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Two Novel 1,2,4,5-Tetrazines that Participate in Inverse Electron Demand Diels−Alder Reactions with an Unexpected Regioselectivity

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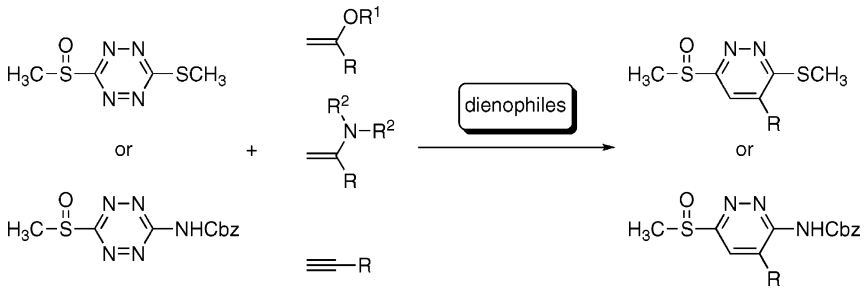
Received August 30, 2005



Two new unsymmetrical 1,2,4,5-tetrazines, 3-methylsulfinyl-6-methylthio-1,2,4,5-tetrazine (**4**) and 3-(benzyloxycarbonyl)amino-6-methylsulfinyl-1,2,4,5-tetrazine (**5**), were prepared, and the scope of their participation in intermolecular inverse electron demand Diels−Alder reactions was defined. As anticipated, sulfoxides **4** and **5** (**4** > **5**) display a reactivity that is substantially greater than that of their corresponding sulfides (**2** and **3**), being derived from their enhanced electron-deficient character and resulting in a wider range of potential dienophile choices or the use of milder reaction conditions. The cycloaddition reactions were expectedly regioselective, typically producing a single cycloadduct, ensuring their synthetic utility, but both were found to proceed with a regioselectivity opposite what would be anticipated and complementary to that observed with **2** and **3**.

Introduction

Electron-deficient heterocyclic azadienes have proven to be useful reagents that often participate in well-defined inverse electron demand Diels−Alder reactions with electron-rich dienophiles, providing rapid access to a range of highly substituted heterocyclic systems.[1] Of these, the substituted 1,2,4,5-tetrazines are the most reactive and most widely utilized heterocyclic azadienes. Typically, symmetrical 1,2,4,5-tetrazines are employed largely because of their synthetic accessibility, and synthetic studies of their utility have necessarily focused only on their relative reactivities.

In the course of our investigations of such reagents and their applications in complex natural products total synthesis,[2−16] we have examined a number of such tetrazines[17,18] and introduced several new useful symmetrical[19] or unsymmetrical[20,21] 1,2,4,5-tetrazines. Of these, dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate

(1) Boger, D. L.; Weinreb, S. M. *Hetero Diels−Alder Methodology in Organic Synthesis*; Academic Press: San Diego, CA, 1987.
(2) Reviews: Boger, D. L. *Tetrahedron* **1983**, *39*, 2869. Boger, D. L. *Chem. Rev.* **1986**, *86*, 781. Boger, D. L. *Chemtracts: Org. Chem.* **1996**, *9*, 149.
(3) Streptonigrin: Boger, D. L.; Panek, J. S.; Duff, S. R. *J. Am. Chem. Soc.* **1985**, *107*, 5745.
(4) OMP: Boger, D. L.; Coleman, R. S.; Panek, J. S.; Yohannes, D. *J. Org. Chem.* **1984**, *49*, 4405.
(5) Lavendamycin: Boger, D. L.; Duff, S. R.; Panek, J. S.; Yasuda, M. *J. Org. Chem.* **1985**, *50*, 5790.
(6) PDE-I and PDE-II: Boger, D. L.; Coleman, R. S. *J. Am. Chem. Soc.* **1987**, *109*, 2717.
(7) CC-1065: Boger, D. L.; Coleman, R. S. *J. Am. Chem. Soc.* **1988**, *110*, 1321, 4796.
(8) Prodigiosin: Boger, D. L.; Patel, M. *J. Org. Chem.* **1988**, *53*, 1405.
(9) Trikentrin A: Boger, D. L.; Zhang, M. *J. Am. Chem. Soc.* **1991**, *113*, 4230.
(10) Isochrysohermidin: Boger, D. L.; Baldino, C. M. *J. Am. Chem. Soc.* **1993**, *115*, 11418.
(11) Ningalin A, Lamellarin O, Lukianol A, and Storniamide A: Boger, D. L.; Boyce, C. W.; Labroli, M. A.; Sehon, C. A.; Jin, Q. *J. Am. Chem. Soc.* **1999**, *121*, 54.
(12) Phomazarin: Boger, D. L.; Hong, J.; Hikota, M.; Ishida, M. *J. Am. Chem. Soc.* **1999**, *121*, 2471.
(13) Ningalin B: Boger, D. L.; Soenen, D. R.; Boyce, C. W.; Hedrick, M. P.; Jin, Q. *J. Org. Chem.* **2000**, *65*, 2479.
(14) Anhydrolycorinone and related alkaloids: Boger, D. L.; Wolkenberg, S. E. *J. Org. Chem.* **2000**, *65*, 9120.

10.1021/jo051832o CCC: $33.50
Published on Web 11/30/2005

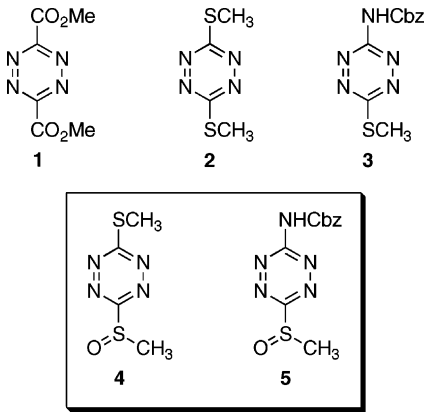


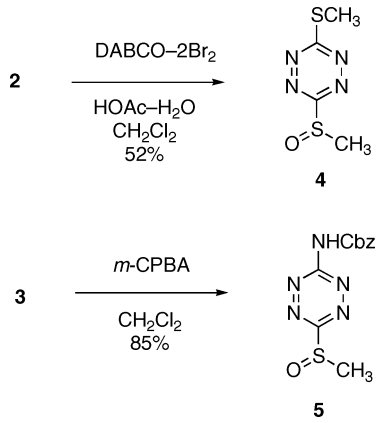
FIGURE 1.

(**1**)[17] and 3,6-bis(thiomethyl)-1,2,4,5-tetrazine (**2**)[18] have been the most widely utilized of the symmetrical tetrazines, and the *N*-acyl-3-amino-6-methylthio-1,2,4,5-tetrazines (e.g., **3**)[21] have proven to be the most widely explored of the unsymmetrical tetrazines participating in well-behaved, effective, and regioselective [4+2] cycloaddition reactions. Herein, we report the preparation of two new and useful unsymmetrical 1,2,4,5-tetrazines, 3-methylsulfinyl-6-methylthio-1,2,4,5-tetrazine (**4**) and 3-(benzyloxycarbonyl)amino-6-methysulfinyl-1,2,4,5-tetrazine (**5**), obtained by the *S* oxidation of **2** and **3**, respectively, and we describe studies defining the scope of their Diels−Alder reactions, Figure 1. As anticipated, both **4** and **5** (**4** > **5**) display a reactivity that is greater than that of either **2** or **3**, being derived from their enhanced electron-deficient character, resulting in a wider range of potential dienophile choices and/or the use of milder reaction conditions for the [4+2] cycloaddition reactions. Moreover, the cycloaddition reactions were expectedly regioselective, typically producing a single cycloadduct, ensuring their synthetic utility. Remarkably, this regioselectivity proved opposite what one would anticipate on the basis of simple zwitterionic models or more sophisticated frontier molecular orbital (FMO) analysis of the [4+2] cycloaddition reactions.

Results and Discussion

Preparation of 1,2,4,5-Tetrazines 4 and 5. To our knowledge, there have been only two reports of the preparation of sulfoxide-substituted 1,2,4,5-tetrazines,[22,23] and only one of these examined their [4+2] cycloaddition reactivity.[23] In these latter studies, only their intramolecular [4+2] cycloaddition reaction with tethered unactivated alkynes was examined, and no studies of their intermolecular Diels−Alder reactions have been disclosed.[23] Both were prepared by the oxidation of the corresponding thioether, enlisting either the DABCO−Br_2 complex[24] or oxone.[23] The former proved effective for selective oxidation of **2** to provide **4** as a blood red crystalline solid in good yield (0.55 equiv of DABCO, 1.1 equiv of Br_2, HOAc−H_2O−CH_2Cl_2, 25 °C, 20 h, 52%) along with small amounts of **2**, Scheme 1. Increasing the amount of oxidant increased the conversion without further increasing the yield of **4**, likely a result of competing over oxidation, and the use of *m*-CPBA (1.1 equiv) also provided **4** but in lower yield. In either case, the over-oxidation led to unidentified water-soluble byproducts that were easily removed in the workup. Tetrazine **4**, like **1**, is not stable to prolonged exposure to silica gel but can be isolated in pure form by washing the crude reaction product with Et_2O/hexane to remove small amounts of unreacted **2** and subsequently recrystallized from EtOAc/hexane (mp 73−74 °C).

SCHEME 1

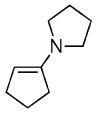
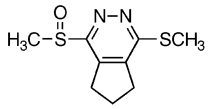
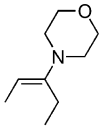
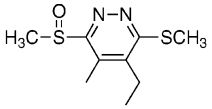
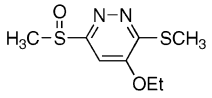
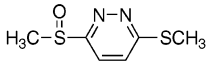
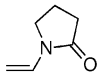
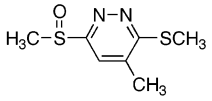
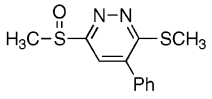
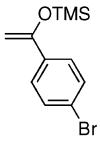
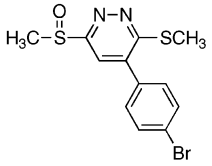
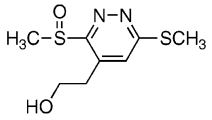
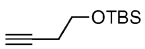
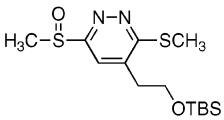


Tetrazine **3** proved essentially unreactive toward DABCO−Br_2 under these conditions but was oxidized to the corresponding sulfoxide with *m*-CPBA (1.1 equiv, CH_2Cl_2, 0 °C, 30 min, 85%). Like **1** and **4**, **5** was not sufficiently stable to prolonged exposure to silica gel to permit purification by chromatography. However, an aqueous workup of the oxidation reaction, including an extraction with saturated aqueous $NaHCO_3$ to remove reagent and *m*-chlorobenzoic acid, provided tetrazine **5** as a blood red oil, sufficiently pure (>95%) for [4+2] cycloaddition studies.

Diels−Alder Reactions of 4. The tetrazine **4** exhibited superb reactivity in prototypical inverse electron demand Diels−Alder reactions and was much more reactive than the corresponding sulfide **2**,[18] Table 1. The reaction of **4** with enamines was essentially instantaneous at 25 °C, and other electron-rich dienophiles including ketene acetals, enol ethers, and enamides readily react smoothly at room temperature to cleanly provide the [4+2] cycloadducts. Notably, no problematic detection of intermediate unaromatized product was observed, and the Diels−Alder products were isolated in uniformly high yields. Remarkably, even unactivated dienophiles including phenylacetylene **6h** and alkyne **6k** reacted smoothly with **4**, albeit slowly at room temperature (ca. 24−48 h), requiring higher reaction temperatures for a rapid reaction (100 °C, 1−9 h, 80−

(15) Roseophilin: Boger, D. L.; Hong, J. *J. Am. Chem. Soc.* **2001**, *123*, 8515.
(16) Ningalin D: Hamasaki, A.; Zimpleman, J. M.; Hwang, I.; Boger, D. L. *J. Am. Chem. Soc.* **2005**, *127*, 10767.
(17) Dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate (**1**): Sauer, J.; Mielert, A.; Lang, D.; Peter, D. *Chem. Ber.* **1965**, *98*, 1435. Boger, D. L.; Coleman, R. S.; Panek, J. S.; Huber, F. X.; Sauer, J. *J. Org. Chem.* **1985**, *50*, 5377. Boger, D. L.; Panek, J. S.; Patel, M. *Org. Synth.* **1991**, *70*, 79.
(18) 3,6-Bis(methylthio)-1,2,4,5-tetrazine (**2**): Sandström, J. *Acta Chem. Scand.* **1961**, *15*, 1575. Boger, D. L.; Sakya, S. M. *J. Org. Chem.* **1988**, *53*, 1415.
(19) 3,6-Bis(3,4-dimethoxybenzoyl)-1,2,4,5-tetrazine: Soenen, D. R.; Zimpleman, J. M.; Boger, D. L. *J. Org. Chem.* **2003**, *68*, 3593.
(20) 3-Methoxy-6-methylthio-1,2,4,5-tetrazine: Sakya, S. M.; Groskopf, K. K.; Boger, D. L. *Tetrahedron Lett.* **1997**, *38*, 3805.
(21) *N*-Acyl-6-amino-3-methylthio-1,2,4,5-tetrazine (e.g., **3**): Boger, D. L.; Schaum, R. P.; Garbaccio, R. M. *J. Org. Chem.* **1998**, *63*, 6329.
(22) Johnson, J. L.; Whitney, B.; Werbel, L. M. *J. Heterocycl. Chem.* **1980**, *17*, 501.
(23) Seitz, G.; Dietrich, S.; Görge, L.; Richter, J. *Tetrahedron Lett.* **1986**, *27*, 2747.
(24) Blair, L. K.; Baldwin, J.; Smith, W. C., Jr. *J. Org. Chem.* **1977**, *42*, 1817.

TABLE 1. [4+2] Cycloaddition Reactions of 4

entry		dienophile (equiv)		conditions		product	% yield
1	**6a**		(1.5)	CH_2Cl_2, 25 °C, 1 min	**7a**		96%
2	**6b**		(2)	CH_2Cl_2, 25 °C, 15 min	**7b**		91%
3	**6c**		(10)	dioxane, 25 °C, 30 min	**7c**		85%
4	**6d**		(10)	dioxane, 25 °C, 30 min	**7d**		96%
5	**6e**		(1.5)	CH_2Cl_2, 25 °C, 16 h		**7d**	66%
6	**6f**		(10)	CH_2Cl_2, 25 °C, 2 h	**7e**		91%
7	**6g**		(5)	CH_2Cl_2, 25 °C, 1 h	**7f**		94%
8	**6h**		(5)	dioxane, 100 °C, 1 h or dioxane, 25 °C, 24 h or dioxane, 25 °C, 48 h		**7f**	90% 54% 72%
9	**6i**		(2)	CH_2Cl_2, 25 °C, 2 h	**7g**		89%
10	**6j**		(5)	CH_2Cl_2, 25 °C, 2 h	**7h**		70% (5–11% regioisomer)
11	**6k**		(5)	dioxane, 100 °C, 9 h	**7i**		89%

90%). As such, tetrazine **4**, by virtue of its enhanced electron-deficient character, exhibits a reactivity that accommodates an unusually wide range of potential dienophiles. Moreover, the [4+2] cycloaddition reactions were regioselective, typically providing a single detectable product. The only exception to this generalization was dihydrofuran (Table 1, entry 10), where a trace of the second regioisomer (5−11%) was detected. Unexpectedly, this regioselectivity proved to be opposite what one would predict from simple zwitterionic models or FMO analysis of the [4+2] cycloaddition reaction. Although this became apparent in assessing the spectroscopic properties of the cycloaddition products (e.g., 1,2-diazine C4−H vs C5−H chemical shift), single-crystal X-ray structures of **7c**, **7f**, and **7g** unambiguously established their structures, Figure 2.[25] Similarly, dienophiles **6j** and **6k** provided regioisomeric products clearly distinguishable as the C4-substituted (C5−H δ 7.36) and

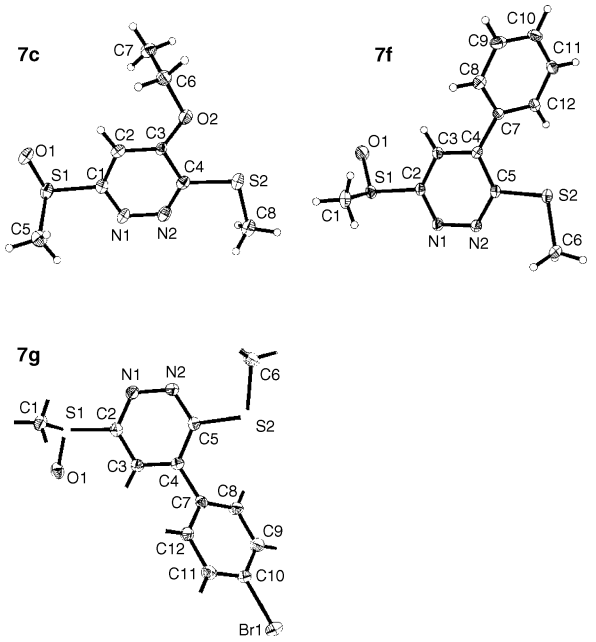
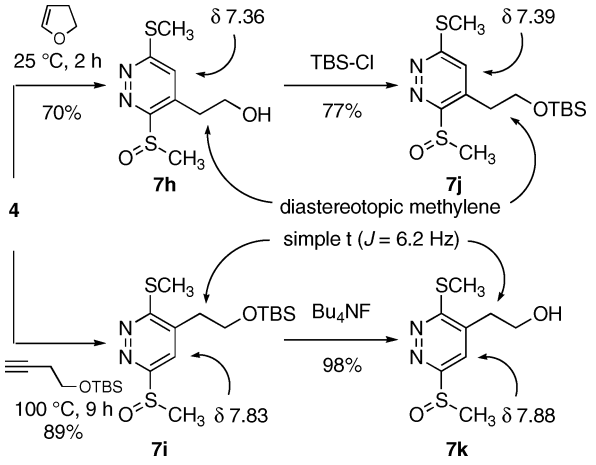


FIGURE 2. ORTEP drawings of **7c**, **7f**, and **7g**.

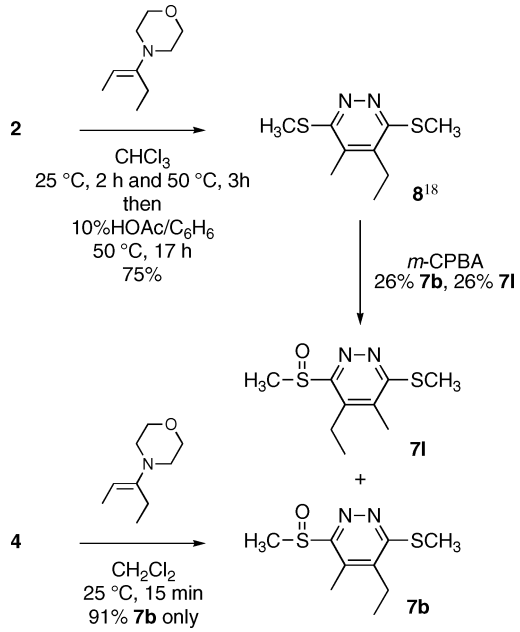
SCHEME 2



C5-substituted (C4−H δ 7.88) 1,2-diazines, with the latter alkyne regioselectivity being consistent with that observed with phenylacetylene (X-ray), Scheme 2. The structure of the cycloadduct **7b**, which lacks the distinguishing aryl CH, was confirmed by comparison of its spectroscopic properties with that of the two possible cycloadducts (**7b** vs **7l**) with **7l**, but not **7b**, exhibiting a characteristic diastereotopic methylene adjacent to the sulfoxide substituent similarly observed with **7h** versus **7k**, Scheme 3. As such, tetrazine **4** exhibits a very useful Diels−Alder reactivity accommodating an unusually wide range of potential dienophiles and proceeds with a reaction regioselectivity opposite what one would predict.

Diels−Alder Reactions of 5. Given the useful but unexpected observations with tetrazine **4**, an analogous but less extensive study of the [4+2] cycloaddition reactions of tetrazine **5** was conducted, Table 2. As anticipated, the reactivity of **5**, by virtue of its enhanced electron-deficient character, substantially exceeded that of **3**. Not only did **5** react with enamines, ketene acetals, and enol ethers rapidly and effectively at room temperature, but also the unactivated dienophile phenylacetylene (**6h**) provided the [4+2] cycloadduct **9f** in excellent conversion (77%) at 25 °C, requiring only 24 h for complete reaction. Although tetrazine **5** was slightly less reactive than **4**, requiring slightly longer reaction times and providing somewhat lower conversions, it was also found to exhibit a superb [4+2] cycloaddition reactivity. Similarly, the regioselectivity of the [4+2] cycloaddition reactions was often excellent, although not always as clean as that observed with **3** or **4**, and, like that of **4**, was found to be opposite that anticipated. This was first evident upon examination of the spectroscopic properties of the products and confirmed by X-ray for **9c**[25] or by correlation with the alternative regioisomeric products available through *S* oxidation of the analogous cycloadducts derived from tetrazine **3**, Scheme 4. These latter studies not only further verified that tetrazines **3** and **5** proceed with opposite regioselectivities in the [4+2] cycloaddition reactions and, more surprisingly, that it is the regioselectivity of **5** that is opposite what one might predict, but they also illustrate that the analogous reactions of **3** require much more vigorous reaction conditions to conduct.

SCHEME 3



Reactivity and Regioselectivity. The regioselectivity of the cycloadditions is not consistent with the expectation that the methylsulfinyl group would control the reaction orientation by stabilizing a partial negative charge at C3 (Table 3). The dienophile addition does not follow an approach predicted by this stabilization and the complementary ability of the thiomethyl or acylamino group to stabilize a partial positive charge on C6. These intuitive predictions are supported by the Austin model 1 (AM1) and MNDO computational studies, where C3 of both **4** and **5** bear a significant partial negative charge, while C6 is more electropositive. Moreover, C6 bears the largest LUMO coefficient, indicating it should dominate the regioselectivity by preferentially combining with the dienophile C2 center, which possesses its largest HOMO coefficient. Thus, both **4** and **5** experimentally display a [4+2] cycloaddition reaction regioselectivity opposite what one would predict on the basis of simple zwitterionic models or FMO analysis of the reactions.

(25) Atomic coordinates for **7c** (CCDC 282318), **7f** (CCDC 282319), **7g** (CCDC 282321), and **9c** (CCDC 282320) have been deposited with the Cambridge Crystallographic Data Centre.

TABLE 2. [4+2] Cycloaddition Reactions of 5

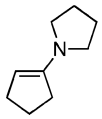
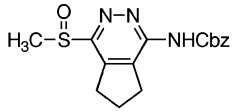
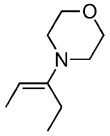
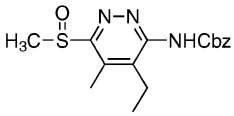
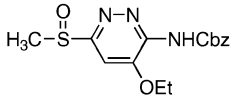
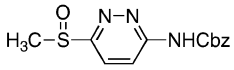
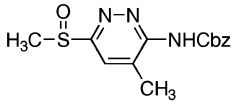
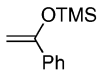
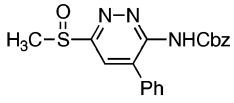
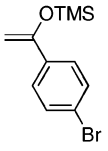
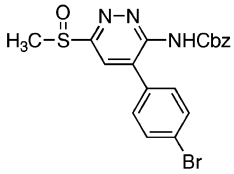
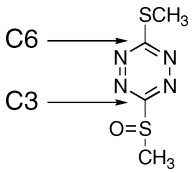
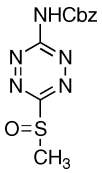
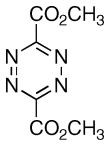
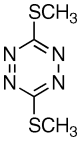
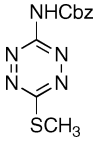
entry		dienophile (equiv)		conditions		product	% yield
1	**6a**		(1.5)	CH_2Cl_2, 25 °C, 5 min	**9a**		77%
2	**6b**		(2)	CH_2Cl_2, 25 °C, 15 min	**9b**		29% (10% regioisomer)
3	**6c**		(10)	dioxane, 25 °C, 30 min	**9c**		47–34% (17% regioisomer)
4	**6d**		(10)	dioxane, 25 °C, 1 h	**9d**		75%
5	**6f**		(10)	CH_2Cl_2, 25 °C, 6 h	**9e**		58% (7% regioisomer)
6	**6g**		(5)	CH_2Cl_2, 25 °C, 2 h	**9f**		83%
7	**6h**		(5)	dioxane, 25 °C, 24 h	**9f**		77%
8	**6i**		(2)	dioxane, 25 °C, 6 h	**9g**		69%

TABLE 3. AM1 Computational Results (LUMO) of 1,2,4,5-Tetrazines

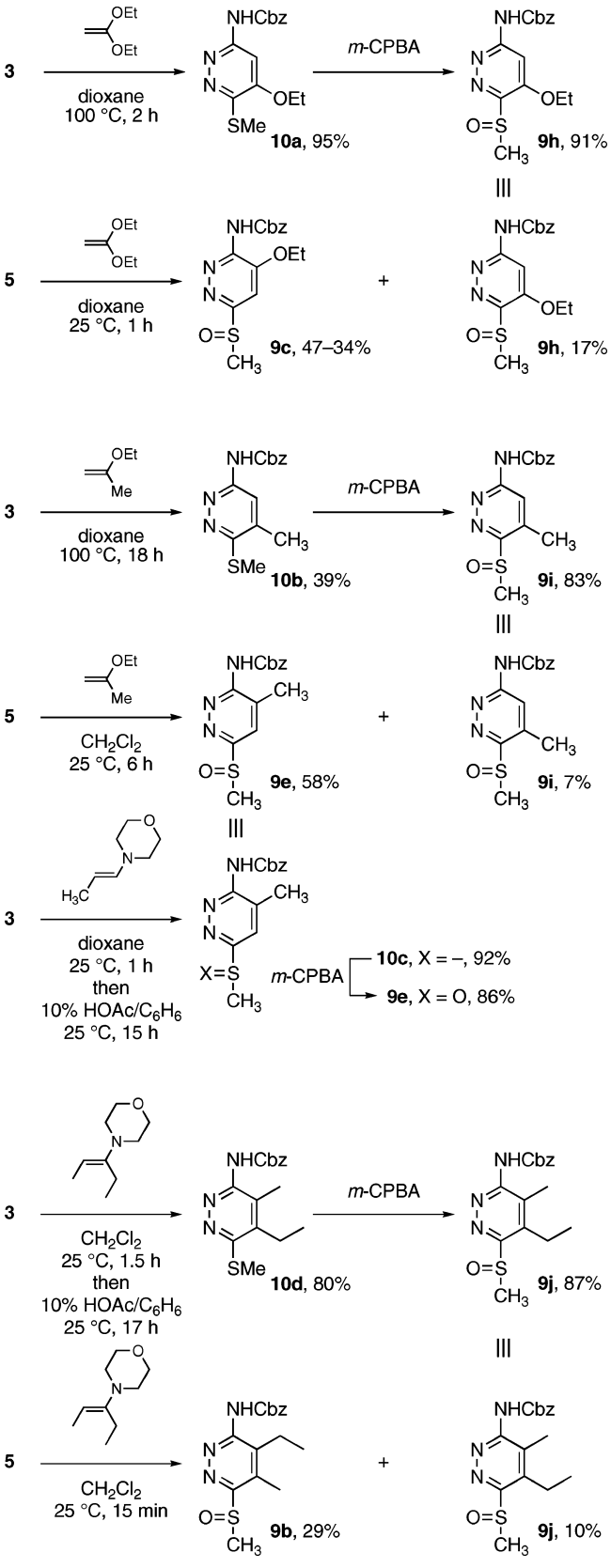
	 **4**	 **5**[a]	 **1**	 **2**	 **3**[a]
LUMO (EV)	−1.871	−1.607	−2.149	−1.365	−1.364
C-3 coefficient	0.530	0.517	0.591	0.584	0.549
C-6 coefficient	0.617	0.625	0.591	0.584	0.596
C-3 net charge	−0.571	−0.586	−0.102	−0.277	−0.301
C-6 net charge	−0.283	0.063	−0.102	−0.277	0.022

[a] Cbz group was replaced with CO_2CH_3 for the calculations.

Only the LUMO energy levels of the FMO analysis accurately reflect the increased reactivity of **4** and **5** (**4** > **5**) relative to **2** and **3**.

Consequently, the origin of the reversed regioselectivity is not clear. It is possible that this is related to a destabilizing steric and/or electronic interaction of the dienophile substituents with the larger and more electronegative methylsulfinyl substituent (e.g., a destabilizing $-NR_2/CH_3SO-$ interaction). In part, this may explain the lower regioselectivity typically observed with **5** versus **4**, including the relative behavior seen in the reaction of **5** with the terminally substituted dienophile **6b**. However, it is also interesting to note that treatment of tetrazine **4** (Et_2NH, THF, 0 to 25 °C) or the cycloadducts **7c**, **7d**, and **7e** (CH_3ONa, CH_3OH, 25−70 °C) with nucleophiles only provided products derived from the displacement of the methylsulfinyl group and not the methyl sulfide. Consequently,

SCHEME 4



it is also possible that the reactions proceed by stepwise addition−cyclization reactions initiated by an analogous nucleophilic addition. Although potentially reasonable for the nucleophilic dienophiles examined, no intercepted simple addition−elimination products (no cyclization) were detected, and such a stepwise reaction course is unlikely for the unactivated alkynes examined.

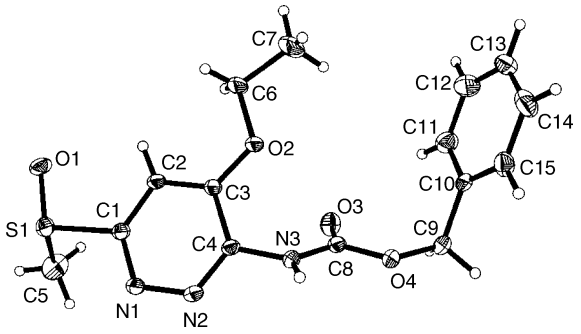


FIGURE 3. ORTEP drawing of **9c**.

Conclusions

The unsymmetrical 1,2,4,5-tetrazines **4** and **5** participate in well-defined and regioselective inverse electron demand Diels−Alder reactions with a wide range of electron-rich and unactivated dienophiles providing the corresponding 1,2-diazines in excellent yields. As anticipated, their enhanced electron-deficient character relative to **2** and **3** provides dienes that react faster and/or under milder reaction conditions and with a wider range of potential dienophiles. The cycloadditions are regioselective, albeit providing products opposite what is predicted using simple zwitterionic models or FMO analysis of the [4+2] cycloaddition reaction.

Experimental Section

3-Methylsulfinyl-6-methylthio-1,2,4,5-tetrazine (4). 3,6-Bis-(methylthio)tetrazine (**2**, 500 mg, 2.87 mmol) was dissolved in 16 mL of a 5:2:1 mixture of HOAc, H_2O, and CH_2Cl_2. The DABCO−$2Br_2$ complex (681 mg, 1.58 mmol) was added, and the mixture was stirred at room temperature for 20 h. Water was added, and the mixture was extracted with CH_2Cl_2, dried ($MgSO_4$), and evaporated. The crude material was washed with Et_2O/hexane (1:1, 3×), providing pure tetrazine **4** (286 mg, 52% yield) as a red solid. An analytically pure sample of **4** was obtained by recrystallization from EtOAc/hexane: mp 73−74 °C (EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.18 (s, 3H), 2.81 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 178.9, 173.0, 40.1, 13.6; IR (film) ν_{max} 1382, 1242, 1122, 1078, 1049, 961, 892 cm^{-1}. HRMS (MALDI−FTMS, *m*/*z*): (M + Na^+) calcd for $C_4H_6N_4OS_2$, 212.9875; found, 212.9878.

6-(Benzyloxycarbonyl)amino-3-(methylsulfinyl)-1,2,4,5-tetrazine (5). 6-(Benzyloxycarbonyl)-amino-3-methylthio-1,2,4,5-tetrazine (**3**, 100 mg, 0.36 mmol) was dissolved in 4 mL of CH_2Cl_2 and cooled to 0 °C. *m*-CPBA (68.5 mg, 0.397 mmol) was added, and the mixture was stirred at 0 °C for 30 min. Saturated aqueous $NaHCO_3$ was added, and the mixture was extracted with CH_2Cl_2, dried ($MgSO_4$), and evaporated to give 90 mg (85%) of essentially pure tetrazine **5** (> 95%) as a red foam: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.91 (br s, 1H), 7.45−7.35 (m, 5H), 5.34 (s, 2H), 3.16 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.9, 160.7, 150.4, 134.6, 128.6, 128.5 (2C), 128.4 (2C), 68.5, 39.6; IR (film) ν_{max} 3196, 3031, 1759, 1557, 1471, 1279, 1211, 1179, 1059, 964, 927, 742 cm^{-1}. HRMS (ESI-TOF, *m*/*z*): (M + Na^+) calcd for $C_{11}H_{11}N_5O_3S$, 316.0475; found, 316.0466.

General Procedure for Cycloadditions. Tetrazine **4** or **5** was dissolved in the reaction solvent (Tables 1 and 2), the dienophile was added at room temperature, and the mixture was stirred at the indicated temperature for the indicated time. After completion of

the reaction, the solvent was removed and the crude material was purified by chromatography on silica gel.

1-(Methylsulfinyl)-4-(methylthio)-6,7-dihydro-*5H*-cyclopenta-[*d*]pyridazine (7a). A total of 10 mg of **4** yielded 11.5 mg of **7a** (96%, white solid) after chromatography (0−5% MeOH/EtOAc): mp 92−93 °C (EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.44−3.30 (m, 2H), 3.07 (s, 3H), 2.83 (t, J = 7.7 Hz, 2H), 2.77 (s, 3H), 2.27−2.16 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 161.7, 160.4, 145.3, 142.3, 39.3, 30.3, 30.1, 23.3, 12.7; IR (film) ν_{max} 1541, 1427, 1291, 1191, 1058, 964 cm^{-1}. HRMS (MALDI−FTMS, *m*/*z*): (M + H$^+$) calcd for $C_9H_{12}N_2OS_2$, 229.0464; found, 229.0466.

5-Ethyl-4-methyl-3-(methylsulfinyl)-6-(methylthio)-pyridazine (7b). A total of 20 mg of **4** yielded 22 mg of **7b** (91%, pale yellow viscous oil) after preparative TLC (EtOAc): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.11 (s, 3H), 2.74 (q, J = 7.5 Hz, 2H), 2.71 (s, 3H), 2.60 (s, 3H), 1.18 (t, J = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.6, 160.4, 141.3, 134.6, 37.1, 21.8, 13.7, 12.7, 11.2; IR (film) ν_{max} 3460, 2972, 2926, 1715, 1652, 1538, 1057 cm^{-1}. HRMS (ESI-TOF, *m*/*z*): (M + H$^+$) calcd for $C_9H_{14}N_2OS_2$, 231.0620; found, 231.0620.

5-Ethoxy-3-(methylsulfinyl)-6-(methylthio)pyridazine (7c). A total of 10 mg of **4** yielded 10.4 mg of **7c** (85%, white solid) after chromatography (0−2% MeOH/EtOAc gradient elution). A single-crystal X-ray structure determination[25] conducted on crystals grown from benzene unambiguously established the structure of **7c**: mp 111.5−112.5 °C (benzene); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.31 (s, 1H), 4.31 (q, J = 7 Hz, 2H), 2.98 (s, 3H), 2.69 (s, 3H), 1.54 (t, J = 7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.6, 157.0, 156.2, 99.5, 65.5, 41.8, 14.0, 12.6; IR (film) ν_{max} 1556, 1353, 1193, 1058, 1033 cm^{-1}. HRMS (MALDI−FTMS, *m*/*z*): (M + H$^+$) calcd for $C_8H_{12}N_2O_2S_2$, 233.0413; found, 233.0412.

3-(Methylsulfinyl)-6-(methylthio)pyridazine (7d). From ethyl vinyl ether (**6d**), 10 mg of **4** yielded 9.5 mg of **7d** (96%, white solid) after chromatography (EtOAc). From vinyl pyrrolidinone (**6e**), 10 mg of **4** afforded 6.5 mg of **7d** (66%) after chromatography (EtOAc): mp 115−117 °C (EtOAc/hexane, lit.[26] mp 118−119 °C); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.91 (d, J = 8.8 Hz, 1H), 7.58 (d, J = 8.8 Hz, 1H), 2.98 (s, 3H), 2.76 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.1, 164.6, 127.4, 121.3, 41.7, 13.4; IR (film) ν_{max} 1557, 1390, 1156, 1053, 974, 854 cm^{-1}. HRMS (MALDI−FTMS, *m*/*z*): (M + H$^+$) calcd for $C_6H_8N_2OS_2$, 189.0151; found, 189.0153.

5-Methyl-3-(methylsulfinyl)-6-(methylthio)pyridazine (7e). A total of 10 mg of **4** yielded 9.6 mg of **7e** (91%, white solid) after chromatography (EtOAc): mp 106−107 °C (EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.74 (s, 1H), 2.95 (s, 3H), 2.74 (s, 3H), 2.36 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 165.4, 164.8, 138.5, 121.0, 41.7, 18.5, 13.4; IR (film) ν_{max} 1558, 1347, 1062 cm^{-1}. HRMS (MALDI−FTMS, *m*/*z*): (M + H$^+$) calcd for $C_7H_{10}N_2OS_2$, 203.0307; found, 203.0308.

3-(Methylsulfinyl)-6-(methylthio)-5-phenylpyridazine (7f). From 1-phenyl-1-(trimethylsilyloxy)ethylene (**6g**), 10 mg of **4** yielded 13 mg of **7f** (94%, white solid) after chromatography (60% EtOAc/hexane). From phenylacetylene (**6h**), 50 mg of **4** yielded 63 mg of **7f** (90%) after chromatography (60% EtOAc/hexane). A single-crystal X-ray structure determination[25] conducted on crystals grown from acetone/H_2O unambiguously established the structure of **7f**: mp 143.2−143.8 °C (acetone/H_2O); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.81 (s, 1H), 7.50 (s, 5H), 3.02 (s, 3H), 2.70 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.0, 163.5, 141.4, 134.3, 130.1, 128.9 (2C), 128.4 (2C), 120.7, 41.7, 14.3; IR (film) ν_{max} 1344, 1193, 1059 cm^{-1}. HRMS (MALDI−FTMS, *m*/*z*): (M + H$^+$) calcd for $C_{12}H_{12}N_2OS_2$, 265.0464; found, 265.0466.

5-(4′-Bromophenyl)-3-(methylsulfinyl)-6-(methylthio)-pyridazine (7g). A total of 30 mg of **4**[27] yielded 48 mg of **7g** (89%, white solid) after chromatography (50−100% EtOAc/hexane). A single-crystal X-ray structure determination[25] conducted on crystals grown from acetone/H_2O unambiguously established the structure of **7g**: mp 149−150 °C (acetone/H_2O); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.79 (s, 1H), 7.64 (d, J = 8.8 Hz, 2H), 7.40 (d, J = 8.8 Hz, 2H), 3.02 (s, 3H), 2.70 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.1, 163.1, 140.1, 133.0, 132.2 (2C), 130.0 (2C), 124.6, 120.6, 41.7, 14.2; IR (film) ν_{max} 1487, 1418, 1328, 1142, 1063, 1009, 843, 821, 753 cm^{-1}. HRMS (ESI-TOF, *m*/*z*): (M + H$^+$) calcd for $C_{12}H_{11}BrN_2OS_2$, 342.9569; found, 342.9571.

4-(2′-Hydroxyethyl)-3-(methylsulfinyl)-6-(methylthio)-pyridazine (7h). A total of 10 mg of **4** yielded 8.5 mg of **7h** (70%, colorless oil) after chromatography (0−10% MeOH/EtOAc). The regioisomer (**7k**) was isolated as a minor product (5−11%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.36 (s, 1H), 4.04−3.98 (m, 1H), 3.87−3.82 (m, 1H), 3.37−3.31 (m, 1H), 3.18 (s, 3H), 3.13−3.08 (m, 1H), 2.74 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.1, 161.7, 139.7, 128.4, 61.7, 38.9, 32.8, 13.3; IR (film) ν_{max} 3383, 1415, 1353, 1193, 1057 cm^{-1}. HRMS (MALDI−FTMS, *m*/*z*): (M + H$^+$) calcd for $C_8H_{12}N_2O_2S_2$, 233.0413; found, 233.0412.

5-[2-(*tert*-Butyldimethylsilyloxy)ethyl]-3-(methylsulfinyl)-6-(methylthio)pyridazine (7i). A total of 10 mg of **4** yielded 16 mg of **7i** (89%, colorless oil) after chromatography (40% EtOAc/hexane): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.83 (s, 1H), 3.96 (t, J = 6.2 Hz, 2H), 2.95 (s, 3H), 2.90 (t, J = 6.2 Hz, 2H), 2.76 (s, 3H), 0.84 (s, 9H), 0.00 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 165.5, 164.4, 139.6, 121.2, 59.6, 41.7, 35.0, 25.7, 18.1, 13.6, −5.4; IR (film) ν_{max} 2928, 1353, 1256, 1096, 1066, 837, 777 cm^{-1}. HRMS (MALDI−FTMS, *m*/*z*): (M + H$^+$) calcd for $C_{14}H_{26}N_2O_2S_2Si$, 347.1278; found, 347.1274.

4-[2-(*tert*-Butyldimethylsilyloxy)ethyl]-3-(methylsulfinyl)-6-(methylthio)pyridazine (7j). A solution of **7h** (7 mg, 0.03 mmol) in DMF (300 μL) was treated with imidazole (3.4 mg, 0.05 mmol) and *t*-butyldimethylsilyl chloride (6.7 mg, 0.045 mmol). The mixture was stirred for 3 h at room temperature before being diluted with EtOAc and washed with water. Preparative TLC (50% EtOAc/hexane) afforded 8 mg (77%) of **7j** as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.39 (s, 1H), 3.98−3.90 (m, 2H), 3.27−3.22 (m, 1H), 3.14 (s, 3H), 3.12−3.09 (m, 1H), 2.74 (s, 3H), 0.84 (s, 9H), −0.01 (s, 3H), −0.02 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 164.7, 161.0, 139.3, 128.5, 61.6, 37.9, 33.0, 25.7 (3C), 18.1, 13.2, −5.5 (2C); IR (film) ν_{max} 2927, 1566, 1360, 1256, 1090, 1065, 836, 777 cm^{-1}. HRMS (MALDI−FTMS, *m*/*z*): (M + H$^+$) calcd for $C_{14}H_{26}N_2O_2S_2Si$, 347.1278; found, 347.1279.

5-(2′-Hydroxyethyl)-3-(methylsulfinyl)-6-(methylthio)-pyridazine (7k). A solution of **7i** (5 mg) in 100 μL of THF was treated with Bu_4NF (1.0 M in THF, 30 μL, 2 equiv) at room temperature, and the mixture was stirred at 25 °C for 1 h. Chromatography (5% MeOH/EtOAc) afforded 3.3 mg of **7k** (98%, white solid): mp 110−112 °C (EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.88 (s, 1H), 4.06 (t, J = 6.2 Hz, 2H), 2.99 (s, 3H), 2.95 (t, J = 6.2 Hz, 2H), 2.77 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.4, 164.7, 139.4, 120.8, 59.3, 41.6, 34.5, 13.7; IR (film) ν_{max} 3377, 1567, 1413, 1362, 1193, 1149, 1057, 958 cm^{-1}. HRMS (MALDI−FTMS, *m*/*z*): (M + H$^+$) calcd for $C_8H_{12}N_2O_2S_2$, 233.0413; found, 233.0412.

4-Ethyl-5-methyl-3-(methylsulfinyl)-6-(methylthio)-pyridazine (7l). A solution of **8** (46 mg, 0.215 mmol) in CH_2Cl_2 (1 mL) was treated with *m*-CPBA (70%, 53 mg, 0.215 mmol, 1 equiv) at 0 °C. The mixture was allowed to warm to room temperature over 1 h before being washed with saturated aqueous $NaHCO_3$. The organic layer was dried over Na_2SO_4, and preparative TLC (SiO_2, EtOAc) afforded **7b** (13 mg, 0.056 mmol, 26%, pale yellow viscous oil) and **7l** (13 mg, 0.056 mmol, 26%, white solid). **7l**: mp 94−96 °C (EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.16−2.92 (m, 2H), 3.10 (s, 3H), 2.72 (s, 3H), 2.28 (s, 3H), 1.24 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.6, 159.8, 140.5, 135.5, 37.6, 20.7, 14.1, 13.8, 13.6; IR (film) ν_{max} 3475, 2926, 1539, 1294, 1206, 1035, 952 cm^{-1}. HRMS (ESI-TOF, *m*/*z*): (M + H$^+$) calcd for $C_9H_{14}N_2OS_2$, 231.0620; found, 231.0629.

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4-(Benzyloxycarbonyl)amino-1-(methylsulfinyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyridazine (9a). A total of 54 mg of **5** yielded 47 mg of **9a** (77%, orange film) after chromatography (0−1% MeOH/EtOAc): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.41−7.34 (m, 5H), 5.23 (s, 2H), 3.38 (t, J = 7.6 Hz, 2H), 3.13−3.02 (m, 2H), 3.00 (s, 3H), 2.26−2.08 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 160.8, 153.4, 153.0, 148.0, 141.5, 135.3, 128.6 (2C), 128.5, 128.2 (2C), 67.8, 39.5, 31.6, 30.4, 24.3; IR (film) ν_{max} 3184, 2960, 1733, 1515, 1232, 1047 cm^{-1}. HRMS (ESI-TOF, *m*/*z*): (M + H$^+$) calcd for $C_{16}H_{17}N_3O_3S$, 332.1063; found, 332.1056.

6-(Benzyloxycarbonyl)amino-5-ethyl-4-methyl-3-(methylsulfinyl)pyridazine (9b). A total of 29 mg of **5** yielded **9b** (9.6 mg, 29%, colorless oil) after preparative TLC (SiO_2, EtOAc). The regioisomer (**9j**) was isolated as a minor product (3.2 mg, 10%, colorless oil). **9b**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.39−7.36 (m, 5H), 5.23 (s, 2H), 3.10 (s, 3H), 2.76 (q, J = 7.6 Hz, 2H), 2.66 (s, 3H), 1.14 (t, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 161.9, 154.2, 153.8, 139.2, 135.3, 128.6 (2C), 128.5, 128.4 (2C), 126.9, 68.0, 37.6, 20.8, 13.3, 12.2; IR (film) ν_{max} 3209, 2976, 1728, 1557, 1498, 1455, 1228, 1051 cm^{-1}. HRMS (ESI-TOF, *m*/*z*): (M + H$^+$) calcd for $C_{16}H_{19}N_3O_3S$, 334.1220; found, 334.1221. Minor isomer **9j**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.77 (s, 1H), 7.39−7.33 (m, 5H), 5.21 (s, 2H), 3.13−2.95 (m, 2H), 3.06 (s, 3H), 2.30 (s, 3H), 1.26 (t, J = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 161.3, 155.3, 153.6, 145.1, 135.3, 133.8, 128.65 (2C), 128.56, 128.3 (2C), 68.0, 38.3, 21.1, 13.9, 13.7; IR (film) ν_{max} 3180, 2973, 1732, 1504, 1231, 1043 cm^{-1}. HRMS (ESI-TOF, *m*/*z*): (M + H$^+$) calcd for $C_{16}H_{19}N_3O_3S$, 334.1220; found, 334.1215.

6-(Benzyloxycarbonyl)amino-5-ethoxy-3-(methylsulfinyl)-pyridazine (9c). A total of 70 mg of **5** yielded 27 mg of **9c** (34%, white solid) after chromatography (0−10% MeOH/CH_2Cl_2) and preparative TLC (SiO_2, 5% MeOH/CH_2Cl_2). The regioisomer (**9h**) was isolated as a minor product (14 mg, 17%, white solid). A single-crystal X-ray structure determination[25] conducted on crystals grown from EtOAc/$CHCl_3$ unambiguously established the structure of **9c**. **9c**: mp 119−121 °C (EtOAc/$CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.48−7.38 (m, 6H), 5.30 (s, 2H), 4.29 (q, J = 8.5 Hz, 2H), 2.96 (s, 3H), 1.52 (t, J = 8.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 165.9, 151.0, 148.8, 147.2, 135.3, 128.63 (2C), 128.58 (2C), 128.54, 102.6, 67.9, 65.9, 41.9, 14.1; IR (film) ν_{max} 1731, 1572, 1503, 1438, 1221, 1042 cm^{-1}. HRMS (MALDI−FTMS, *m*/*z*): (M + H$^+$) calcd for $C_{15}H_{17}N_3O_4S$, 336.1012; found, 336.1016. Minor isomer **9h**: mp 144−145 °C (EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.59 (br s, 1H), 7.89 (s, 1H), 7.42−7.36 (m, 5H), 5.26 (s, 2H), 4.29 (q, J = 7.0 Hz, 2H), 3.00 (s, 3H), 1.53 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 157.7, 157.3, 152.9, 152.1, 135.1, 128.7 (2C), 128.6, 128.2 (2C), 98.5, 67.8, 65.5, 37.3, 14.0; IR (film) ν_{max} 1731, 1572, 1512, 1228, 1152, 1050, 1029 cm^{-1}. HRMS (MALDI−FTMS, *m*/*z*): (M + H$^+$) calcd for $C_{15}H_{17}N_3O_4S$, 336.1012; found, 336.1017.

6-(Benzyloxycarbonyl)amino-3-(methylsulfinyl)pyridazine (9d). A total of 16 mg of **5** yielded 12 mg of **9d** (75%, white solid) after chromatography (10% EtOAc/hexane): mp 155.5−155.8 °C (EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.55 (d, J = 9.4 Hz, 1H), 8.39 (br s, 1H), 8.16 (d, J = 9.4 Hz, 1H), 7.42−7.39 (m, 5H), 5.28 (s, 2H), 2.94 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 165.2, 155.6, 152.7, 134.9, 128.78, 128.75 (2C), 128.4 (2C), 124.9, 118.6, 68.0, 41.9; IR (film) ν_{max} 1721, 1573, 1519, 1228, 1056 cm^{-1}. HRMS (MALDI−FTMS, *m*/*z*): (M + H$^+$) calcd for $C_{13}H_{13}N_3O_3S$, 292.0756; found, 292.0758.

6-(Benzyloxycarbonyl)amino-5-methyl-3-(methylsulfinyl)-pyridazine (9e). A total of 77 mg of **5** yielded 43 mg of **9e** (54%, colorless oil) after chromatography (0−10% EtOAc/hexane). The regioisomer (**9i**) was isolated as a minor product (5.5 mg, 7%, white solid). **9e**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.01 (s, 1H), 7.76 (br s, 1H), 7.42−7.35 (m, 5H), 5.24 (s, 2H), 2.94 (s, 3H), 2.45 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.8, 155.1, 153.5, 136.5, 135.1, 128.68 (2C), 128.64, 128.4 (2C), 125.8, 68.1, 41.8, 18.4; IR (film) ν_{max} 1732, 1506, 1234, 1049 cm^{-1}. HRMS (MALDI−FTMS, *m*/*z*): (M + H$^+$) calcd for $C_{14}H_{15}N_3O_3S$, 306.0907; found, 306.0913. Minor isomer **9i**: mp 139−141 °C (EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.22 (s, 1H), 8.15 (br s, 1H), 7.43−7.37 (m, 5H), 5.26 (s, 2H), 3.08 (s, 3H), 2.69 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 160.2, 155.8, 152.7, 141.6, 135.0, 128.7 (2C), 128.3 (2C), 119.1, 67.9, 37.6, 17.7; IR (film) ν_{max} 3182, 2923, 1733, 1558, 1505, 1409, 1224, 1152, 1047, 744 cm^{-1}. HRMS (MALDI−FTMS, *m*/*z*): (M + H$^+$) calcd for $C_{14}H_{15}N_3O_3S$, 306.0907; found, 306.0912.

6-(Benzyloxycarbonyl)amino-3-(methylsulfinyl)-5-phenyl-pyridazine (9f). From 1-phenyl-1-(trimethylsilyloxy)ethylene (**6f**), 9.2 mg of **5** yielded 9.5 mg of **9f** (83%, white solid) after chromatography (60−100% EtOAc/hexane). From phenylacetylene (**6g**), 10.4 mg of **5** yielded 10 mg of **9f** (77%) after preparative TLC (SiO_2, EtOAc): mp 119−121 °C (EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.07 (s, 1H), 7.52−7.49 (m, 5H), 7.35−7.33 (m, 3H), 7.28−7.27 (m, 2H), 5.07 (s, 2H), 3.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.7, 152.7, 152.0, 135.5, 135.1, 133.8, 129.9, 129.5 (2C), 128.55 (2C), 128.52, 128.4 (2C), 127.5 (2C), 124.5, 67.8, 41.9; IR (film) ν_{max} 1731, 1495, 1213, 1045, 743, 697 cm^{-1}. HRMS (MALDI−FTMS, *m*/*z*): (M + H$^+$) calcd for $C_{19}H_{17}N_3O_3S$, 368.1063; found, 368.1064.

6-(Benzyloxycarbonyl)amino-5-(4′-bromophenyl)-3-(methylsulfinyl)pyridazine (9g). A total of 33 mg of **5**[27] yielded 34 mg of **9g** (69%, white solid) after chromatography (50−100% EtOAc/hexane): mp 162−163 °C (toluene/$CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.07 (s, 1H), 7.92 (brs, 1H), 7.57−7.55 (m, 2H), 7.40−7.34 (m, 5H), 7.22−7.20 (m, 2H), 5.03 (s, 2H), 3.00 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.2, 152.7, 152.2, 135.3, 135.0, 133.4, 132.5 (2C), 128.7 (2C), 128.6, 128.5 (2C), 128.4 (2C), 124.5, 124.2, 67.9, 41.8; IR (film) ν_{max} 3176, 2960, 1733, 1488, 1393, 1250, 1214, 1055, 751 cm^{-1}. HRMS (MALDI−FTMS, *m*/*z*): (M + H$^+$) calcd for $C_{19}H_{16}BrN_3O_3S$, 446.0168; found, 446.0166.

6-(Benzyloxycarbonyl)amino-4-ethoxy-3-(methylthio)-pyridazine (10a). A solution of **3** (20 mg, 0.072 mmol) in dioxane (300 μL) was treated with ketene diethyl acetal (**6c**, 94 μL, 10 equiv). The mixture was heated at 100 °C in a closed vessel for 2 h. Chromatography (30% EtOAc/hexane) afforded 22 mg of **10a** (95%, white solid): mp 167−168 °C (EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.07 (br s, 1H), 7.59 (s, 1H), 7.42−7.34 (m, 5H), 5.23 (s, 2H), 4.21 (q, J = 7.0 Hz, 2H), 2.59 (s, 3H), 1.50 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 155.8, 153.6, 153.3, 150.8, 135.5, 128.6 (2C), 128.4, 128.0 (2C), 96.1, 67.3, 64.7, 14.0, 12.2; IR (film) ν_{max} 2923, 1723, 1589, 1571, 1515, 1373, 1357, 1239, 1156, 1117, 1034, 750 cm^{-1}. HRMS (MALDI−FTMS, *m*/*z*): (M + H$^+$) calcd for $C_{15}H_{17}N_3O_3S$, 320.1063; found, 320.1059.

6-(Benzyloxycarbonyl)amino-4-methyl-3-(methylthio)-pyridazine (10b). A solution of **3** (20 mg, 0.072 mmol) in dioxane (300 μL) was treated with 2-methoxypropene (**6e**, 69 μL, 10 equiv). The mixture was heated in a closed vessel at 100 °C for 18 h. Chromatography (20% EtOAc/hexane) afforded **10b** (8 mg, 39%, white solid): mp 151−152 °C (EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.96 (s, 1H), 7.82 (br s, 1H), 7.43−7.35 (m, 5H), 5.23 (s, 2H), 2.67 (s, 3H), 2.28 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 158.5, 153.0, 152.2, 138.3, 135.4, 128.6 (2C), 128.5, 128.2 (2C), 116.8, 67.5, 18.5, 13.1; IR (film) ν_{max} 1721, 1570, 1502, 1232, 1149, 1110, 1041, 750, 695 cm^{-1}. HRMS (MALDI−FTMS, *m*/*z*): (M + H$^+$) calcd for $C_{14}H_{15}N_3O_2S$, 290.0958; found, 290.0956.

6-(Benzyloxycarbonyl)amino-5-methyl-3-(methylthio)-pyridazine (10c). A solution of **3** (25 mg, 0.090 mmol) in dioxane (0.2 mL) was treated with 1-morpholinopropene[28] (57 mg, 0.45 mmol, 5 equiv). The mixture was stirred at 25 °C for 1 h before the solvent was removed. The residue was dissolved in 10% HOAc/

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benzene (0.2 mL) and stirred at 25 °C for 15 h. Neutralization with saturated aqueous $NaHCO_3$, extraction (CH_2Cl_2), and chromatography (40% EtOAc/hexane) afforded **10c** (24 mg, 92%, white solid): mp 117−119 °C (EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.53 (s, 1H), 7.40−7.32 (m, 5H), 7.17 (s, 1H), 5.20 (s, 2H), 2.63 (s, 3H), 2.27 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 145.3, 135.6, 128.6 (2C), 128.3, 128.2 (2C), 67.6, 17.7, 13.2 (four peaks are undetected); IR (film) ν_{max} 3208, 2926, 1727, 1497, 1239, 1101 cm^{-1}. HRMS (ESI-TOF, *m*/*z*): ($M + H^+$) calcd for $C_{14}H_{15}N_3O_2S$, 290.0958; found, 290.0957.

6-(Benzyloxycarbonyl)amino-4-ethyl-5-methyl-3-(methylthio)-pyridazine (10d). A solution of **3** (23 mg, 0.083 mmol) in CH_2Cl_2 (0.17 mL) was treated with 3-morpholino-2-pentene[28] (**6b**, 26 mg, 0.166 mmol, 2 equiv). The mixture was stirred at 25 °C for 1.5 h before the removal of the solvent. The residue was treated with 10% HOAc/benzene (0.2 mL), and the mixture was stirred at 25 °C for 17 h. Neutralization with saturated aqueous $NaHCO_3$, extraction (CH_2Cl_2), and preparative TLC (SiO_2, 33% EtOAc/hexane) afforded **10d** (21 mg, 80%, pale yellow oil): mp 124−126 °C (CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.41−7.32 (m, 5H), 5.20 (s, 2H), 2.70 (q, J = 7.6 Hz, 2H), 2.64 (s, 3H), 2.23 (s, 3H), 1.17 (t, J = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 141.6, 135.8, 128.5 (2C), 128.3, 128.2 (2C), 67.6, 22.3, 13.5, 13.3, 11.5 (four peaks are undetected); IR (film) ν_{max} 3170, 2971, 1731, 1499, 1237, 1071 cm^{-1}. HRMS (ESI-TOF, *m*/*z*): ($M + H^+$) calcd for $C_{16}H_{19}N_3O_2S$, 318.1271; found, 318.1279.

General Procedure for the Oxidation of 8 or 10. A solution of **8** or **10** in CH_2Cl_2 was treated with *m*-CPBA (1 equiv) at 0 °C. The reaction mixture was allowed to warm to room temperature over 0.5−1 h. Washing with saturated aqueous $NaHCO_3$, drying with Na_2SO_4, and chromatography afforded **7** or **9**.

Acknowledgment. We gratefully acknowledge the financial support of the National Institutes of Health (CA42056) and the Skaggs Institute for Chemical Biology.

Supporting Information Available: ^{1}H NMR spectra of all new compounds and details of the X-ray structures of **7c**, **7f**, **7g**, and **9c**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO051832O