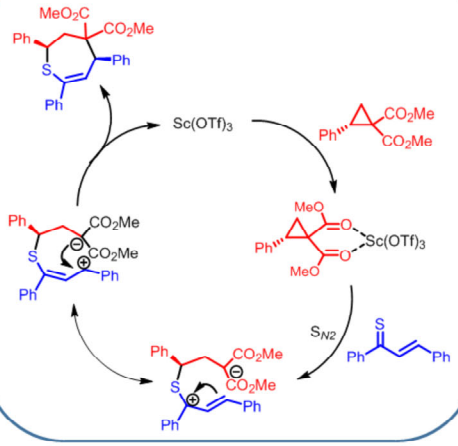
Tomilov's group developed a procedure for the preparation of indenes **2** and polycyclic lactones **3**. The ring-opened reactive intermediate **A** may be either generated *in situ* or isolated as an alkene. Under short reaction times of ca. 20–60 min, indenes **2** are obtained selectively, whereas with increased reaction time polycyclic lactones **3** are formed. The following reaction mechanism is suggested. First, the reactive intermediate **A** attacks the carbonyl group of the aldehyde, and subsequent cyclization through the S_EAr mechanism followed by elimination of a water molecule affords the indenes **2** in high yield. If the reaction is not terminated at this stage, the indene double bond attacks a second aldehyde molecule (and this aldehyde may be different from the one employed at the previous stage), leading to lactonization. A water molecule is eliminated, and cyclization by the S_EAr mechanism affords the products **3** with preferential formation of one diastereomer.



Kerr and coworkers described a [3+2] annulation reaction of a DAC and 3-phenyl-2H-azirine leading to an unusual azabicyclic scaffold. A plausible reaction mechanism involves ring opening of the $Dy(OTf)_3$-activated cyclopropane by the nucleophilic nitrogen producing a zwitterionic intermediate. This iminium ion undergoes a Mannich-like ring closure to the product **4**. The range of substituents in the DAC is fairly wide, with aryl, heteroaryl, vinyl, acetato, and phthalimido substituents tolerated. Notably, the cycloadducts are produced as single *trans* diastereomers. The following rationale for the observed diastereoselectivity is proposed. Zwitterionic species **A** may undergo Mannich-style ring closure via transition state **B** with R in a pseudoequatorial position in the newly formed 5-membered ring leading to the formation of the observed diastereomer **C**.

Formal [4+3] cycloaddition of DAC and thiochalcone

Proposed reaction mechanism

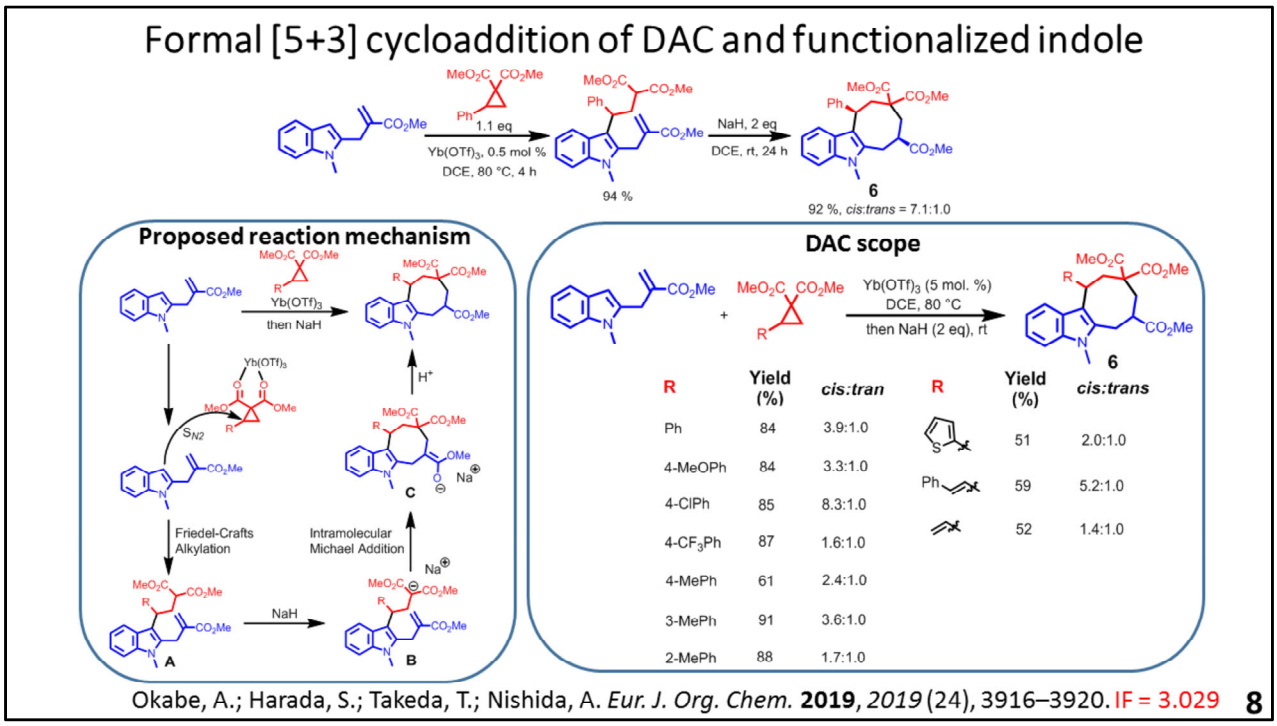


Substrate scope

R^1	Ar^1	Ar^2	Yield (%)	R^1	Ar^1	Ar^2	Yield (%)
Ph	Ph	Ph	85	Ph	4-ClPh	Ph	80
4-ClPh	Ph	Ph	77	Ph	4-MePh	Ph	66
4-OAcPh	Ph	Ph	73	Ph	2-Naphtyl	Ph	62
4-CNPh	Ph	Ph	82	Ph	2-Thiophenyl	Ph	49
2-MePh	Ph	Ph	65	Ph	Ferrocenyl	2-Thiophenyl	43
4-NO_2Ph	Ph	Ph	67	Ph	Ph	2-Thiophenyl	71
3-CF_3Ph	Ph	Ph	75				
C_6F_5	Ph	Ph	67				
NPhth	Ph	Ph	38				
2-Naphtyl	Ph	Ph	58				
Vinyl	Ph	Ph	61				

Augustin, A. U.; Merz, J. L.; Jones, P. G.; Młostoń, G.; Werz, D. B. *Org. Lett.* **2019**, *21* (23), 9405–9409. IF = 6.555 **7**

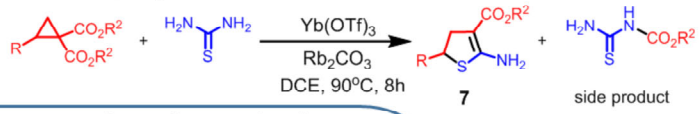
Werz and coworkers reported a formal [4+3] cycloaddition reaction of a DAC and a thiochalcone, which affords 7-membered tetrahydrothiepines. The reaction mechanism proposed by the authors is as follows. The DAC coordinates to $Sc(OTf)_3$, and the complex formed undergoes an S_{N2}-type reaction with the thiochalcone. A zwitterion is formed with inversion of the configuration of the phenyl substituent in the DAC. Intramolecular cyclization at the less-hindered terminal carbon of the allyl system leads to the 7-membered product **5**. DACs bearing diverse aryl substituents were found to perform well. A small number of thiochalcones with aryl substituents other than phenyl were also investigated. The reported yields range from moderate to high. The reaction was observed to be stereospecific, affording only the *cis* diastereomer.



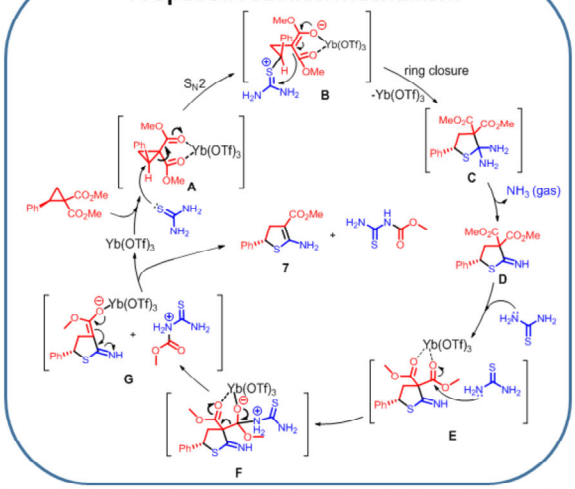
Okabe, A.; Harada, S.; Takeda, T.; Nishida, A. *Eur. J. Org. Chem.* **2019**, *2019* (24), 3916–3920. IF = 3.029 **8**

Nishida and coworkers reported a formal [5+3] cycloaddition between a DAC and a specially substituted indole derivative leading to the formation of an 8-membered ring. The following reaction mechanism is proposed. The DAC chelates to $Yb(OTf)_3$ through the two ester groups, which polarizes and activates the C–C bond in the cyclopropane ring. The indole attacks the donor-substituted carbon atom of the DAC resulting in the alkylated product **A**. Deprotonation by NaH forms the anionic species **B**, which upon intramolecular Michael addition cyclizes into the compound **C**. Subsequent protonation affords product **6**. The authors developed a one-pot variant of the procedure, which foregoes the isolation of the intermediate **A**. The use of different aryl substituents in the DAC was investigated, and the yields of the target products were found to be high. Thiophenyl, vinyl and phenylvinyl groups lead to a marked decrease of yield. In all cases, preference for the formation of the *cis* diastereomer was observed.

[3+2] Cycloaddition of DAC to thiourea



Proposed reaction mechanism

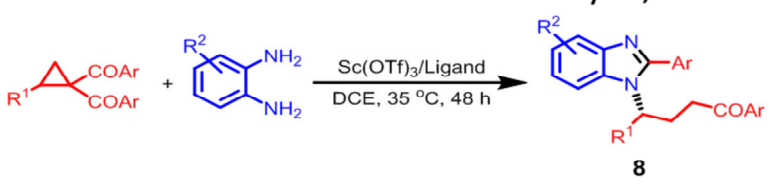


R	R^2	Yield (%)
Ph	Me	92
Ph	Et	87
Ph	Bn	89
Bn	Me	80
Cy	Me	82
4-FPh	Me	72
Napthyl	Me	85
4-OMePh	Me	82
4-BrPh	Me	75

Xie, M.-S.; Zhao, G.-F.; Qin, T.; Suo, Y.-B.; Qu, G.-R.; Guo, H.-M. *Chem. Commun.* **2019**, *55* (11), 1580–1583. IF = 6.164 **9**

Reaction of a DAC with thiourea to afford 2-amino-dihydrothiophenes under combined Lewis acid and Brønsted base catalysis was reported. The authors suggest the following reaction mechanism. Under activation by $Yb(OTf)_3$, the DAC is attacked by thiourea in an S_N2 manner, leading to ring opening with concomitant inversion of the phenyl substituent configuration. The resulting enolate **B** attacks the $C{=}S^+$ bond of the thiourea and undergoes intramolecular ring closure. The aminal **C** eliminates an ammonia molecule to form imine **D**. A second equivalent of thiourea attacks the activated ester group via "transition state" **E** to form the tetrahedral intermediate **F**. Intermediate **F** cleaves the esterified thiourea and forms enolate **G**, which after protonation yields the final product **7**. High yields were observed for both aromatic and aliphatic substituents in the DAC.

Enantioselective reaction of aryl 1,2-diamines with DACs



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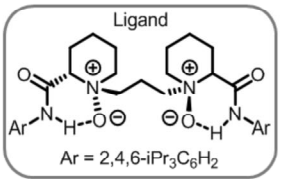
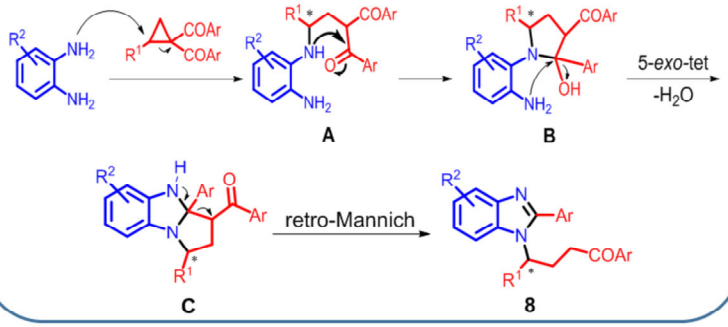


Proposed reaction mechanism



R¹	R²	Ar	Yield (%)	ee (%)
Ph	H	Ph	97	95
4-MeOPh	H	Ph	99	89
4-FPh	H	Ph	96	94
2-Naphthyl	H	Ph	97	93
Vinyl	H	Ph	86	90
Me	H	Ph	73	86
Ph	H	4-MePh	92	97
Ph	H	4-FPh	98	97
Ph	MeO	Ph	99	95
Ph	NO_2	Ph	65	95
Ph	Cl	Ph	94	95
Ph	Ph	Ph	92	95

Xia, Y.; Lin, L.; Chang, F.; Liao, Y.; Liu, X.; Feng, X. *Angew. Chem. Int. Ed.* **2016**, *55* (40), 12228–12232. IF = 12.257 **10**

A highly efficient asymmetric reaction of DACs with aryl 1,2-diamines to produce benzimidazoles containing a chiral side chain was reported. The high enantioselectivity is achieved through the use of $Sc(OTf)_3$ in combination with a chiral *N,N*-dioxide ligand as a catalyst. The authors propose the following reaction mechanism. 1,2-Diaminobenzene adds to the DAC, and intermediate **A** undergoes intramolecular cyclization affording species **B**. 5-*exo*-tet cyclization to give **C** is facilitated by the good leaving ability of a water molecule. Then **C** undergoes a retro-Mannich reaction to deliver the desired benzimidazole **8** while simultaneously establishing stereochemistry in the side chain. The products **8** are obtained in excellent yield with superb enantioselectivities. The reaction sequence proceeds under mild conditions and exhibits broad substrate scope, with both aryl and alkyl substituents in the DAC performing well.

Conclusion

DACs enable the generation of a diverse range of carbo- and heterocycles with:

- ✔ High substituent scope
- ✔ High diastereoselectivity
- ✔ High enantioselectivity
- ✔ Complex polycyclic architectures
- ✔ Potential biological activity

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In summary, we have demonstrated the huge synthetic utility of DACs in the preparation of a diverse range of carbo- and heterocycles with broad substituent scope. Diastero- and enantioselective variations were examined. Complex bicyclic and polycyclic systems can be established easily and highly effectively through these transformations.

Literature

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5. Augustin, A. U.; Merz, J. L.; Jones, P. G.; Młostoń, G.; Werz, D. B. *Org. Lett.* **2019**, *21* (23), 9405–9409. IF = 6.555

6. Okabe, A.; Harada, S.; Takeda, T.; Nishida, A. *Eur. J. Org. Chem.* **2019**, *2019* (24), 3916–3920. IF = 3.029

7. Xie, M.-S.; Zhao, G.-F.; Qin, T.; Suo, Y.-B.; Qu, G.-R.; Guo, H.-M. *Chem. Commun.* **2019**, *55* (11), 1580–1583. IF = 6.164

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Thank you for your attention!