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Chameleon-Like Activating Nature of the Spirooxindole Group in Donor−Acceptor Cyclopropanes

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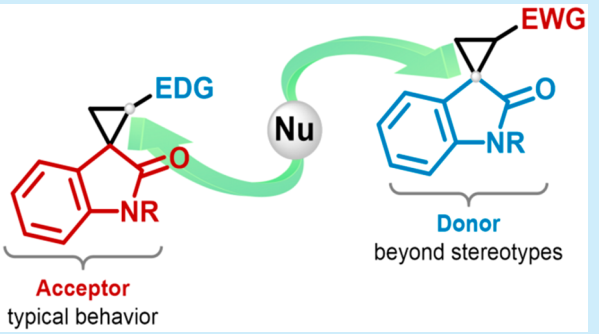
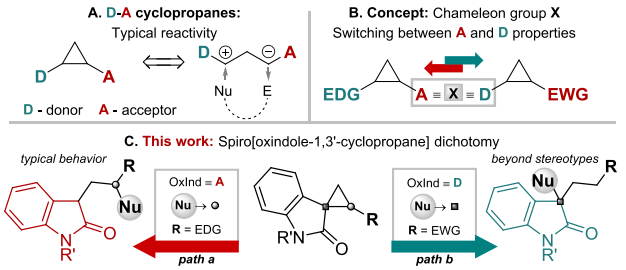
Supporting Information

ABSTRACT: The concept of a chameleon activating group is considered in the context of donor−acceptor cyclopropane chemistry. When spiro-conjugated with cyclopropane, oxindole can act as an acceptor or a donor depending on the electronic nature of vicinal substituents. This dichotomy is reflected in the alteration of chemoselectivity of spiro[oxindole-1,3′-cyclopropane] ring opening with nucleophiles.



Donor−acceptor (D−A) cyclopropanes[1] are well-known as versatile building blocks in synthetic chemistry.[2] Their most common reactivity is associated with 1,3-zwitterionic behavior providing opportunities for reactions of such cyclopropanes with both nucleophiles and electrophiles as well as ambiphilic compounds[3] (Scheme 1A). This reactivity is

Scheme 1. General Concept



furnished by donor and acceptor substituents located at neighboring C atoms of the three-membered ring. In the context of D−A cyclopropanes, C═O, C≡N, or NO_2 groups are the most common activating acceptors, whereas Ar, CH_2═CH, RO, R_2N, or, more rarely, Alk substituents serve as donors. Among those, there are groups which act as unambiguous acceptors or unambiguous donors regardless of the electronic properties of neighboring groups and reaction conditions. Meanwhile, in a broad sense, donating and accepting abilities are not fixed parameters since some functionalities are able to exhibit chameleon behavior depending on their surroundings or other factors.[4] However, in the context of extensively researched D−A cyclopropanes, this question has not been addressed (Scheme 1B). In our current work, we implemented the concept of a chameleon D−A group by using spiro[oxindole-1,3′-cyclopropanes] as D−A cyclopropanes wherein the activating oxindole unit can act as both donor and acceptor (Scheme 1C).

As an acceptor, oxindole is a quite weak activating group. Therefore, despite spiro-activation that facilitates ring opening of spiro[oxindole-1,3′-cyclopropanes] which can contain an additional electron-donating group at the vicinal position to the oxindole moiety, these reactions usually require harsher conditions compared to those for common 2-substituted cyclopropane-1,1-diesters. The systematic study of the synthetic value of spiro[oxindole-1,3′-cyclopropanes] was initiated by Carreira and co-workers who successfully applied Lewis-acid-catalyzed (3 + 2)-cycloaddition of these compounds to imines for the synthesis of pharmaceutically important spiro[oxindole-3,3′-pyrrolidines].[5,6] Recently, Yan and Zhou et al. demonstrated possibilities for these cyclopropanes (when additionally activated with an electron-withdrawing *N*-protecting group) to undergo (3 + 3)-cycloadditions to nitrones and (3 + 2)-cycloaddition to aldehydes, producing spirooxindoleoxazines and furans, respectively.[7] The same authors described ring-opening reactions with dithiane and aniline derivatives.[7] Moreover, other examples of spiro[oxindole-1,3′-cyclopropane] reactivity were reported, including nucleophilic ring opening with dimethylamine[8] and (3 + 2)-cycloaddition to alkenes[9a,b] and isatines.[9c] Our group reported reactions of spiro[oxindole-1,3′-cyclopropanes] with pseudohalides, such as the azide and cyanate ions, as convenient approaches to spiro[oxindole-3,3′-pyrrolidine] derivatives.[10] In all of these cases, the primary nucleophilic attack is directed toward the cyclopropane C2 atom substituted with a donor group (R = H, Alk, Vinyl, Ar) (Scheme 1C, path a).

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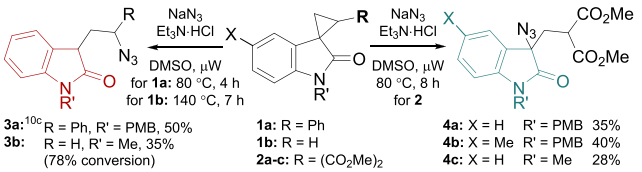
The replacement of an electron-donating group R with an electron-withdrawing one leads to simultaneous switching in the activating role of the oxindole unit, from accepting to donating. This results in an anomalous model of reactivity wherein a nucleophile attacks the quaternary spiro-C atom (Scheme 1C, path b). To the best of our knowledge, only two random examples can illustrate this unusual inverse reactivity of spiro[oxindole-1,3′-cyclopropanes]: their nucleophilic ring opening with aniline[11a] and water.[11b] Therefore, this reactivity is underexplored.

Herein, we describe an approach to exploiting the chameleon D−A nature of the oxindole group in the context of ring opening of spiro[oxindole-1,3′-cyclopropanes] with anionic and neutral *N*-nucleophiles, such as the azide ion and primary amines. Cyclopropanes **1** and **2** were chosen as model substrates, wherein the oxindole moiety was located vicinally in relation to donating or accepting substituents.

Our recent study showed that nucleophilic ring opening of **1a** with the azide ion efficiently proceeded in DMSO at 80 °C in 4 h leading to azidoethyloxindole **3** (Scheme 2).[10c]

Scheme 2. Nucleophilic Ring Openings of 1 and 2 with the Azide Ion

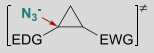


However, a similar experiment with cyclopropane **2a** revealed a change in the chemoselectivity of the nucleophilic attack. In this case, it was directed toward the spiro-C atom with azide **4a** yielded eventually. The nucleophilic ring opening of **2b,c** occurred under identical conditions, leading to **4b,c**.

The priority of the nucleophilic attack on the quaternary spiro-C atom of cyclopropanes **2** was supported by DFT calculations at the B3LYP/SVP/COSMO level of theory using the ORCA 3.0[12] program package. S_N2-like ring opening of D−A cyclopropanes with the azide ion was used as a suitable mechanistic model due to the satisfactory agreement of variation trends for the calculated energy barriers with the changes in reaction conditions.[13]

The comparison of energy barriers $\Delta G^{\ddagger}_{298}$, calculated for the N_3^- attack on the model N-unprotected D−A cyclopropanes **1a′** and **2a′**, as well as electrophilic cyclopropane **1b′**, where the only substituent is the oxindole group (Table 1), points toward a synergetic effect for vicinal substitution even when both C1 and C2 positions are occupied with nominally electron-withdrawing groups. This kind of synergetic effect is also revealed in our experiments with cyclopropanes **1a,b** and **2a−c** (Scheme 2).

Table 1. Energy Barriers for Cyclopropane Ring Opening with the Azide Ion

	EDG	EWG	$\Delta G^{\neq}_{298}$ [kcal/mol]
1a′	Ph	(*N*-H)OxInd	27.6
2a′	(*N*-H)OxInd	$(CO_2Me)_2$	28.0
1b′	-	(*N*-H)OxInd	31.1

The energy barrier $\Delta H^{\ddagger}$ of N_3^- attack on the quaternary C2 atom of **2a′** accompanied by cleavage of the longest C1−C2 bond is, respectively, 7.2 and 11.6 kcal/mol lower than those for the attack on the secondary C3 atom, resulting in cleavage of the C2−C3 and C1−C3 bonds (Figure 1). Surprisingly, the attack of N_3^- on the C1 atom is the second best option, resulting in C1−C2 bond cleavage with only a 4.9 kcal/mol penalty. Moreover, it can be partially associated with a higher acidity of malonate in comparison with oxindole (pK_a 15.9 vs 18.5),[14] providing for a difference in the stability of the corresponding ring-opened anions (according to DFT, ΔH_{298} = 3.3 kcal/mol). Therefore, the main factors controlling the selectivity of the S_N2 attack are the following: (1) C−C bond length: a cyclopropane undergoes ring opening via cleavage of the longest bond (although no correlation between bond lengths and kinetic trends was observed for different D−A cyclopropanes)[15] and (2) the ability of functional groups to stabilize the negative charge in the resulting ring-opened anion. Meanwhile, degree of substitution of electrophilic sites has a minor impact on the regioselectivity of the nucleophilic attack that is preferably directed toward the quaternary or tertiary C atoms rather than the secondary one. The activation of electrophilic sites C2 together with simultaneous deactivation of unsubstituted sites C3 toward nucleophilic attacks is observed upon going from electrophilic cyclopropane **1b′** to cyclopropanes **1a′** and **2a′**. The same differences are observed between mainstream D−A cyclopropanes (2-arylcyclopropane-1,1-diesters) and their electrophilic counterparts (cyclopropane-1,1-diesters).[13a]

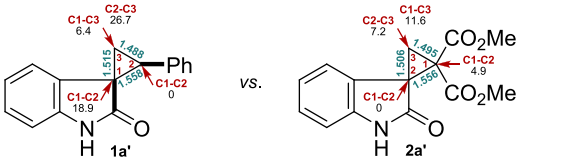


Figure 1. Bond lengths [Å] and relative TS energies $\Delta H^{\ddagger}$ [kcal/mol] of the S_N2 ring opening in **1a′** and in **2a′** with N_3^-: DFT data.

Next, we examined cyclopropanes **1** and **2** in reactions with primary amines. To check the typical direction of nucleophilic ring opening, we carried out reactions of **1a** with aniline under Lewis acid catalysis. In our initial experiments, $Ni(ClO_4)_2 \cdot 6H_2O$ was examined as a typical catalyst for reactions of other carbonyl-derived D−A cyclopropanes with amines.[16] When performed at 40 °C in CH_2Cl_2 under reflux, the reaction did not proceed at all (Table 2, entry 1), whereas an increase in temperature to 110 °C (toluene under reflux) facilitated a reaction: complete conversion of **1a** was observed in 24 h (entry 2). Under these harsh conditions, the typical product of nucleophilic ring opening (**5**) was formed along with its oxidized derivative **6**. A brief screening of other Lewis acids revealed that MgI_2 and $Yb(OTf)_3$ induced a more rapid reaction of **1a** with aniline, so that amine **5** ended up being the major product (entries 3 and 4). Meanwhile, $Sc(OTf)_3$ was less efficient, leading to increased reaction time which resulted in complete oxidation, forming aminocarbinol **6** exclusively (entry 5). This result differs from that reported by Yan, Zhou, and co-workers for the reaction between spiro[oxindole-1,3′-cyclopropane] **1c** activated with an electron-withdrawing N-protecting group and *p*-toluidine.[6a] In their case, the reaction

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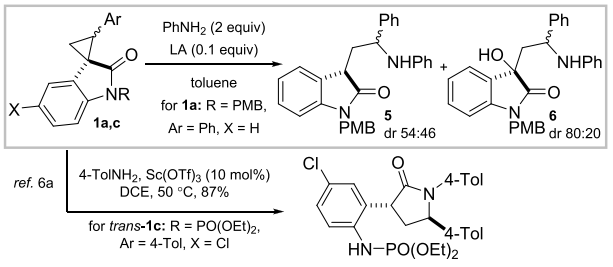
Table 2. Example of Typical Nucleophilic Ring Opening of Cyclopropanes 1 with Anilines



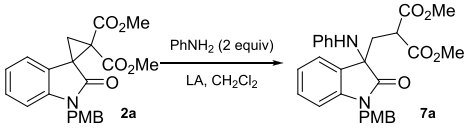
entry	LA	T [°C]	t [h]	yield **5**/**6** [%][a]
1	$Ni(ClO_4)_2·6H_2O$	40[b]	3	-[c]
2	$Ni(ClO_4)_2·6H_2O$	110	24	11/19
3	MgI_2	110	3	45/8
4	$Yb(OTf)_3$	110	6	19/-
5	$Sc(OTf)_3$	110	12	-/29

[a]Isolated yield. [b]CH_2Cl_2 was used as a solvent. [c]No reaction.

proceeded with cleavage of the five-membered ring in the bicyclic system of oxindole, yielding the aryl-substituted γ-lactame.

The reactions of cyclopropane **2a** with aniline proceeded via an inverse nucleophilic attack on the spiro-C atom, leading to amine **7a** (Table 3). The use of $Ni(ClO_4)_2·6H_2O$ in CH_2Cl_2 at

Table 3. Reaction of Cyclopropane 2a with Aniline: Optimization of the Reaction Conditions



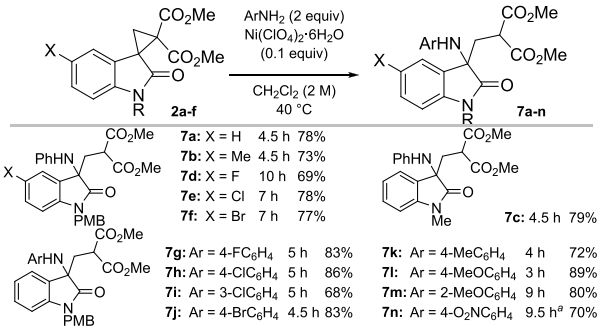
entry	LA (equiv)	T [°C]/t [h]	yield [%][a]/conversion [%]
1	$Ni(ClO_4)_2$[b] (0.1)	25/24	72/90
2	$Ni(ClO_4)_2$[b] (0.1)	40/4.5	78/>95
3	$Ni(ClO_4)_2$[b] (0.1)	83[c]/1	69/>95
4	$Co(ClO_4)_2$[b] (0.1)	25/24	37/78
5	$Zn(ClO_4)_2$[b] (0.1)	25/24	12/48
6	MgI_2 (0.1)	40/4.5	57/>95
7	$Yb(OTf)_3$ (0.1)	25/48	17/32
8	$BF_3·Et_2O$ (1.1)	25/48	-[d]
9	$FeCl_3$ (0.5)	25/48	-[d]
10	$SnCl_4$ (1.2)	25/48	-[e]
11	$TiCl_4$ (1.2)	25/48	-[d]

[a]Isolated yield. [b]Hexahydrates were used. [c]1,2-$C_2H_4Cl_2$ was used as a solvent. [d]No reaction. [e]Complex mixture of unidentified products.

ambient temperature did not provide a complete conversion of **2a** into **7a** even in 24 h (entry 1). A slight increase in temperature up to 40 °C allowed for a complete conversion of **2a** in 4.5 h (entry 2). A further increase in temperature led to a decrease in reaction time, although the yield of **7a** declined (entry 3). $Co(ClO_4)_2·6H_2O$, $Zn(ClO_4)_2·6H_2O$, MgI_2, and $Yb(OTf)_3$ were found to be less efficient as catalysts for the studied reaction (entries 4–7). The use of $BF_3·Et_2O$ or $FeCl_3$ (entries 8 and 9) did not induce a reaction, whereas the presence of stronger Lewis acids ($SnCl_4$ or $TiCl_4$) initiated the oligomerization of the reactants (entries 10 and 11). Therefore, the use of $Ni(ClO_4)_2·6H_2O$ in CH_2Cl_2 at 40 °C was found to be the most efficient for nucleophilic ring opening of **2a** with aniline (entry 2).

Using these conditions, we examined a series of cyclopropanes **2** in reactions with anilines (Scheme 3). Amines **7**

Scheme 3. Reaction of Cyclopropanes 2 with Anilines: Substrate Scope

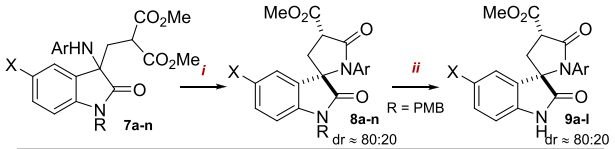


[a]Reaction was carried out in 1,2-$C_2H_4Cl_2$ under reflux.

were obtained in good to high yields (68–89%) regardless of the electronic effects of substituents in oxindole or aniline. We demonstrated that the introduction of halogens into the oxindole unit (**2d–f**) led to deceleration of nucleophilic ring opening. The same effect was observed when anilines with hindered (2-methoxyaniline) or electron-deficient (4-nitroaniline) nucleophilic centers were employed. To carry out the latter reaction, harsher conditions were required (namely, prolonged heating in 1,2-$C_2H_4Cl_2$ under reflux). At the same time, the use of highly nucleophilic 4-methoxyaniline consistently led to slight acceleration of the main reaction.

The synthesized γ-aminocarbonyl compounds **7** can be easily transformed into spiro[oxindole-3,2′-pyrrolidones] **8** under Brønsted acid catalysis (Scheme 4). In most cases, complete conversion of **7** was achieved in 1 h. However, due to the *ortho*-effect, amine **7m** was transformed into lactame **8m** in 7 h. This led to a slight decrease in the yield of **8m** compared to other lactams **8** within this series. The studied reactions exhibited good diastereoselectivity, affording **8**, predominantly

Scheme 4. Transformation of Amines 7 into Spiro[oxindole-3,2′-pyrrolidones] 8 and Their Further Deprotection*



8a:	X = H	R = PMB	Ar = Ph	80%	**8h:**	X = H	R = PMB	Ar = 4-ClC6H4	88%
8b:	X = Me	R = PMB	Ar = Ph	82%	**8i:**	X = H	R = PMB	Ar = 3-ClC6H4	93%
8c:	X = H	R = Me	Ar = Ph	75%	**8j:**	X = H	R = PMB	Ar = 4-BrC6H4	80%
8d:	X = F	R = PMB	Ar = Ph	76%	**8k:**	X = H	R = PMB	Ar = 4-MeC6H4	94%
8e:	X = Cl	R = PMB	Ar = Ph	87%	**8l:**	X = H	R = PMB	Ar = 4-MeOC6H4	84%
8f:	X = Br	R = PMB	Ar = Ph	86%	**8m:**[a]	X = H	R = PMB	Ar = 2-MeOC6H4	61%
8g:	X = H	R = PMB	Ar = 4-FC6H4	92%	**8n:**	X = H	R = PMB	Ar = 4-O2NC6H4	78%

9a:	X = H	Ar = Ph	47%	**9g:**	X = H	Ar = 4-ClC6H4	55%
9b:	X = Me	Ar = Ph	50%	**9h:**	X = H	Ar = 3-ClC6H4	45%
9c:	X = F	Ar = Ph	60%	**9i:**	X = H	Ar = 4-BrC6H4	54%
9d:	X = Cl	Ar = Ph	46%	**9j:**	X = H	Ar = 4-MeC6H4	62%
9e:	X = Br	Ar = Ph	48%	**9k:**	X = H	Ar = 4-MeOC6H4	56%
9f:	X = H	Ar = 4-FC6H4	60%	**9l:**	X = H	Ar = 4-O2NC6H4	55%

*Conditions: *i.* TsOH (0.2 equiv), toluene (0.15 M), 110 °C, 1 h; *ii.* TfOH (2.5 equiv), TFA (50 equiv), CH_2Cl_2 (0.08 M), 25 °C. [a]Reaction was carried out for 7 h.

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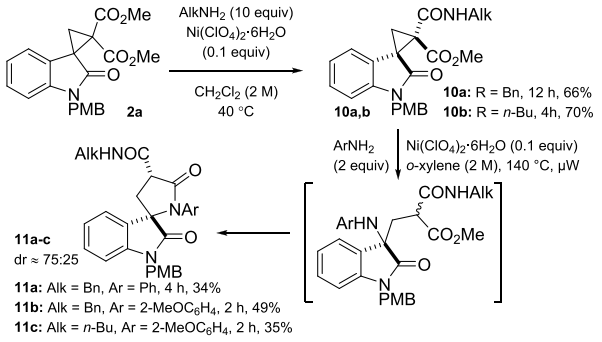
as *trans*-isomers (dr ≈ 80:20). Relative configuration was assigned according to the results of a NOESY experiment for **8a**.

It is noteworthy that N-PMB-protected spiro[oxindole-3,2′-pyrrolidones] **8** can be readily deprotected into *N*-H-spirooxindoles **9** (Scheme 4).

Our attempts to involve aliphatic amines in the studied reaction did not result in nucleophilic ring opening of model cyclopropane **2a**; instead, nucleophilic acyl substitution occurred, affording amidoesters **10a,b** (Scheme 5). The

Scheme 5. Transformations of 2a with Aliphatic Amine Participation



cyclopropanes **10** were confirmed to be less reactive when compared to their diester analogues **2**. The heating of **10** with anilines in the presence of $Ni(ClO_4)_2·6H_2O$ in CH_2Cl_2 or 1,2-$C_2H_4Cl_2$ under reflux did not induce the required reaction; therefore, harsher conditions were used (140 °C). These triggered a domino reaction involving nucleophilic ring opening and sequential γ-lactamization while yielding spiro-[oxindole-3,2′-pyrrolidones] **11** (Scheme 5).

In conclusion, it was revealed that, in the chemistry of D−A cyclopropanes, the spirooxindole moiety can act as a chameleon D−A group, switching between donor and acceptor roles. In the presence of vicinal donors, the oxindole fragment acts as an acceptor, directing the nucleophilic attack on the vicinal tertiary C atom of a cyclopropane. The vicinal acceptor causes the spirooxindole unit to exhibit uncharacteristic donor behavior with the nucleophilic attack directed toward the quaternary spiro-C atom. This dichotomy in the reactivity of spiro[oxindole-1,3′-cyclopropanes] was demonstrated in their reactions with the azide ion and anilines used as model nucleophiles. The results of our DFT studies supported the higher probability of a nucleophilic attack on the more substituted electrophilic sites of such D−A cyclopropanes.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b04153.

Experimental procedures, analytical data, details of DFT calculations, and copies of ^1H and ^{13}C NMR spectra (PDF)

Accession Codes

CCDC 1948999 and 1954544 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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