

Enantioselective Construction of Oxa- and Aza-Angular Triquinanes through Tandem $[4 + 1]/[3 + 2]$ Cycloaddition of Sulfur Ylides and Nitroolefins

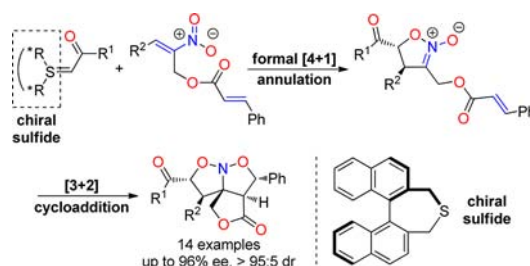
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ABSTRACT



A formal $[4 + 1]/[3 + 2]$ cycloaddition sequence of sulfur ylides and alkene-tethered nitroolefins has been developed. The use of (*R*)-binol-derived chiral sulfide leads to an asymmetric process that allows the construction of oxa- and aza-angular triquinanes in good to excellent diastereo- and enantioselectivities.

The angular triquinanes and their heteroatom-substituted analogues form the core architecture of numerous natural products which display a broad and interesting range of biological activities.^{1–3} Consequently, these complex polycyclic frameworks have become interesting targets for the synthetic organic chemistry community. Recently, several strategies have been developed for the synthesis of

heterotriquinanes, including cascade radical methods,⁴ tandem enyne/ring closing metathesis approaches,⁵ and others.⁶ Despite these successes, the search for new efficient, especially stereospecific approaches to such a motif bearing three fused rings and multiple consecutive stereogenic centers, including a chiral quaternary center, remains a substantial challenge.

Over the past decade, sulfur ylides⁷ were used as diverse reagents to construct complex cyclic molecules beyond three-membered rings. For instance, we recently developed a $[4 + 1]/[3 + 2]$ cycloaddition of sulfur ylides with nitroolefins,⁸ wherein a transiently generated cyclic

(1) (a) Mehta, G.; Srikrishna, A. *Chem. Rev.* **1997**, 97, 671. (b) Singh, V.; Thomas, B. *Tetrahedron* **1998**, 54, 3647. (c) Marchand, A. P. *Synlett* **1991**, 73. (d) Kouno, I.; Mori, K.; Kawano, N.; Sato, S. *Tetrahedron Lett.* **1989**, 30, 7451. (e) Schmidet, T. J.; Müller, E.; Fronczek, F. R. *J. Nat. Prod.* **2001**, 64, 411.

(2) Yang, X.-Y.; Feng, T.; Li, Z.-H.; Sheng, Y.; Yin, X.; Leng, Y.; Liu, J.-K. *Org. Lett.* **2012**, 14, 5382.

(3) (a) Smith, M. J.; Mazzola, E. P.; Sims, J. J.; Midland, S. L.; Keen, N. T.; Burton, V.; Stayton, M. M. *Tetrahedron Lett.* **1993**, 34, 223. (b) Midland, S. L.; Keen, N. T.; Sims, J. J.; Midland, M. M.; Stayton, M. M.; Burton, V.; Smith, M. J.; Mazzola, E. P.; Graham, K. J.; Clardy, J. J. *Org. Chem.* **1993**, 58, 2940. (c) Wood, J. L.; Jeong, S.; Salcedo, A.; Jenkins, J. J. *Org. Chem.* **1995**, 60, 286.

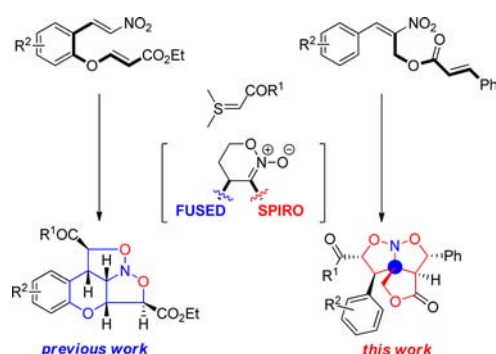
(4) (a) Yadav, J. S.; Kumar, P. T. K.; Gadgil, V. R. *Tetrahedron Lett.* **1992**, 33, 3687. (b) Gurjar, M. K.; Ravindranadh, S. V.; Kumar, P. *Chem. Commun.* **2001**, 917. (c) Enholm, E. J.; Jia, Z. J. *J. Org. Chem.* **1997**, 62, 174. (d) Sha, C.-K.; Santhosh, K. C.; Lih, S.-H. *J. Org. Chem.* **1998**, 63, 2699. (e) Gharpure, S. J.; Niranjana, P.; Porwal, S. K. *Org. Lett.* **2012**, 14, 5476.

(5) (a) Kaliappan, K. P.; Nandurdikar, R. S. *Chem. Commun.* **2004**, 2506. (b) Kaliappan, K. P.; Nandurdikar, R. S.; Shaikh, M. M. *Tetrahedron* **2006**, 62, 5064. (c) Ramakrishna, K.; Kaliappan, K. P. *Synlett* **2011**, 2580.

(6) (a) Tormo, J.; Moyano, A.; Pericàs, M. A.; Riera, A. *J. Org. Chem.* **1997**, 62, 4851. (b) Seo, J.; Fain, H.; Blanc, J.-B.; Montgomery, J. *J. Org. Chem.* **1999**, 64, 6060. (c) MacDougall, J. M.; Moore, H. W. *J. Org. Chem.* **1999**, 64, 7445. (d) Verma, S. K.; Fleischer, E. B.; Moore, H. W. *J. Org. Chem.* **2000**, 65, 8564. (e) Ader, T. A.; Champey, C. A.; Kuznetsova, L. V.; Li, T.; Lim, Y.-H.; Rucando, D.; Sieburth, S. McN. *Org. Lett.* **2001**, 3, 2165. (f) Liao, J.-H.; Maulide, N.; Augustyns, B.; Marko, I. E. *Org. Biomol. Chem.* **2006**, 4, 1464. (g) Clive, D. L. J.; Cole, D. C.; Tao, Y. *J. Org. Chem.* **1994**, 59, 1396.

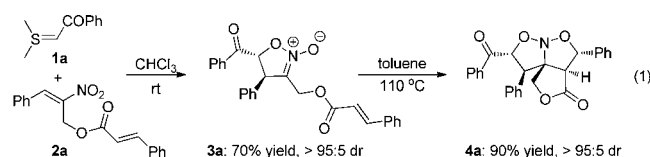
nitronate was involved. This cascade reaction provided rapid access to fused heterocyclic compounds in high yields and stereoselectivities. On the basis of the success of the initial study, we became interested in the possibility of expanding the synthetic utility of this strategy to prepare a variety of heterotriquinanes. Herein, we report the tandem intermolecular [4 + 1] and intramolecular [3 + 2] cycloaddition process of sulfur ylides and α -tethered nitroolefins⁹ affording the previously unknown tetrahydrofuro[3,4-*c*]-isoxazolo[2,3-*b*]isoxazol-3(1*H*)-ones in good yields. This sequence involves the formation of four new σ bonds and five consecutive stereogenic centers in excellent stereoselectivities (Scheme 1).

Scheme 1. Reaction Design



To test our hypothesis, we initially studied the reaction of phenylacetyl sulfur ylide **1a** with (*E*)-2-nitro-3-phenylallyl cinnamate **2a** in CHCl_3 . When the reaction was performed with **1a** and **2a** at room temperature, the only isolated product was the formal [4 + 1] adduct **3a** (eq 1). Compared with the previous [4 + 1]/[3 + 2] cycloaddition to synthesize fused oxa- and aza-cycles, this reaction is more challenging because of the steric repulsion to forge the last two rings including a quaternary center in the [3 + 2] cycloaddition. Luckily, the intramolecular [3 + 2] cycloaddition of isolated nitronate **3a** was facilitated by heating in toluene at

110 °C for 6 h, to give the desired triquinane **4a** in 90% isolated yield with > 95:5 dr.



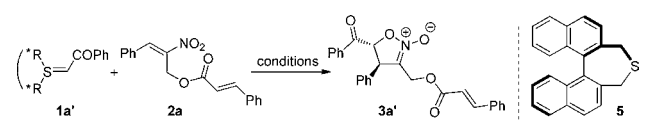
In order to carry out the enantioselective version, the strategy of chiral substrate control was applied to this transformation. Thus, a series of chiral sulfur ylides were prepared with atropisomeric sulfide **5** as the starting material.¹⁰ The reaction of chiral ylide **1a'** with acrylate-tethered nitrostyrene **2a** was initially examined in CH_2Cl_2 at 0 °C, and it was found that enantioenriched nitronate **3a'** was formed in good yield (Table 1, entry 1, 77% yield and 26% ee). A survey of reaction media showed that this asymmetric [4 + 1] process was remarkably influenced by the polarity of solvents (Table 1, entries 1–9). Weakly polar solvents, such as toluene and benzene, improved the enantioselectivity to 76% ee at 0 °C and rt, respectively (Table 1, entries 8 and 9). Then we examined a toluene and benzene mixture at lower temperature in an effort to elevate the stereoselectivity of this process (Table 1, entries 10–13). We found that the reaction in toluene and benzene with a ratio of 1:1 at –40 °C provided **3a** in 84% ee (Table 1, entry 12). The reaction conditions were further

(7) For selected reviews, see: (a) Lu, L.-Q.; Chen, J.-R.; Xiao, W.-J. *Acc. Chem. Res.* **2012**, *45*, 1278. (b) Li, A.-H.; Dai, L.-X.; Aggarwal, V. K. *Chem. Rev.* **1997**, *97*, 2341. (c) Aggarwal, V. K.; Winn, C. L. *Acc. Chem. Res.* **2004**, *37*, 611. (d) McGarrigle, E. M.; Myers, E. L.; Illa, O.; Shaw, M. A.; Riches, S. L.; Aggarwal, V. K. *Chem. Rev.* **2007**, *107*, 5841. (e) Sun, X.-L.; Tang, Y. *Acc. Chem. Res.* **2008**, *41*, 937. For selected examples, see: (f) Kokotos, C. G.; Aggarwal, V. K. *Chem. Commun.* **2006**, 2156. (g) Unthank, M. G.; Hussain, N.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2006**, *45*, 7066. (h) Liao, W.-W.; Li, K.; Tang, Y. *J. Am. Chem. Soc.* **2003**, *125*, 13030. (i) Wang, Q.-G.; Deng, X.-M.; Zhu, B.-H.; Ye, L.-W.; Sun, X.-L.; Li, C.-Y.; Zhu, C.-Y.; Shen, Q.; Tang, Y. *J. Am. Chem. Soc.* **2008**, *130*, 5408. (j) Loebach, J. L.; Bennett, D. M.; Danheiser, R. L. *J. Am. Chem. Soc.* **1998**, *120*, 9690. (k) Gais, H.-J.; Reddy, L. R.; Babu, G. S.; Raabe, G. *J. Am. Chem. Soc.* **2004**, *126*, 4859. (l) Schomaker, J. M.; Pulgam, V. R.; Borhan, B. *J. Am. Chem. Soc.* **2004**, *126*, 13600. (m) Oswald, M. F.; Raw, S. A.; Taylor, R. J. K. *Chem. Commun.* **2005**, 2253. (n) Sone, T.; Lu, G.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 1677. (o) Chen, Z.-L.; Zhang, J.-L. *Chem.—Asian J.* **2009**, *4*, 1527. (p) Kramer, S.; Skrydstrup, T. *Angew. Chem., Int. Ed.* **2012**, *51*, 4681. (q) Chen, J.-R.; Dong, W.-R.; Candy, M.; Pan, F.-F.; Jörres, M.; Bolm, C. *J. Am. Chem. Soc.* **2012**, *134*, 6924. (r) Yang, Q.-Q.; Xiao, C.; Lu, L.-Q.; An, J.; Tan, F.; Li, B.-J.; Xiao, W.-J. *Angew. Chem., Int. Ed.* **2012**, *51*, 9137.

(8) (a) Lu, L.-Q.; Cao, Y.-J.; Liu, X.-P.; An, J.; Yao, C.-J.; Ming, Z.-H.; Xiao, W.-J. *J. Am. Chem. Soc.* **2008**, *130*, 6946. (b) Lu, L.-Q.; Li, F.; An, J.; Zhang, J.-J.; An, X.-L.; Hua, Q.-L.; Xiao, W.-J. *Angew. Chem., Int. Ed.* **2009**, *48*, 9542. (c) Lu, L.-Q.; Zhang, J.-J.; Li, F.; Cheng, Y.; An, J.; Chen, J.-R.; Xiao, W.-J. *Angew. Chem., Int. Ed.* **2010**, *49*, 4495. (d) Lu, L.-Q.; Ming, Z.-H.; An, J.; Li, C.; Chen, J.-R.; Xiao, W.-J. *J. Org. Chem.* **2012**, *77*, 1072. (e) Lu, L.-Q.; Li, F.; An, J.; Cheng, Y.; Chen, J.-R.; Xiao, W.-J. *Chem.—Eur. J.* **2012**, *18*, 4073.

(9) Alkene-tethered nitroolefins are often used as heterodienes in cycloadditions. For a review, see: (a) Denmark, S. E.; Thorarensen, A. *Chem. Rev.* **1996**, *96*, 137. For leading references, see: (b) Denmark, S. E.; Moon, Y.-C.; Senanayake, C. B. W. *J. Am. Chem. Soc.* **1990**, *112*, 311. (c) Denmark, S. E.; Stolle, A.; Dixon, J. A.; Guagnano, V. *J. Am. Chem. Soc.* **1995**, *117*, 2100. (d) Denmark, S. E.; Guagnano, V.; Dixon, J. A.; Stolle, A. *J. Org. Chem.* **1997**, *62*, 4610. (e) Denmark, S. E.; Dixon, J. A. *J. Org. Chem.* **1998**, *63*, 6167. (f) Denmark, S. E.; Middleton, D. S. *J. Org. Chem.* **1998**, *63*, 1604. (g) Denmark, S. E.; Gomez, L. *Org. Lett.* **2001**, *3*, 2907. (h) Denmark, S. E.; Gomez, L. *J. Org. Chem.* **2003**, *68*, 8015. (i) Denmark, S. E.; Baiazitov, R. Y. *Org. Lett.* **2005**, *7*, 5617.

(10) (a) Imashiro, R.; Yamanaka, T.; Seki, M. *Tetrahedron: Asymmetry* **1999**, *10*, 2845. (b) Miyake, Y.; Oyamada, A.; Nishibayashi, Y.; Uemura, S. *Heteroat. Chem.* **2002**, *13*, 270. References for the synthesis of these axially chiral sulfides: (c) Cram, D. J.; Helgeson, R. C.; Koga, K.; Kyba, E. P.; Madan, K.; Sousa, L. R.; Siegel, M. G.; Moreau, P.; Gokel, G. W.; Timko, J. M.; Sogah, G. D. Y. *J. Org. Chem.* **1978**, *43*, 2758. (d) Fabbri, D.; Delogu, G.; Lucchi, O. D. *J. Org. Chem.* **1993**, *58*, 1748. (e) Fabbri, D.; Pulacchini, S.; Gladiali, S. *Synlett* **1996**, 1054. (f) Stará, I. G.; Stary, P.; Tichý, M.; Závada, J.; Fiedler, P. *J. Org. Chem.* **1994**, *59*, 1326. For other enantiopure sulfides, see: (g) Furukawa, N.; Sugihara, Y.; Fujihara, H. *J. Org. Chem.* **1989**, *54*, 4222. (h) Li, A.-H.; Dai, L.-X.; Hou, X.-L.; Huang, Y.-Z.; Li, F.-W. *J. Org. Chem.* **1996**, *61*, 489. (i) Saito, T.; Akiba, D.; Sakairi, M.; Kanazawa, S. *Tetrahedron Lett.* **2001**, *42*, 57. (j) Aggarwal, V. K.; Thompson, A.; Jones, R. V. H.; Standen, M. *Tetrahedron: Asymmetry* **1995**, *6*, 2557. (k) Aggarwal, V. K.; Ford, J. G.; Thompson, A.; Jones, R. V. H.; Standen, M. C. H. *J. Am. Chem. Soc.* **1996**, *118*, 7004. (l) Aggarwal, V. K.; Charmant, J.; Dudin, L.; Porcelloni, M.; Richardson, J. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5467. (m) Myllymäki, V. T.; Lindvall, M. K.; Koskinen, A. M. P. *Tetrahedron* **2001**, *57*, 4629. (n) Minière, S.; Reboul, V.; Metzner, P.; Fochi, M.; Bonini, B. F. *Tetrahedron: Asymmetry* **2004**, *15*, 3275. (o) Winn, C. L.; Bellenie, B. R.; Goodman, J. M. *Tetrahedron Lett.* **2002**, *43*, 5427. (p) Davoust, M.; Brière, J.-F.; Jaffrès, P. A.; Metzner, P. *J. Org. Chem.* **2005**, *70*, 4166.

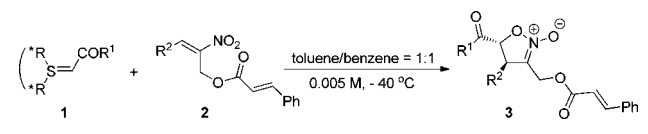
Table 1. Optimization of Reaction Conditions for Asymmetric [4 + 1] Annulation^a


entry	solvent	temp (°C)	concn (M)	yield ^b (%)	ee ^c (%)
1	CH ₂ Cl ₂	0	0.05	77	26
2	CHCl ₃	0	0.05	97	25
3	Et ₂ O	0	0.05	49	42
4	THF	0	0.05	58	49
5	DMF	0	0.05	48	19
6	CH ₃ CN	0	0.05	62	27
7	CH ₃ OH	0	0.05	35	3
8	toluene	0	0.05	75	76
9	benzene	rt	0.05	74	76
10 ^d	toluene/ benzene	0	0.05	74	80
11	toluene/ benzene	−25	0.05	86	80
12	toluene/ benzene	−40	0.05	93	84
13	toluene/ benzene	−78	0.05	92	84
14	toluene/ benzene	−40	0.1	83	77
15	toluene/ benzene	−40	0.01	89	89
16	toluene/ benzene	−40	0.005	95	92

^a Unless noted, reactions were performed with **1a'** (0.30 mmol), **2a** (0.20 mmol) in the noted solvent at the indicated temperature. ^b Isolated yield. ^c Determined by chiral HPLC analysis. ^d The ratio of toluene and benzene is 1:1.

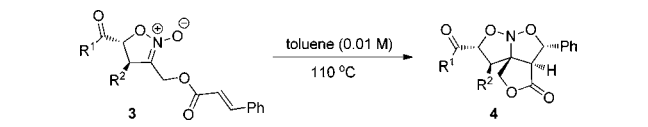
optimized by adjusting the concentration (Table 1, entries 14–16). Finally, the superior levels of asymmetric induction and efficiency exhibited in a toluene and benzene mixture at −40 °C (Table 1, entry 16, 95% yield and 92% ee) prompted us to use these conditions for further exploration.

With the optimal conditions established, the substrate scope of this annulation was then investigated and representative results are listed in Table 2. Significant structural variation in sulfur ylides could be carried out. Note that the reaction is quite general with respect to the electronic contribution of the substituent in the aryl ring of sulfur ylides (Table 2, entries 1–6, 87–94% isolated yield, 86–94% ee, and >95:5 dr). As highlighted in entries 6–8 of Table 2, variation in the position of the substituent on the aryl group of the ylides is also tolerated without remarkable effects on the chemical yield and stereoselectivities of the transformation. To our delight, the scope of sulfur ylides could be significantly extended to the hetero-aryllacyl sulfur ylide, and the corresponding enantio-enriched nitronate was obtained in excellent yield and stereoselectivities (Table 2, entry 9, 95% yield, >95:5 dr, and 90% ee).

Table 2. Scope of Substrates in Asymmetric [4 + 1] Annulation^a


entry	R ¹	R ²	yield ^b (%)	dr ^c	ee ^d (%)
1	Ph	Ph	3a' , 93	>95:5	92
2	4-MePh	Ph	3b , 87	>95:5	90
3	4-MeOPh	Ph	3c , 91	>95:5	94
4	4-FPh	Ph	3d , 94	>95:5	86
5	4-ClPh	Ph	3e , 93	>95:5	86
6	4-BrPh	Ph	3f , 91	>95:5	88
7	2-FPh	Ph	3g , 78	>95:5	90
8	3-BrPh	Ph	3h , 90	>95:5	86
9	thiophenyl	Ph	3i , ^e 95	>95:5	90
10	Ph	4-MeOPh	3j , 89	>95:5	96
11	Ph	4-ClPh	3k , 95	>95:5	90
12	Ph	3,4-(MeO) ₂ Ph	3l , 91	>95:5	94
13	Ph	2-naphthyl	3m , 87	>95:5	90

^a Unless noted, reactions were performed with **1** (0.30 mmol), **2** (0.20 mmol) in toluene/benzene (1:1, 40 mL) at −40 °C. ^b Isolated yield. ^c Determined by ¹H NMR methods. ^d Determined by HPLC analysis. ^e The absolute configuration of product **3i** was established by X-ray analysis.

Table 3. Scope of Substrates in [3 + 2] Cycloaddition^a


entry	R ¹	R ²	yield ^b (%)	dr ^c	ee ^d (%)
1	Ph	Ph	4a , ^e 83	>95:5	92
2	4-MePh	Ph	4b , 76	>95:5	90
3	4-MeOPh	Ph	4c , 91	>95:5	94
4	4-FPh	Ph	4d , 82	>95:5	86
5	4-ClPh	Ph	4e , 72	>95:5	86
6	4-BrPh	Ph	4f , 81	>95:5	88
7	2-FPh	Ph	4g , 68	>95:5	90
8	3-BrPh	Ph	4h , 81	>95:5	86
9	thiophenyl	Ph	4i , 90	>95:5	90
10	Ph	4-MeOPh	4j , 84	>95:5	96
11	Ph	4-ClPh	4k , 70	>95:5	92
12	Ph	3,4-(MeO) ₂ Ph	4l , 80	>95:5	94
13	Ph	2-naphthyl	4m , 82	>95:5	92

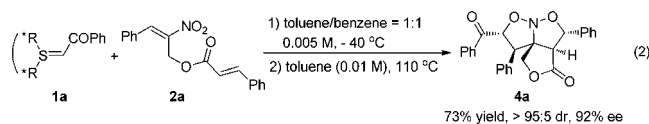
^a Unless noted, reactions were performed with **3** in toluene (0.01 M) at 110 °C. ^b Isolated yield. ^c Determined by ¹H NMR methods. ^d Determined by HPLC analysis. ^e The absolute configuration of product **4a** was established by X-ray analysis.

As revealed in entries 1 and 10 to 13 of Table 2, this asymmetric [4 + 1] annulation was also general with respect to the nitroolefin component. Significant structural variation on the benzene ring was well tolerated. The

electronic nature of the benzene ring did not greatly affect the yield, and usually excellent stereoselectivities were achieved (89–95% yields, > 95:5 dr, 90–96% ee). Furthermore, the disubstituted nitrostyrene derivative could readily participate in this reaction and afforded the corresponding nitronate in good stereoselectivities (Table 2, entry 12). It was also found that the naphthalene-derived nitroolefin was a suitable reaction partner, generating product **3m** in 87% yield and 90% ee (Table 2, entry 13).¹¹

The two stereogenic centers which were created in the [4 + 1] process might undergo racemization easily. As highlighted in Table 3, to our delight, the substrate-induced asymmetric [3 + 2] cycloaddition provided the desired triquinanes smoothly and efficiently in good yields and excellent diastereoselectivities in refluxing toluene (Table 3, entries 1–13).

Furthermore, we were pleased to find that the heterotriquinanes could also be comparably obtained directly without isolating the nitronate intermediate. For example, when the (*E*)-2-nitro-3-phenylallyl cinnamate **2a** was consumed, the reaction mixture was concentrated and then warmed to 110 °C in toluene to give the desired triquinane **4a** in 73% yield, with 92% ee and greater than 95:5 dr (eq 2).

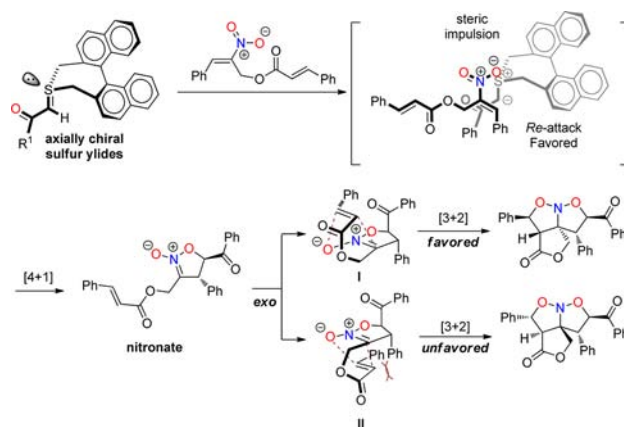


In light of previous work,^{8c,d} one can rationalize the origin of stereodiscrimination in this tandem reaction. The sulfur ylides attack the *Re* face of nitroolefins in order to minimize the steric interaction of the side chain in alkene-tethered nitroolefins with the binaphthalene motif in the chiral ylide component. Then the folding of the dipolarophile tether occurred in an *exo* fashion through the transition state **I**, because of the unfavorable steric interaction between the phenyl group and the dipolarophile tether. The absolute configuration of triquinane **4a** was

(11) The reaction with the alkylacyl-substituted sulfur ylide was very slow even at room temperature, and the reaction with aliphatic nitroolefin derivative was complex.

(12) CCDC 904983 (**3i**) and 905855 (**4a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Scheme 2. Proposed Model



unambiguously confirmed to be (3*aS*, 4*S*, 8*R*, 9*R*, 9*aS*) by X-ray crystallographic analysis of the optically pure nitronate **3i** and racemic **4a**, and the stereochemistry of other products could be tentatively assigned by assuming an analogous enantioinduction (Scheme 2).¹²

In summary, we have described a tandem formal [4 + 1]/[3 + 2] cycloaddition of sulfur ylides and alkene-tethered nitroolefins. This strategy gave optically active oxa- and aza-triquinanes in a concise way, with excellent stereoselectivities by using the low cost and readily available chiral sulfur ylides. Further investigations on the synthetic transformation and bioactivity screening are currently underway in our laboratory.

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Supporting Information Available. Experimental procedures and compound characterization data including X-ray crystal data (CIF) for **3i** and **4a**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.