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Highly Diastereoselective Synthesis of 1-Pyrrolines *via* $SnCl_4$-Promoted [3 + 2] Cycloaddition between Activated Donor–Acceptor Cyclopropanes and Nitriles

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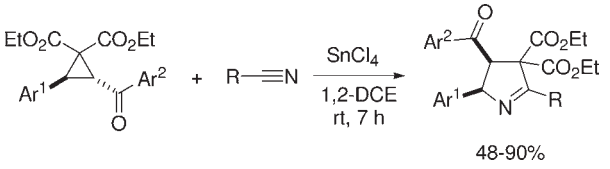
ABSTRACT

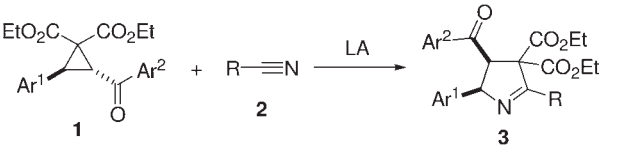


Activated donor–acceptor cyclopropanes underwent formal [3 + 2] cycloaddition with nitriles in the presence of $SnCl_4$. The product 1-pyrrolines were isolated as single *cis*-diastereomers in moderate to good yields.

The formal [3 + 2] cycloaddition reaction of donor–acceptor (D–A) cyclopropanes has emerged as a powerful tool for the construction of various five-membered carbo- and heterocycles.[1] The reactions involve *in situ* generation of 1,3-dipoles through Lewis acid promoted ring opening of the D–A cyclopropanes, followed by addition to dipolarophiles that bear C–C or C–X (X = O, N) multiple bonds. The special features of the reactions include high atom economy and excellent regio- and stereoselectivities observed in the products.

The use of nitriles as dipolarophiles in such cycloaddition reactions remained unexplored until the publication of a seminal work by Pagenkopf and co-workers in 2003.[2] Although this methodology affords the product 1-pyrrolines in excellent yields, it is applicable specifically to carbohydrate-derived or pyran ring-fused, lactonized D–A cyclopropanes prepared by intramolecular cyclopropanation. In the case of similar nonlactonized cyclopropanes prepared by intermolecular cyclopropanation, the reaction failed to stop at the 1-pyrroline stage and further structural transformation spontaneously occurred to yield pyrroles.[3] To address this issue, we planned to examine D–A cyclopropanes **1** as the 1,3-dipole precursors for cycloaddition reactions with nitriles (Scheme 1). It is obvious that the presence of a *gem*-diester moiety will arrest any further structural transformation in the product 1-pyrrolines.

Scheme 1. Synthesis of 1-Pyrrolines **3** via [3 + 2] Cycloaddition between Donor–Acceptor Cyclopropanes **1** and Nitriles **2**



(1) For recent reviews, see: (a) Reissig, H.-U.; Zimmer, R. *Chem. Rev.* **2003**, *103*, 1151. (b) Yu, M.; Pagenkopf, B. L. *Tetrahedron* **2005**, *61*, 321. (c) Carson, C. A.; Kerr, M. A. *Chem. Soc. Rev.* **2009**, *38*, 3051. (d) De Simone, F.; Waser, J. *Syntheis* **2009**, 3353.

(2) Yu, M.; Pagenkopf, B. L. *J. Am. Chem. Soc.* **2003**, *125*, 8122. For cycloaddition between other types of cyclopropanes and nitriles, see: (a) Mizuno, K.; Nire, K.; Sugita, H.; Otsuji, Y. *Tetrahedron Lett.* **1993**, *34*, 6563. (b) Herbertz, T.; Roth, H. D. *J. Am. Chem. Soc.* **1996**, *118*, 10954. (c) Huang, J.-W.; Shi, M. *Synlett* **2004**, 2343. (d) Li, W.; Shi, M. *J. Org. Chem.* **2008**, *73*, 4151.

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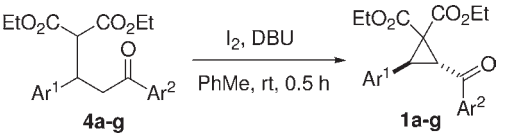
Although the D−A cyclopropanes **1** and other related cyclopropanes have previously been employed for the synthesis of substituted tetrahydrofurans,[4−7] their use in the synthesis of 1-pyrrolines remains unexplored. Thus, the present methodology would provide an easy and efficient access to densely substituted 1-pyrrolines, possibly in a highly diastereoselective manner. It is noteworthy to mention that the 1-pyrroline ring is featured in several naturally occurring compounds[8] and many 1-pyrroline derivatives have been recognized as valuable intermediates in synthetic and medicinal chemistry.[8b] In addition to conventional cyclization methods,[9] many other methods such as thermal or photochemical rearrangements of cyclopropylimines,[10] 1,3-dipolar cycloadditions of azomethine[11,12] and nitrile[13] ylides with alkenes, intramolecular hydroamination of aminoalkynes,[14] and partial hydrogenation of pyrroles[15] have been reported for the synthesis of 1-pyrrolines.

The D−A cyclopropanes **1** used in the present study could be prepared by either the oxidative cyclization of the Michael adducts of malonates with chalcones **4** using PhIO/Bu_4NI[16] or the Michael-initiated ring closure (MIRC) between diethyl benzylidenemalonates and chloroacetophenones.[17] In the present study, we have developed an alternative procedure which involves the ring closure of the Michael adducts **4** using I_2 and DBU. This reagent combination has been previously used for the intermolecular cyclopropanation of fullerene C_{60} with diethylmalonate.[18] Accordingly, when the Michael adducts **4a**−**g** were stirred with I_2 and DBU in toluene at room temperature for 30 min, the cyclopropanes **1a**−**g** were produced in excellent yields (Table 1). The main advantage of our procedure is the formation of cyclopropanes **1a**−**g** as single *trans*-diastereomers with no sign of *cis*-diastereomers. It has been reported that a diastereomeric mixture of similar cyclopropanes could be isomerized to more stable single *trans*-diastereomers by treatment with DBU.[19] This phenomenon would account for the exclusive formation of the *trans*-diastereomers in our present study.

Table 1. Preparation of Precursor D−A Cyclopropanes **1**



entry	Ar^1	Ar^2	yield (%)[a]
1	C_6H_5	C_6H_5	92 (**1a**)
2	4-MeC_6H_4	C_6H_5	90 (**1b**)
3	4-$MeOC_6H_4$	C_6H_5	93 (**1c**)
4	4-ClC_6H_4	C_6H_5	94 (**1d**)
5	4-$NO_2C_6H_4$	C_6H_5	89 (**1e**)
6	C_6H_5	4-$NO_2C_6H_4$	89 (**1f**)
7	4-ClC_6H_4	2-thienyl	85 (**1g**)

[a] Isolated yield; all are single *trans*-diastereomers.

In order to explore the [3 + 2] cycloaddition reactions of D−A cyclopropanes **1** with nitriles, the reaction between **1a** and benzonitrile (**2a**) was chosen as a model reaction to optimize the reaction conditions. The results are summarized in Table 2.

To start, the reaction was conducted with 1 equiv of **1a** and 5 equiv of **2a** using a stoichiometric amount of the Lewis acid, $AlCl_3$ in CH_2Cl_2 at room temperature. Pleasingly, the *cis*-1-pyrroline **3a** was obtained as the only isolable product in 52% yield (entry 1). When conducted at 0 °C, the reaction did not take place (entry 2). The use of $SnCl_4$ as the Lewis acid gave the product **3a** in a slightly better yield (55%), and the reaction time was also reduced to 8 h (entry 3). This reaction also failed when conducted at 0 °C (entry 4). Switching the solvent to 1,2-dichloroethane increased the yield to 66% while reducing the reaction time to 7 h (entry 5). When nitromethane was used as the solvent, the yield was reduced to 40% (entry 6). When conducted at 0 °C in 1,2-dichloroethane, the reaction failed (entry 7). The yield was reduced slightly when the reaction was conducted at 60 °C (entry 8) or the amount of the Lewis acid was decreased to 50 mol % (entry 9). When the amount of the Lewis acid was reduced further to 20 mol %, the reaction was incomplete even after 24 h and the isolated yield was only 19% (entry 10). The use of $TiCl_4$ formed the product only in trace amounts (entry 11) while $BF_3 \cdot Et_2O$ decomposed the starting cyclopropane (entry 12). Other Lewis acids, *viz.*, $InBr_3$, $In(OTf)_3$, $Sc(OTf)_3$, and $Yb(OTf)_3$,

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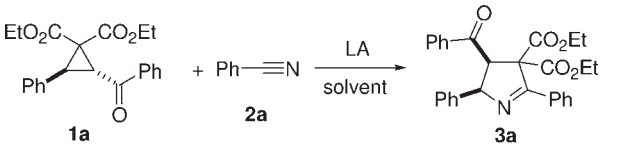
Table 2. Optimization of Reaction Conditions for Cycloaddition of **1a** with **2a**[a]



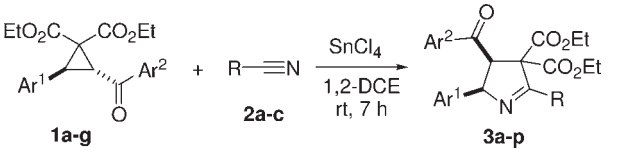
entry	Lewis acid (equiv)	solvent	temp	time (h)	yield of **3a** (%)[b]
1	$AlCl_3$ (1.0)	DCM	rt	14	52
2	$AlCl_3$ (1.0)	DCM	0 °C	12	NR[c]
3	$SnCl_4$ (1.0)	DCM	rt	8	55
4	$SnCl_4$ (1.0)	DCM	0 °C	12	NR[c]
5	$SnCl_4$ (1.0)	1,2-DCE	rt	7	66
6	$SnCl_4$ (1.0)	$MeNO_2$	rt	12	40
7	$SnCl_4$ (1.0)	1,2-DCE	0 °C	12	NR[c]
8	$SnCl_4$ (1.0)	1,2-DCE	60 °C	6	60
9	$SnCl_4$ (0.5)	1,2-DCE	rt	8	62
10	$SnCl_4$ (0.2)	1,2-DCE	rt	24	19
11	$TiCl_4$ (1.0)	1,2-DCE	rt	10	trace[d]
12	$BF_3 \cdot Et_2O$ (1.0)	1,2-DCE	0 °C-rt	8	dec.[e]
13	$InBr_3$ (1.0)	1,2-DCE	rt	12	NR[c]
14	$In(OTf)_3$ (1.0)	1,2-DCE	rt	12	NR[c]
15	$Sc(OTf)_3$ (1.0)	1,2-DCE	rt	12	NR[c]
16	$Yb(OTf)_3$ (1.0)	1,2-DCE	rt	12	NR[c]

[a] The reaction was conducted with **1a** (1 mmol), **2a** (5 mmol), Lewis acid (*x* equiv), and solvent (2 mL). [b] Isolated yield. [c] No reaction. [d] Only a trace of **3a** was formed. [e] **1a** was decomposed.

were all ineffective in bringing about the reaction (entries 13–16). Therefore, the optimal reaction conditions for the cycloaddition were identified as 1 equiv of $SnCl_4$ in 1,2-dichloroethane at room temperature.

Next, the scope of the cycloaddition was investigated with respect to various D–A cyclopropanes and nitriles under the optimized reaction conditions. The results are summarized in Table 3. Like **2a**, 4-methoxybenzonitrile (**2b**) also underwent cycloaddition readily with **1a**, furnishing **3b** in a comparable yield (entries 1 and 2). When acetonitrile (**2c**) was used as the dipolarophile in the reaction, the yield steeply increased to 89% (entry 3). The presence of a *p*-Me, *p*-OMe, or *p*-Cl group on the Ar^1 moiety of the cyclopropanes seemed to have no influence on the yield of the products (entries 4–12). However, the yield was dramatically reduced to 10%, in addition to the reaction time becoming longer (48 h), when a *p*-NO_2 group was present on the Ar^1 moiety (entry 13). Obviously, this could be the result of destabilization of the incipient positive charge on the adjacent carbon of the dipole by the *p*-$NO_2C_6H_4$ moiety during the course of the reaction (see mechanism). This is further supported by the fact that the presence of the *p*-NO_2 group on the Ar^2 moiety of the cyclopropane does not cause any detriment to the yield (entries 14 and 15). The reaction was also found to be tolerant to the presence of a thiophene moiety in the starting cyclopropane (entry 16). A sharp increase in the yield of the product was consistently found in all cycloadditions in which acetonitrile was employed as the dipolarophile (entries 3, 6, 9, 12, and 15). This may be attributable to the markedly different electronic and steric nature of methyl group as compared with aryl groups. A complete *cis*-diastereoselectivity was observed in the isolated product in all cases, and the observation was unequivocally supported by the X-ray analysis of one of the products, **3b** (Figure 1).[20]

Table 3. [3 + 2] Cycloaddition between Donor–Acceptor Cyclopropanes **1** and Nitriles **2**



entry	Ar^1	Ar^2	R	yield (%)[a]
1	C_6H_5	C_6H_5	C_6H_5	66 (**3a**)
2	C_6H_5	C_6H_5	4-$MeOC_6H_4$	62 (**3b**)
3	C_6H_5	C_6H_5	Me	89 (**3c**)
4	4-MeC_6H_4	C_6H_5	C_6H_5	52 (**3d**)
5	4-MeC_6H_4	C_6H_5	4-$MeOC_6H_4$	54 (**3e**)
6	4-MeC_6H_4	C_6H_5	Me	88 (**3f**)
7	4-$MeOC_6H_4$	C_6H_5	C_6H_5	59 (**3g**)
8	4-$MeOC_6H_4$	C_6H_5	4-$MeOC_6H_4$	67 (**3h**)
9	4-$MeOC_6H_4$	C_6H_5	Me	86 (**3i**)
10	4-ClC_6H_4	C_6H_5	C_6H_5	51(**3j**)
11	4-ClC_6H_4	C_6H_5	4-$MeOC_6H_4$	48 (**3k**)
12	4-ClC_6H_4	C_6H_5	Me	89 (**3l**)
13	4-$NO_2C_6H_4$	C_6H_5	4-$MeOC_6H_4$	10 (**3m**)[b]
14	C_6H_5	4-$NO_2C_6H_4$	4-$MeOC_6H_4$	62 (**3n**)
15	C_6H_5	4-$NO_2C_6H_4$	Me	90 (**3o**)
16	4-ClC_6H_4	2-thienyl	4-$MeOC_6H_4$	52 (**3p**)

[a] Isolated yield. [b] The reaction time was 48 h.

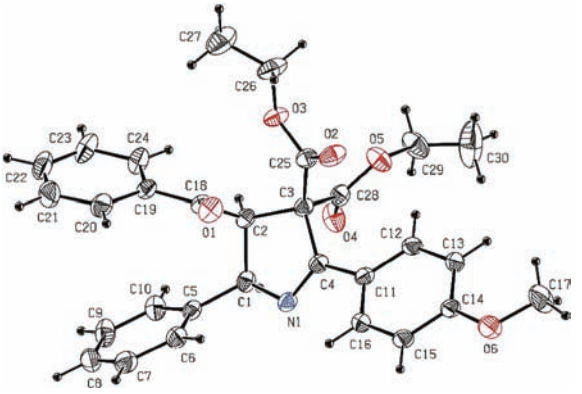
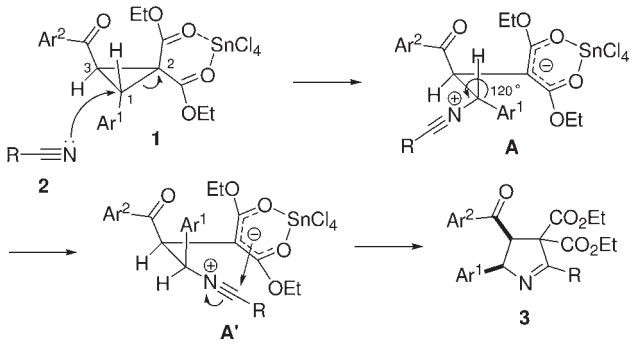


Figure 1. ORTEP plot of the crystal structure of **3b** (at 30% probability level).

(20) CCDC 827601 for compound **3b**. See the Supporting Information for details.

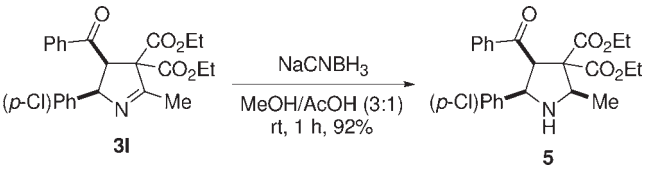
Scheme 2. Plausible Reaction Mechanism



The mechanism outlined in Scheme 2 could be postulated to explain the formation of the 1-pyrrolines as single *cis*-diastereomers. The mechanism is analogous to the one reported for the [3 + 2] cycloaddition reaction between similar D−A cyclopropanes and aldehydes.[5c,7,21] The Lewis acid coordinates with the malonate moiety of cyclopropanes thereby weakening the C1−C2 bond and making C1 vulnerable to nucleophilic attack. The lone pair on the nitrogen atom of the nitrile attacks C1 in S_N2 fashion to generate the 1,5-dipole **A**. The C1−C3 bond of **A** undergoes a 120° rotation to form the conformer **A′** which brings the aryl substituents at C1 and C3 to a *cis*-orientation despite steric crowding and, also, the nitrile carbon in the vicinity of the malonate carbanion for the ensuing nucleophilic attack. The rotation is instantly followed by the nucleophilic attack furnishing 1-pyrrolines with the substituents at C1 and C3 frozen in the *cis*-configuration.

The products are resourceful intermediates and could be transformed in to a wide range of other compounds using standard imine chemistry. For example, reduction of **3l** with $NaCNBH_3$ gave the *cis*-pyrrolidine **5** in 92% yield (Scheme 3).

Scheme 3. Synthetic Transformation of 1-Pyrroline **3l**



In summary, we have developed an $SnCl_4$-promoted [3 + 2] cycloaddition strategy for the highly diastereoselective synthesis of 1-pyrrolines from D−A cyclopropanes and nitriles. The various aspects of the strategy including the synthetic applications of the resulting 1-pyrrolines and the replacement of nitriles with other carbon−heteroatom dipolarophiles are under investigation.

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Supporting Information Available. Experimental procedures and characterization data for all products, including copies of ^1H and ^{13}C NMR spectra and X-ray structural information of **3b** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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