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Carbanion-Induced [3 + 2] Annulation of Donor–Acceptor Cyclopropanes

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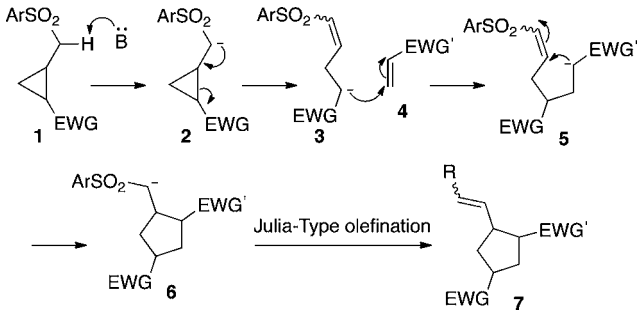
Supporting Information

ABSTRACT: The [3 + 2] annulation of donor–acceptor cyclopropanes and ylidenemalonates, in which an α-*p*-tosyl carbanion functions as a donor substituent, is described. A notable feature of the annulation is that the auxiliary *p*-tosylmethyl group can be removed via a cycloreversion during the tandem annulation sequence.

Donor–acceptor (D–A)-substituted cyclopropanes have been used as versatile synthetic blocks in organic syntheses due to a ring opening facilitated by vicinally positioned electron-donor and -acceptor groups.[1] In recent years, they have attracted renewed interest due to the development of improved methods for their synthesis and new combinations of donors and acceptors.[2,3] A large variety of combinations of donor and acceptor groups, the electronic nature of which should define the reactivity, is possible, in principle. Werz and co-workers evaluated the influence of various combinations of D–A groups on ring-enlargement reactions of D–A cyclopropanes on the basis of DFT calculations.[4] Although the synergistic push–pull effect can facilitate the strain-driven ring opening, Lewis acids are typically used to further promote reactivity by coordinating with an acceptor group such as an ester.[5] In contrast, promotion of the reaction by activation of a donor group is rarely found, and there are only a few examples of anion-induced reactions of D–A cyclopropanes, though simple ring-opening reactions of cyclopropanes without further synthetic manipulation, such as an annulation, have been reported.[6−8] One of us also reported that a carbanion generated by a Brook rearrangement cleaves a carbon–carbon bond in vicinally cyano-substituted cyclopropane to give an α-nitrile carbanion.[9] The main reasons might be the difficulty in (1) removing or manipulating the carbon functionality containing an electron-withdrawing group that is generally required for generating a carbanion after the ring-opening reactions and (2) controlling the reactivity of anionic species generated during the course of the reaction that tend to polymerize. In this paper, we report an all-carbon [3 + 2] annulation methodology based on carbanion-induced reactions of D–A cyclopropanes.

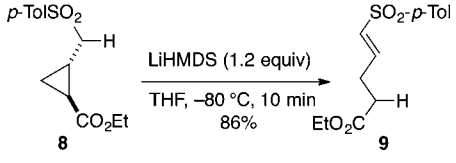
Our initial approach to overcome the difficulty relied on Julia-type[10] desulfonylative manipulation of an α-sulfonyl carbanion (**6** → **7**) generated via a tandem sequence that involves a base-induced ring opening of D–A cyclopropane (**1** → **2** → **3**) followed by an inter- and intramolecular Michael addition of the generated carbanions to Michael acceptors (**3** + **4** → **5** and **5** → **6**) (Scheme 1).

Scheme 1. Carbanion-Induced [3 + 2] Annulation of D–A Cyclopropanes



The feasibility of the carbanion-induced ring-opening reaction[7b] was first explored with *p*-tosylmethylcyclopropanecarboxylate **8**, which was prepared from ethyl *trans*-2-formylcyclopropane-1-carboxylate[11] via a three-step sequence: (1) $NaBH_4$ reduction, (2) iodination of the resulting alcohol, and (3) sulfonylation with *p*-$TolSO_2Na$.[12] The best result was obtained when the reaction was conducted with $LiN(SiMe_3)_2$ (LiHMDS) in THF at −80 °C for 10 min to give ring-opening product **9** in 86% yield, indicating that the combination of an α-tosyl anion and an ester group can function well as a D–A substituent on a cyclopropane ring (Scheme 2). The yields of the reaction varied depending on the base used. When LDA

Scheme 2. Base-Induced Ring Opening of *p*-Tosylmethylcyclopropanecarboxylate (8)



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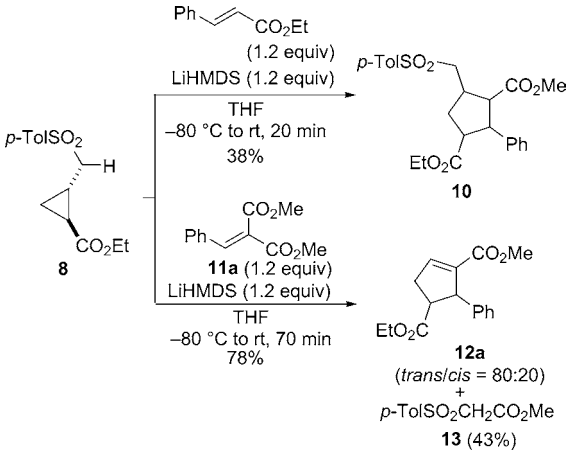
and NaHMDS were used, the yields were decreased to 52 and 59%, respectively, implying sensitivity of the generated anionic species to polymerization.

Since the electronic nature of the electron-withdrawing group (EWG′) in Michael acceptor **4** should affect the reactivity of the two-fold Michael additions[13] (**3** + **4** → **5** and **5** → **6**) in the opposite way, we decided to examine the annulation using ethyl cinnamate and benzylidenemalonate **11a**, which have different abilities as Michael acceptors (Scheme 3). To suppress undesired side reactions, such as

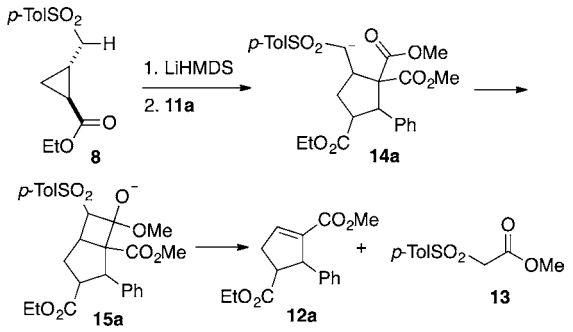
Scheme 3. Reactions of 8 with Ethyl Cinnamate or Dimethylbenzylidenemalonate



anion-induced polymerization, LiHMDS was added to a THF solution of **8** and a Michael acceptor at −80 °C, and the solution was warmed to room temperature. While the reaction with ethyl cinnamate gave the expected annulation product **10** as a single diastereomer, the reaction with benzylidenemalonate resulted in the formation of a cyclopentenecarboxylate derivative **12a** that lacks tosyl and methoxycarbonyl groups.

Isolation of methyl *p*-tosylacetate **13** in addition to **12a** led us to propose a mechanism that involves the formation of a four-membered ring intermediate **15a** followed by a formal cycloreversion with concomitant liberation of **13** (**15a** → **12a**) (Scheme 4). To the best of our knowledge, this type of

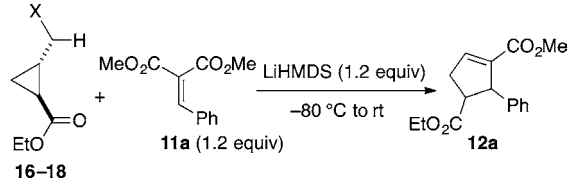
Scheme 4. Plausible Pathway for the Formation of 12a



reaction via formation/cleavage of a four-membered ring is unkown, although the formation of cyclopentene derivatives via a *β*-lactone followed by liberation of CO_2 has been reported.[14]

To explore the scope of the unusual [3 + 2] annulation of D−A cyclopropanes accompanied by elimination of an *α*-carbanion-stabilizing moiety, reactions of the corresponding dimethylphosphono-, cyano-, and ethoxycarbonyl derivatives **16**−**18** were examined.[15] In all cases, the same type of reaction occurred to provide **12a** in variable yields (Table 1). The

Table 1. [3 + 2] Annulation of Cyclopropanecarboxylates Having Various Electron-Withdrawing Groups with 11a

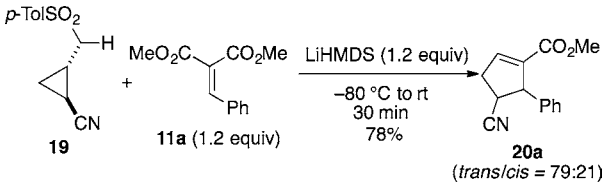


entry	sm	X	time (h)	yield (%)	*trans*/*cis*
1	**16**	$P(O)(OMe)_2$	0.5	trace	*trans*
2	**16**	$P(O)(OMe)_2$	12	45	*trans*
3	**17**	CN	0.5	trace	*trans*
4	**17**	CN	12	32	*trans*
5	**18**	CO_2Et	0.5	28	85:15
6	**18**	CO_2Et	5	77	71:29

derivatives, however, were found to be too sluggish to react at an acceptable rate in comparison with the *p*-tosyl derivative. The fact that a diastereomeric mixture of uncyclized addition products was obtained as the major products in all cases except for entry 6 suggests that the rate of cyclization for compounds **16**−**18** is slower than that for **8**.

A cyano group on a cyclopropane ring was also found to function as an acceptor substituent, providing the [3 + 2] annulation products in a similar manner (Scheme 5).[15]

Scheme 5. [3 + 2] Annulation Using Cyanocyclopropane Derivative 19



The scope of the [3 + 2] annulation was examined using **8** and **19** for several representative alkylidene- or arylidenemalonates. The results are shown in Scheme 6. In the case of ethylidenemalonates **11e** and **11f**, addition of the ylidenemalonate after treatment of **8** with LiHMDS gave better results, probably due to suppression of competitive deprotonation of the acidic methyl or methylene proton of the ylidenemalonates. While pretreatment of **19** with LiHMDS followed by addition of an ylidenemalonate resulted in significant decomposition, addition of LiHMDS to a mixture of **19** and **11e** or **11f** resulted in acceptable yields.

Reactions of the ester derivative **8** gave yields better than those of the corresponding cyano derivative **19**. Although the diastereomeric selectivity is moderate and variable depending on the substrate, selective formation of the major diastereomers can be achieved by quenching the reaction at lower temperatures. For example, stopping the reaction of **8** with **11a** at 0 °C resulted in the formation of *trans*-**12a** as a single diastereomer in 74% yield together with an uncyclized addition product.

In conclusion, we have demonstrated a new type of [3 + 2] annulation of D−A cyclopropanes in which an *α*-sulfonyl

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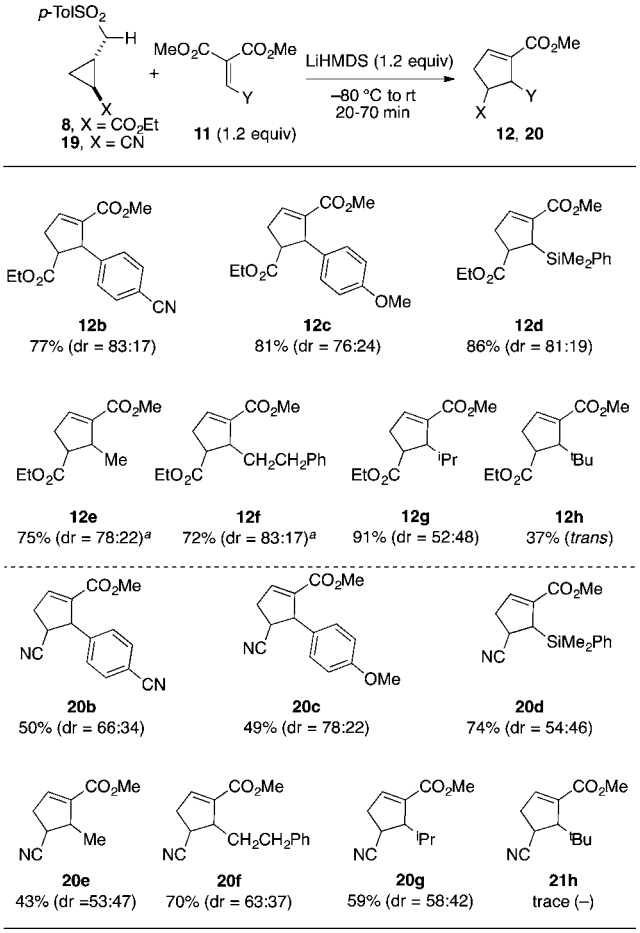
Scheme 6. [3 + 2] Annulation Using 8 and 19



[a]Ylidenemalonate **11** was added after treatment of **8** with LiHMDS.

carbanion functions as a donor group and the donor group can be eliminated via a formal cycloreversion in a four-membered intermediate. The results present the first example of a carbanion-induced [3 + 2] annulation of D–A cyclopropanes, which will open the way to a new phase of D–A cyclopropane chemistry.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01865.

All experimental and analytical data (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Reissig, H.-U. *Top. Curr. Chem.* **1988**, *144*, 74–135. (b) Reissig, H.-U.; Zimmer, R. *Chem. Rev.* **2003**, *103*, 1151–1196. (c) Yu, M.; Pagenkopf, B. L. *Tetrahedron* **2005**, *61*, 321–347.

(2) (a) Cavitt, M. A.; Phun, L. H.; France, S. *Chem. Soc. Rev.* **2014**, *43*, 804–818. (b) Schneider, T. F.; Kaschel, J.; Werz, D. B. *Angew. Chem., Int. Ed.* **2014**, *53*, 5504–5523. (c) Grover, H. K.; Emmett, M. R.; Kerr, M. A. *Org. Biomol. Chem.* **2015**, *13*, 655–671. (d) Kulinkovich, O. G. *Cyclopropanes in Organic Synthesis*; John Wiley & Sons, Inc: Hoboken, NJ, 2015; pp 43–47.

(3) (a) Ortega, V.; G. Csákÿ, A. *J. Org. Chem.* **2016**, *81*, 3917–3923. (b) Sabbatani, J.; Maulide, N. *Angew. Chem., Int. Ed.* **2016**, *55*, 6780–6783. (c) Sanchez-Diez, E.; Vesga, D. L.; Reyes, E.; Uria, U.; Carrillo, L.; Vicario, J. L. *Org. Lett.* **2016**, *18*, 1270–1273. (d) Budynina, E. M.; Ivanov, K. L.; Chagarovskiy, A. O.; Rybakov, V. B.; Trushkov, I. V.; Melnikov, M. Y. *Chem. - Eur. J.* **2016**, *22*, 3692–3696. (e) Novikov, R. A.; Tarasova, A. V.; Korolev, V. A.; Shulishov, E. V.; Timofeev, V. P.; Tomilov, Y. V. *J. Org. Chem.* **2015**, *80*, 8225–8235. (f) Cheng, Q.-Q.; Qian, Y.; Zavalij, P. Y.; Doyle, M. P. *Org. Lett.* **2015**, *17*, 3568–3571. (g) Ghosh, A.; Pandey, A. K.; Banerjee, P. *J. Org. Chem.* **2015**, *80*, 7235–7242. (h) Xu, H.; Hu, J.-L.; Wang, L.; Liao, S.; Tang, Y. *J. Am. Chem. Soc.* **2015**, *137*, 8006–8009. (i) Halskov, K. S.; Kniep, F.; Lauridsen, V. H.; Iversen, E. H.; Donslund, B. S.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2015**, *137*, 1685–1691. (j) Garve, L. K. B.; Barkawitz, P.; Jones, P. G.; Werz, D. B. *Org. Lett.* **2014**, *16*, 5804–5807. (k) Talukdar, R.; Tiwari, D. P.; Saha, A.; Ghorai, M. K. *Org. Lett.* **2014**, *16*, 3954–3957. (l) Zhu, M.; Liu, J.; Yu, J.; Chen, L.; Zhang, C.; Wang, L. *Org. Lett.* **2014**, *16*, 1856–1859. (m) Mackay, W. D.; Fistikci, M.; Carris, R. M.; Johnson, J. S. *Org. Lett.* **2014**, *16*, 1626–1629. (n) Novikov, R. A.; Tarasova, A. V.; Korolev, V. A.; Timofeev, V. P.; Tomilov, Y. V. *Angew. Chem., Int. Ed.* **2014**, *53*, 3187–3191. (o) Sathishkannan, G.; Srinivasan, K. *Chem. Commun.* **2014**, *50*, 4062–4064.

(4) Schneider, T. F.; Werz, D. B. *Org. Lett.* **2011**, *13*, 1848–1851.

(5) (a) Beal, R. B.; Dombroski, M. A.; Snider, B. B. *J. Org. Chem.* **1986**, *51*, 4391–4399.

(6) For oxyanion-induced reactions, see: (a) Wenkert, E.; Mueller, R. A.; Reardon, E. J., Jr.; Sathe, S. S.; Scharf, D. J.; Tosi, G. *J. Am. Chem. Soc.* **1970**, *92*, 7428–7436. (b) Wenkert, E. *Acc. Chem. Res.* **1980**, *13*, 27–31. Kunkel, E.; Reichelt, I.; Reissig, H. U. *Liebigs Ann. Chem.* **1984**, *1984*, 802–819. (c) Marino, J. P.; Laborde, E. *J. Am. Chem. Soc.* **1985**, *107*, 734–735. (d) Cheng, Q.-Q.; Yedoyan, J.; Arman, H.; Doyle, M. F. *Angew. Chem., Int. Ed.* **2016**, *55*, 5573–5576.

(7) For carbanion-induced reactions, see: (a) Stirling, C. *Chem. Rev.* **1978**, *78*, 517–567. (b) Tomažič, A.; Ghera, E. *Tetrahedron Lett.* **1981**, *22*, 4349–4352. (c) Reichelt, I.; Reissig, H.-U. *Liebigs Ann.* **1984**, *1984*, 828–830.

(8) For palladium-catalyzed annulation reaction, see: (a) Shimizu, I.; Ohashi, Y.; Tsuji, J. *Tetrahedron Lett.* **1985**, *26*, 3825–3828. For free-radical-mediated annulation reaction, see: (b) Feldman, K. S.; Romanelli, A. R.; Ruckle, R. E., Jr.; Miller, R. F. *J. Am. Chem. Soc.* **1988**, *110*, 3300–3302.

(9) (a) Okugawa, S.; Takeda, K. *Org. Lett.* **2004**, *6*, 2973–2975. (b) Okugawa, S.; Masu, H.; Yamaguchi, K.; Takeda, K. *J. Org. Chem.* **2005**, *70*, 10515–10523.

(10) (a) Julia, M.; Paris, J.-M. *Tetrahedron Lett.* **1973**, *14*, 4833–4836. (b) Markó, I. E.; Pospíšil, J. *Science of Synthesis*, de Meijere, A., Ed.; Georg Thieme: Stuggart, 2009; Vol. *47a*, p 105.

(11) Payne, G. B. *J. Org. Chem.* **1967**, *32*, 3351–3355.

(12) Sasaki, M.; Takeda, K. *Org. Lett.* **2004**, *6*, 4849–4851.

(13) Spino, C.; Deslongchamps, P. *Tetrahedron Lett.* **1990**, *31*, 3969–3972.

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Org. Lett. 2016, 18, 3858–3861

(14) (a) Nair, V.; Vellalath, S.; Poonoth, M.; Suresh, E. *J. Am. Chem. Soc.* **2006**, *128*, 8736−8737. (b) Wadamoto, M.; Phillips, E. M.; Reynolds, T. E.; Scheidt, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 10098−10099. (c) Phillips, E. M.; Roberts, J. M.; Scheidt, K. A. *Org. Lett.* **2010**, *12*, 2830−2833. (d) Cardinal-David, B.; Raup, D. *J. Am. Chem. Soc.* **2010**, *132*, 5345−5347.
(15) For preparation of **16**−**19**, see the Supporting Information.

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