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Organocatalytic Domino Reaction of Cyanosulfones: Access to Complex Cyclohexane Systems with Quaternary Carbon Centers

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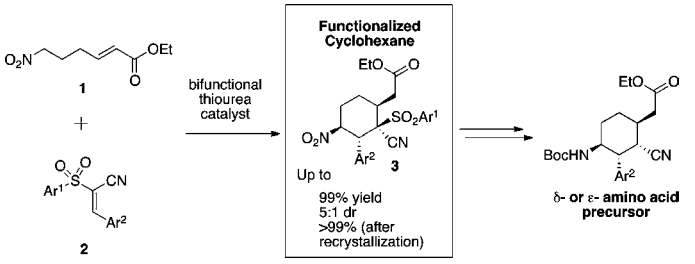
ABSTRACT



When ε-nitro-α,β-unsaturated esters are added to conjugated cyanosulfones in the presence of a bifunctional thiourea catalyst, a highly stereoselective domino reaction occurs to generate complex cyclohexanes with up to four stereogenic centers, one of which is quaternary in nature. Therefore, it is demonstrated that, like nitro compounds, sulfones can undergo an asymmetric intramolecular conjugate addition to α,β-unsaturated esters in the presence of a bifunctional organocatalyst.

Cascade reactions, which can construct multiple bonds and lead to complex molecules in a single step, are of great interest to the synthetic community.[1] Such reactions can have many advantages, as they are atom-economical[2] and have reduced synthetic steps, minimizing the amount of purification required and removing the need for protecting group strategies. Highly functionalized cyclohexane rings are a class of molecules whose synthesis has benefited from this cascade approach.[3] These systems are ubiquitous in nature and, as such, are important medicinal and agrochemical targets. Of particular note in recent times is the use of asymmetric organocatalysis in cascade chemistry, which has contributed toward the synthesis of an impressive diversity of complex structures.[4]

Recent work in our laboratories has focused on the use of bifunctional organocatalysts in the stereoselective addition of nitronates to conjugated esters to generate enantiopure cyclohexane systems. We have achieved this in both a direct manner[5a] and within a cascade process involving sequential Michael additions, where we demonstrated the use of this methodology toward the synthesis of lycorane-like

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(1) See: (a) Pellissier, H. *Adv. Syn. Catal.* **2012**, *354*, 237. (b) Tietze, L. F.; Brasche, G.; Gericke, K. M. In *Domino Reactions in Organic Synthesis*; Wiley-VCH: Weinheim, 2006.

(2) (a) Trost, B. M. *Science* **1991**, *254*, 1471. (b) Trost, B. M. *Angew. Chem., Int. Ed.* **1995**, *107*, 258.

(3) For recent examples of the use of domino reactions towards the synthesis (both organocatalytic and nonorganocatalytic) of complex cyclohexanes, see: (a) Mao, Z. F.; Jia, Y. M.; Xu, Z. Q.; Wang, R. *Adv. Synth. Catal.* **2012**, *354*, 1401. (b) Shi, D. J.; Xie, Y. J.; Zhou, H.; Xia, C. G.; Huang, H. M. *Angew. Chem., Int. Ed.* **2012**, *51*, 1248. (c) Shen, H.; Yang, K. F.; Shi, Z. H.; Jiang, J. X.; Lai, G. Q.; Xu, L. W. *Eur. J. Org. Chem.* **2011**, 5031. (d) Zhang, B.; Cai, L. C.; Song, H. B.; Wang, Z. H.; He, Z. J. *Adv. Synth. Catal.* **2010**, *352*, 97. (e) Tan, B.; Chua, P. J.; Li, Y. X.; Zhong, G. F. *Org. Lett.* **2008**, *10*, 2437. (f) Corbu, A.; Gauron, G.; Castro, J. M.; Dakir, M.; Arseniyadis, S. *Org. Lett.* **2007**, *9*, 4745. (g) Hong, B.-C.; Liao, W.-K.; Dange, N. S.; Liao, J.-H. *Org. Lett.* **2013**, *15*, 468. See also: (h) Enders, D.; Hüttl, M. R. M.; Grondal, C.; Raabe, G. *Nature* **2006**, *441*, 861 (refs 5 and 6).

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structures.[6] Pleasingly, others have since utilized our approach in the synthesis of a range of related lycoranes.[7] As a further extension of our work, we decided to explore the use of conjugated cyanosulfones **2** as an initial Michael acceptor. We hypothesized that addition of nitro compound **1** to such a substrate would reveal a catalyst-bound *C*-nucleophile for a subsequent and final asymmetric ring-closing Michael addition. We further hypothesized that catalyst activation would occur in the same way as we have previously proposed,[5a,6] whereby one of the thiourea nitrogens would activate the electrophile and the other, in tandem with the nitrogen of the protonated amine, would activate the nucleophile (Figure 1).[8] The resulting sulfones are synthetically useful compounds and can be further modified in a number of ways.[9] Our initial system for screening started with the simple nitro compound **1** and the conjugated cyanosulfone **2a**. Using a range of bifunctional thiourea catalysts,[10] we were gratified to see that the expected transformation occurred (Table 1, entries 1–6), and it was determined that catalyst **8** gave the most promising overall results in terms of balance between yield, diastereoselectivity, and enantioselectivity (entry 5). Using this catalyst, we found that changing the solvent had a profound effect on enantioselectivity (entries 7–12), and among those tested, diethyl ether was found to give optimal results. Decreasing the temperature (entries 13–15), however, had a detrimental effect on the enantioselectivity, and surprisingly, catalyst loading appeared to have little influence on the overall outcome of the process (entries 16–19).

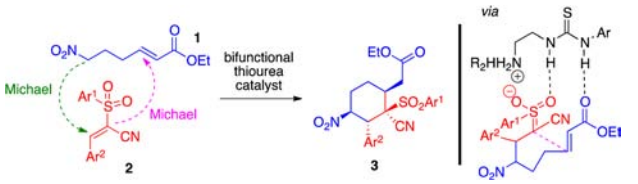
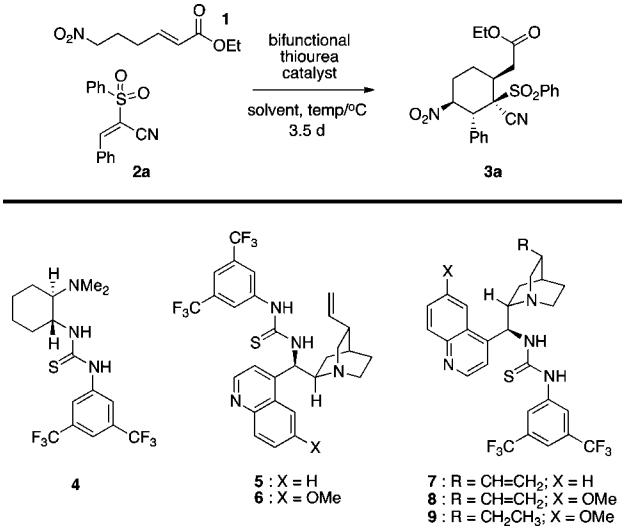


Figure 1. Domino reaction with conjugated cyanosulfones: concept and proposed transition state.

Table 1. Optimization of the Domino Reaction



entry	catalyst (mol %)	solvent	temp, °C	% yield[a]	dr[b]	ee[c,d] (%)
1[e]	**4** (10)	CH_2Cl_2	20	97	10:3	46
2[e]	**5** (10)	CH_2Cl_2	20	99	4:1	57
3[e]	**6** (10)	CH_2Cl_2	20	94	2.7:1	46
4	**7** (10)	CH_2Cl_2	20	97	25:4	65
5	**8** (10)	CH_2Cl_2	20	99	25:4	68
6	**9** (10)	CH_2Cl_2	20	97	11:2	69
7	**8** (10)	DCE	20	99	25:4	72
8	**8 (10)**	**Et_2O**	**20**	**94**	**25:4**	**78**
9	**8** (10)	PhMe	20	98	25:6	78
10	**8** (10)	THF	20	92	25:4	70
11	**8** (10)	MeCN	20	94	5:1	55
12	**8** (10)	MeOH	20	87	25:4	38
13[f]	**8** (10)	CH_2Cl_2	−40	64	25:9	68
14[f]	**8** (10)	Et_2O	−40	66	25:9	68
15[f]	**8** (10)	PhMe	−40	61	25:6	70
16	**8** (1)	Et_2O	20	42	25:7	77
17	**8** (5)	Et_2O	20	92	5:1	78
18	**8** (20)	Et_2O	20	92	25:4	78
19	**8** (30)	Et_2O	20	97	25:3	77

[a] Based on isolated product. [b] Determined by ^{1}H NMR spectroscopy. The minor diastereosiomer was found to be the (1*R*)-epimer. [c] Determined by HPLC using a chiral stationary phase. [d] Absolute configuration determined by Cu-source X-ray crystallography of **3j** and ascribed by analogy. [e] *ent*-**3a** was produced. [f] Reaction stopped after 7.5 days.

(4) For selected reviews, see: (a) Walji, A. M.; MacMillan, D. W. C. *Synlett* **2007**, 1477. (b) Enders, D.; Grondal, C.; Hüttl, M. R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570. (c) Dondoni, A.; Massi, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 4638. (d) MacMillan, D. W. C. *Nature* **2008**, *455*, 304. (e) Nielsen, M.; Worgull, D.; Zweifel, T.; Gschwend, B.; Bertelsen, S.; Jørgensen, K. A. *Chem. Commun.* **2011**, *47*, 632. (f) Cobb, A. J. A. In *Enantioselective Organocatalyzed Reactions II*; Mahrwald, R., Ed.; Springer-Verlag: Weinheim, 2011; Chapter 1. (g) Grondal, C.; Jeanty, M.; Enders, D. *Nat. Chem.* **2010**, *2*, 167. For recent examples, see: (h) Albertshofer, K.; Anderson, K. E.; Barbas, C. F., III. *Org. Lett.* **2012**, 5968. (i) Wan, J.-P.; Loh, C. C. J.; Pan, F.; Enders, D. *Chem. Commun.* **2012**, *48*, 10049. (j) Rubush, D. M.; Morges, M. A.; Rose, B. J.; Thamm, D. H.; Rovis, T. *J. Am. Chem. Soc.* **2012**, *134*, 13554. (k) Dong, X.-Q.; Fang, X.; Tao, H.-Y.; Zhou, X.; Wang, C.-J. *Chem. Commun.* **2012**, 7238. (l) Barber, D. M.; Sanganee, H. J.; Dixon, D. J. *Org. Lett.* **2012**, *14*, 5290. (m) Xie, X.; Peng, C.; He, G.; Leng, H. J.; Wang, B. A.; Huang, W.; Han, B. *Chem. Commun.* **2012**, *48*, 10487. (n) Coulthard, G.; Erb, W.; Aggarwal, V. K. *Nature* **2012**, *489*, 278. (o) Roy, S.; Chen, K. *Org. Lett.* **2012**, *14*, 2496. (p) Albertshofer, K.; Tan, B.; Barbas, C. F., III. *Org. Lett.* **2012**, *14*, 1834.

(5) (a) Nodes, W. J.; Nutt, D. R.; Chippindale, A. M.; Cobb, A. J. A. *J. Am. Chem. Soc.* **2009**, *131*, 16016. (b) Nodes, W. J.; Rajkumar, S.; Shankland, K.; Cobb, A. J. A. *Synlett* **2010**, 3011. For alternative methods to synthesise the substrates described in ref 5a, see: (c) Guo, L.; Chi, Y. G.; Almeida, A. M.; Guzei, A.; Parker, B. K.; Gellman, S. H. *J. Am. Chem. Soc.* **2009**, *131*, 16018. (d) Xu, Y. J.; Lin, L. Q.; Kanai, M.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2011**, *133*, 5791.

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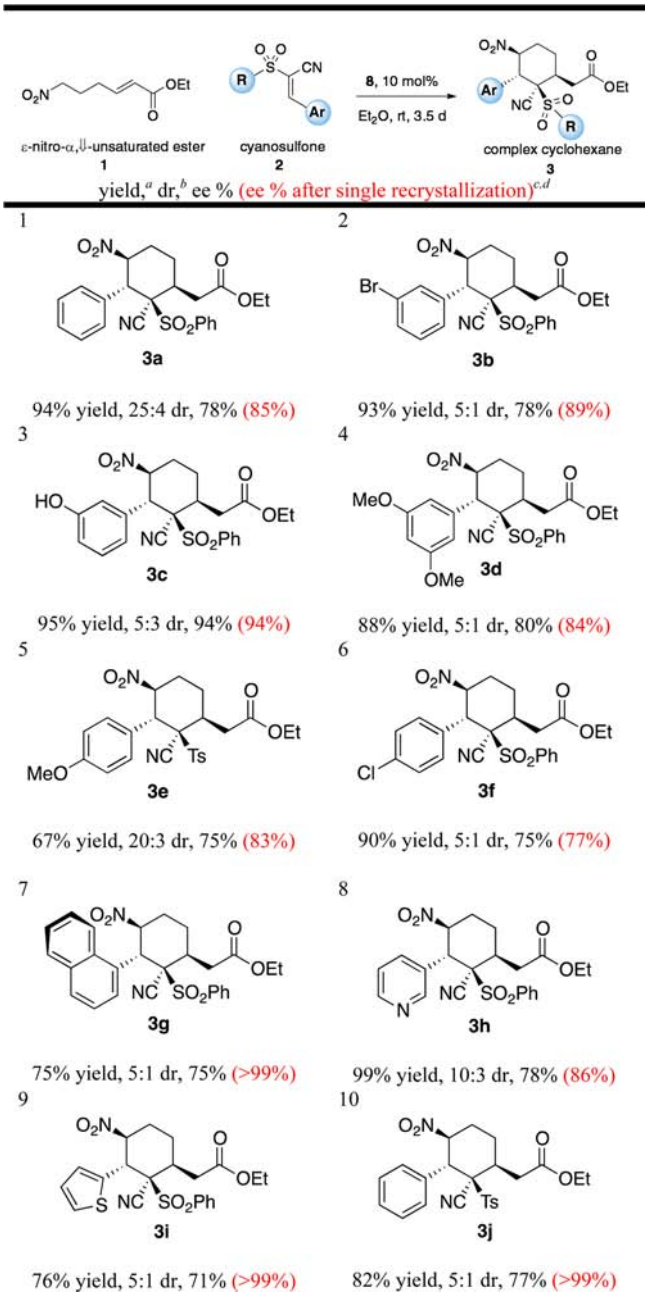
(7) Wang, Y.; Luo, Y.-C.; Zhang, H.-B.; Xu, P.-F. *Org. Biomol. Chem.* **2012**, *10*, 8211.

(8) A computational study by Wang and co-workers has added credence to this argument. See: Zhu, J.-L.; Zhang, Y.; Liu, C.; Zheng, A.-M.; Wang, W. *J. Org. Chem.* **2012**, *77*, 9813.

(9) (a) Simpkins, N. S. In *Sulphones in Organic Synthesis (Tetrahedron Organic Chemistry Series*; Pergamon Press: Oxford, 1993; Vol. 10. For reviews on the use of sulfones in organocatalysis, see: (b) Nielsen, M.; Jacobsen, C. B.; Holub, N.; Paixão, M. W.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2010**, *49*, 2668. (c) Alba, A.-N. R.; Companyó, X.; Rios, R. *Chem. Soc. Rev.* **2010**, *39*, 2018.

Scheme 1. Enantioselective Cascade: Cyanosulfone Scope



[a] Based on isolated product. [b] Determined by ^{1}H NMR spectroscopy. The minor diastereosiomer was found to be the (1*R*)-epimer. [c] Determined by HPLC using a chiral stationary phase. [d] Absolute configuration determined by Cu-source X-ray crystallography of **3j** and ascribed by analogy.

Using the optimized conditions (entry 8, bold) we selected a range of conjugated arylcyanosulfones **2** for the reaction with nitroester **1** and were pleased to find that they all exhibited good reactivity (Scheme 1). Most satisfyingly, however, was our observation that the enantiomeric excess could be enhanced significantly by a single recrystallization. Our recrystallization of the cyclohexane adduct **3j** gave an enantiopure crystal that was subjected to single-crystal X-ray analysis, which allowed the absolute configuration to be assigned (Figure 2).[11] The absolute stereochemical configurations of the other products were assigned by analogy with this analysis.

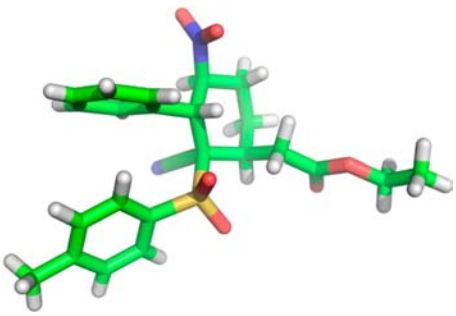


Figure 2. Molecular structure of **3j**, with absolute stereochemistry as determined by X-ray crystallography.[11]

The diastereomeric ratio for all substrates was fairly similar, being around 5:1, wherein it was found that the minor diastereoisomer was the (1*R*)-epimer, which presumably results from the conjugated ester presenting its opposite face to the nitronate prior to cyclization.

Interestingly, the X-ray crystal structure of compound **3g** shows a conformational preference for the (*P*)-atropisomeric position, where the intramolecular distances from the centroid of the benzene ring to the centroids of the naphthalene rings are 3.953 and 4.871 Å (Figure 3). Calculations (B3LYP/6-31G* energies after an OPLSA conformation search[12]) demonstrate that the observed geometry of **3g** is the thermodynamically preferred one by a ratio of 500:1 and do not provide evidence of a high energy barrier between the atropisomers. However, the possibility of a catalytic influence upon axial chirality has not been totally ruled out and is the subject of ongoing investigation.

Finally, we have used Raney-Ni under 1 atm of hydrogen to convert **3a** to the useful functionalized cyclohexane

(10) See: (a) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672. (b) Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 119. (c) Okino, T.; Nakamura, S.; Furukawa, T.; Takemoto, Y. *Org. Lett.* **2004**, *6*, 625. (d) Vakulya, B.; Varga, S.; Csámpai, A.; Soós, T. *Org. Lett.* **2005**, *7*, 1967. (e) Li, B.-J.; Jiang, L.; Liu, M.; Chen, Y.-C.; Ding, L.-S.; Wu, Y. *Synlett* **2005**, 603. (f) McCooey, S. H.; Connon, S. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 6367. (g) Ye, J.; Dixon, D. J.; Hynes, P. S. *Chem. Commun.* **2005**, 4481.

(11) Compound **3g** was also assigned in this fashion, and as expected, the stereochemistry was identical to **3j**. Both the Flack parameters and the Hooft probabilities indicate strongly that the absolute configurations of the refined crystal structures are correct. **3j**: Flack parameter −0.019(11); Hooft probabilities P2(true) = 1, P3(true) = 1, P3(rac-twin) = 0, P3(false) = 0, Hooft y = −0.012(2). **3g**: Flack parameter 0.022(17); Hooft probabilities P2(true) = 1, P3(true) = 1, P3(rac-twin) = 0, P3(false) = 0, Hooft y = 0.007(12). (a) Flack, H. D. *Acta Crystallogr., Sect. A: Found. Crystallogr.* **1983**, *39*, 876. (b) Hooft, R. W. W.; Straver, L. H.; Spek, A. L. *J. Appl. Crystallogr.* **2008**, *41*, 96.

(12) Calculations carried out using BatchMin (version 9.7) and Jaguar (version 7.6) from Schrodinger, LLC, New York, NY, 2009. See also: (a) Jorgensen, W. L.; Maxwell, D. S.; Tirado-Rives, J. *J. Am. Chem. Soc.* **1996**, *118*, 11225. (b) Becke, A. D. *Phys. Rev. A* **1988**, *38*, 3098. (c) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785. (d) Krishnan, R.; Binkley, J. S.; Seeger, R.; Pople, J. A. *J. Chem. Phys.* **1980**, *72*, 650. (e) Gill, P. M. W.; Johnson, B. G.; Pople, J. A.; Frisch, M. *J. Chem. Phys. Lett.* **1992**, *197*, 499.

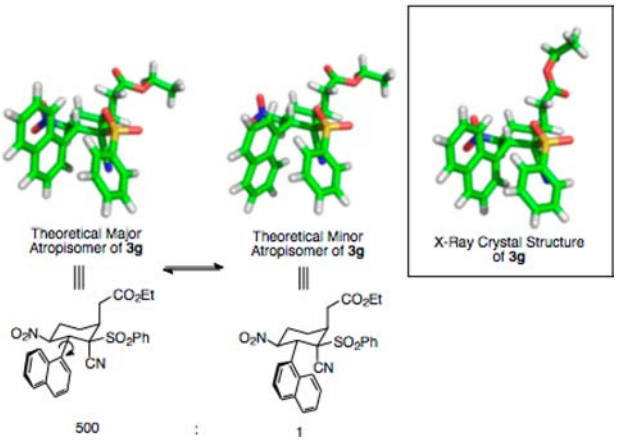
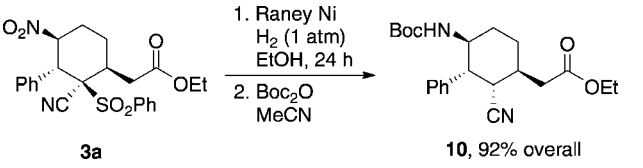


Figure 3. Calculations (B3LYP/6-31G* energies after an OPLSA conformation search) indicate a strong thermodynamic preference (500:1 at room temperature) for the (*P*)-atropisomer of **3g**.[12,13]

product **10** (Scheme 2). Under these conditions, there is no scrambling of the C-2 stereogenic center, where the axial position of the nitrile, itself unaffected by the reducing conditions, is retained. Cyclohexane system **10** is envisaged to be a useful "three-way junction" within peptide chemistry, as there is the potential to have two orthogonally reactive *N*-termini (one generating an δ-amino acid and the other an ε-amino acid) as well as a single *C*-terminus.

(13) For an explanation of our atropisomer assignment, see the Supporting Information.

Scheme 2. Desulfonylation Using Raney Ni



In conclusion, we have demonstrated that bifunctional thiourea catalysts have the ability to control the asymmetric reactivity of nitro- and sulfone substituted compounds to generate highly enantioenriched products with up to four contiguous stereocenters, one of which is quaternary in nature. Future work will involve both the theoretical study of the mechanism of reaction, as well as the use of this new amino acid precursor within peptide chemistry.

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Supporting Information Available. Experimental procedures, NMR characterization, HPLC traces, and X-ray data (CIF) for compounds **3g** and **3j**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.