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Dearomatization of Electron-Deficient Nitrogen Heterocycles via Cobalt-Catalyzed Asymmetric Cyclopropanation

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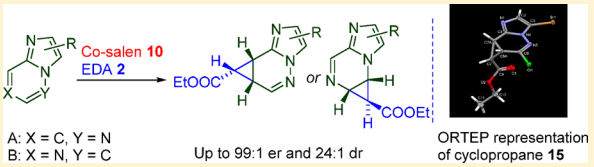
Supporting Information

ABSTRACT: The dearomatization of a series of electron-deficient nitrogen heterocycles has been achieved through a cobalt-catalyzed asymmetric cyclopropanation reaction. This reaction proceeds with high levels of enantio- and diastereoselectivity to afford unique cyclopropanes that can be further functionalized to provide complex heterocyclic building blocks.



INTRODUCTION

Cyclopropanes are important structural motifs found in numerous pharmaceutical scaffolds and natural products.[1,2] In drug discovery, the rigid conformations adopted by cyclopropanes make them important bioisosteric replacements for motifs like aziridines or oxiranes.[3,4] As a result, there is an intense interest in identifying new methodologies to access functionalized cyclopropanes, especially in an asymmetric fashion. Metal-catalyzed asymmetric cyclopropanation employing diazo compounds has proven to be a particularly fertile area of research resulting in the majority of synthetic options for functionalizing simple olefinic compounds.[5−11] In contrast to the large number of olefinic examples reported, only limited examples of catalytic asymmetric cyclopropanations of aromatic double bonds have appeared in the literature. These examples have been largely limited to simple electron-rich systems such as indoles[12a] and benzofurans,[12b] with no examples of electron-deficient heteroaromatics described. Correspondingly, the discovery of an aromatic cyclopropanation of electron-poor heteroaromatics would provide an opportunity to access a previously unexplored new class of pharmacophores. Herein, we report a highly efficient cobalt-catalyzed asymmetric cyclopropanation of fused heteroaromatic systems that provides access to a range of unique heterocyclic cyclopropanes (Figure 1).

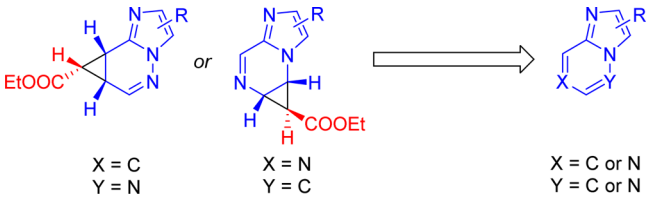


Figure 1. Approach to access heterocyclic cyclopropanes via dearomatizing cyclopropanation.

RESULTS AND DISCUSSION

Our initial investigations focused on the reaction of ethyl 6-chloroimidazo[1,2-*b*]pyridazine-2-carboxylate (**1**) with ethyl diazoacetate (EDA) (**2**) employing a broad set of conditions (Table 1). Interestingly, known rhodium[6] and copper[9] cyclopropanation catalysts (Table 1, entries 1−3) failed to provide any conversion to cyclopropane **3**. A promising level of reactivity was observed with cobalt-porphyrin **7** (Table 1, entry 4) as catalyst, providing the *trans*-cyclopropane product **3′** in 38% conversion but with poor enantioselectivity. Encouraged by the reactivity provided by chiral cobalt(II) porphyrin, we evaluated other chiral cobalt(II) catalysts.[10] When the unhindered Co-salen **8** (Table 1, entry 5) was employed as catalyst, 55% conversion to *cis*-cyclopropane **3** was obtained with no observed enantioselectivity. Improved enantio- and diastereoselectivities were obtained with Co-salen **9**, albeit with only 10% conversion to *cis*-cyclopropane product **3** (Table 1, entry 6). To our delight, the classical ^{t}Bu-Co-salen **10**, provided the *cis*-cyclopropane **3** in 96% conversion, 95:5 er and 20:1 dr (Table 1, entry 7), highlighting the privileged position this ligand framework holds in asymmetric catalysis.[13] Both the cyclohexanediamine backbone and substitution on the salicylimine portion of the salen ligand were essential for high reactivity and selectivity.

Having identified an efficient catalyst, we sought to optimize the reaction to provide the best reactivity and selectivity. The efficiency of the transformation was highly sensitive to the nature of the reaction medium (Figure 2). In general, polar aromatic solvents provided good conversions and enantioselectivities. Chlorobenzene proved optimal with *cis*-cyclopropanation product **3** in 98% conversion and 96:4 er. Other commonly used solvents such as THF and CH_2Cl_2 provided the product in similarly high er but with lower conversions, while reactivity was significantly suppressed in acetonitrile. A variety of additives were also studied for potential benefits to reactivity and selectivity (Table 2).[14] Introduction of both *N*-

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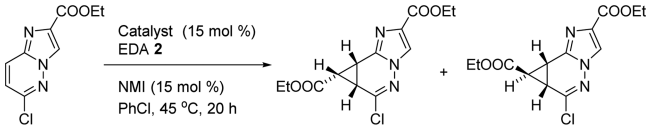
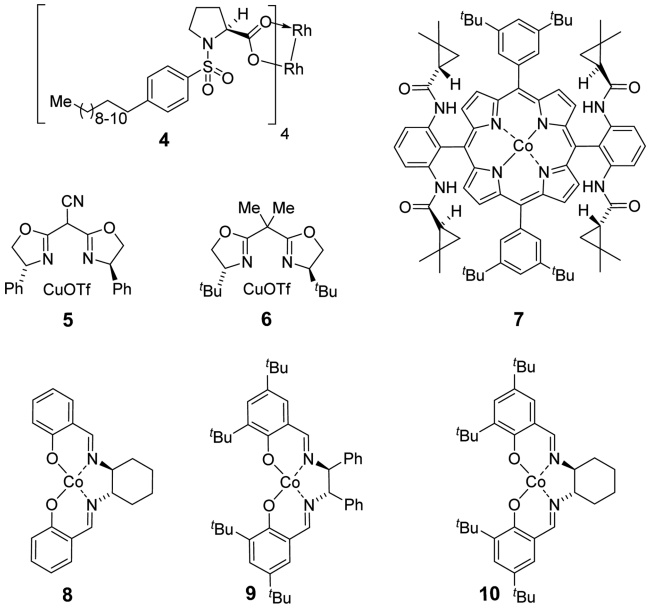
Table 1. Results of Catalyst Screening for Asymmetric Cyclopropanation of Heteroaromatic Substrate[a]



1 **3** *cis* **3'** *trans*

entry	catalyst	conv[c] (%)	3:3'[c]	er[d]
1	Rh_2(*S*-DOSP)$_4$[b] (**4**)	0	–	–
2	Cu box[b] (**5**)	0	–	–
3	Cu box[b] (**6**)	0	–	–
4	Co-porphyrin (**7**)	38	1:30	67:33
5	Co-salen (**8**)	55	6:1	49:51
6	Co-salen (**9**)	10	20:1	88:12
7	Co-salen (**10**)	96	20:1	95:5

[a]Conditions: **1** (0.1 mmol), catalyst, *N*-methylimidazole (NMI), EDA **2** (0.13 mmol), chlorobenzene (0.7 mL), 45 °C, 20 h. [b]Reaction performed without NMI. [c]Determined by UPLC. [d]er of major isomer was determined by chiral SFC.



methyl- and *N*-butylimidazoles provided an increase in reactivity of the cyclopropanation reaction, affording *cis*-cyclopropane **3** in high yield and maintaining the established 96:4 er. The use of imidazole resulted in significant reduction in yield as well as enantioselectivity. Other additives such as thiazole, pyridine, and DMAP furnished the desired product in high yields, but with lower enantiomeric ratios. Further increase in the equivalents of additive *N*-methylimidazole (NMI) increased the initial rate but did not affect the overall productivity of cyclopropanation.

With optimized reaction conditions in hand, we explored the scope of the asymmetric cyclopropanation using a variety of imidazopyridazines and imidazopyrazines (Scheme 1). Both 2-ethyl carboxylate and 2-(trifluoromethyl)imidazopyridazine provided the *cis*-cyclopropane products **3**[15] and **12**, respectively, in good yields and excellent diastereo- and enantioselectivities. The less reactive cyclopropanating agent ^{t}Bu diazoacetate reacted efficiently with 2-ethyl carboxylate imidazopyridazine to afford the corresponding *cis*-cyclopropane **11** in 82% yield, with 20:1 dr and 94:6 er. On the other hand,

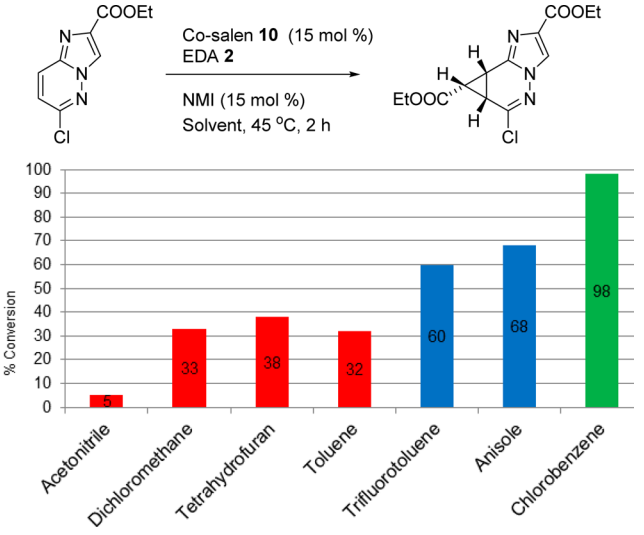
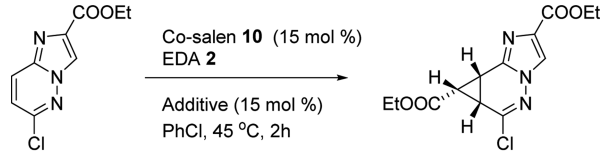


Figure 2. Selected results of solvent screening for asymmetric cyclopropanation of 6-chloroimidazo[1,2-*b*]pyridazine-2-carboxylate. Conditions: **1** (0.1 mmol), Co-salen **10**, NMI, EDA **2** (0.13 mmol), solvent (0.7 mL), 45 °C, 2 h. Conversions were determined by UPLC. *Cis* product formed as major diastereomer with dr = 20:1. er remained unchanged.

Table 2. Additive Screening for Asymmetric Cyclopropanation of 6-Chloroimidazo[1,2-*b*]pyridazine-2-carboxylate[a]



1 **3**

entry	additive	conv[b,c] (%)	er (cis)[d]
1	imidazole	68	89:11
2	*N*-methylimidazole	100	96:4
3	*N*-^{n}butylimidazole	100	96:4
4	thiazole	95	93:7
5	pyridine	92	92:8
6	4-(dimethylamino)pyridine	100	93:7
7	none	30	88:12

[a]Conditions: **1** (0.1 mmol), Co-salen **10**, additive, EDA **2** (0.13 mmol), chlorobenzene (0.7 mL), 45 °C, 2 h. [b]Determined by UPLC. [c]*Cis* product formed as major diastereomer with dr = 20:1. [d]Determined by chiral SFC.

modest yields and selectivities were observed for reactions with 3-substituted imidazopyridazines (**13**–**15**). Cyclopropanation of imidazopyrazine analogues proceeded in good yields and enantioselectivities albeit with diminished diastereoselectivities (**16**–**19**) compared to analogous imidazopyridazines. Substitution of an electron-withdrawing group at the 2-position of imidazopyrazine again proved optimal. Interestingly, the parent imidazopyrazine provided the desired cyclopropane **19**[16] in 47% yield and a remarkable 99:1 er.

To further expand the scope of this transformation, we studied the cyclopropanation reaction using other substituted fused polynitrogenated heterocycles (Scheme 2). 6-Chloro-[1,2,4]triazolo[4,3-*b*]pyridazine (**20**) underwent cyclopropanation to give the desired product **21** in 92% yield, with high

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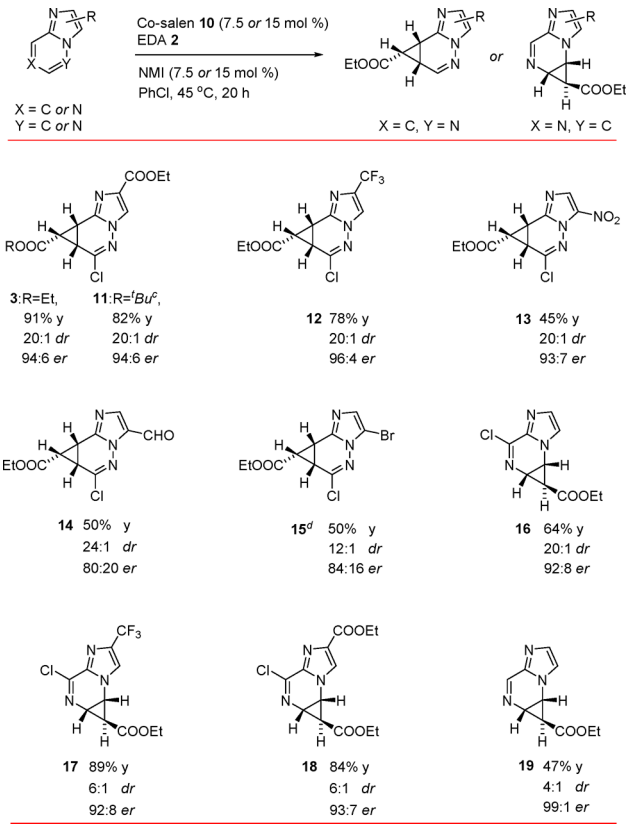
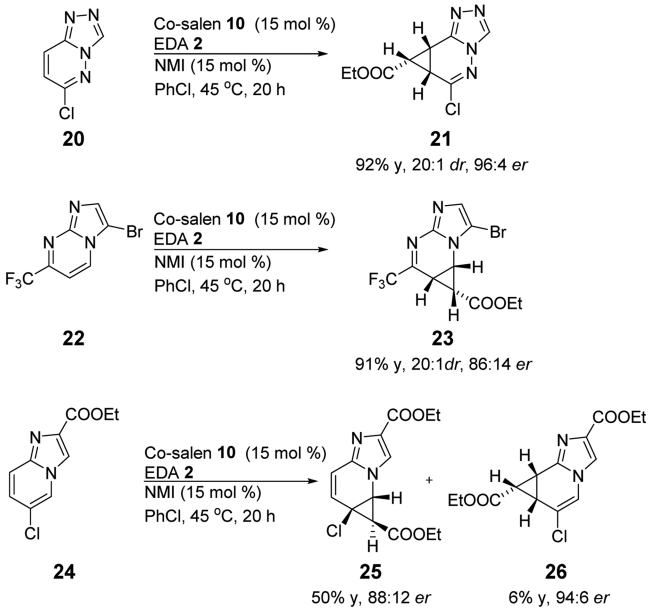
Scheme 1. Co-salen Catalyzed Asymmetric Cyclopropanation of Imidazopyrazine and Imidazopyridazine Substrates[a,b]



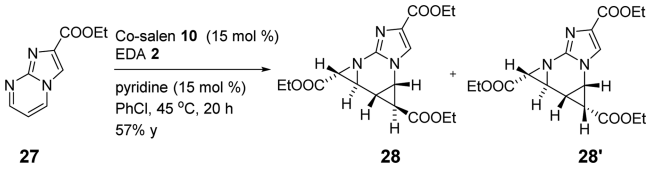
[a]Conditions: heterocycle (1 mmol), Co-salen **10**, NMI, EDA **2** (1.3 mmol), chlorobenzene (7 mL), 45 °C, 20 h. [b]er of major isomer was determined by chiral SFC. [c]Using [t]Bu diazoacetate. [d]Determination of absolute configuration by X-ray crystallography.

Scheme 2. Co-salen Catalyzed Asymmetric Cyclopropanation of Heteroaromatic Substrates[a,b]



[a]Conditions: heterocycle (1 mmol), EDA **2** (1.3 mmol), chlorobenzene (7 mL), 45 °C, 20 h. [b]er of major isomer was determined by chiral SFC.

Scheme 3. Co-salen Catalyzed Asymmetric Aziridination of Ethyl Imidazo[1,2-*a*]pyrimidine-2-carboxylate[a−d]



[a]Conditions: heterocycle **27** (0.5 mmol), EDA **2** (1.3 mmol), chlorobenzene (3.5 mL) 45 °C, 20 h. [b]**28**:**28′** = 5:1. [c]78:22 er for **28** as determined by chiral SFC. [d]1:1 dr using NMI.

enantio- and diastereoselectivity. To our delight, cyclopropanation of 3-bromo-7-(trifluoromethyl)imidazo[1,2-*a*]-pyrimidine (**22**) also gave desired product **23** in excellent yield and high diastereoselectivity (91% yield, 20:1 dr, 86:14 er). When ethyl 6-chloroimidazo[1,2-*a*]pyridine-2-carboxylate (**24**) was subjected to cyclopropanation conditions, product **25** was obtained in 50% yield (6:1 dr, 88:12 er).

Initial attempts at forming aziridines using this chemistry showed promising results (Scheme 3). When ethyl imidazo-[1,2-*a*]pyrimidine-2-carboxylate (**27**) was subjected to cyclopropanation conditions, cyclopropanation and aziridination reaction proceeded competitively giving products **28** and **28′** in 57% isolated yield and 5:1 dr.[17] To our knowledge, this is the first example of a cobalt-catalyzed aziridination reaction where the aziridine ring is formed on the carbon−nitrogen double bond of heterocyclic substrate, and we are currently working to understand and optimize for this reactivity.

In summary, we have developed an efficient Co-salen catalyzed asymmetric cyclopropanation of fused heteroaromatics. This protocol provides access to a range of unique heterocyclic cyclopropanes in high diastereomeric and enantiomeric ratios via dearomatization of heteroaromatic rings. This method represents a significant advance in asymmetric cyclopropanations. For the first time, electron-deficient nitrogen heteroarenes have become suitable substrates for asymmetric cyclopropanation using the privileged Co-salen catalyst. This transformation has also been extended to asymmetric aziridination to access unique heterocyclic scaffolds. Futher applications of Co-salen catalyzed asymmetric cyclopropanations of heteroarenes are under investigation within our laboratories, and the results will be reported in due course.

EXPERIMENTAL SECTION

General Methods. All reactions were carried out under nitrogen atmosphere in a glovebox or using standard Schlenk techniques. Reagents were purchased from commercial sources and used without further purification unless otherwise noted. ^{1}H NMR spectra were recorded on either a 500 or 600 MHz spectrometer at ambient temperature. Data are reported as follows: chemical shift in parts per million (δ, ppm) from either residual $CHCl_3$ (7.26 ppm) or methanol-d_3 (3.31 ppm), multiplicity (s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, m = multiplet, om = overlapped multiplet, and dd = doublet of a doublet), coupling constants (Hz), and number of protons (H). ^{13}C NMR spectra were recorded on either a 500 or 600 MHz spectrometer at ambient temperature. Chemical shifts are reported in ppm from either $CDCl_3$ (77.16 ppm) or methanol-d_4 (49.00 ppm). HRMS data were obtained

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on a Q-ToF mass spectrometer using positive polarity electrospray ionization mode, (+)ESI. Absolute configuration was determined on product **15** by X-ray analysis and was extrapolated to other products by analogy. Reactions were monitored using UPLC−MS. Crude reactions were purified using flash column chromatography.

General Procedure for Cyclopropanation Reactions. A 25 mL three-necked round-bottom flask was purged with nitrogen. To this flask were added (*R*,*R*)-(−)-*N*,*N*′-Bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminocobalt(II) catalyst (0.15 mmol, 90 mg) and substrate (1 mmol) under nitrogen. The flask was evacuated and backfilled with nitrogen three times using Schlenk techniques. *N*-Methylimidazole (0.15 mmol, 12 μL) was diluted with 7 mL of dry chlorobenzene, and the solution was then added to the three-necked flask. The reaction mixture was heated and stirred at 45 °C for 15 min after which ethyl diazoacetate (1.3 mmol, 158 μL) was added dropwise. The reaction was stirred under nitrogen for 20 h and then concentrated to a crude residue under vacuum. Purification was performed by column chromatography (using 10−30% acetone/hexanes) to give the desired product.

*Diethyl 6-Chloro-6a,7a-dihydro-7H-cycloprop[d]imidazo-[1,2-b]pyridazine-2,7-dicarboxylate (**3**).* 91% yield (284 mg), 94:6 er, brown wax. The general procedure was employed using 7.5% catalyst and 7.5% NMI. ^{1}H NMR (600 MHz, CD_3OD) δ: 7.85 (s, 1H), 4.37 (q, J = 7.1 Hz, 2H), 4.12−3.91 (m, 2H), 3.28 (dd, J = 8.5, 8.5 Hz, 1H) (observed as apparent triplet), 2.82 (dd, J = 8.8, 8.7 Hz, 1H), 2.60 (dd, J = 9.0, 9.0 Hz, 1H) (observed as apparent triplet), 1.38 (t, J = 7.1 Hz, 3H), 1.16 (t, J = 7.1 Hz, 3H) ppm. ^{13}C NMR (151 MHz, CD_3OD) δ: 165.8, 162.4, 149.9, 132.2, 130.6, 123.5, 61.9, 70.0, 26.2, 21.1, 18.1, 14.5, 14.0 ppm. Enantiomeric excess was determined by SFC: column OJ-3, mobile phase MeOH/IBA. HRMS calcd for $C_{13}H_{15}ClN_3O_4^+$: 312.0746, found 312.0747.

*7-tert-Butyl 2-Ethyl 6-chloro-6a,7a-dihydro-7H-cycloprop-[d]imidazo[1,2-b]pyridazine-2,7-dicarboxylate (**11**).* 82% (278 mg), 94:6 er, white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.83 (s, 1H), 4.37 (q, J = 7.1 Hz, 2H), 3.20 (dd, J = 8.5, 8.6 Hz, 1H), 2.75 (dd, J = 8.4, 9.3 Hz, 1H), 2.52 (dd, J = 9.1, 9.2 Hz, 1H), 1.39 (t, J = 7.1 Hz, 3H), 1.29 (s, 9H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 164.6, 162.3, 150.3, 132.6, 131.4, 123.3, 83.1, 60.9, 27.8, 25.7, 20.7, 19.4, 14.4 ppm. Enantiomeric excess was determined by SFC: column OJ-3, mobile phase IPA/IBA. HRMS calcd for $C_{15}H_{19}ClN_3O_4^+$: 340.1059, found 340.1067.

*Ethyl 6-Chloro-2-(trifluoromethyl)-6a,7a-dihydro-7H-cycloprop[d]imidazo[1,2-b]pyridazine-7-carboxylate (**12**).* 78% yield (239 mg), 96:4 er, brown solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.55 (s, 1H), 4.09−3.98 (m, 2H), 3.26 (dd, J = 8.6, 8.6 Hz, 1H) (observed as apparent triplet), 2.84 (dd, J = 8.5, 9.2 Hz, 1H), 2.62 (dd, J = 9.0, 9.0 Hz, 1H) (observed as apparent triplet), 1.17 (t, J = 7.2 Hz, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ: 165.6, 149.8, 132.3, 130.2 (q, $J_{C,F}$ = 39.8 Hz, 1C), 121.1 (q, $J_{C,F}$ = 266.8 Hz, 1C), 117.9 (q, $J_{C,F}$ = 3.7 Hz, 1C), 61.9, 26.0, 20.9, 17.7, 13.9 ppm. ^{19}F NMR (470 MHz, $CDCl_3$) δ: −63.34 ppm. Enantiomeric excess was determined by SFC: column AD-3, mobile phase IPA/IBA. HRMS calcd for $C_{11}H_{10}ClF_3N_3O_2^+$: 308.0408, found 308.0416.

*Ethyl 6-Chloro-3-nitro-6a,7a-dihydro-7H-cycloprop[d]-imidazo[1,2-b]pyridazine-7-carboxylate (**13**).* 45% yield (128 mg), 93:7 er, white solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.95 (s, 1H), 4.12−4.02 (m, 2H), 3.44 (dd, J = 8.6, 8.6 Hz, 1H) (observed as apparent triplet), 3.08 (dd, J = 8.8, 8.8 Hz, 1H) (observed as apparent triplet), 2.88 (dd, J = 8.9, 8.9 Hz, 1H) (observed as apparent triplet), 1.20 (t, J = 7.2 Hz, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ: 165.6, 152.1, 136.2, 135.9, 131.0, 62.1, 26.5, 21.7, 17.0, 13.9 ppm. Enantiomeric excess was determined by SFC: column AD-3, mobile phase IPA/IBA. HRMS calcd for $C_{10}H_{10}ClN_4O_4^+$: 285.0385, found 285.0389.

*Ethyl 6-Chloro-3-formyl-6a,7a-dihydro-7H-cycloprop[d]-imidazo[1,2-b]pyridazine-7-carboxylate (**14**).* 50% yield (133 mg), 80:20 er, brown wax. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 10.01 (s, 1H), 7.77 (s, 1H), 4.09−3.99 (m, 2H), 3.38 (dd, J = 8.5, 8.5 Hz, 1H) (observed as apparent triplet), 2.93 (dd, J = 8.7, 8.7 Hz, 1H) (observed as apparent triplet), 2.73 (dd, J = 9.1, 9.1 Hz, 1H) (observed as apparent triplet), 1.16 (t, J = 7.1 Hz, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 179.1, 165.5, 150.6, 135.0, 134.0, 129.1, 62.2, 26.4, 21.2, 17.5, 14.0 ppm. Enantiomeric excess was determined by SFC: column AD-3, mobile phase MeOH/IBA. HRMS calcd for $C_{11}H_{11}ClN_3O_3^+$: 268.0483, found 268.0480.

*Ethyl (6aS,7R,7aS)-3-Bromo-6-chloro-6a,7a-dihydro-7H-cycloprop[d]imidazo[1,2-b]pyridazine-7-carboxylate (**15**).* 50% (159 mg), 84:16 er, brown solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.00 (s, 1H), 4.09−3.98 (m, 2H), 3.24 (dd, J = 8.5, 8.5 Hz, 1H) (observed as apparent triplet), 2.82 (dd, J = 9.1,8.8 Hz, 1H), 2.57 (dd, J = 8.9, 8.9 Hz, 1H) (observed as apparent triplet), 1.14 (t, J = 7.1 Hz, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 165.8, 148.6, 132.5, 127.8, 61.9, 26.5, 21.9, 17.6, 14.0 (one carbon resonance not observed due to low sensitivity) ppm. Enantiomeric excess was determined by SFC: column OD-3, mobile phase MeOH/IBA. HRMS calcd for $C_{10}H_{10}BrClN_3O_2^+$: 317.9639, found 317.9643. The absolute configuration was determined by X-ray crystallography.

*Ethyl 3-Chloro-1a,7a-dihydro-1H-cycloprop[e]imidazo-[1,2-a]pyrazine-1-carboxylate (**16**).* 64% yield (153 mg), 92:8 er, brown solid. The general procedure was employed using 7.5% catalyst and 7.5% NMI. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35 (d, J = 0.8 Hz, 1H), 7.32 (d, J = 0.9 Hz, 1H), 4.35 (dd, J = 3.3, 6.5 Hz, 1H), 4.29−4.20 (om, 3H), 1.52 (dd, J = 3.4, 3.4 Hz, 1H) (observed as apparent triplet), 1.30 (t, J = 7.2 Hz, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.4, 146.3, 132.5, 132.0, 122.0, 62.2, 44.4, 39.9, 26.4, 14.3 ppm. Enantiomeric excess was determined by SFC: column OD-3, mobile phase MeOH/IBA. HRMS calcd for $C_{10}H_{11}ClN_3O_2^+$: 240.0534, found 240.0542.

*Ethyl 3-Chloro-5-(trifluoromethyl)-1a,7a-dihydro-1H-cycloprop[e]imidazo[1,2-a]pyrazine-1-carboxylate (**17**).* 89% yield (273 mg), 92:8 er, brown sticky solid (major isomer) and white crystalline solid (minor isomer). The general procedure was employed using 7.5% catalyst and 7.5% NMI. Major *trans*-product. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.72 (s, 1H), 4.40 (dd, J = 6.5, 3.5 Hz, 1H), 4.30 (dd, J = 6.5, 3.7 Hz, 1H), 4.28−4.24 (m, 2H), 1.63 (dd, J = 3.6, 3.6 Hz, 1H) (observed as apparent triplet), 1.32 (t, J = 7.2 Hz, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ: 169.6, 145.4, 135.6, 134.3 (q, $J_{C,F}$ = 23.8 Hz, 1C), 121.2 (q, $J_{C,F}$ = 3.6 Hz, 1C), 120.5 (q, $J_{C,F}$ = 267.8 Hz, 1C), 62.4, 44.0, 39.7, 26.5, 14.1 ppm. ^{19}F NMR (470 MHz, CDCl3) δ: −63.00 ppm. Enantiomeric excess was determined by SFC: column IC, mobile phase MeOH/IBA. HRMS calcd for $C_{11}H_{10}ClF_3N_3O_2^+$: 308.0408, found 308.0417. Minor *cis*-product. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.57 (s, 1H), 4.23−4.28 (m, 2H), 3.97−4.03 (m, 2H), 2.51 (dd, J = 9.2, 7.45 Hz, 1H), 1.12 (t, J = 7.15 Hz, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 164.4, 148.2, 121.3 (q, J_{CF} = 3.6 Hz, 1C), 61.7, 41.6, 37.1, 15.8, 14.0 ppm (Note: only one ^{13}C resonance from the

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J. Org. Chem. 2016, 81, 3070−3075

imidazole ring was observed due to poor sensitivity from insufficient sample quantity). ^{19}F NMR (470 MHz, $CDCl_3$) δ: −62.83 ppm. HRMS calcd for $C_{11}H_{10}ClF_3N_3O_2^+$: 308.0408, found 308.0418.

Diethyl (1R,1aS,7aR)-3-Chloro-1a,7a-dihydro-1H-cycloprop[e]imidazo[1,2-a]pyrazine-1,5-dicarboxylate ***(18)***. 84% yield (261 mg), 93:7 er, brown solid. The general procedure was employed using 7.5% catalyst and 7.5% NMI. Major *trans*-product. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.98 (s, 1H) 4.40−4.37 (om, 3H), 4.26−4.21 (om, 3H), 1.59 (dd, J = 3.6, 3.6 Hz, 1H) (observed as apparent triplet), 1.38 (t, J = 7.1 Hz, 3H), 1.31 (t, J = 7.15 Hz, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ: 169.7, 161.7, 146.1, 135.8, 132.6, 126.7, 62.4, 61.5, 44.0, 39.9, 26.9, 14.5, 14.3 ppm. Enantiomeric excess was determined by SFC: column AD-3, mobile phase MeOH/IBA. HRMS calcd for $C_{13}H_{15}ClN_3O_4$+: 312.0746, found 312.0745. Minor *cis*-product. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.90 (s, 1H) 4.39 (dd, J = 6.6, 6.6 Hz, 1H) (observed as apparent triplet), 4.37−4.31 (m, 2H), 4.23 (dd, J = 9.6, 6.2 Hz, 1H), 3.97−3.89 (m, 2H), 2.50 (dd, J = 9.6, 7.2 Hz, 1H), 1.37 (t, J = 7.1 Hz, 3H), 1.12 (t, J = 7.2 Hz, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ 164.5, 162.0, 148.5, 135.2, 135.0, 127.1, 61.5, 61.3, 41.6, 37.2, 16.0, 14.5, 14.0 ppm. HRMS calcd for $C_{13}H_{15}ClN_3O_4^+$: 312.0746, found 312.0743.

Ethyl 1a,7a-Dihydro-1H-cycloprop[e]imidazo[1,2-a]-pyrazine-1-carboxylate ***(19)***. 47% yield (96 mg), 99:1 er, brown solid. Minor product (formed presumably by ring opening of minor cyclopropanation product), was coeluted with major product. Major product. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.29 (s, 1H), 7.28 (d, J = 0.8 Hz, 1H), 7.24 (broad s, 1H) 4.33 (dd, J = 6.5, 3.3 Hz, 1H), 4.27−4.17 (om, 3H), 1.37 (dd, J = 3.6, 3.6 Hz, 1H) (observed as apparent triplet), 1.30 (t, J = 7.2 Hz, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ: 171.0, 149.4, 134.4, 131.6, 119.8, 62.0, 43.5, 40.0, 26.5, 14.2 ppm. Enantiomeric excess was determined by SFC: column LUX Cellulose-4, mobile phase MeOH/IBA. HRMS calcd for $C_{10}H_{12}N_3O_2^+$: 206.0925, found 206.0922. Minor product. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 9.05 (s, 1H), 7.83 (s, 1H), 7.79 (s, 1H), 7.67 (s, 1H), 4.27−4.17 (om, 1H), 3.93 (s, 2H), 1.22 (t, J = 7.2 Hz, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ: 167.5, 142.8, 141.0, 135.9, 129.7, 124.9, 111.5, 61.8, 36.3, 14.0 ppm.

Ethyl 6-Chloro-6a,7a-dihydro-7H-cyclopropa[d][1,2,4]-triazolo[4,3-b]pyridazine-7-carboxylate ***(21)***. 92% yield (221 mg), 96:4 er, brown solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.45 (s, 1H), 4.09−3.98 (m, 2H), 3.43 (dd, J = 8.5, 8.5 Hz, 1H) (observed as apparent triplet), 2.89 (dd, J = 9.1, 8.4 Hz, 1H), 2.75 (dd, J = 9.0, 9.0 Hz, 1H) (observed as apparent triplet), 1.16 (t, J = 7.1 Hz, 3H), ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 165.6, 151.4, 140.3, 138.6, 62.1, 26.0, 18.9, 18.6, 14.0 ppm. Enantiomeric excess was determined by SFC: column IC, mobile phase MeOH/IBA. HRMS calcd for $C_9H_{10}ClN_4O_2^+$: 241.0487, found 241.0494.

Ethyl 6-Bromo-2-(trifluoromethyl)-1a,7a-dihydro-1H-cycloprop[e]imidazo[1,2-a]pyrimidine-1-carboxylate ***(23)***. 91% yield (319 mg), 86:14 er, brown solid. Minor isomer was hydrolyzed under column conditions. Major *cis*-product: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.25 (s, 1H), 4.41 (dd, J = 7.6, 7.1 Hz, 1H), 4.0 (q, J = 7.2 Hz, 2H), 2.84 (dd, J = 10.3, 8.0 Hz, 1H), 2.59 (dd, J = 10.3, 6.8 Hz, 1H), 1.09 (t, J = 7.1 Hz, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 164.1, 151.9 (q, $J_{C,F}$ = 38.2 Hz, 1C), 142.6, 131.1, 119.5 (q, $J_{C,F}$ = 276.4 Hz, 1C), 118.7, 62.1, 36.0, 17.5, 16.0, 13.9 ppm. Enantiomeric excess was determined by SFC: column IC-3, mobile phase MeOH/IBA. HRMS calcd for $C_{11}H_{10}BrF_3N_3O_2^+$: 351.9903, found 351.9912.

Diethyl 6-Chloro-6a,7a-dihydro-7H-cycloprop[c]imidazo-[1,2-a]pyridine-2,7-dicarboxylate ***(25)***. 50% yield (155 mg), 88:12 er, brown wax. Major *trans*-product: ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.87 (s, 1H), 6.73 (d, J = 10.0 Hz, 1H), 6.57 (d, J = 9.8 Hz, 1H), 4.82 (broad s, 1H), 4.33 (q, J = 6.3 Hz, 2H), 4.30−4.21 (m, 2H), 1.98 (d, J = 3.8 Hz, 1H), 1.34 (t, J = 7.1 Hz, 3H), 1.30 (t, J = 7.1 Hz, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 166.3, 162.3, 139.9, 134.9, 130.3, 124.8, 117.5, 62.4, 60.9, 44.8, 42.6, 31.5, 14.4, 14.3 ppm. Enantiomeric excess was determined by SFC: column OD-3, mobile phase MeOH/IBA. HRMS calcd for $C_{14}H_{16}ClN_2O_4^+$: 311.0793, found 311.0794. Minor *cis*-product: ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.95 (s, 1H), 6.85 (d, J = 9.4 Hz, 1H), 6.34 (d, J = 10.1 Hz, 1H), 4.80 (broad s, 1H), 4.30 (q, J = 6.5 Hz, 2H), 3.91 (q, J = 7.1 Hz, 2H), 2.79 (d, J = 6.2 Hz, 1H), 1.32 (t, J = 6.8 Hz, 3H), 1.05 (t, J = 7.1 Hz, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ: 163.1, 161.2, 141.5, 132.1, 127.1, 125.7, 118.1, 61.6, 61.3, 44.0, 42.1, 26.4, 14.4, 13.9 ppm. Enantiomeric excess was determined by SFC: column OJ-3, mobile phase MeOH/IBA. HRMS calcd for $C_{14}H_{16}ClN_2O_4^+$: 311.0793, found 311.0803.

Diethyl (6aS,7R,7aS)-6-Chloro-6a,7a-dihydro-7H-cycloprop[c]imidazo[1,2-a]pyridine-2,7-dicarboxylate ***(26)***. 6% yield (19 mg), 94:6 er, brown wax. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.54 (s, 1H), 7.05 (s, 1H), 4.32 (q, J = 6.5 Hz,, 2H), 3.98 (q, J = 7.0 Hz, 2H), 3.17 (t, J = 8.2 Hz, 1H), 2.67 (t, J = 9.1 Hz, 1H), 2.38 (t, J = 8.8 Hz, 1H), 1.34 (t, J = 6.5 Hz, 3H), 1.13 (t, J = 7.0 Hz, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ: 166.4, 162.4, 138.9, 133.5, 122.1, 121.6, 117.9, 61.1, 60.8, 27.3, 21.3, 16.2, 14.5, 14.1 ppm. Enantiomeric excess was determined by SFC: column OD-3, mobile phase MeOH/IBA. HRMS calcd for $C_{14}H_{16}ClN_2O_4^+$: 311.0793, found 311.0799.

Triethyl 4a,5a,5b,6-Tetrahydro-5H-azirino[1,2-c]-cycloprop[e]imidazo[1,2-a]pyrimidine-2,5,6-tricarboxylate ***(28)***. 57% yield (104 mg), 78:22 er, brown solid. Major product (**28**). ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.51 (s, 1H), 4.32 (q, J = 7.1 Hz, 2H), 4.25−4.15 (om, 4H), 3.85 (dd, J = 8.6, 2.8 Hz, 1H), 3.48 (d, J = 3.3 1H), 2.96 (d, J = 3.3 Hz, 1H), 2.49 (dd, J = 8.7, 5.3 Hz, 1H), 2.24 (dd, J = 5.3, 2.9 Hz, 1H), 1.34 (t, J = 7.2 Hz, 3H), 1.29 (om, 6H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ: 168.8, 166.6, 162.2, 143.4, 131.5, 122.7, 61.9, 61.8, 60.6, 46.7, 38.9, 35.6, 31.0, 16.0, 14.4, 14.1, 14.0 ppm. Enantiomeric excess was determined by SFC: column LUX Cellulose-4, mobile phase MeOH/IBA. HRMS calcd for $C_{17}H_{22}N_3O_6^+$ 364.1503, found 364.1513. Minor product (**28′**). ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.45 (s, 1H), 4.27 (q, J = 7.2 Hz, 2H), 4.15 (q, J = 7.1 Hz, 2H), 4.01 (q, J = 7.0 Hz, 2H), 3.94 (dd, J = 7.1, 8.4 Hz, 1H), 3.36 (dd, J = 3.1 Hz, <1 Hz, 1H) (observed as apparent doublet), 2.93 (d, J = 3.1 Hz, 1H), 2.37 (ddd, J = 8.8, 8.8, <1 Hz, 1H) (observed as apparent triplet), 2.22 (dd, J = 6.8, 8.9 Hz, 1H), 1.31 (t, J = 7.2 Hz, 3H), 1.24 (t, J = 7.2 Hz, 3H), 1.11 (t, J = 7.1 Hz, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ: 167.2, 166.9, 162.5, 145.6, 131.0, 123.0, 61.7, 61.3, 60.5, 46.6, 37.4, 32.7, 25.7, 14.3, 14.1, 13.9, 13.7 ppm. Enantiomeric excess was determined by SFC: column OD-3, mobile phase MeOH/IBA. HRMS calcd for $C_{17}H_{22}N_3O_6^+$: 364.1503, found 364.1518.

■ ASSOCIATED CONTENT

Supporting Information

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HRMS and NMR spectra for all new compounds; SFC chromatograms for racemic and chiral compounds (PDF)
Crystal data for compound **15** (PDF)
X-ray crystallographic data of compound **15** (CIF)

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Notes

The authors declare no competing financial interest.

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(13) To our knowledge, this is the first example of using Co-salen **10** for asymmetric cyclopropanation of heteroarenes (a) For a minireview on privileged chiral catalysts, see: Yoon, T. P.; Jacobsen, E. N. *Science* **2003**, *299*, 1691. (b) For a review of chiral salen complexes, see: Larrow, J. F.; Jacobsen, E. N. *Top. Organomet. Chem.* **2004**, *6*, 123. (c) For cyclopropanation of simple olefins using Co-salen, see ref 10.

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(15) For substrate **1**, 5 mol % catalyst can be used without compromising the yield.

(16) Substitution on imidazopyrazine is not required for cyclopropanation.

(17) With a substoichiometric amount of EDA, product **28** was obtained as major product. Monocyclopropanation product was not detected by UPLC–MS analysis.

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J. Org. Chem. 2016, 81, 3070–3075