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Development of Chiral, Bifunctional Thiosquaramides: Enantioselective Michael Additions of Barbituric Acids to Nitroalkenes

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Supporting Information

ABSTRACT: We report a general method for the synthesis of chiral thiosquaramides, a class of bifunctional catalysts not previously described in the literature. Thiosquaramides are found to be more acidic and significantly more soluble in nonpolar solvents than their oxosquaramide counterparts, and they are excellent catalysts for the unreported, enantioselective conjugate addition reaction of the barbituric acid pharmacaphore to nitroalkenes, delivering the chiral barbiturate derivatives in high yields and high enantioselectivities, even with catalyst loadings as low as 0.05 mol%.

Conceptual insights and key advances in catalyst design have fueled many breakthroughs in asymmetric catalysis. Over the past two decades, chemists have witnessed unparalleled growth in enantioselective reactions promoted by chiral organic catalysts, such as bases, secondary amines, and hydrogen bond donors. In the last category, early examples of enantioselection through hydrogen bond activation paved the way for broader application of this modality to asymmetric catalysis,[1,2] with the development of bifunctional catalysts playing a pivotal role in propelling this activation paradigm into the discovery of new enantioselective processes.[3] Among the earliest and most-enabling bifunctional catalysts are those based on the thiourea scaffold, wherein the two donor hydrogens serve to organize and activate the reaction substrate.[4] In the hope of expanding the classes of reactions that can be rendered enantioselective, we examined many new scaffolds for bifunctional catalysis, particularly those in which the distance between the donor hydrogens was significantly greater than found in thioureas, and introduced chiral squaramides as bifunctional hydrogen bonding catalysts.[5] Squaramides are easily synthesized, through two addition−elimination reactions, and this has allowed the development of a large number of derivatives. Squaramides have proven to be excellent catalysts and have been adopted widely for the development of new methodology.[6,7] Despite their widespread use, the inherent properties of squaramides, such as low solubility in nonpolar solvents and a limited ability to modulate the pK_a of the donor hydrogens, restricts their performance in some reactions. Faced with these limitations, we have developed chiral dithiosquaramides as bifunctional catalysts and report herein their use in the unreported enantioselective conjugate addition reaction of the barbituric acid pharmacaphore to nitroalkenes.

The high effectiveness of squaramides stands in contrast to their poor solubility in nonpolar solvents, which are commonly employed for hydrogen bond mediated reactions. The reason for the low solubility is that squaramides self-aggregate through dual H-bonds into head-to-tail ladder networks and precipitate.[8,9] Among the structural modifications to overcome this issue, we considered the prospect of converting the carbonyl groups to thiocarbonyls.[10] Replacement of even one of the carbonyl groups to a thiocarbonyl was expected to disrupt ladder formation and, as a result, increase solubility. Furthermore, this interconversion was also expected to increase the acidity of the N−H bonds, as observed when going from an amide to a thioamide or urea to a thiourea (Figure 1).[11−13]

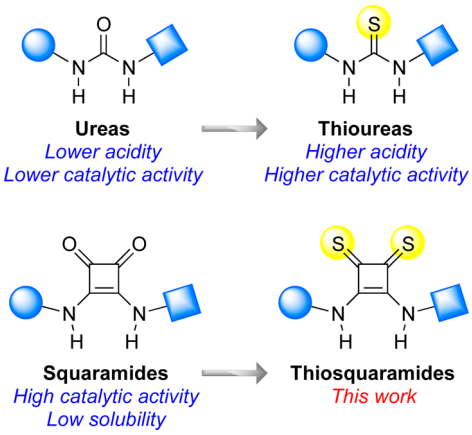

Figure 1. Development of relevant chiral organocatalyst scaffolds.

This ability to dial up the acidity of squaramides by converting one or both carbonyls to thiocarbonyls presented an opportunity to expand the catalyst's reaction footprint.

The selection of barbituric acid derivatives to test the capability of new thiosquaramides was motivated by their known biomedical applications. Historically used as sedatives, anti-convulsants, and analgesics, barbiturates have recently been shown to possess anti-tumor, immune system modulatory, and anti-depressive activity.[14] The varied biological properties of barbituric acids and the limited reports on their use in enantioselective reactions,[15] and none using organic catalysts, prompted us to select them as nucleophiles for demonstrating the effectiveness of chiral thiosquaramide catalysts.

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Direct synthesis of chiral, bifunctional thiosquaramides by dithionation of the corresponding "oxo"-squaramides eluded us for many years.[16] Even in instances where the desired product was observed, the isolation of a pure bifunctional thiosquaramide was complicated by its decomposition during silica gel chromatography and the presence of various byproducts. An alternative approach was thus explored. The preferred route to bifunctional thiosquaramides proceeded through the butyl squarate ester **1**, rather than the more common vinylogous methyl ester (Figure 2). Treatment of vinylogous

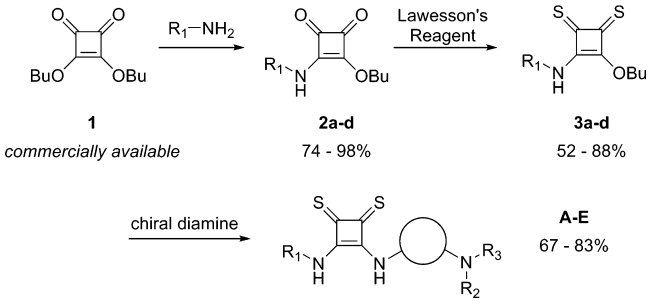


Figure 2. Synthesis of bifunctional thiosquaramides via the vinylogous butyl ester.

butyl ester–amide **2** with 1 equiv of Lawesson's reagent gave the easily isolated dithionation product **3**, which is moderately stable at room temperature.[17] Carrying out these steps on the corresponding methyl ester gave little or no product, depending on the substrate. Coupling of **3** with a chiral diamine provided bifunctional catalysts **A**–**E**, which were purified by trituration to give yellow to amber, bench-stable solids. As expected, unlike their widely used oxo-counterparts, which are at best sparingly soluble in common organic solvents, thiosquaramides are significantly more soluble in a range of solvents. At room temperature, squaramide **F** has a solubility of <0.1 mg/mL in toluene, whereas thiosquaramide **E** has a solubility of >3 mg/mL. We have also determined the pK_a of select chiral squaramides and thiosquaramides using various methods (computational, NMR titration, and Bordwell) and have found thiosquaramides to be 4–5 pK_a units more acidic than the corresponding oxosquaramides.[18,19] We expect this increased acidity to confer greater hydrogen bonding capability to the thiosquaramide N–H bonds.

To gain insight on the structural changes imparted upon substitution of the two oxygens with sulfurs, we secured the X-ray crystal structure of bifunctional thiosquaramide **A** (Figure 3). Two rotameric forms of the compound are

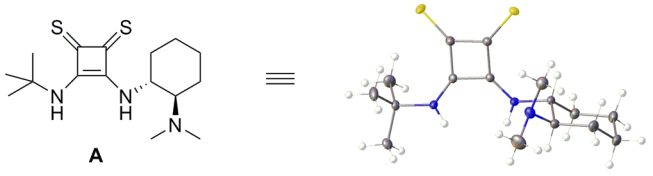
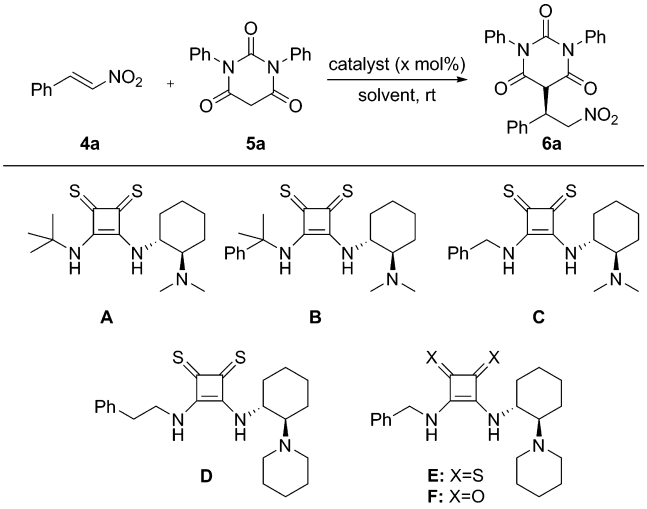


Figure 3. X-ray crystal structure of a bifunctional thiosquaramide.

observed in the structure, of which the one with the dimethylamino group pointing forward is shown. The planar geometry about the two squarate nitrogens is consistent with sp^2 hybridization expected at these atoms, and the *anti*/*anti* conformation, with the N–H bonds syn to each other, is as observed for most squaramides.[7a,9] In the two rotameric forms of **A**, the two N–H hydrogen atoms are positioned 2.43 and 2.64 Å apart, as opposed to ~2.1 Å for thioureas[20] and ~2.7 Å for squaramides (see Crystallographic Information File).[5a] The smaller H–H distance in thiosquaramide **A** likely results from the steric and electronic repulsion between the *tert*-butyl group and the proximal thiocarbonyl group. Hartree–Fock calculations for the same structure at the 3-21G level of theory gives the H–H distance as 2.60 Å, indicating that the smaller H–H distance is due to the interactions with the sulfur atoms rather than packing forces or other interactions in the crystal structure.[21] As anticipated, intermolecular hydrogen bonds to give ladder structures, found in analogous oxosquaramides, are not seen.[22]

The procedure described above was used to synthesize several chiral thiosquaramides (**A**–**E**), and the new bifunctional catalysts were evaluated as catalysts for the unreported enantioselective conjugate addition of *N*,*N*′-diphenylbarbituric acid to *β*-nitrostyrene (Table 1). Among the catalysts

Table 1. Evaluation of Catalysts and Other Reaction Conditions



entry[a]	catalyst	mol%	solvent	time, h	conv,[b] %	ee,[c] %
1	**A**	0.5	PhMe	0.5	>98	54
2	**B**	0.5	PhMe	0.5	>98	45
3	**C**	0.5	PhMe	0.5	>98	88
4	**D**	0.5	PhMe	0.5	>98	91
5	**E**	0.5	PhMe	0.5	>98	97
6	**F**	0.5	PhMe	0.5	>98	95
7	**E**	0.5	MeOH	6	>98	38
8	**E**	0.5	acetone	1.5	>98	87
9	**E**	0.5	$CHCl_3$	0.5	>98	91
10	**E**	0.5	EtOAc	0.5	>98	92
11	**E**	0.5	CH_2Cl_2	0.5	>98	94
12	**E**	0.1	PhMe	2	>98	97
13	**E**	0.05	PhMe	10	>98	96
14	**E**	0.02	PhMe	10	83	72

[a]Reactions were carried out using 0.2 mmol of **5a** and 0.22 mmol of **4a**. [b]Conversion was determined by ^{1}H NMR spectroscopy. [c]Enantiomeric excess measured after halogenation (see Supporting Information).

possessing the *N*,*N*-dimethylated cyclohexanediamine unit, reduction in steric bulk on the distal thiosquaramide nitrogen corresponded with higher ee for the Michael addition product (entries 1–3). Of the piperidine containing thiosquaramides

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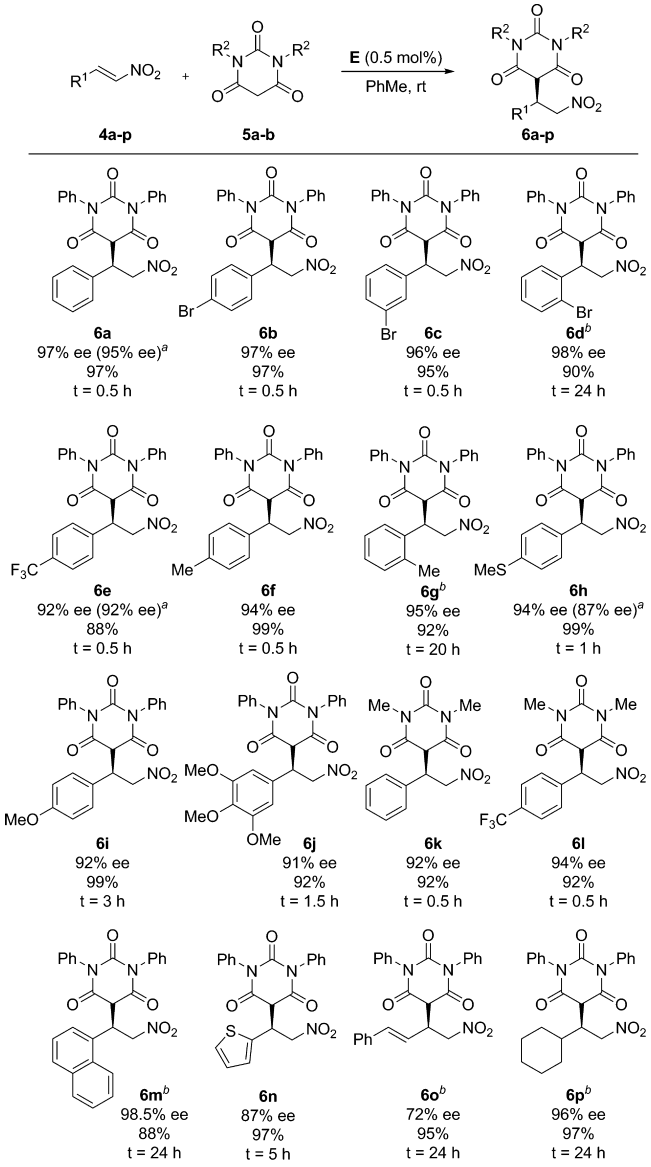
Chart 1. Conjugate Addition of Barbituric Acids to Nitroolefins



All reactions were carried out using 0.22 mmol of nitroolefin and 0.2 mmol of barbituric acid, and yields given are of isolated products. Enantiomeric excess was determined after chlorination, and the absolute stereochemistry shown is tentative, based on the crystal structure of **7f** (see Figure 4 and Supporting Information, including the Crystallographic Information File, for further details). [a]Enantiomeric excesses in parentheses correspond to reactions carried out with squaramide catalyst **F**. [b]5 mol% of the catalyst was used.

examined, the benzyl-substituted catalyst performed better than the one possessing a phenethyl unit (entries 4 and 5). Catalyst **F**, the oxo-analogue of **E**, was also effective, but gave lower enantioselectivity (entries 5 and 6). The seemingly small difference in ee observed with catalysts **E** and **F** (97% vs 95%) corresponds to selectivity ratios of 70:1 and 40:1, respectively.[23] Further screening of conditions showed thiosquaramide **E** to afford excellent yields and high enantioselectivities in all solvents examined except methanol, and the optimal solvent was found to be toluene. No reaction took place in the absence of a catalyst. Further reduction of catalyst loading to 0.1 mol% increased the reaction time only slightly, from 0.5 to 2 h, with

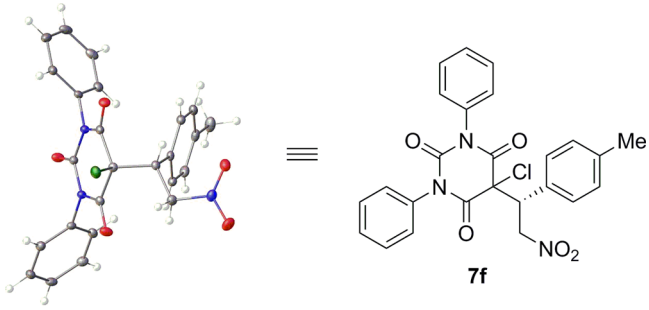


Figure 4. X-ray crystal structure of a chlorinated barbiturate.

no effect on ee. Even at a catalyst loading of 0.05 mol%, the reaction proceeded smoothly, going to full conversion within 10 h, with essentially no diminution in ee. The reaction worked even when the catalyst level was reduced to 0.02 mol%, but gave the product in 72% ee. The conjugate addition can also be carried out on gram-scale, affording 1.65 g of the product in 96% yield and 96.5% ee. Importantly, nearly all of these catalyzed reactions, as well as those shown Chart 1, were carried out without special precautions, under an air atmosphere and using reagent grade solvents right out of a bottle.[24]

The scope of this thiosquaramide catalyzed conjugate addition of barbiturates was examined next. Different combinations of nitroolefins and *N,N′*-disubstituted barbituric acids were reacted in the presence of 0.5 mol% of catalyst **E** (Chart 1). The reactions gave high yields and high enantioselectivities for most of the reactants examined.[25] Brominated nitrostyrenes gave excellent results, although the rate of the reaction was considerably slower for the substrate giving **6d**, presumably due to the steric hindrance caused by the ortho-substituent, necessitating higher catalyst loading (5 mol%). A similar effect on rate was observed with other hindered substrates, and with alkenyl and alkyl substituted nitroalkenes. For comparison purposes, the corresponding squaramide (**F**) was employed for the catalysis of two additional reactions, under otherwise identical conditions (**6e** and **6h**, enantiomeric excess given in parentheses). The absolute stereochemistry of **6f**, and by analogy all other conjugate addition products, was determined by X-ray crystallography of its chlorination product **7f** (Figure 4).

In conclusion, we have developed a general method for the synthesis of chiral thiosquaramides, a class of bifunctional catalysts not previously described in the literature. Thiosquaramides can be prepared in only three steps from commercially available materials, and they are more acidic and significantly more soluble in nonpolar solvents than their "oxo"-squaramide counterparts. Thiosquaramides are excellent catalysts for the unreported, enantioselective conjugate addition reaction of the barbituric acid pharmacaphore to nitroalkenes, delivering the chiral barbiturate derivatives in high yields and high enantioselectivities, even with catalyst loadings as low as 0.05 mol%.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b01115.

X-ray crystallographic data for thiosquaramide **A** (CIF)
X-ray crystallographic data for **7f** (CIF)
Experimental procedures and detailed characterization data of all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) For selected pioneering examples of enantioselective hydrogen-bond donor catalysis, see: (a) Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 4901. (b) Wenzel, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 12964. (c) Huang, Y.; Unni, A. K.; Thadani, A. N.; Rawal, V. H. *Nature* **2003**, *424*, 146. (d) Nugent, B. M.; Yoder, R. A.; Johnston, J. N. *J. Am. Chem. Soc.* **2004**, *126*, 3418.

(2) For reviews of hydrogen-bond donor catalysis, see: (a) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713. (b) *Hydrogen Bonding in Organic Synthesis*; Pihko, P. M., Ed.; Wiley-VCH: Weinheim, 2009. (c) Türkmen, Y. E.; Zhu, Y.; Rawal, V. H. Brønsted Acids In *Comprehensive Enantioselective Organocatalysis*; Dalko, P. I., Ed.; Wiley-VCH: Weinheim, 2013; Vol. *2*, Chapter 10.

(3) For reviews of bifunctional thiourea catalysis, see: (a) Takemoto, Y. *Chem. Pharm. Bull.* **2010**, *58*, 593. (b) Siau, W.-Y.; Wang, J. *Catal. Sci. Technol.* **2011**, *1*, 1298.

(4) For early examples of thiourea-based bifunctional catalysis, see: (a) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672. (b) Yoon, T.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2005**, *44*, 466.

(5) For the first applications of squaramides as asymmetric organocatalysts, see: (a) Malerich, J. P.; Hagihara, K.; Rawal, V. H. *J. Am. Chem. Soc.* **2008**, *130*, 14416. (b) Lee, J. W.; Ryu, T. H.; Oh, J. S.; Bae, H. Y.; Jang, H. B.; Song, C. E. *Chem. Commun.* **2009**, 7224. (c) Zhu, Y.; Malerich, J. P.; Rawal, V. H. *Angew. Chem., Int. Ed.* **2010**, *49*, 153.

(6) For selected recent applications of squaramides, see: (a) Albrecht, L.; Dickmeiss, G.; Acosta, F. C.; Rodríguez-Escrich, C.; Davis, R. L.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2012**, *134*, 2543. (b) Yang, K. S.; Nibbs, A. E.; Türkmen, Y. E.; Rawal, V. H. *J. Am. Chem. Soc.* **2013**, *135*, 16050. (c) Manoni, F.; Connon, S. J. *Angew. Chem., Int. Ed.* **2014**, *53*, 2628.

(7) (a) Aciro, C.; Jones, L. H.; Storer, R. I. *Chem. Soc. Rev.* **2011**, *40*, 2330. (b) Alemán, J.; Parra, A.; Jiang, H.; Jørgensen, K. A. *Chem. - Eur. J.* **2011**, *17*, 6890. (c) Auvil, T. J.; Schafer, A. G.; Mattson, A. E. *Eur. J. Org. Chem.* **2014**, *2014*, 2633. (d) Chauhan, P.; Mahajan, S.; Kaya, U.; Hack, D.; Enders, D. *Adv. Synth. Catal.* **2015**, *357*, 253.

(8) (a) Portell, A.; Barbas, R.; Braga, D.; Polito, M.; Puigjaner, C.; Prohens, R. *CrystEngComm* **2009**, *11*, 52. (b) Prohens, R.; Portell, A.; Alcobé, X. *Cryst. Growth Des.* **2012**, *12*, 4548. (c) Portell, A.; Font-Bardia, M.; Bauzá, A.; Frontera, A.; Prohens, R. *Cryst. Growth Des.* **2014**, *14*, 2578. (d) Portell, A.; Bardia-Font, M.; Bauzá, A.; Frontera, A.; Prohens, R. *CrystEngComm* **2016**, *18*, 6437.

(9) Ladder arrangement was also observed for the chiral, bifunctional squaramide we had examined (see ref 5a). A reconstructed image from the CIF file (Cambridge Structural Database Refcode: NOLRIQ; CCDC No. 712821) from ref 5a is included in the Supporting Information.

(10) The synthesis of achiral thiosquaramides was reported recently: Busschaert, N.; Elmes, R. B. P.; Czech, D. D.; Wu, X.; Kirby, I. L.; Peck, E. M.; Hendzel, K. D.; Shaw, S. K.; Chan, B.; Smith, B. D.; Jolliffe, K. A.; Gale, P. A. *Chem. Sci.* **2014**, *5*, 3617.

(11) Studies on pK_a values of thioureas and squaramides: (a) Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456. (b) Bordwell, F. G.; Algrim, D. J.; Harrelson, J. A. *J. Am. Chem. Soc.* **1988**, *110*, 5903. (c) Bordwell, F. G.; Ji, G. Z. *J. Am. Chem. Soc.* **1991**, *113*, 8398. (d) Li, X.; Deng, H.; Zhang, B.; Li, J.; Zhang, L.; Luo, S.; Cheng, J. − P. *Chem. - Eur. J.* **2010**, *16*, 450. (e) Jakab, G.; Tancon, C.; Zhang, Z.; Lippert, K. M.; Schreiner, P. R. *Org. Lett.* **2012**, *14*, 1724. (f) Ni, X.; Li, X.; Wang, Z.; Cheng, J. − P. *Org. Lett.* **2014**, *16*, 1786. (g) See also ref 7..

(12) Increased acidity of a catalyst has been found to correlate with increased activity and capability. See, inter alia: (a) Wittkopp, A.; Schreiner, P. R. *Chem. - Eur. J.* **2003**, *9*, 407. (b) Jensen, K. H.; Sigman, M. S. *Angew. Chem., Int. Ed.* **2007**, *46*, 4748. (c) Jensen, K. H.; Sigman, M. S. *J. Org. Chem.* **2010**, *75*, 7194. (d) Parmar, D.; Sugiono, E.; Raja, S.; Rueping, M. *Chem. Rev.* **2014**, *114*, 9047.

(13) For a computation study, see: Lu, T.; Wheeler, S. E. *Chem. - Eur. J.* **2013**, *19*, 15141.

(14) (a) Gulliya, K. S. Anti-Cancer Uses for Barbituric Acid Analogs. U.S. Patent 5674870A, Oct 7, 1997. (b) Gulliya, K. S. Uses for Barbituric Acid Analogs. U.S. Patent 5869494A, Feb 9, 1999. (c) Kaur, M.; Verma, P.; Singh, P. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3054. (d) Dhorajiya, B. D.; Ibrahim, A. S.; Badria, F. A.; Dholakiya, B. Z. *Med. Chem. Res.* **2014**, *23*, 839. (e) Penthala, N. R.; Ketkar, A.; Sekhar, K. R.; Freeman, M. L.; Eoff, R. L.; Balusu, R.; Crooks, P. A. *Bioorg. Med. Chem.* **2015**, *23*, 7226.

(15) To the best of our knowledge, the only use of barbituric acids as nucleophiles in asymmetric catalysis has been in palladium-catalyzed allylation reactions: (a) Brunner, H.; Deml, I.; Dirnberger, W.; Nuber, B.; Reißer, W. *Eur. J. Inorg. Chem.* **1998**, *1998*, 43. (b) Brunner, H.; Deml, I.; Dirnberger, W.; Ittner, K.-P.; Reißer, W.; Zimmermann, M. *Eur. J. Inorg. Chem.* **1999**, *1999*, 51. (c) Trost, B. M.; Schroeder, G. M. *J. Org. Chem.* **2000**, *65*, 1569.

(16) For reports of thionation of squaric acid derivatives, see: (a) Eggerding, D.; West, R. *J. Org. Chem.* **1976**, *41*, 3904. (b) Frauenhoff, G. R.; Takusagawa, F.; Busch, D. H. *Inorg. Chem.* **1992**, *31*, 4002. (c) Müller, M.; Heileman, M. J.; Moore, H. W.; Schaumann, E.; Adiwidjaja, G. *Synthesis* **1997**, *1997*, 50.

(17) Monothiosquarate can be prepared by limiting the amount of the thionating agent. Studies on the synthesis and catalyst properties of monothiosquaramides will be reported in due course.

(18) Using the method of overlapping indicators (Bordwell's method), the pK_a of dithiosquaramide **A** was determined to be 13.96, whereas that for the corresponding dioxosquaramide was 18.88.

(19) Please see Supporting Information for a summary of our extensive studies on pK_a determination of numerous squaramides and thiosquaramides.

(20) Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X. N.; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 119.

(21) Calculated for a single molecule in vacuum: *Spartan '08*, Wavefunction, Inc., Irvine, CA.

(22) Similar to the situation with thioureas, in the absence of other hydrogen bond acceptors, thiosquaramides crystallize in a head-to-tail arrangement with each thiosquaramide unit perpendicular to the next unit. See: Custelcean, R. *Chem. Commun.* **2008**, 295.

(23) Please see Supporting Information for a comparison with relevant thioureas and squaramides.

(24) Please see Supporting Information for a complete optimization table.

(25) The conjugate addition products have long retention times and broad peaks when examined by chiral HPLC, presumably a result of their high acidity and the presence of significant enol content. The chloro and bromo derivatives of the products (cf., **7f**) form in quantitative yield upon treatment with NCS or NBS, elute quickly, and give sharper peaks.

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