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Highly Enantioselective, Hydrogen-Bond-Donor Catalyzed Additions to Oxetanes

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Supporting Information Placeholder

ABSTRACT: A precisely designed chiral squaramide derivative is shown to promote the highly enantioselective addition of trimethylsilyl bromide (TMSBr) to a broad variety of 3-substituted and 3,3-disubstituted oxetanes. The reaction provides direct and general access to synthetically valuable 1,3-bromohydrin building blocks from easily accessed achiral precursors. The products are readily elaborated both by nucleophilic substitution and through transition-metal-catalyzed cross-coupling reactions. The enantioselective catalytic oxetane ring opening was employed as part of a 3-step, gram-scale synthesis of pretomanid, a recently-approved medication for the treatment of multi-drug-resistant tuberculosis. Heavy-atom kinetic isotope effect (KIE) studies are consistent with enantiodetermining delivery of bromide from the H-bond-donor (HBD) catalyst to the activated oxetane. While the nucleophilicity of the bromide ion is expected to be attenuated by association to the HBD, overall rate acceleration is achieved by enhancement of Lewis acidity of the TMSBr reagent through anion-abstraction.

Chiral anion-binding catalysis has emerged as a powerful strategy for enantioselective additions to cationic intermediates through their non-covalent association to catalyst-bound spectator anions.[1,2] In most applications identified to date, the chiral catalyst-anion complex mediates stereoinduction in the addition of an external nucleophile (Figure 1A). An interesting variation to the anion-binding catalysis concept arises when the catalyst-bound anion also acts as the nucleophile in the enantiodetermining bond construction.[3,4] At least in principle, such an approach can provide more precise control over stereoselectivity through specific association of both nucleophile and electrophile to the chiral catalyst. However, H-bonding from the catalyst would also be expected to attenuate the reactivity of the nucleophile relative to an uncatalyzed, racemic pathway.[5] This fundamental reactivity challenge can be circumvented if the catalyst also promotes the generation of the reactive ion-pair, as demonstrated elegantly by Gouverneur[3f,g] in the specific context of phase-transfer reactions of alkali metal fluorides (Figure 1B). Following the recent discovery that H-bond donors such as chiral squaramides can activate silyl triflates via anion binding to promote enantioselective transformations,[6] we were drawn to an alternative and possibly general approach to catalysis of nucleophile delivery by applying the anion-binding principle to activation of Lewis acids bearing nucleophilic counterions. Anion abstraction from the promoter should result in enhanced Lewis acidity, providing a general platform to access highly-reactive, cationic, electrophilic intermediates ion paired with a catalyst-bound nucleophilic anion (Figure 1C).

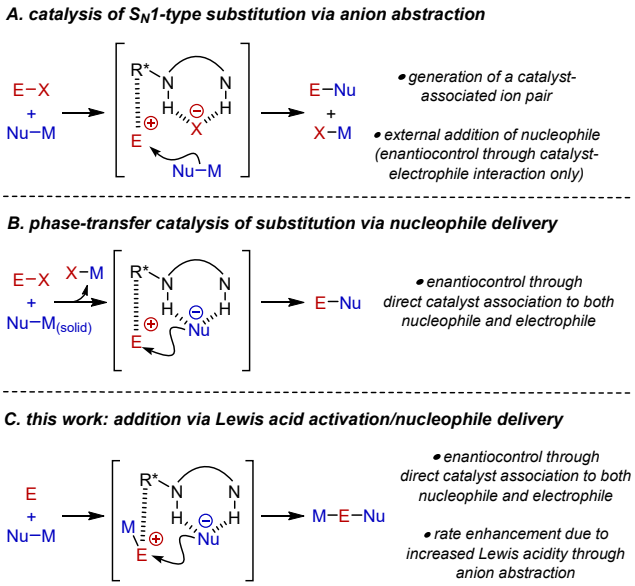

Figure 1. (A) Conventional approach to anion-binding catalysis in which the catalyst binds a spectator anion. (B) Alternative reactive mode in anion-binding catalysis involving delivery of the bound anionic nucleophile to a cationic electrophile. Hydrogen bonding attenuates the reactivity of the nucleophile, but rate acceleration has been achieved via phase-transfer catalysis. (C) Catalyst-promoted ionization of an anionic nucleophile from a neutral Lewis acid-nucleophile complex allows for H-bond donor catalyzed anion delivery.

We chose to explore the anion-binding effect on nucleophile-bearing Lewis acids in the context of additions of TMSBr to prochiral oxetanes (Fig. 2A). Enantioselective

ring-opening of 3-substituted oxetanes provides a route to valuable 3-carbon chiral building blocks from simple, synthetically-accessible precursors.[7] Several examples of enantioselective openings of 3-susbtituted oxetanes with intramolecular nucleophiles have been identified.[8,9] However, more generally applicable highly enantioselective reactions involving intermolecular nucleophilic addition are limited to two pioneering examples from Sun and coworkers involving chiral phosphoric acid-catalyzed addition of mercaptobenzothiazole and HCl.[10] Here we report the successful application of a chiral squaramide catalyst to promote the ring-opening addition of TMSBr to prochiral oxetane substrates with unprecedented substrate scope.

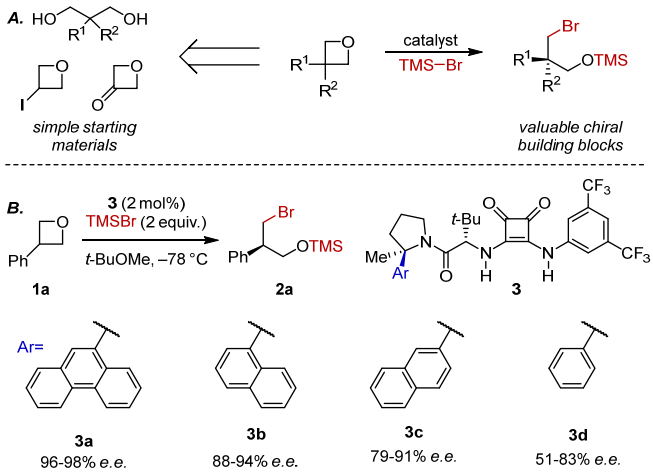

Figure 2. A) Model reaction: enantioselective opening of oxetanes with TMSBr. B) Catalyst screening data for a series of arylpyrrolidino squaramides.

The addition of TMSBr to 3-phenyloxetane (**1a**) was selected as a model reaction.[11] Squaramide hydrogen-bond-donor catalysts[6,12] bearing a 2-arylpyrrolidino amide were identified as particularly effective, with the the aryl substituent having a marked effect on enantioselectivity and reproducibility (Fig. 2B). Systematic reaction and catalyst development (Fig. S1–S5) led to the identification of 9-phenanthryl squaramide **3a** as the optimal catalyst for the synthesis of silylated bromohydrin **2a**, catalyzing its formation in quantitative yields and with 96-98% e.e. over >20 runs.[13]

Squaramide **3a** was found to catalyze the opening of a broad range of 3-subsituted and 3,3-disubstituted oxetanes in high levels of e.e. (Figure 3). With 3-aryl oxetanes, both electron donating and withdrawing substituents could be introduced, with only ortho substitution impacting enantioselectivity adversely (**1a–h**). Weakly Lewis basic functional groups such as nitriles (**1f**) and esters (**1g**) had no deleterious effect on the reaction, and aryl ether spectator groups remained intact (**1h**). Oxetanes bearing protected alcohol and amine functionality (**1i–m**) as well as simple saturated alkyl groups (**1n-p**) all underwent reaction with high enantioselectivity. The reaction could even be extended successfully to certain 3,3'-disubstituted oxetane substrates, which underwent stereoselective ring opening to provide products bearing fully substituted stereocenters (**1q–v**) with moderate-to-high enantioselectivity.

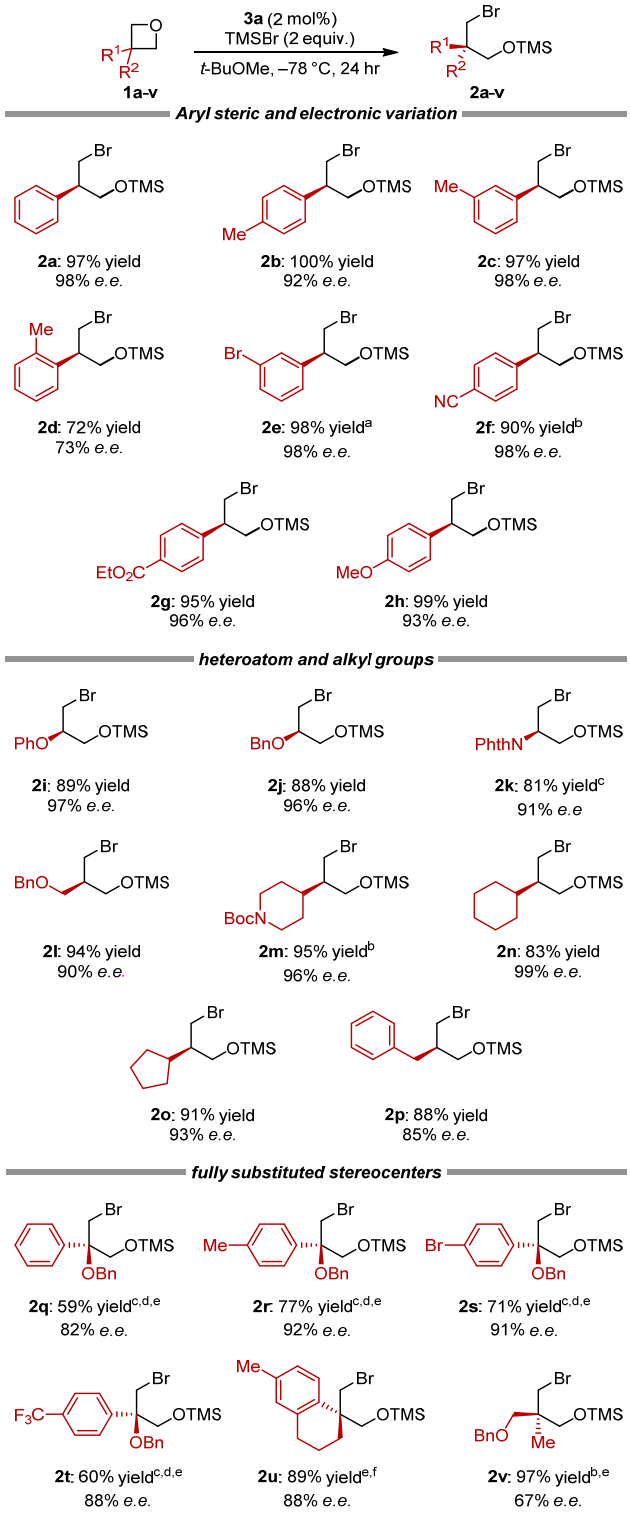

Figure 3. Isolated yield and enantiomeric enrichments measured for the asymmetric oxetane opening at 0.4 mmol scale. See SI for details on methods for e.e. determination, reproducibility studies, and the assignment of absolute configuration. [a] Isolated as a 12.5 : 1 ratio of ROTMS to ROH product. [b] 48-hr reaction time. [c] –25 °C. [d] 72-hr reaction time. [e] 7.5 mol% **3a**. [f] –65 °C.

Alkyl bromide **2a** was examined as a model substrate for potential product derivatizations (Fig. 4A) and was found to undergo facile substitution with azide, cyanide, and thiophenolate nucleophiles. Recent advances in transition-metal-catalyzed cross-coupling chemistry[14] provide further opportunities for product elaborations; for example, we found that **2a** engaged effectively in cobalt-catalyzed arylations.[15] Moreover, the polarity of the electrophilic alkyl bromide could be inverted either by copper-catalyzed borylation,[16] or through metal-halogen exchange, allowing **2a** to function as the nucleophilic partner in a C(sp^2)–C(sp^3) cross coupling.[17] Overall, the diverse range of products that can be accessed directly from **2a** illustrates the synthetic versatility of these chiral bromohydrin building blocks.

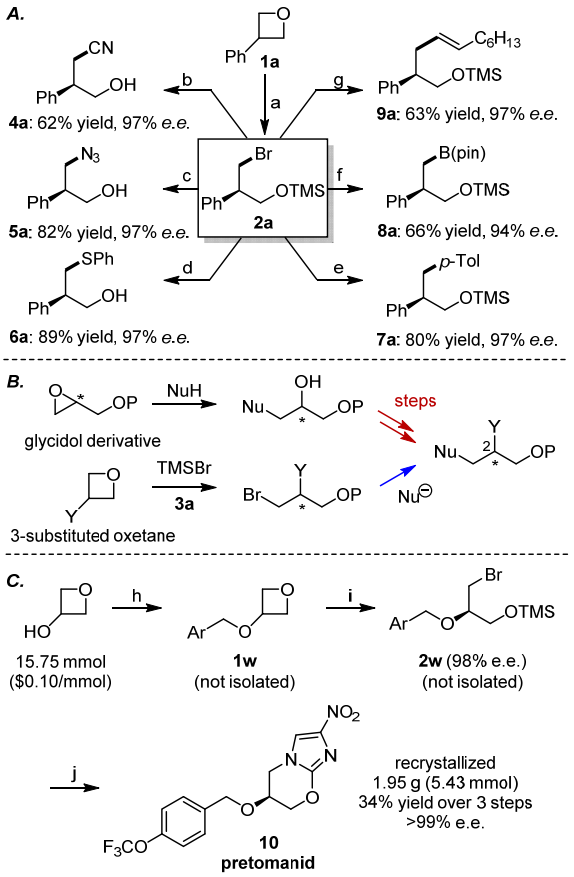

Figure 4. A) Product elaborations: all reported yields are for the entire sequence of reactions starting from **1a** a) standard reaction conditions with 0.4 mmol **1a;** b) NaCN; c) NaN_3; d) NaSPh; e) p-TolMgBr, $Co(acac)_3$, TMEDA; f) B_2Pin_2, CuCl, Xantphos, *t*-BuOK; g) NaI in MeCN then solvent swap to Et_2O, *t*-BuLi, $ZnCl_2$, $Pd(dppf)Cl_2$, R-I. See SI for detailed procedures. B) Glycidol- and oxetane-based strategies to C3 chiral derivatives. C) Gram-scale synthesis of pretomanid: Ar = 4-(trifluoromethoxy)phenyl h) 4-(trifluormethoxy)benzyl bromide (1.2 equiv.), NaH (1.2 equiv.), 2-Me-THF (1.0 M), 60 °C, 12 hr; i) **3a** (2 mol%), TMSBr (1.1 equiv.), *t*-BuOMe (0.25 M), –80 °C, 24 hr; j) 2-chloro-4-nitroimidazole (2.0 equiv.), Et_3N (2.1 equiv.), NaI (1.0 equiv.) DMF (0.25 M), 115 °C, 24 hr, then cool to 23 °C and add MeOH (1.0 M) and NaOH (5.0 equiv.), 30 min.

The oxetane-opening methodology presents an interesting alternative to well-established synthetic strategies for accessing three-carbon chiral building blocks based on glycidol or epichlorohydrin derivatives (Figure 4B).[18] In particular, the identity of the C2 group can be set in the prochiral oxetane substrate, thereby avoiding potentially multi-step late-stage functional-group manipulations required in routes involving epoxide ring-opening. This advantage is illustrated in the synthesis of the recently approved tuberculosis drug pretomanid[19] (Figure 4C), which was prepared previously by Reider, Sorensen and coworkers in an elegant 5-step route from enantioenriched (*R*)-3-chloro-1,2-propanediol.[20a] Readily accessible oxetane **1w** underwent highly enantioselective ring-opening to yield TMS-protected bromohydrin **2w** in 98% e.e.[21] Gratifyingly, 2-chloro-4-nitroimadzole, which was identified in the Reider and Sorensen synthesis as a non-explosive alternative to 2,4-dinitroimidazole,[20a] underwent alkylation by **2w** with complete regioselectivity followed by S_NAr annulation to yield the desired product. Both intermediates were formed in sufficient purity to be carried forward without purification, and only a recrystallization of the final product was required to access analytically-pure pretomanid (**10**) in >99% e.e. The synthetic route avoids protecting-group manipulation steps and provides access to pretomanid in just 3 steps.

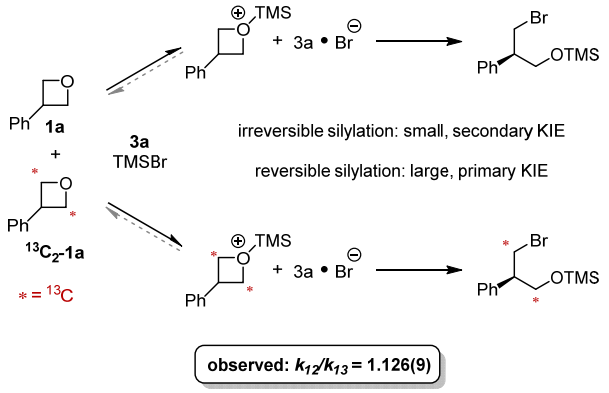

Figure 5. One-pot competition KIE between **1a** and $^{13}C_2$-**1a**. A primary KIE of 1.126(9) was measured, indicating that oxetane silylation must be reversible, supporting enantiodetermining bromide delivery.

As an initial step toward establishing the basis for exquisite enantiocontrol in oxetane ring-opening reactions with squaramide **3a**, we endeavored to determine whether bromide delivery was indeed the enantiodetermining step as proposed at the outset of reaction development. To address this question, the ^{12}C / ^{13}C KIE at the site of bromide attack was determined through analysis of starting material recovered at partial conversion from a one-pot competition between doubly labeled oxetane $^{13}C_2$-**1a** and unlabeled isotopologue **1a** (Fig. 5).[22] If bromide-promoted ring opening were substrate-committing, and thus, enantiodetermining, a primary KIE consistent with C–O bond cleavage would be expected. In contrast, if a step preceding ring opening such as oxetane silylation were irreversible then only a small, secondary KIE would be anticipated. Irreversible silylation

would not necessarily preclude enantiodetermining bromide delivery, but it would allow for the possibility that silylation of **1a** was enantiodetermining.[23] Subjection of a mixture of **1a** and $^{13}C_2$-**1a** to the catalytic reaction conditions led to the observation of a large, primary KIE (k_{12}/k_{13} = 1.126(9)), fully consistent with reversible silylation and enantioselectivity-determining bromide delivery (see SI for full details of the KIE studies).

In conclusion, the chiral squaramide-catalyzed addition of TMSBr to 3-aryl, 3-alkyl, and 3-heteroatom substituted oxetanes as well as certain 3,3-disubstituted oxetanes provides a general enantioselective synthesis of protected 1,3-bromohydrin derivatives. The products of these reactions can be elaborated through a variety of nucleophilic substitution reactions, and the utility of the method is illustrated in the 3-step, gram-scale synthesis of the TB drug pretomanid. Heavy-atom KIE studies are consistent with enantiodetermining bromide delivery by the catalyst to an activated oxetane. This strategy overcomes the intrinsic deactivation of nucleophiles that accompanies association with an H-bond donor and holds promise as a broadly applicable approach to asymmetric catalysis of addition reactions.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:

Experimental and characterization data of catalyst and substrate syntheses, procedures and analytical data for enantioselective reactions, procedure and analytical data for product elaborations, details of KIE experiment (PDF)

Crystallographic data for **26a** (derivative of **2a**) (CIF)

Crystallographic data for **26o** (derivative of **2o**) (CIF)

Crystallographic data for **2t** (CIF)

Crystallographic data for **26u** (derivative of **2u**) (CIF)

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Author Contributions

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) Doyle, A. G.; Jacobsen, E. N. Small-molecule H-bond donors in asymmetric catalysis. *Chem. Rev.* **2007,** *107,* 5713-5743. (b) Brak, K.; Jacobsen, E. N. Asymmetric ion-pairing catalysis. *Angew. Chem., Int. Ed.* **2013,** *52,* 534-561.

(2) Chiral Brønsted acids have also been employed effectively to generate analogous chiral ion-pair intermediates through association of protonated species to the conjugate base of the chiral acid catalyst. For a recent reviews see ref. 1b and: Parmar, D.; Sugiono, E.; Raja, S.; Rueping, M. Complete field guide to asymmetric BINOL-phosphate derived Bronsted acid and metal catalysis: history and classification by mode of activation; Bronsted acidity, hydrogen bonding, ion pairing, and metal phosphates. *Chem. Rev.* **2014,** *114,* 9047-9153.

(3) (a) Zuend, S. J.; Coughlin, M. P.; Lalonde, M. P.; Jacobsen, E. N. Scaleable catalytic asymmetric Strecker syntheses of unnatural α-amino acids. *Nature* **2009,** *461,* 968-970. (b) Zuend, S. J.; Jacobsen, E. N.; Mechanism of amido-thiourea catalyzed enantioselective imine hydrocyanation: transition state stabilization via multiple non-covalent interactions. *J. Am. Chem. Soc.* **2009,** *131,* 15358-15374. (c) Birrell, J. A.; Desrosiers, J.-N.; Jacobsen, E. N. Enantioselective acylation of silyl ketene acetals through fluoride anion-binding catalysis. *J. Am. Chem. Soc.* **2011,** *133,* 13872-13875. (d) De, C. K.; Mittal, N.; Seidel, D. A dual-catalysis approach to the asymmetric Steglich rearrangement and catalytic enantioselective addition of *O*-acylated azalactones to isoquinolines. *J. Am. Chem. Soc.* **2011,** *133,* 16802-16805. (e) Jarvis, C. L.; Hirschi, J. S.; Vetticatt, M. J.; Seidel, D. Catalytic enantioselective synthesis of lactams through formal [4+2] cycloaddition of imines with homophthalic anhydride. *Angew. Chem., Int. Ed.* **2017,** *56,* 2670-2674. (f) Pupo, G.; Ibba, F.; Ascough, D. M. H.; Vicini, A. C.; Ricci, P.; Christensen, K. E.; Pfeifer, L.; Morphy, J. R.; Brown, J. M.; Paton, R. S.; Gouverneur, V. Asymmetric nucleophilic fluorination under hydrogen bonding phase-transfer catalysis. *Science* **2018,** *360,* 638-642. (g) Pupo, G.; Vicini, A. C.; Ascough, D. M. H.; Ibba, F.; Christensen, K. E.; Thompson, A. L.; Brown, J. M.; Paton, R. S.; Gouverneur, V. Hydrogen bonding phase-transfer catalysis with potassium fluoride: enantioselective synthesis of β-fluoroamines. *J. Am. Chem. Soc.* **2019,** *141,* 2878-2883.

(4) Nucleophilic attack by catalyst-bound anions on neutral electrophiles is frequently proposed in reactions catalyzed by bifunctional hydrogen-bond donors. See ref. 4a and 4b for representative mechanistic studies, and ref. 4c for an example of halide delivery in a hydrochlorinative aziridine opening. (a) Hamza, A.; Schubert, G.; Soos, T.; Papai, I. Theoretical studies on the bifunctionality of chiral thiourea-based organocatalysts: competing routes to C-C bond formation. *J. Am. Chem. Soc.* **2006,** *128,* 13151-13160. (b) Izzo, J. A.; Myshchuk, Y.; Hirschi, J. S.; Vetticatt, M. J. Transition state analysis of an enantioselective Michael addition by a bifunctional thiourea organocatalyst. *Org. & Biomol. Chem.* **2019,** *17,* 3934-3939. (c) Mita, T.; Jacobsen, E. N. Bifunctional asymmetric catalysis with hydrogen chloride: enantioselective ring opening of aziridines catalyzed by a phosphinothiourea. *Synlett* **2009,** *10,* 1680-1684.

(5) Anslyn, E. V.; Dougherty, D. A. *Modern Physical Organic Chemistry;* University Science Books: Sausalito, CA, 2006: pp 643-646.

(6) (a) Banik, S. M.; Levina, A.; Hyde, A. M.; Jacobsen, E. N. Lewis acid enhancement by hydrogen-bond donors for asymmetric catalysis. *Science* **2017,** *10,* 761-764. (b) Wendlandt, A. E.; Vangal, P.; Jacobsen, E. N. Quaternary stereocenters via an enantioconvergent catalytic S_N1 reaction. *Nature* **2018,** *556,* 447-451.

(7) (a) Burkhard, J. A.; Wuitschik, G.; Rogers-Evans, M.; Muller, K.; Carreira, E. M. Oxetanes as versatile elements in drug discovery and synthesis. *Angew. Chem., Int. Ed.* **2010,** *49,* 9052-9067. (b) Wuitschik, G.; Carreira, E. M.; Wagner, B.; Fischer, H.; Parilla, I.; Schuler, F.; Rogers-Evans, M.; Müller, K. Oxetanes in drug discovery: structural and synthetic insights. *J. Med. Chem.* **2010,** *53,* 3227-3246. (c) Ahmad, S.; Yousaf, M.; Mansha, A.; Rasool, N.; Zahoor, A. F.; Hafeez, F.; Rizvi, S. M. A. Ring-opening reactions of oxetanes: a review of methodology development and synthetic applications. *Synth. Comm.* **2016,** *46,* 1397-1416. (d) Bull, J. A.; Croft, R. A.; Davis, O. A.; Doran, R.; Morgan, K. F. Oxetanes: recent advances in synthesis, reactivity, and medicinal chemistry. *Chem. Rev.* **2016,** *116,* 12150-12233.

(8) (a) Loy, R. N.; Jacobsen, E. N. Enantioselective intramolecular openings of oxetanes catalyzed by (salen)Co(III) complexes: access to enantioenriched tetrahydrofurans. *J. Am. Chem. Soc.* **2009,** *131,* 2786-2787. (b) Chen, Z.; Wang, B.; Wang, Z.; Zhu, G.; Sun, J. Complex bioactive alkaloid-type polycycles through efficient catalytic asymmetric multicomponent aza-Diels-Alder reactions of indoles with oxetane as directing group. *Angew. Chem., Int. Ed.* **2013,** *52,* 2027-2031. (c) Chen, Z.; Wang, Z.; Sun, J. Catalytic enantioselective synthesis of tetrahydroisoquinolines and their analogues bearing a C4 stereocenter: formal synthesis of (+)-(8*S*,13*R*)-cyclocelabenzine. *Chem. Eur. J.* **2013,** *19,* 8426-8430. (d) Wang, Z.; Chen, Z.; Sun, J. Catalytic asymmetric nucleophilic openings of 3-substituted oxetanes. *Org. & Biomol. Chem.* **2014,** *12,* 6028-6032. (e) Yang, W.; Sun, J. Organocatalytic enantioselective synthesis of 1,4-dioxanes and other oxa-heterocycles by oxetane desymmetrization. *Angew. Chem., Int. Ed.* **2016,** *55,* 1868-1871. (f) Zhang, R.; Guo, W.; Duan, M.; Houk, K. N.; Sun, J. Asymmetric desymmetrization of oxetanes for the synthesis of chiral tetrahydrothiophenes and tetrahydroselenophenes. *Angew. Chem., Int. Ed.* **2019,** *58,* 18055-18060. An enantioselective ring expansion of 3-substituted oxetanes has also been developed: (g) Yin, Q.; You, S-L. Asymmetric chlorination/ring expansion for the synthesis of α-quaternary cycloalkanones. *Org. Lett.* **2014,** *14,* 1810-1813.

(9) Several enantioselective reactions have also been developed that employ 2-substituted oxetanes as substrates for ring expansion: (a) Nozaki, H.; Moriuti, S.; Takaya, H.; Noyori, R. Asymmetric induction in carbenoid reactions by means of a dissymmetric copper chelate. *Tet. Lett.* **1966,** *7,* 5239-5244. (b) Nozaki, H.; Takaya, H.; Moritui, S.; Noyori, R. Homogeneous catalysis in the decomposition of diazo compounds by copper chelates: asymmetric carbenoid reactions. *Tetrahedron* **1968,** *24,* 3655-3669. (c) Ito, K.; Katsuki, T. Asymmetric carbene C-O insertion reaction using optically active bipyridine-copper complex as a catalyst. Ring expansion of oxetanes to tetrahydrofurans. *Chem. Lett.* **1994,** *23,* 1857-1860. (d) Ito, K.; Yoshitake, M.; Katsuki, T. Enantioselective synthesis of *trans*-whisky lactone by using newly developed asymmetric ring expansion reaction of oxetane as a key step. *Chem. Lett.* **1995,** *24,* 1027-1028. (e) Ito, K.; Yoshitake, M.; Katsuki, T. Enantiospecific ring expansion of oxetanes: stereoselective synthesis of tetrahydrofurans. *Heterocycles* **1996,** *42,* 305-317. (f) Ito, K.; Fukuda, T.; Katsuki, T. A new methodology for efficient construction of 2,7-dioxabicyclo[3.3.0]octane derivatives. *Synlett* **1997,** *4,* 387-389. (g) Ito, K.; Fukuda, T.; Katsuki, T. A new enantiospecific approach to the bislactone structure: formal syntheses of (+)-avenaciolide and (-)-isoavenaciolide. *Heterocycles* **1997,** *46,* 401-411. (h) Lo, M. M.-C.; Fu, G. C. Applications of planar-chiral heterocycles in enantioselective catalysis: Cu(I)/bisazaferrocene-catalyzed asymmetric expansion of oxetanes to tetrahydrofurans. *Tetrahedron* **2001,** *57,* 2621-2634. (i) Guo, B.; Schwarzwalder, G.; Njardarson, J. T. Catalytic ring expansion of vinyl oxetanes: asymmetric synthesis of dihydropyrans using chiral counterion catalysis. *Angew. Chem., Int. Ed.* **2012,** *51,* 5675-5678.

(10) (a) Wang, Z.; Chen, Z.; Sun, J. Catalytic enantioselective intermolecular desymmetrization of 3-substituted oxetanes. *Angew. Chem., Int. Ed.* **2013,** *52,* 6685-6688. (b) Yang, W.; Wang, Z.; Sun, J. Enantioselective oxetane ring opening with chloride: unusual use of wet molecular sieves for the controlled release of HCl. *Angew. Chem., Int. Ed.* **2016,** *55,* 6954-6958. For pioneering examples of moderately enantioselective intermolecular oxetane openings with organolithium reagents, see: (c) Mizuno, M.; Kanai, M.; Iida, A.; Tomioka, K. Chiral ligand controlled enantioselective opening of oxirane and oxetane. *Tet. Asymm.* **1996,** *7,* 2483-2484. (d) Mizuno, M.; Kanai, M.; Iida, A.; Tomioka, K. An external chiral ligand controlled enantioselective opening of oxirane and oxetane by organolithiums. *Tetrahedron* **1997,** *53,* 10699-10708.

(11) Kricheldorf, H. R.; Morber, G.; Regel, W. Syntheses of alkyl bromides from ethers and bromotrimethylsilane. *Synthesis* **1981,** *5,* 383-384.

(12) Malerich, J. P.; Hagihara, K.; Rawal, V. H. Chiral squaramide derivatives are excellent hydrogen bond donor catalysts. *J. Am. Chem. Soc.* **2008,** *130,* 14416-14417.

(13) Variability in the e.e. was observed to be catalyst-dependent and traced to the effect of adventious water. The addition of up to 4 mol% of H_2O or other protic additives had little effect on the enantioselectivity of ring opening of **1a** catalyzed by **3a** (Fig. S6 entries 1 and 2, Fig. S7 entry 1), but higher loadings of protic additives led to decreases in enantioselectivity ranging from moderate (Fig. S6 entries 3 and 4, Fig. S7 entry 2) to significant (Fig. S7 entry 3). The effect of catalytic amounts of HBr and the unqiue features that allow **3a** to catalyze the transformation with consistently high levels of e.e. are the subject of ongoing study, and will be discussed in a separate report.

(14) (a) Luh, T-Y.; Leung, M-K.; Wong, K.-T. Transition metal-catalyzed activation of aliphatic C-X bonds in carbon-carbon bond formation. *Chem. Rev.* **2000,** *100,* 3187-3204. (b) Netherton, M. R.; Fu, G. C. Nickel-catalyzed cross-couplings of unactivated alkyl halides and pseudohalides with organometallic compounds. *Adv. Synth. Catal.* **2004,** *346,* 1525-1532. (c) Frisch, A. C.; Beller, M. Catalysts for cross-coupling reactions with non-activated alkyl halides. *Angew. Chem., Int. Ed.* **2004,** *44,* 674-688. (d) Terao, J.; Kambe, N. Transition metal-catalyzed C-C bond formation reactions using alkyl halides. *Bull. Chem. Soc. Jpn.* **2006,** *79,* 663-672. (e) Cahiez, G.; Moyeux, A. Cobalt-catalyzed cross-coupling reactions. *Chem. Rev.* **2010,** *110,* 1435-1462.

(15) Cahiez, G.; Chaboche, C.; Duplais, C.; Moyeux, A. A new efficient catalytic system for the chemoselective cobalt-catalyzed cross-coupling of aryl Grignard reagents with primary and secondary alkyl bromides. *Org. Lett.* **2009,** *11,* 277-280.

(16) Ito, H.; Kubota, K. Copper(I)-catalyzed boryl substitution of unactivated alkyl halides. *Org. Lett.* **2012,** *14,* 890-893.

(17) Jana, R.; Pathak, T. P.; Sigman, M. S. Advances in transition metal (Pd,Ni,Fe)-catalyzed cross-coupling reactions using alkyl-organometallics as reaction partners. *Chem. Rev.* **2011,** *111,* 1417-1492.

(18) (a) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. Catalytic Asymmetric Epoxidation and Kinetic

Resolution: Modified Procedures Including in Situ Derivatization. *J. Am. Chem. Soc.* **1987,** *109,* 5765-5780. (b) Hanson, R. M. The Synthetic Methodology of Nonracemic Glycidol and Related 2,3-Epoxy Alcohols. *Chem. Rev.* **1991,** *91,* 437-475. (c) Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. Asymmetric Catalysis with Water: Efficient Kinetic Resolution of Terminal Epoxides by Means of Catalytic Hydrolysis. *Science* **1997,** *277,* 936-938. (d) Furrow, M. E.; Schaus, S. E.; Jacobsen, E. N. Practical Access to Highly Enantioenriched C-3 Building Blocks via Hydrolytic Kinetic Resolution. *J. Org. Chem.* **1998,** *63,* 6776-6777. (e) Kasai, N.; Suzuki, T.; Furukawa, Y. Chiral C3 epoxides and halohydrins: Their preparation and synthetic application. *J. Mol. Cat. B: Enzymatic* **1998,** *4,* 237-252. (f) Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. Highly Selective Hydrolytic Kinetic Resolution of Terminal Epoxides Catalyzed by Chiral (salen)Co^{III} Complexes. Practical Synthesis of Enantioenriched Terminal Epoxides and 1,2-Diols. *J. Am. Chem. Soc.* **2002,** *124,* 1307-1315. (g) Larrow, J. F.; Hemberger, K. E.; Jasmin, S.; Kabir, H.; Morel, P. Commercialization of the hydrolytic kinetic resolution of racemic epoxides: toward the economical large-scale production of enantiopure epichlorohydrin. *Tet. Asymm.* **2003,** *14,* 3589-3592. (h) Larrow, J. F.; Quigley, P. F. Industrial Applications of the Jacobsen Hydrolytic Kinetic Resolution Technology. In Comprehensive Chirality; Carreira, E. M., Yamamoto, H., Eds.; Elsevier: Amsterdam, 2012; Vol. 9, pp 129–146. (i) Singh, G. S.; Mollet, K.; D'hooghe, M.; De Kimpe, N. Epihalohydrins in Organic Synthesis. *Chem. Rev.* **2013,** *113,* 1441-1498.

(19) TB Alliance: News: FDA Approves New Treatment for Highly Drug-Resistant Forms of Tuberculosis (August 14, 2019). https://www.tballiance.org/news/fda-approves-new-treatment-highly-drug-resistant-forms-tuberculosis (accessed April 11, 2020).

(20) (a) Marsini, M. A.; Reider, P. J.; Sorensen, E. J. A Concise and Convergent Synthesis of PA-824. *J. Org. Chem.* **2010,** *75,* 7479-7482. For other syntheses of pretomanid see: (b) Baker, W. R.; Shaopei, C.; Keeler, E. L. Nitro-[2,1-*b*]imidazopyran Compounds and Antibacterial Uses Thereof. U.S. Patent 6087358, 2000. (c) Orita, A.; Miwa, K.; Otera, J. Integration of Solventless Reaction in a Multi-Step Process: Application to an Efficient Synthesis of PA-824. *Adv. Synth. Catal.* **2007,** *349,* 2136-2144. (d) Thompson, A. M.; Blaser, A.; Anderson, R. F.; Shinde, S. S.; Franzblau, S. G.; Ma, Z.; Denny, W. A.; Palmer, B. D. Synthesis, Reduction Potentials, and Antitubercular Activity of Ring A/B Analogues of the Bioreductive Drug (6*S*)-2-Nitro-6-{[4-(trifluoromethoxy)benzyl]oxy}-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (PA-824). *J. Med. Chem.* **2009,** *52,* 637-645. (e) Thompson, A. M.; O'Connor, P. D.; Marshall, A. J.; Blaser, A.; Yardley, V.; Maes, L.; Gupta, S.; Launay, D.; Braillard, S.; Chatelain, E.; Wan, B.; Franzblau, S. G.; Ma, Z.; Cooper, C. B.; Denny, W. A. Development of (6*R*)-2-Nitro-6-[4-(trifluoromethoxy)phenoxy]-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (DNDI-8219): A New Lead for Visceral Leishmaniasis. *J. Med. Chem.* **2018,** *61,* 2329-2352.

(21) The catalytic reaction was found to slow down on larger scale, but this could be compensated for by increasing the concentration to 0.25 M. The basis for the dependence of rate on reaction scale is related to the effect of adventitious water noted in ref. 13 and will be discussed fully in a separate report.

(22) The one-pot intermolecular competition experiment is the only option that allows accurate and diagnostic determination of the KIE in this system. For a lucid discussion of the applications of intramolecular, one-pot, and two-pot competition KIE experiments see: Simmons, E. M.; Hartwig, J. F. On the Interpretation of Deuterium Kinetic Isotope Effects in C—H Bond Functionalizations by Transition Metal Complexes. *Angew. Chem., Int. Ed.* **2012,** *51,* 3066-3072.

(23) For an example where substrate activation rather than anion delivery is proposed to be enantiodetermining, see ref. 3b.

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