Copper-Catalyzed Conjugate Additions to Isocyanoalkenes

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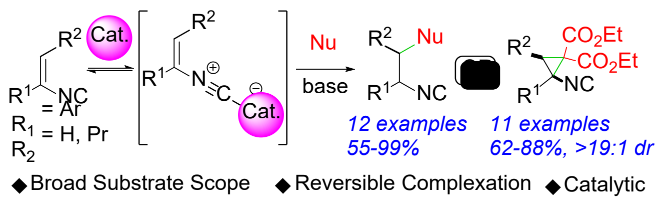
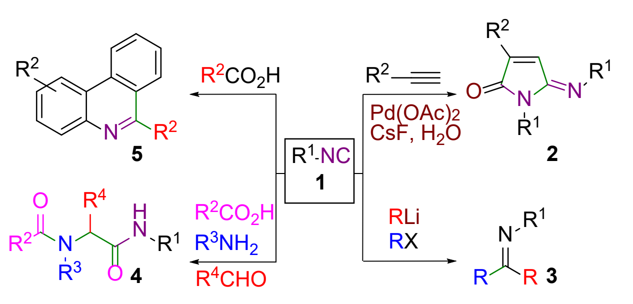
Supporting Information Placeholder



ABSTRACT: A copper iodide-Pyox complex catalyzes the first conjugate addition of diverse sulfur, nitrogen, and carbon nucleophiles to isocyanoalkenes. The anionic addition generates metalated isocyanoalkanes capable of S_Ni displacements, providing a rapid route to a series of functionalized, cyclic isocyanoalkanes. The Cu(I)I-Pyox complex efficiently catalyzes a first-in-class conjugate addition affording a range of complex, functionalized isocyanoalkanes that are otherwise challenging to synthesize while laying a foundation for catalytic reactions that maintain the isocyanide group.

Introduction Isocyanides are chemical chameleons by virtue of the terminal, ambiphilic carbon that reacts with nucleophiles,[1] electrophiles,[2] radicals,[3] and transition metals.[4] The exceptional reactivity of isocyanides stems from the unusual bonding of the divalent, terminal carbenoid carbon whose evolution to a more stable tetravalent configuration is the driving force for many reactions: insertions (Scheme 1, **1** → **2**), additions (**1** → **3**), multicomponent reactions (**1** → **4**), and radical cyclizations (**1** → **5**).[5] The exceptionally diverse reactivity profile provides rapid access to heterocycles such as **2** and **5**, nucleosides, peptidomimetics (cf. **4**), and natural product analogs.[6]

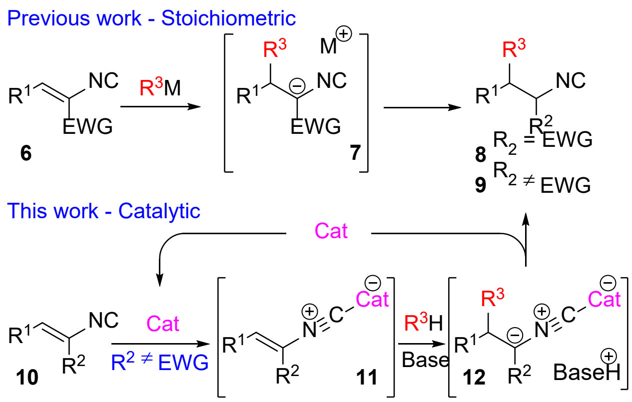
Scheme 1. Representative Isocyanides Reactions.



In contrast to the diverse suite of reactions that deploy the terminal isocyanide carbon as a lynchpin, there are relatively few methods for synthesizing the types of substituted isocyanides required for pharmaceutical discovery.[7] The fruitful use of conjugate additions to access complex scaffolds is, for additions to isocyanoalkenes, limited to a few stoichiometric, anionic conjugate additions (Scheme 2, **6** → **7** → **8**).[8] The absence of any catalytic conjugate addition to isocyanoalkenes reflects the extremely strong binding of most potential transition metal complexes that might serve as catalysts; isocyanides tenaciously complex transition metals making them very effective scavengers for removing trace metals.[9] Not surprisingly, catalytic manipulations of isocyanides that maintain the isocyanide functionality are extremely rare.[10] The difficulty reflects the strong σ-bond donation from the isocyanide carbon to the transition metal d-orbitals coupled with a π-donation from the metal to the isocyanide π* orbital[11] which favor insertion and addition reactions over reversable complexation.

Catalyzing conjugate additions to isocyanoalkenes requires overcoming two main challenges: irreversible complexation of the catalyst to the isocyanide and selective delivery of the nucleophile to the alkene rather than the inherently more reactive carbenoid isocyanide carbon.[12] A highly efficacious copper(I) catalyst is described that reversibly complexes isocyanoalkenes to generate nitrilium-like intermediates **11** that are activated toward anionic conjugate addition (Scheme 2, **10** → **11** → **12** → **9**). In contrast to previous work, the transformation is catalytic and does not require isocyanoalkenes bearing an additional electron withdrawing group (cf. **10** with **6**).

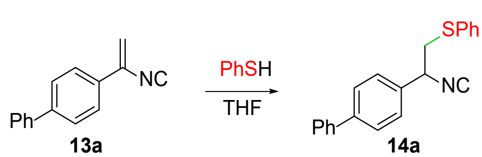
Scheme 2. Conjugate Additions to Isocyanoalkenes.



Results and Discussion. An initial screening in which the isocyanoalkene **13a** was treated with a series of nucleophiles[13] in the presence or absence of metal complexes[14] afforded mainly products resulting from addition to the terminal isocyanide carbon. The strategy for identifying a potential catalyst was therefore redesigned by first developing an uncatalyzed addition with highly nucleophilic PhSK and then adding metal salts as potential catalysts to accelerate the conjugate additions with the goal of ultimately identifying a complex capable of catalyzing the addition of carbon and nitrogen nucleophiles.

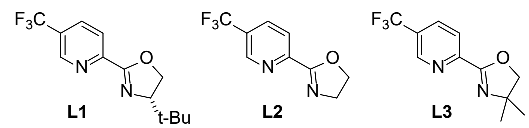
Sporadic, reversible, complexation of isocyanides to copper (I) salts hinted at the viability of copper complexes as catalysts for conjugate additions to isocyanoalkenes.[15] Copper(I)-isocyanide complexes are unusual in reversibly forming complexes because although the σ-donation from the isocyanide is strong, there is minimal π-donation from copper to the isocyanide.[16] In the event, addition of PhSK generated from PhSH and K_2CO_3 (10 mol%), provided the phenylsulfanylisocyanide **14a** (Table 1, entry 1). A control experiment with no base gave only trace amounts of the phenylsulfanylisocyanide **14a** (Table 1, entry 2). Screening a series of copper salt-ligand combinations (see Figure S1 in the SI for details) identified the combination of catalytic CuI[17] and commercially available Pyox (**L1**)[18] with K_2CO_3 as an efficacious promoter for the addition of PhSH to **13a** (Table 1, entry 3). Cs_2CO_3 was found to promote a faster reaction than K_2CO_3, though the soluble bases KHMDS and Et_3N dramatically accelerated the addition allowing complete conversion to **14a** at -78 °C within 30 and 20 min, respectively (Table 1, entries 5 and 6). NaH promoted the fastest conversion of **13a** to **14a** requiring only 8 min at -78 °C; no conjugate addition was observed in a control reaction in the absence of CuI/CF_3Pyox (Table 1, cf. entries 7 and 8). Varying the structure of the PyOx catalyst in reactions with CuI and **L2** and **L3** gave virtually the same reaction profile as with **L1** (Table 1, cf. entry 7 with entries 9, and 10).[19]

Table 1. Addition of PhSH to Isocyanoalkene 9a.



Entry	Base (equiv)	CuI/Pyox*[a] (mol %)	T (°C)	Time (h)	Yield[b]
1	K_2CO_3 (0.1)	-	25	18 h	75%
2	-	-	25	72 h	trace
3	K_2CO_3 (0.1)	2.5	25	2 h	64%
4	Cs_2CO_3 (0.3)	2.5	25	1 h	70%
5	KHMDS (1.0)	2.5	-78	30 min	78%
6	Et_3N (1.0)	2.5	-78	20 min	79%
7	NaH (0.1)	2.5	-78	8 min	85%
8	NaH (0.1)	-	-78	40 min	-
9	NaH (0.1)	2.5 **L2**	-78	8 min	67%
10	NaH (0.1)	2.5 **L3**	-78	8 min	87%

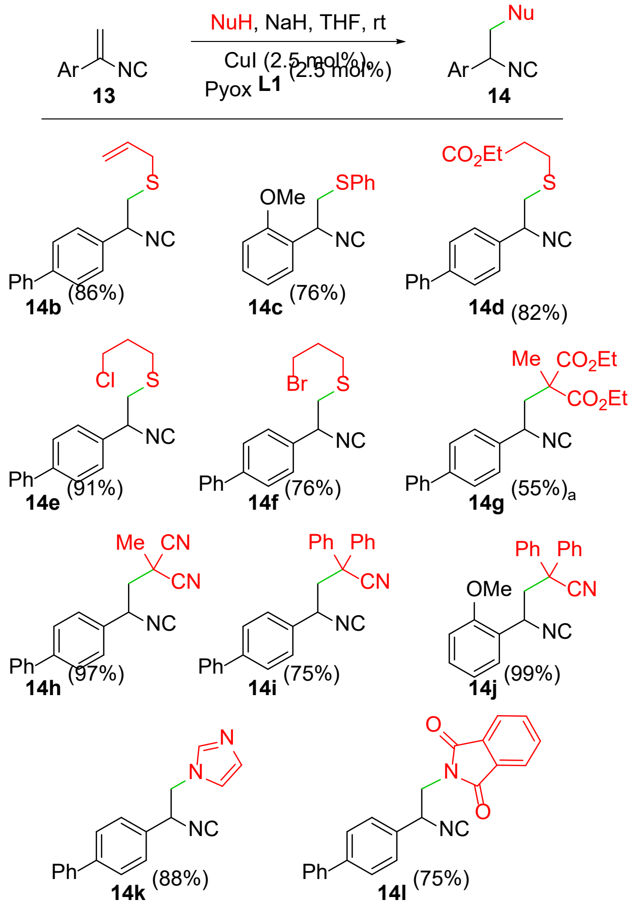
[a] Ligand **L1** (5 mol %) was used unless stated otherwise. [b] Isolated yield after chromatography on C-2 silica.[20]



Identifying Cu(I)-Pyox as an efficient catalyst provided the foundation for expanding the conjugate addition to diverse sulfur, nitrogen, and carbon nucleophiles (Scheme 3). Addition of allylsulfide to **13a** readily afforded **14b** under conditions identical to that with thiophenol. In contrast, the conjugate addition of thiophenol to the *o*-substituted isocyanoalkene **13b** (**13**, Ar = *o*-$MeOC_6H_4$) to afford **14c** required elevating the reaction from -78 °C to rt; presumably, the *syn*-pentane-like interaction between the *o*-methoxy substituent and the alkene in **13b** prevents planarity which retards the conjugate addition. Ethyl 3-mercaptopropanoate reacted efficiently with **13a** to afford **14d** while the addition of chloropropylthiol or bromopropylthiol to **13a** afforded **14e** and **14f**, respectively (Scheme 3).[21]

The successful conjugate addition of sulfenylates prompted an evaluation of anionic carbon nucleophiles (Scheme 3). Using the same Cu(I)-Pyox combination with diethyl methylmalonate smoothly provided the diester **14g**, a class of ester-isocyanides that are otherwise challenging to synthesize.[22] Addition of methylmalononitrile to **13a** with Cu(I)-Pyox and NaH provided a very efficient route to the isocyanonitrile **14h**; analogous conjugate additions with the significantly less acidic diphenylacetonitrile provided isocyanonitriles **14i** and **14j**. The nitrogen nucleophiles imidazole and phthalimide were equally as effective in the conjugate addition, affording the corresponding heterocycle-containing isocyanides **14k** and **14l**, respectively.

Scheme 3. Cu-Catalyzed Additions to Isocyanoalkenes.

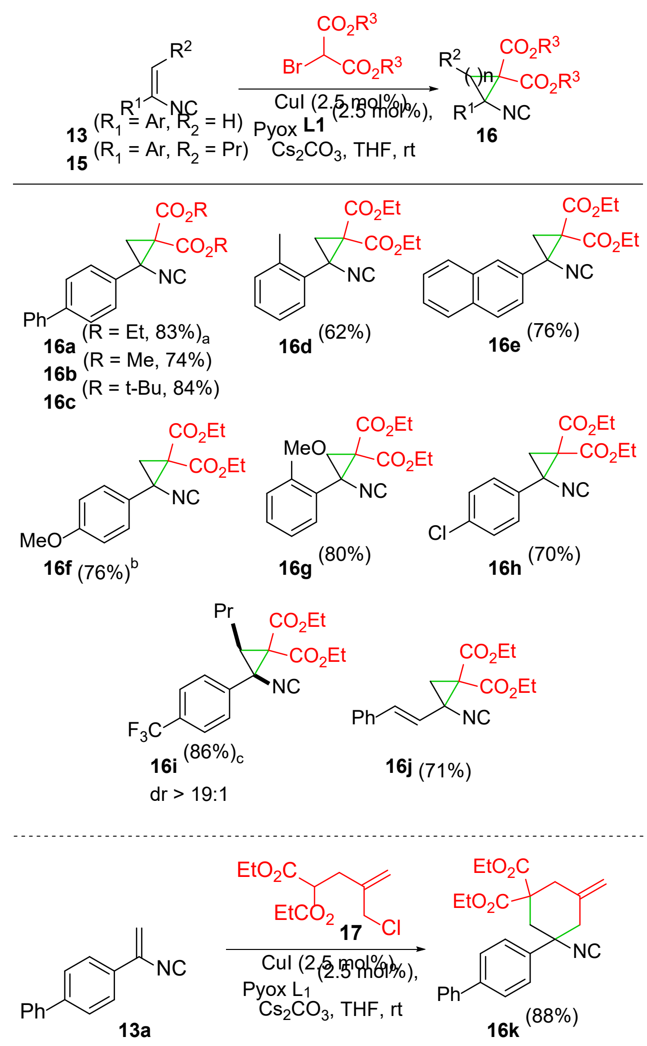


[a] Cs_2CO_3 was used in place of NaH.

The successful addition of carbon nucleophiles suggested generating carbocyclic isocyanides by harnessing the intermediate metalated isocyanide in an S_Ni displacement.[23] The conjugate addition-cyclization of bromomalonates was particularly appealing because the resulting isocyanocyclopropanes are precursors of functionalized cyclopropylamines,[24] valuable γ-turn mimetics that feature as pharmacophores[25] in cancer treatment.[26] Cu(I)-Pyox proved optimal[27] in catalyzing the addition of diethyl bromomalonate to **13a** with Cs_2CO_3 in THF[28] to afford **16a** (Scheme 4). A brief survey of bases revealed that NaH formed the isocyanocyclopropane **16a** more rapidly (20 min at rt), but less efficiently than Cs_2CO_3 (67% and 83%, respectively).[29]

Catalytic Cu(I)/Pyox in combination with bromomalonates efficiently generated a range of isocyanocyclopropanes (Scheme 4). Modulating the steric demand of the malonate alkyl ester substituent by changing from ethyl to methyl had minimal effect, (cf. **16a** with **16b**) whereas the *t*-butyl malonate required 95 h for full conversion to the *t*-butyl ester-isocyanide **16c**. Isocyanoalkenes **13** with aromatic substituents, aromatics with electron withdrawing or electron donating substituents, or cinnamyl substituents, were equally well tolerated in forming the corresponding ester-isocyanides (**16a-e**, **16f-i**, and **16j**, respectively).[30] The addition of diethyl bromomalonate to the β-substituted isocyanoalkene **15** (R^1 = *p*-$CF_3C_6H_4$) afforded the penta-substituted cyclopropane **16i** as the only detectable diastereomer. Extending the addition-cyclization to the allyl malonate **17**[31] afforded the six-membered isocyanide **16k**.

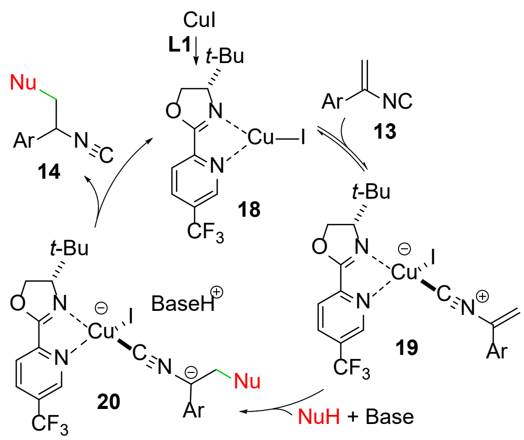
Scheme 4. Cu-Catalyzed Conjugate Addition-Cyclizations.



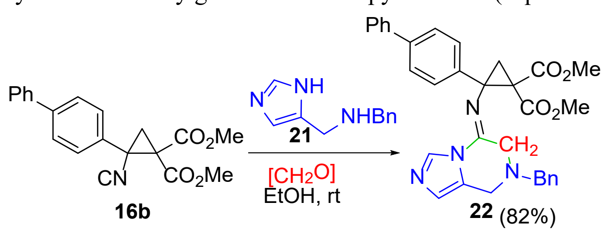
Reactions were performed on a 0.1 – 1.0 mmol scale with Nuc (1.1-1.5 equiv), CuI (2.5 mol%), **L1** (2.5 mol%), Cs_2CO_3 (1.2 equiv), THF (0.1 M), rt, 0.5-95 h. [a] The yield on a 1.0 mmol scale was 70%. [b] K_2CO_3 was employed rather than Cs_2CO_3. [c] Performed at 50 °C for 20 h for complete conversion.

Mechanistically, the conjugate additions likely proceed via complexation of the isocyanide to a tetrahedral Cu(I)I-Pyox complex **18**.[32] ^{13}C NMR of the isocyanoalkene **13a** with Cu(I)I in d_8-THF showed signal suppression of the ^{13}C NMR isocyanide carbon, the olefinic carbon, the proximal quaternary carbon, and the *ortho*-methine carbons (see Figure S2 in the SI for details), consistent with a fast, reversible complexation of copper to the terminal isocyanide carbon (Scheme 5, **18** ⇆ **19**). Association of iodide in the copper-isocyanide complex **18** appears likely because addition of iodide scavengers ($AgBF_4$, AgOTf, $NaBPh_4$) afforded a much less efficient catalyst. Complex **19** activates the alkene toward anionic conjugate addition by creating a nitrilium-like intermediate while preventing nucleophilic attack on the terminal carbon.[33] Nucleophilic addition to **19** generates **20** whose protonation (Scheme 3) or cyclization (Scheme 4) sets the configuration at the chiral center; an inability to coax asymmetry in the conjugate addition is consistent with location of the chiral ligand distal to the newly formed chiral center. The resulting, neutral copper-isocyanide complex releases the isocyanoalkane **14** and frees the catalyst for further turnover.

Scheme 5. Proposed Catalytic Cycle.



Isocyanocyclopropanes provide a direct route to cyclopropylamides that are potent pharmacophores and serve as precursors to nucleosides[34] and heterocycles.[35] As an illustration of the potential for isocyanocyclopropanes in multi-component cascades, **16b** was treated with imidazole **21** and paraformaldehyde to efficiently generate imidazopyrazine **22** (Equation 1).



(1)

Conclusions Cu(I)-Pyox catalyzes the first-in-kind conjugate addition of diverse nucleophiles to isocyanoalkenes while maintaining the isocyanide group. The delicate activation promotes conjugate addition with a range of sulfur, nitrogen, and carbon nucleophiles through activation of the isocyanoalkene by reversible binding of the catalyst. The intermediate metalated isocyanides can be protonated or trapped to generate isocyanides with complex molecular architectures that are otherwise challenging to access. Identification of the key mechanistic features in the active copper catalyst provide an extremely promising foundation for developing additional copper-catalyzed reactions while providing a valuable synthetic route to a diverse array of functionalized isocyanides.

Experimental Section

General Experimental Conditions: Tetrahydrofuran (THF) was freshly distilled from Na/benzophenone ketyl prior to use. All reactions were performed in dry glassware under an atmosphere of dry nitrogen. Other reagents were purchased as analytical or ACS grade and used without further purification unless stated otherwise. Saturated, aqueous ammonium chloride was buffered to pH = 7.0 by addition of ammonium hydroxide. Reactions that required a microwave heat source were performed in sealed 2 mL microwave reaction vials (Biotage #355629) equipped with a Teflon-coated stir bar and were maintained at a constant temperature using a Biotage® Initiator+ microwave reactor, equipped with an IR-sensor. Thin layer chromatography (TLC) was performed with glass-backed, 250 µm thickness, F254 hard layer SiliaPlate TLC Plates purchased from Silicycle. TLC plates were visualized by exposure to short wavelength UV light (254 nm). Flash chromatography was performed using the Buchi Reveleris X2 Automated Flash Chromatography System with commercial or self-prepared cartridges filled with SilicaFlash ® silica gel P60 (30-400 mesh) purchased from Silicycle or with "C-2 silica" prepared as previously described.[20] ^{1}H NMR and ^{13}C NMR high resolution nuclear magnetic resonance spectra were recorded at room temperature on a Varian Mercury Plus 400 (400 MHz/101 MHz) or a Varian Unity Inova 500 (500 MHz/126 MHz) spectrometer. Chemical shifts were referenced to $CDCl_3$ (δ 7.26) for 1H NMR and $CDCl_3$ (δ 77.16) for 13C NMR. ^{1}H NMR data are reported as follows: chemical shift, multiplicity (s =singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublet, m = multiplet, br = broad resonance, etc.), integration, and coupling constant (Hz). ^{1}H and ^{13}C NMR data are reported in parts per million (ppm) on the δ scale and referenced to tetramethylsilane or the proton residual of $CHCl_3$ for ^{1}H NMR and the carbon signal of $CDCl_3$ for ^{13}C NMR. High-resolution mass spectra were obtained on a Thermo-Electron LTQ-FT 7T Fourier transform ion cyclotron resonance (FT-ICR) spectrometer with an atmospheric pressure chemical ionization (APCI) source with direct infusion run in positive ion mode at 5 kV. Enantiomeric ratios (er's) were determined by performing chiral high pressure liquid chromatography (HPLC) analysis on a Shimadzu Nexera X2 instrument with a Daicel Chiral Technologies Inc. CHIRALPAK® IE, amylose-based (Amylose tris(3,5-dichlorophenylcarbamate) immobilized on 5 µm silica-gel) column (4.6 mm x 250 mm).

General Isocyanoalkene Synthesis Procedure: Isocyanoalkenes were prepared following a modification of the published procedure.[36] A solution of alkyllithium (1.2 equiv) was added to a -60 °C, THF (0.08 M) solution of the nitrile (1.0 equiv) and CuCN (0.02 equiv). After 15-30 min, neat isopropyl formate (5.0 equiv) was added and then the mixture was heated to 50 °C. After 12-20 h, when the tautomerization was complete as judged by TLC analysis, the reaction was allowed to cool to rt and then cooled to -60 °C. Neat triethylamine (9.0 equiv) was added followed by the dropwise addition of neat phosphoryl chloride (3.0 equiv). Upon completion, as monitored by TLC, the reaction mixture was poured into saturated, aqueous sodium carbonate, the phases were separated and then the aqueous phase was extracted with EtOAc (3 x 15 mL). The combined organic extract was washed with water (1 x 20 mL) and brine (1 x 20 mL), dried (Na_2SO_4), filtered, and then concentrated under reduced pressure. The crude product was purified by flash chromatography.

1-(1-isocyanovinyl)-2-methoxybenzene (13b). Prepared following the general isocyanoalkene synthesis procedure with 2-methoxybenzonitrile (500 mg, 3.76 mmol), CuCN (6.7 mg, 75 µmol), THF (37 mL, 80 mM), MeLi (2.83 mL, 4.50 mmol) except that isopropyl formate (1.88 mL, 18.8 mmol) was added to a -30 °C solution for 40 min before the mixture was heated to 50 °C. After 48 h, the reaction mixture was allowed to cool and then diisopropylamine (4.61 mL, 33.8 mmol) and $POCl_3$ (1.05 mL, 11.3 mmol) were added. Purification (dry-loaded with Celite onto a 12 g silica gel cartridge, 10% EtOAc/Hexanes) afforded 357 mg (60%) of the isocyanoalkene **13b** as a yellow liquid: IR (ATR): 3007, 2839, 2112, 1601 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (dd, J = 7.8, 1.7 Hz, 1H), 7.39-7.33 (m, 1H), 7.02 (tdd, J = 7.8, 1.0, 0.5 Hz, 1H), 6.96 (br d, J = 8 Hz, 1H), 6.01 (t, J = 5.2 Hz, 1H), 5.79-5.76 (m, 1H), 3.90 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 172.5, 161.9, 157.2, 130.8, 129.2, 121.1, 120.7, 119.5, 111.4, 55.6; HRMS (+APCI) m/z: [M + H]$^+$ Calcd. for $C_{10}H_{10}NO$ 160.0762; Found 160.0758.

(Z)-1-(1-isocyanopent-1-en-1-yl)-4-(trifluoromethyl)benzene (15a). Prepared following the general isocyanoalkenes synthesis procedure with 4-(trifluoromethyl)benzonitrile (500 mg, 2.92 mmol), CuCN (5.2 mg, 0.060 mmol), THF (30 mL, 0.10 M), BuLi (2.19 mL, 3.50 mmol). After 2 h at -60 °C, isopropyl formate (1.46

mL, 14.6 mmol) was added, the mixture was heated to 50 °C for 25 h, cooled and then diisopropylamine (3.59 mL, 26.3 mmol) and $POCl_3$ (0.81 mL, 8.8 mmol) were added to afford, after purification (dry-loaded with Celite onto a 12 g silica gel cartridge, 100% Hexanes eluent), 106 mg (23%) of the isocyanoalkene **15a** as a yellow oil: IR (ATR): 2966, 2877, 2118, 1686 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.73-7.54 (m, 4H), 6.39 (t, *J* = 7.4 Hz, 1H), 2.48 (q, *J* = 7.4 Hz, 2H), 1.58 (sext, *J* = 7.4 Hz, 2H), 1.02 (t, *J* = 7.4 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 167.4, 135.8 (q, ^4J = 1.4 Hz), 133.5, 130.8 (q, ^2J = 32 Hz), 125.8 (q, ^3J = 3.8 Hz), 125.08, 125.05, 123.8 (q, ^1J = 270 Hz), 31.3, 21.7, 13.8; HRMS (+APCI) m/z: [M + H]$^+$ Calcd. for $C_{13}H_{13}F_3N$ 240.1000; Found 240.0994.

Diethyl 2-(2-(chloromethyl)allyl)malonate (17). Prepared following a modification of the published procedure.[37] Neat diethylmalonate (0.476 mL, 3.12 mmol) was added dropwise to a 0 °C, DMF suspension (15 mL, 0.20 M) of NaH (43.0 mg, 1.78 mmol) and then the reaction mixture was allowed to warmed to rt. After 55 min, the reaction was transferred by syringe to a DMF solution (15 mL, 0.31 M) of methallyl dichloride (0.541 mL, 4.68 mmol). After 14 h, aqueous 1.0 M HCl (20 mL) was added and then the mixture was extracted with diethyl ether (4 x 20 mL). The combined organic extract was washed with water (1 x 30 mL) and brine (1 x 30 mL), dried ($MgSO_4$), filtered, and then concentrated under reduced pressure. The crude product was purified by flash chromatography (12 g silica gel cartridge, 5% EtOAc/Hexanes eluent) to afford 210 mg (27%) of **i** as a colorless liquid: IR (ATR): 2983, 1729, 1646 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.25-5.19 (m, 1H), 5.02 (td, *J* = 1.4, 1 Hz, 1H), 4.20 (q, *J* = 7.0 Hz, 2H), 4.19 (q, *J* = 7.0 Hz, 2H) 4.06 (d, *J* = 1 Hz, 2H), 3.62 (t, *J* = 7.9 Hz, 1H), 2.79 (br d, 7.9 Hz, 2H), 1.26 (t, *J* = 7 Hz, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 168.7, 141.5, 116.6, 61.6, 50.4, 47.8, 32.0, 14.0; HRMS (+APCI) m/z: [M + H]$^+$ Calcd. for $C_{11}H_{18}O_4Cl$ 249.0894; Found 249.0891.

General Isocyanoalkene Conjugate Addition Procedure: Neat nucleophile (1.5 equiv) was added to a rt, THF solution (0.10 M) of isocyanoalkene (1.0 equiv), base (0.30 – 1.0 equiv), copper iodide (0.025 equiv), and (*S*)-4-tert-butyl-2-(5-(trifluoromethyl)pyridin-2-yl)-4,5-dihydrooxazole (0.025 equiv). The reaction was monitored by TLC (1 – 10 h for cesium carbonate or 5 min – 24 h for NaH) and when complete, saturated, aqueous ammonium chloride was added. The phases were separated, the aqueous phase was extracted with EtOAc (3 x 2 mL), and then the combined organic phase was washed with water (1 x 10 mL) and brine (1 x 10 mL), dried (Na_2SO_4), and filtered. The crude isocyanide was concentrated under reduced pressure and was then purified by silica gel chromatography.

(2-([1,1'-Biphenyl]-4-yl)-2-isocyanoethyl)(phenyl)sulfane (14a). Prepared following the general isocyanoalkene conjugate addition procedure with 4-(1-isocyanovinyl)-1,1'-biphenyl (**13a**)[36] (30.0 mg, 146 mmol), Cs_2CO_3 (14.3 mg, 43.0 mmol), Cu(I)I (0.70 mg, 4.0 mmol), (*S*)-4-(*tert*-butyl)-2-(5-(trifluoromethyl)pyridin-2-yl)-4,5-dihydrooxazole (1.0 mg, 4.0 mmol), and thiophenol (20 mL, 200 mmol) for 1 h at rt to afford, after purification (dry-loaded with Celite onto C-2 silica, 10% EtOAc/Hexanes eluent), 39 mg (85%) of the isocyanosulfide **14a** as a colorless oil: IR (ATR): 3032, 2138 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.62-7.55 (m, 4H), 7.48-7.41 (m, 4H), 7.40-7.26 (m, 6H), 4.76 (dd, *J* = 7.9, 5.9 Hz, 1H), 3.43-3.31 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 158.6, 141.9, 140.2, 134.7, 134.0, 131.2, 129.3, 128.9, 127.7, 127.7, 127.5, 127.1, 126.7, 57.9, 42.8; HRMS (+APCI) m/z: [M + H]$^+$ Calcd. for $C_{21}H_{18}NS$ 316.1160; Found 316.1154.

1-Phenyl-2-(phenylthio)ethan-1-amine (i). Prepared following a modification of the published procedure.[38] Four drops of concentrated, aqueous HCl (12 M) was added to a rt, ethanolic solution (0.2 M) of **14a** (30.0 mg, 95 μmol). After 18 h, the ethanol was removed under reduced pressure and then the residue was dissolved in CH_2Cl_2 (5 mL) that was then washed with water (5 mL). The aqueous phase was separated, neutralized with 2M NaOH until pH = 7 as determined by monitoring with pH paper, and then extracted with CH_2Cl_2 (3 x 5 mL), dried (Na_2SO_4), and concentrated under reduced pressure to afford, after purification (dry-loaded with Celite onto 4g silica gel cartridge, 0 to 100% EtOAc/Hexanes gradient eluent), 29 mg (99%) of the primary amine **i** as a colorless oil: IR (ATR): 3366, 3288, 3028, 2921, 2860 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.59-7.54 (m, 4H), 7.46-7.38 (m, 6H), 7.36-7.27 (m, 3H), 7.23-7.18 (m, 1H), 4.14 (dd, *J* = 9.4, 4.0 Hz, 1H), 3.34 (dd, *J* = 13.4, 4.0 Hz, 1H), 3.06 (dd, *J* = 13.4, 9.4 Hz, 1H), 1.87 (s, 2H); $^{13}C\{^1H\}$ NMR (400 MHz, $CDCl_3$) δ 143.2, 140.8, 140.5, 135.8, 129.8, 129.0, 128.8, 127.34, 127.27, 127.1, 126.8, 126.4, 54.4, 43.8; HRMS (+APCI) m/z: [M - NH_2] Calcd. for $C_{20}H_{17}S$ 289.1051; Found 289.1049.

(E)-N-(1-([1,1'-biphenyl]-4-yl)-2-(phenylthio)ethyl)-1-(2-((S)-dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaborepin-4-yl)phenyl)methanimine (ii). Prepared following the published general procedure:[39] 2-Formylphenylboronic acid (7.8 mg, 52 μmol), and (*S*)-BINOL (17 mg, 57μmol) were added to a $CDCl_3$ (1.0 mL) suspension of the amine **i** (10 mg, 52 μmol), and 4 Å molecular sieves. After 5 min at rt, an aliquot was removed and the ^1H NMR spectrum of **ii** was obtained to determine the enantiomeric ratio (1:1.0) of the staring primary amine **i** by comparing the imine C-H for the (*R*) and (*S*) complexes: ^1H NMR (400 MHz, $CDCl_3$) δ 8.48 (s, 1H), 8.29 (s, 1H) Δ δ = 0.19 ppm.

(2-([1,1'-biphenyl]-4-yl)-2-isocyanoethyl)(allyl)sulfane (14b). Prepared following the general isocyanoalkene conjugate addition procedure with 4-(1-isocyanovinyl)-1,1'-biphenyl (**13a**)[36] (30.0 mg, 146 μmol), NaH (5.26 mg, 219 μmol), Cu(I)I (0.7 mg, 3.7 μmol), (*S*)-4-(*tert*-butyl)-2-(5-(trifluoromethyl)pyridin-2-yl)-4,5-dihydrooxazole (1.0 mg, 3.7 μmol), and allylmercaptan (16.3 mg, 219 μmol) for 30 min at -78 °C to afford, after purification (dry-loaded with Celite onto a C-2 silica gel,[20] 3% EtOAc/Hexanes eluent), 35 mg (86%) of the isocyanoallylsulfane **14b** as a clear oil: IR (ATR): 3030, 2919, 2139, 1633 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.67-7.56 (m, 4H), 7.50-7.42 (m, 4H), 7.41-7.35 (m, 1H), 5.84-5.71 (m, 1H), 5.18-5.01 (m, 2H), 4.85 (dd, *J* = 7.7, 5.7 Hz, 1H), 3.20-3.06 (m, 2H), 3.00 (dd, *J* = 14.1, 7.7 Hz, 1H), 2.93 (dd, *J* = 14.1, 5.7 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 158.4, 141.9, 140.2, 135.0, 133.9, 128.9, 127.7, 127.6, 127.1, 126.7, 118.1, 58.8, 38.2, 35.4; HRMS (+APCI) m/z: [M - NC] $C_{17}H_{17}S$ 253.1051; Found 253.1048.

(2-Isocyano-2-(2-methoxyphenyl)ethyl)(phenyl)sulfane (14c). Prepared following the general isocyanoalkene conjugate addition procedure with 1-(1-isocyanovinyl)-2-methoxybenzene (**13b**) (30.0 mg, 188 μmol), Cs_2CO_3 (18.4 mg, 56.5 μmol), Cu(I)I (0.9 mg, 5 μmol), (*S*)-4-(*tert*-butyl)-2-(5-(trifluoromethyl)pyridin-2-yl)-4,5-dihydrooxazole (1.3 mg, 5.0 μmol), and thiophenol (29 μL, 280 μmol), for 14 h at 50 °C to afford, after purification (dry-loaded with Celite onto a 4g gel silica cartridge, 20% EtOAc/Hexanes eluent), 29 mg (76%) of the isocyanosulfide **14c** as a yellow oil: IR (ATR): 3067, 2140 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.51 (ddt, *J* = 7.6, 1.7, 0.5 Hz, 1H), 7.46-7.42 (m, 2H), 7.34-7.29 (m, 3H), 7.27-7.22 (m, 1H), 7.02 (td, *J* = 7.6, 1.0 Hz, 1H), 6.84 (dd, *J* = 8.2, 1.0 Hz, 1H), 5.16 (dd, *J* = 9.3, 3.7 Hz, 1H), 3.76 (s, 3H), 3.42 (dd, *J* = 14.1, 3.7 Hz, 1H), 3.12 (dd, *J* = 14.1, 9.3 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 157.7, 155.4, 134.6, 130.7, 130.0, 129.0, 127.0, 126.9, 123.9, 121.1, 110.5, 55.3, 53.7, 40.4; HRMS (+APCI) m/z: [M + H]$^+$ Calcd for $C_{16}H_{16}NOS$ 270.0953; Found 270.0949.

Ethyl 3-((2-([1,1'-biphenyl]-4-yl)-2-isocyanoethyl)thio)propanoate (14d) Prepared following the general isocyanoalkene conjugate addition procedure with 4-(1-isocyanovinyl)-1,1'-biphenyl (**13a**)[36] (30.0 mg, 146 μmol), NaH (3.5 mg, 150 μmol), Cu(I)I (0.7 mg, 4 μmol), (*S*)-4-(*tert*-butyl)-2-(5-(trifluoromethyl)pyridin-2-yl)-4,5-dihydrooxazole (1.0 mg, 3.7 μmol), and ethyl-3-mercaptopropionate (29.4 mg, 219 μmol), for 10 min at rt to afford, after purification (dry-loaded with Celite onto a 4g silica gel cartridge, 10% EtOAc/Hexanes eluent), 35 mg (82%) of the isocyanosulfanylester **14d** as a yellow oil: IR (ATR): 3059, 2138, 1728 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67-7.56 (m, 4H), 7.50-7.42 (m, 4H), 7.41-7.35 (m, 1H), 4.89 (dd, *J* = 7.7, 5.8 Hz, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.09 (dd, *J* = 14.0, 7.7 Hz, 1H), 3.03 (dd, *J* = 14.0, 5.8 Hz, 1H), 2.82 (t, *J* = 7.1 Hz, 2H), 2.59 (t, *J* = 7.1 Hz, 2H), 1.26 (t, *J* = 7.1 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 171.6, 158.6, 141.9, 140.1, 134.9, 128.9, 127.7, 127.7, 127.1, 126.6, 60.8, 58.8, 40.6, 34.9, 27.9, 14.2; HRMS (+APCI) m/z: [M - NC] Calcd for $C_{19}H_{21}O_2S$ 313.1262; Found 313.1272.

(2-([1,1'-biphenyl]-4-yl)-2-isocyanoethyl)(3-chloropropyl)sulfane (14e) Prepared following the general isocyanoalkene conjugate addition procedure with 4-(1-isocyanovinyl)-1,1'-biphenyl (**13a**)[36] (50.0 mg, 244 μmol), NaH (8.8 mg, 365 μmol), Cu(I)I (1.2 mg, 6.1 μmol), (*S*)-4-(*tert*-butyl)-2-(5-(trifluoromethyl)pyridin-2-yl)-4,5-dihydrooxazole (1.7 mg, 6.1 μmol), and 3-chloro-1-propanethiol (29.6 mg, 268 μmol) for 28 min at -78 °C to afford, after purification (dry-loaded with Celite onto a C-2 silica gel,[20] 0-3% EtOAc/Hexanes gradient eluent), 59.8 mg (91%) of the isocyanosulfanylchloride **14e** as an oil: IR (ATR): 3030, 2137 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68-7.56 (m, 4H), 7.50-7.43 (m, 4H), 7.41-7.35 (m, 1H), 4.88 (dd, *J* = 7.6, 5.7 Hz, 1H), 3.63 (t, *J* = 6.2 Hz, 2H), 3.07 (dd, *J* = 14.0, 7.6 Hz, 1H), 3.01 (dd, *J* = 14.0, 5.7 Hz, 1H), , 2.70 (t, *J* = 7.0 Hz, 2H), 2.05-1.96 (m, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 158.7, 142.0, 140.1, 134.8, 128.9, 127.8, 127.7, 127.1, 126.7, 58.9, 43.2, 43.4, 32.1, 30.0; HRMS (+APCI) m/z: $[M + H]^+$ Calcd for $C_{18}H_{19}NClS$ 316.0927; Found 316.0926.

(2-([1,1'-Biphenyl]-4-yl)-2-isocyanoethyl)(3-bromopropyl)sulfane (14f). Prepared following the general isocyanoalkene conjugate addition procedure with 4-(1-isocyanovinyl)-1,1'-biphenyl (**13a**)[36] (30.0 mg, 146 μmol), NaH (8.8 mg, 365 μmol), Cu(I)I (0.7 mg, 3.7 μmol), (*S*)-4-(*tert*-butyl)-2-(5-(trifluoromethyl)pyridin-2-yl)-4,5-dihydrooxazole (1.0 mg, 3.7 μmol), and 3-bromopropane-1-thiol (24.9 mg, 161 μmol), 30 min at -78 °C to afford, after purification (dry-loaded with Celite onto a C-2 silica gel,[20] 10% EtOAc/Hexanes eluent), 40.1 mg (76%) of the isocyanosulfanylbromide **14f** as a colorless oil: IR (ATR): 3030, 2921, 2137 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67-7.56 (m, 4H), 7.50-7.42 (m, 4H), 7.41-7.35 (m, 1H), 4.87 (dd, *J* = 7.6, 5.8 Hz, 1H), 3.49 (t, *J* = 6.3 Hz, 2H), 3.07 (dd, *J* = 14.0, 7.6 Hz, 1H), 3.01 (dd, *J* = 14.0, 5.8 Hz, 1H), 2.69 (t, *J* = 7.0 Hz, 2H), 2.14-2.04 (m, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 158.7, 142.0, 140.1, 134.8, 128.9, 127.8, 127.7, 127.1, 126.7, 58.9, 40.41, 32.2, 31.8, 31.2; HRMS (+APCI) m/z: [M - NC] Calcd for $C_{17}H_{18}BrS$ 333.0313; Found 333.0307.

Diethyl 2-(2-([1,1'-biphenyl]-4-yl)-2-isocyanoethyl)-2-methylmalonate (14g) Prepared following the general isocyanoalkene conjugate addition procedure with 4-(1-isocyanovinyl)-1,1'-biphenyl (**13a**)[36] (30.0 mg, 146 μmol), Cs_2CO_3 (14.3 mg, 43.9 μmol), Cu(I)I (0.7 mg, 4 μmol), (*S*)-4-(*tert*-butyl)-2-(5-(trifluoromethyl)pyridin-2-yl)-4,5-dihydrooxazole (1.0 mg, 4 μmol), and diethyl 2-methylmalonate[40] (38.2 mg, 219 μmol) for 29 h at rt to afford, after purification (dry-loaded with Celite onto a C-2 silica gel column,[20] 5% EtOAc/Hexanes eluent), 30 mg (55%) of the isocyanoester **14g** as a yellow oil: IR (ATR): 2982, 2136, 1726 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64-7.56 (m, 4H), 7.51-7.42 (m, 4H), 7.39-7.34 (m, 1H), 5.00 (dd, *J* = 9.2, 3.5 Hz, 1H), 4.30-4.16 (m, 2H), 4.24 (q, *J* = 7.1 Hz, 2H), 2.51 (dd, *J* = 14.9, 9.2 Hz, 1H), 2.44 (dd, *J* = 14.9, 3.5 Hz, 1H), 1.60 (s, 3H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.29 (t, *J* = 7.1 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) 171.3, 171.1, 158.6, 141.5, 140.3, 137.0, 128.9, 127.7, 127.6, 127.1, 126.3, 61.9, 61.8, 54.8, 52.5, 44.6, 20.6, 14.0, 13.9; HRMS (+APCI) m/z: [M - NC] Calcd for $C_{22}H_{25}O_4$ 353.1753; Found 353.1751.

2-(2-([1,1'-biphenyl]-4-yl)-2-isocyanoethyl)-2-methylmalononitrile (14h). Prepared following the general isocyanoalkene conjugate addition procedure with 4-(1-isocyanovinyl)-1,1'-biphenyl (**13a**)[36] (20.0 mg, 97 μmol), Cs_2CO_3 (9.5 mg, 29 μmol), Cu(I)I (0.5 mg, 2 μmol), (*S*)-4-(*tert*-butyl)-2-(5-(trifluoromethyl)pyridin-2-yl)-4,5-dihydrooxazole (0.7 mg, 2 μmol), and 2-methylmalononitrile[41] (12.0 mg, 146 μmol) for 10 min at rt to afford, after purification (dry-loaded with Celite onto a 4g silica gel cartridge, 10% EtOAc/Hexanes eluent), 27 mg (97%) of the isocyanonitrile **14h** as a white oil: IR (ATR): 3027, 2155, 2136 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71-7.66 (m, 2H), 7.61-7.57 (m, 2H), 7.52-7.43 (m, 4H), 7.41-7.36 (m, 1H), 5.08 (dd, *J* = 8.9, 4.9 Hz, 1H), 2.66 (dd, *J* = 14.6, 8.9 Hz, 1H), 2.44 (dd, *J* = 14.6, 4.9 Hz, 1H), 1.95 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) 162.3, 142.9, 139.8, 133.7, 129.0, 128.3, 128.0, 127.2, 126.6, 114.7, 114.6, 55.1, 45.8, 29.7, 25.8; HRMS (+APCI) m/z: [M - NC] Calcd. for $C_{18}H_{15}N_2$ 259.1235; Found 259.1233.

4-([1,1'-biphenyl]-4-yl)-4-isocyano-2,2-diphenylbutanenitrile (14i). Prepared following the general isocyanoalkene conjugate addition procedure with 4-(1-isocyanovinyl)-1,1'-biphenyl (**13a**)[36] (30.0 mg, 146 μmol), NaH (3.5 mg, 146 μmol), Cu(I)I (0.7 mg, 3.7 μmol), (*S*)-4-(*tert*-butyl)-2-(5-(trifluoromethyl)pyridin-2-yl)-4,5-dihydrooxazole (1.0 mg, 3.7 μmol), and diphenylacetonitrile (226 mg, 1.17 mmol), 1.5 h at 0 °C to afford, after purification (dry-loaded with Celite onto a C-2 silica gel,[20] 0-5% EtOAc/Hexanes gradient eluent), 43.5 mg (75%) of the isocyanonitrile **14i** as a colorless oil: IR (ATR): 3031, 2922, 2240, 2137 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60-7.53 (m, 4H), 7.48-7.32 (m, 15H), 4.83 (dd, *J* = 8.7, 3.9 Hz, 1H), 3.20 (dd, *J* = 14.4, 8.7 Hz, 1H), 2.91 (dd, *J* = 14.4, 3.9 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 159.9, 141.9, 140.1, 138.8, 138.7, 136.0, 129.3, 129.2, 128.9, 128.7, 128.5, 127.9, 127.7, 127.1, 127.0, 126.9, 126.5, 120.9, 55.3, 50.0, 47.4; HRMS (+APCI) m/z: $[M + H]^+$ Calcd. for $C_{29}H_{23}N_2$ 399.1861; Found 399.1863.

4-Isocyano-4-(2-methoxyphenyl)-2,2-diphenylbutanenitrile (14j). Prepared following the general isocyanoalkene conjugate addition procedure with 1-(1-isocyanovinyl)-2-methoxybenzene (**13b**) (20.0 mg, 126 μmol), NaH (3.0 mg, 130 μmol), Cu(I)I (0.6 mg, 3.1 μmol), (*S*)-4-(*tert*-butyl)-2-(5-(trifluoromethyl)pyridin-2-yl)-4,5-dihydrooxazole (0.9 mg, 3.1 μmol), and diphenylacetonitrile (36.4 mg, 188 μmol) for 5 h at 0 °C to afford, after purification (dry-loaded with Celite onto a C-2 silica gel,[20] 0-5% EtOAc/Hexanes gradient eluent), 40.8 mg (99%) of the isocyanonitrile **14j** as a colorless oil: IR (ATR): 3073, 2925, 2853, 2138 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47-7.29 (m, 12H), 7.01 (td, *J* = 7.6, 1.1 Hz, 1H), 6.83 (dd, *J* = 8.3, 1.1 Hz, 1H), 5.12 (dd, *J* = 8.9, 3.6 Hz, 1H), 3.77 (s, 3H), 2.96 (dd, *J* = 14.2, 8.9 Hz, 1H), 2.87 (dd, *J* = 14.2, 3.6 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 159.2, 155.2, 139.3, 139.0, 130.0, 129.1, 128.9, 128.4, 128.3, 127.07, 127.06, 126.9, 125.2, 121.0, 120.95, 110.7, 55.2, 50.7, 49.8, 44.8; HRMS (+APCI) m/z: [M - NC] Calcd. for $C_{23}H_{20}ON$ 326.1545; Found 326.1544.

1-(2-([1,1'-biphenyl]-4-yl)-2-isocyanoethyl)-1H-imidazole (14k). Prepared following the general isocyanoalkene conjugate addition procedure with 4-(1-isocyanovinyl)-1,1'-biphenyl (**13a**)[36] (30.0 mg, 146 μmol), NaH (3.5 mg, 146 μmol), Cu(I)I (0.7 mg, 3.7 μmol), (*S*)-4-(*tert*-butyl)-2-(5-(trifluoromethyl)pyridin-2-yl)-4,5-dihydrooxazole (1.0 mg, 3.7 μmol), and imidazole (79.6 mg, 1.17 mmol) for 5 h at 0 °C to afford, after purification (dry-loaded with Celite onto a 4 g silica gel cartridge, 0-6% MeOH/CH_2Cl_2 gradient eluent), 35.0 mg (88%) of the isocyanoimidazole **14k** as a yellow oil: IR (ATR): 3111, 3031, 2934, 2139, 1670 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66–7.55 (m, 4H), 7.50–7.42 (m, 2H), 7.42–7.36 (m, 1H), 7.34 (t, J = 1.2 Hz, 1H), 7.31–7.27 (m, 2H), 7.07 (t, J = 1.2 Hz, 1H), 6.90 (t, J = 1.2 Hz, 1H), 5.02 (t, J = 5.9 Hz, 1H), 4.37 (d, J = 5.9 Hz, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 161.1, 142.6, 139.8, 137.6, 131.9, 130.1, 129.0, 128.0, 127.96, 127.1, 126.5, 119.4, 59.2, 53.1; HRMS (+APCI) m/z: [M + H]$^{+}$ Calcd. for $C_{18}H_{16}N_3$ 274.1344; Found 274.1339.

2-(2-([1,1'-biphenyl]-4-yl)-2-isocyanoethyl)isoindoline-1,3-dione (14l). Prepared following the general isocyanoalkene conjugate addition procedure with 4-(1-isocyanovinyl)-1,1'-biphenyl (**13a**)[36] (30.0 mg, 146 µmol), NaH (7.0 mg, 292 µmol), Cu(I)I (0.7 mg, 3.7 µmol), (*S*)-4-(*tert*-butyl)-2-(5-(trifluoromethyl)pyridin-2-yl)-4,5-dihydrooxazole (1.0 mg, 3.7 µmol), and phthamilidine (53.8 mg, 365 µmol) for 97 h at 50 °C to afford, after purification (dry-loaded with Celite onto a 4 g silica gel cartridge, 0–5% MeOH/CH_2Cl_2 gradient eluent), 38.0 mg (75%) of the isocyanophthamilide **14l** as a yellow solid (mp 138.4–139.4 °C): IR (ATR): 3031, 2947, 2139, 1776, 1714 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93–7.88 (m, 2H), 7.80–7.74 (m, 2H), 7.67–7.62 (m, 2H), 7.61–7.56 (m, 2H), 7.56–7.51 (m, 2H), 7.48–7.42 (m, 2H), 7.40–7.35 (m, 1H), 5.28 (dd, J = 9.7, 5.4 Hz, 1H), 4.28 (dd, J = 13.9, 9.7 Hz, 1H), 3.91 (dd, J = 13.9, 5.4 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 167.7, 159.8, 142.2, 140.1, 134.4, 132.7, 131.7, 128.9, 127.9, 127.8, 127.1, 126.8, 123.8, 56.3, 44.1; HRMS (+APCI) m/z: [M - NC] Calcd. for $C_{22}H_{16}O_2N$ 326.1181; Found 326.1179.

General Isocyanocyclopropane Synthesis Procedure: Neat ester (1.1 equiv) was added to a rt, THF solution (0.10 M) of isocyanoalkene (1.0 equiv), Cs_2CO_3 (1.2 equiv), Cu(I)I (0.025), and ligand (0.025 equiv). Upon completion, as determined by monitoring by TLC, saturated, aqueous ammonium chloride was added. The phases were separated and then the aqueous phase was extracted with EtOAc (3 x 2 mL). The combined organic extract was washed with water (1 x 10 mL) and brine (1 x 10 mL), dried (Na_2SO_4), filtered, and then concentrated under reduced pressure. The crude product was purified by flash chromatography.

Diethyl 2-([1,1'-biphenyl]-4-yl)-2-isocyanocyclopropane-1,1-dicarboxylate (16a). Prepared following the general isocyanocyclopropane synthesis procedure with 4-(1-isocyanovinyl)-1,1'-biphenyl (**13a**)[36] (20.0 mg, 97.4 µmol), Cs_2CO_3 (34.9 mg, 107 µmol), Cu(I)I (0.5 mg, 2. 4 µmol), (*S*)-4-(*tert*-butyl)-2-(5-(trifluoromethyl)pyridin-2-yl)-4,5-dihydrooxazole (0.7 mg, 2.4 µmol), and diethyl bromomalonate (25.6 mg, 107 µmol) for 2 h at rt to afford, after purification (dry-loaded with Celite onto C-2 silica gel,[20] 5% EtOAc/Hexanes eluent), 29.0 mg (83%) of the isocyanocyclopropane **16a** as a colorless oil: IR (ATR) 2981, 2129, 1736 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64–7.54 (m, 4H), 7.53–7.34 (m, 5H), 4.40 (q, J = 7.1 Hz, 2H), 3.94–3.81 (m, 2H), 2.50 (ABq, Δv = 37.6 Hz, J = 6.8, 2H), 1.40 (t, J = 7.1 Hz, 3H), 0.91 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 164.8, 164.4, 158.6, 142.4, 140.0, 130.7, 128.9, 128.5, 127.9, 127.3, 127.1, 62.9, 62.2, 46.6, 43.1, 23.3, 14.1, 13.5; HRMS (+APCI) m/z: [M + H]$^{+}$ Calcd. for $C_{22}H_{22}O_4N$ 364.1549; Found 364.1546.

Dimethyl 2-([1,1'-biphenyl]-4-yl)-2-isocyanocyclopropane-1,1-dicarboxylate (16b). Prepared following the general isocyanocyclopropane synthesis procedure with 4-(1-isocyanovinyl)-1,1'-biphenyl (**13a**)[36] (30.0 mg, 150 µmol), Cs_2CO_3 (57.1 mg, 175 µmol), Cu(I)I (0.7 mg, 3.7 µmol), (*S*)-4-(*tert*-butyl)-2-(5-(trifluoromethyl)pyridin-2-yl)-4,5-dihydrooxazole (1.0 mg, 3.7 µmol), and dimethyl bromomalonate (33.9 mg, 161 µmol) for 4 h at rt to afford, after purification (dry-loaded with Celite onto C-2 silica gel,[20] 5% EtOAc/Hexanes eluent), 36.2 mg (74%) of the isocyanocyclopropane **16b** as a yellow solid (mp 114.8–115.8 °C): IR (ATR) 2953, 2130, 1740 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64–7.56 (m, 4H), 7.52–7.34 (m, 5H), 3.94 (s, 1H), 3.42 (s, 1H), 2.53 (ABq, Δv = 34.1 Hz, J = 6.8 Hz, 2H); ^{13}C{^{1}H} NMR (400 MHz, $CDCl_3$) δ 165.2, 164.8, 158.9, 142.5, 139.9, 130.5, 128.9, 128.5, 127.9, 127.3, 127.2, 53.8, 53.1, 46.8, 43.3, 23.7; HRMS (+APCI) m/z: [M + H]$^{+}$ Calcd. for $C_{20}H_{18}O_4N$ 336.1236; Found 336.1231. HPLC (Daicel Chiral Technologies Inc. CHIRALPAK® IE, ethyl acetate/hexanes = 10/90, flow rate = 2.0 mL/min, l = 238 nm) tR = 8.9 min (major), 10.5 min (minor) indicated er = 1.05:1.00. *Preparation of Dimethyl 2-([1,1'-biphenyl]-4-yl)-2-isocyanocyclopropane-1,1-dicarboxylate (16b) on a One Millimole Scale.* Repeated the preparation of **16b** on a one mmol scale with 4-(1-isocyanovinyl)-1,1'-biphenyl (**13a**)[36] (206.0 mg, 1.00 mmol), Cs_2CO_3 (392.4 mg, 1.20 mmol), Cu(I)I (4.8 mg, 0.025 mmol), (*S*)-4-(*tert*-butyl)-2-(5-(trifluoromethyl)pyridin-2-yl)-4,5-dihydrooxazole (6.8 mg, 0.025 mmol), and dimethyl bromomalonate (233.0 mg, 1.10 mmol) for 105 h at rt to afford, after purification (dry-loaded with Celite onto C-2 silica gel,[20] 5% EtOAc/Hexanes eluent), 235.0 mg (70%) of the isocyanocyclopropane **16b** as a yellow solid spectrally identical to material previously isolated.

Di-tert-butyl 2-([1,1'-biphenyl]-4-yl)-2-isocyanocyclopropane-1,1-dicarboxylate (16c). Prepared following the general isocyanocyclopropane synthesis procedure with 4-(1-isocyanovinyl)-1,1'-biphenyl (**13a**)[36] (30.0 mg, 146 µmol), Cs_2CO_3 (57.1 mg, 175 µmol), Cu(I)I (0.7 mg, 3.7 µmol), (*S*)-4-(*tert*-butyl)-2-(5-(trifluoromethyl)pyridin-2-yl)-4,5-dihydrooxazole (1.0 mg, 3.7 µmol), and di-*tert*-butyl bromomalonate (47.5 mg, 161 µmol) for 2 h at rt to afford, after purification (dry-loaded with Celite onto C-2 silica gel,[20] 5% EtOAc/Hexanes eluent), 51.4 mg (84%) of the isocyanocyclopropane **16c** as a yellow oil: IR (ATR) 2981, 2133, 1733 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62–7.55 (m, 4H), 7.51–7.43 (m, 4H), 7.40–7.35 (m, 1H), 2.35 (ABq, Δv = 65.3 Hz, J = 6.7, 2H), 1.60 (s, 9H), 1.11 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 163.9, 163.5, 157.8, 142.2, 140.1, 131.3, 128.9, 128.6, 127.8, 127.2, 127.1, 83.4, 82.8, 46.0, 44.4, 28.0, 27.3, 22.7; HRMS (+APCI) m/z: [M + H]$^{+}$ Calcd. for $C_{26}H_{30}NO_4$ 420.2175; Found 420.2184.

Diethyl 2-isocyano-2-(o-tolyl)cyclopropane-1,1-dicarboxylate (16d). Prepared following the general isocyanocyclopropane synthesis procedure with 1-(1-isocyanovinyl)-2-methylbenzene[36] (30.0 mg, 210z µmol), Cs_2CO_3 (81.9 mg, 251 µmol), Cu(I)I (1.0 mg, 5.2 µmol), (*S*)-4-(*tert*-butyl)-2-(5-(trifluoromethyl)pyridin-2-yl)-4,5-dihydrooxazole (1.4 mg, 5.2 µmol), and diethyl bromomalonate (65.1 mg, 272 µmol) for 44 h at rt to afford, after purification (dry-loaded with Celite onto C-2 silica gel,[20] 0-5% EtOAc/Hexanes gradient eluent), 38.8 mg (62%) of the isocyanocyclopropane **16d** as a yellow oil: IR (ATR) 2926, 2126, 1731 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.25 (m, 2H), 7.23–7.16 (m, 2H), 4.46–4.36 (m, 2H), 3.88 (q, J = 7.1 Hz, 2H), 2.54 (s, 3H), 2.41 (ABq, Δv = 16.3 Hz, J = 6.4 Hz, 2H), 1.40 (t, J = 7.1 Hz, 3H), 0.91 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 164.9, 164.6, 157.9, 138.8, 131.1, 130.4, 129.8, 129.2, 126.0, 62.8, 62.1, 53.2, 42.0, 24.2, 19.1, 14.1, 13.5; HRMS (+APCI) m/z: [M + H]$^{+}$ Calcd. for $C_{17}H_{20}NO_4$ 302.1393; Found 302.1385.

Diethyl 2-isocyano-2-(naphthalen-2-yl)cyclopropane-1,1-dicarboxylate (16e). Prepared following the general isocyanocyclopropane synthesis procedure with 2-(1-isocyanovinyl)naphthalene[36] (30.0 mg, 167 µmol), Cs_2CO_3 (65.5 mg, 201 µmol), Cu(I)I (0.8 mg, 4.2 µmol), (*S*)-4-(*tert*-butyl)-2-(5-(trifluoromethyl)pyridin-2-yl)-4,5-dihydrooxazole (1.1 mg, 4.2 µmol), and diethyl bromomalonate (52.0 mg, 218 µmol) for 46 h at rt to afford, after purification (dry-loaded with Celite onto C-2 silica gel,[20] 10% EtOAc/Hexanes eluent), 42.8 mg (76%) of the isocyanocyclopropane **16e** as a colorless oil: IR (ATR) 2923, 2129, 1732 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88–7.81 (m, 4H), 7.60–7.50 (m, 3H), 4.41 (q, J = 7.2 Hz, 2H), 3.83–3.68 (m, 2H), 2.58 (ABq, Δv = 70.4 Hz, J = 6.8 Hz, 2H), 1.42 (t, J = 7.1 Hz, 3H), 0.78 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 165.0, 164.5, 162.0, 133.6, 132.8, 129.3, 128.8, 128.4, 127.9, 127.7, 127.3, 127.0, 125.3, 63.0, 62.2, 47.1, 43.2, 23.5, 14.3, 13.6; HRMS (+APCI) m/z: $[M + H]^+$ Calcd. for $C_{20}H_{20}O_4N$ 338.1393; Found 338.1392.

Diethyl 2-isocyano-2-(4-methoxyphenyl)cyclopropane-1,1-dicarboxylate (16f). Prepared following the general isocyanocyclopropane synthesis procedure with 1-(1-isocyanovinyl)-4-methoxybenzene[36] (30.0 mg, 188 μmol), Cs_2CO_3 (92.1 mg, 283 μmol), Cu(I)I (0.9 mg, 4.7 μmol), (*S*)-4-(*tert*-butyl)-2-(5-(trifluoromethyl)pyridin-2-yl)-4,5-dihydrooxazole (1.3 mg, 4.7 μmol), and diethyl bromomalonate (67.6 mg, 283 μmol) for 2.5 h at rt to afford, after purification (dry-loaded with Celite onto a 4 g silica gel cartridge, 10% EtOAc/Hexanes eluent), 45.0 mg (76%) of the isocyanocyclopropane **16f** as a yellow oil: IR (ATR) 2963, 2129, 1735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37-7.31 (m, 2H), 6.95-6.80 (m, 2H), 4.36 (q, J = 7.1 Hz, 2H), 3.91-3.81 (m, 2H), 3.80 (s, 3H), 2.41 (ABq, Δv = 42.7 Hz, J = 6.7 Hz, 2H), 1.37 (t, J = 7.1 Hz, 3H), 0.94 (t, J = 7.1, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 165.1, 164.6, 160.5, 158.1, 129.7, 124.0, 114.1, 62.9, 62.2, 55.5, 43.0, 26.1, 23.5, 14.3, 13.8; HRMS (+APCI) m/z: [M - NC] Calcd. for $C_{16}H_{19}O_5$ 291.1233; Found 291.1235

Diethyl 2-isocyano-2-(2-methoxyphenyl)cyclopropane-1,1-dicarboxylate (16g). Prepared following the general isocyanocyclopropane synthesis procedure with 1-(1-isocyanovinyl)-2-methoxybenzene (**13b**) (30.0 mg, 188 μmol), Cs_2CO_3 (73.7 mg, 226 μmol), Cu(I)I (0.9 mg, 4.7 μmol), (*S*)-4-(*tert*-butyl)-2-(5-(trifluoromethyl)pyridin-2-yl)-4,5-dihydrooxazole (1.3 mg, 4.7 μmol), and diethyl bromomalonate (58.6 mg, 245 μmol) for 19 h at rt to afford, after purification (dry-loaded with Celite onto C-2 silica gel,[20] 0-5% EtOAc/Hexanes gradient eluent), 48.0 mg (80%) of the isocyanocyclopropane **16g** as a yellow oil: IR (ATR) 2982, 2129, 1726 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 (td, J = 8, 1.7 Hz, 1H), 7.30 (dd, J = 7.6, 1.7 Hz, 1H), 6.94 (t, J = 7.6 Hz, 1H), 6.89 (d, J = 8 Hz, 1H), 4.40 (q, J = 7.1 Hz, 2H), 3.93-3.78 (m, 2H), 3.88 (s, 3H), 2.33 (ABq, Δv = 35.9 Hz, J = 6.4 Hz, 2H), 1.41 (t, J = 7.1 Hz, 3H), 0.96 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 165.4, 165.2, 158.2, 131.2, 130.1, 121.1, 120.6, 120.4, 111.0, 62.5, 61.7, 55.5, 43.9, 41.4, 24.7, 14.2, 13.6; HRMS (+APCI) m/z: $[M + H]^+$ Calcd. for $C_{17}H_{20}NO_5$ 318.1342; Found 318.1331.

Diethyl 2-(4-chlorophenyl)-2-isocyanocyclopropane-1,1-dicarboxylate (16h). Following the general procedure for the synthesis of isocyanocyclopropanes with 1-chloro-4-(1-isocyanovinyl)benzene[36] (42.0 mg, 257 μmol), Cs_2CO_3 (100.7 mg, 308 μmol), Cu(I)I (1.2 mg, 6.4 μmol), (*S*)-4-(*tert*-butyl)-2-(5-(trifluoromethyl)pyridin-2-yl)-4,5-dihydrooxazole (1.7 mg, 6.4 μmol), and diethyl bromomalonate (67.5 mg, 282 μmol) for 19 h at rt to afford, after purification (dry-loaded with Celite onto C-2 silica gel,[20] 0-5% EtOAc/Hexanes gradient eluent), 57.0 mg (70%) of isocyanocyclopropane **16h** as a colorless oil: IR (ATR) 2984, 2129, 1730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40-7.33 (m, 4H), 4.38 (q, J = 7.1 Hz, 1H), 4.37 (q, J = 7.1 Hz, 1H), 3.95-3.82 (m, 2H), 2.43 (ABq, Δv = 27.0, J = 6.8 Hz, 2H), 1.38 (t, J = 7.1 Hz, 3H), 0.96 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 164.6, 164.2, 159.0, 135.7, 130.4, 129.5, 128.9, 62.9, 62.3, 46.1, 42.9, 23.3, 14.1, 13.6; HRMS (+APCI) m/z: $[M + H]^+$ Calcd. for $C_{16}H_{17}NO_4Cl$ 322.0846; Found 322.0838.

Diethyl 2-isocyano-3-propyl-2-(4-(trifluoromethyl)phenyl)cyclopropane-1,1-dicarboxylate (16i). Prepared following the general isocyanocyclopropane synthesis procedure with (*Z*)-1-(1-isocyanopent-1-en-1-yl)-4-(trifluoromethyl)benzene (**15a**, 20.0 mg, 83 μmol), Cs_2CO_3 (32.7 mg, 100 μmol), Cu(I)I (0.4 mg, 2 μmol), (*S*)-4-(*tert*-butyl)-2-(5-(trifluoromethyl)pyridin-2-yl)-4,5-dihydrooxazole (0.6 mg, 2 μmol), and diethyl bromomalonate (12 μL, 130 μmol) for 20 h at 50 °C to afford, after purification (4g silica gel cartridge, 10% EtOAc/Hexanes eluent), 29 mg (86%) of isocyanocyclopropane **16i** as a yellow oil: IR (ATR): 2964, 2876, 2126, 1735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.60 (dd, J = 33.9, 8.1 Hz, 4H), 4.37 (q, J = 7.1 Hz, 2H), 3.97-3.84 (m, 2H), 2.63-2.57 (m, 1H), 2.05-1.90 (m, 1H), 1.74-1.61 (m, 3H), 1.38 (t, J = 7.1 Hz, 3H), 1.08 (t, J = 7.1 Hz, 3H), 0.98 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 164.9, 163.3, 161.1, 137.0 (q, ^4J = 1.6 Hz), 131.5 (q, ^2J = 32.5 Hz), 128.9, 125.7 (q, ^3J = 3.8 Hz), 123.6 (q, ^1J = 273.7 Hz), 62.5, 62.3, 49.4, 44.7, 32.1, 27.1, 21.6 14.0, 13.8, 13.6; ^{19}F NMR (400 MHz, $CDCl_3$) δ -62.9; HRMS (+APCI) m/z: $[M + H]^+$ Calcd. $C_{20}H_{23}F_3NO_4$ 398.1579; Found 398.1579.

Diethyl (E)-2-isocyano-2-styrylcyclopropane-1,1-dicarboxylate (16j). Prepared following the general isocyanocyclopropane synthesis procedure with (*E*)-(3-isocyanobuta-1,3-dien-1-yl)benzene[36] (7.0 mg, 45 μmol), Cs_2CO_3 (17.3 mg, 54.0 μmol), Cu(I)I (0.2 mg, 1 μmol), (*S*)-4-(*tert*-butyl)-2-(5-(trifluoromethyl)pyridin-2-yl)-4,5-dihydrooxazole (0.3 mg, 1 μmol), and diethyl bromomalonate (80 μL, 50 μmol) for 25 min at rt to afford, after purification (4g silica gel cartridge, 5% EtOAc/Hexanes eluent), 10 mg (71%) of isocyanocyclopropane **16j** as a colorless oil: IR (ATR) 3031, 2983, 2132, 1731 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41-7.27 (m, 5H), 6.94 (d, J = 15.7 Hz, 1H), 6.10 (d, J = 15.7 Hz, 1H), 4.39-4.31 (m, 2H), 4.23 (q, J = 7.1 Hz, 2H), 2.26 (ABq, Δv = 121.8 Hz, J = 6.6 Hz, 2H), 1.36 (t, J = 7.1 Hz, 3H), 1.26 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (400 MHz, $CDCl_3$) δ 165.5, 164.7, 159.8, 135.2, 133.8, 128.8, 128.5, 126.7, 119.7, 77.2, 62.8, 62.6, 42.7, 26.5, 14.1, 14.0; HRMS (+APCI) m/z: $[M + H]^+$ Calcd. for $C_{18}H_{20}O_4N$ 314.1393; Found 314.1391.

Diethyl 3-([1,1'-biphenyl]-4-yl)-3-isocyano-5-methylenecyclohexane-1,1-dicarboxylate (16k). Prepared following the general isocyanocyclopropane synthesis procedure with 4-(1-isocyanovinyl)-1,1'-biphenyl (**13a**)[36] (20.0 mg, 97.4 μmol), Cs_2CO_3 (38 mg, 120 μmol), Cu(I)I (0.5 mg, 2 μmol), (S)-4-(*tert*-butyl)-2-(5-(trifluoromethyl)pyridin-2-yl)-4,5-dihydrooxazole (0.7 mg, 2 μmol), and diethyl 2-(2-(chloromethyl)allyl)malonate[37] (36.4 mg, 146 μmol), 24 h at room temperature to afford, after purification (4g silica gel cartridge, 20% EtOAc/Hexanes eluent), 36 mg (88%) of the isocyanocyclopropane **16k** as a yellow oil: IR (ATR): 3036, 2128, 1731 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.68-7.58 (m, 6H), 7.50-7.44 (m, 2H), 7.41-7.36 (m, 1H), 5.29 (q, J = 1.6 Hz, 1H), 5.13 (q, J = 1.7 Hz, 1H), 4.39-4.32 (m, 1H), 4.29-4.14 (m, 3H), 3.32 (dt, J = 13.7, 2 Hz, 1H), 2.94 (dt, J = 14.7, 2 Hz, 1H), 2.72-2.56 (m, 3H), 2.30 (dq, J = 13.7, 2 Hz, 1H), 1.32 (t, J = 7.1 Hz, 3H), 1.26 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (400 MHz, $CDCl_3$) δ 171.0, 169.1, 159.8, 141.4, 140.1, 139.5, 137.4, 128.9, 127.7, 127.5, 127.1, 125.2, 116.8, 64.7, 62.1, 61.8, 54.4, 47.3, 40.7, 37.9, 14.0, 13.8; HRMS (+APCI) m/z: $[M + H]^+$ Calcd. for $C_{26}H_{28}O_4N$ 418.2019; Found 418.2022.

Dimethyl (E)-2-([1,1'-biphenyl]-4-yl)-2-((7-benzyl-7,8-dihydroimidazo[1,5-a]pyrazin-5(6H)-ylidene)amino)cyclopropane-1,1-dicarboxylate (22): Prepared following a modification of the published procedure.[42] An ethanolic solution (0.2 M) of N-((1*H*-imidazol-5-yl)methyl)-1-phenylmethanamine (12 mg, 60 μmol), paraformaldehyde (1.8 mg, 50 μmol), and isocyanide **16b** (20 mg, 60 μmol) were stirred at rt. After 90 h, the reaction mixture was concentrated under reduced pressure and then purified (silica gel column 2 cm x 10 cm, 3% MeOH/CH_2Cl_2 eluent) to afford 26 mg (82%) of the benzoimadazopyrazine **22** as a yellow oil: IR (ATR): 3029, 2952, 2822, 1731 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.06-8.01 (m, 2H), 7.73-7.68 (m, 2H), 7.67-7.62 (m, 2H), 7.51-7.44 (m, 2H), 7.43-7.32 (m, 5H), 7.32-7.26 (m, 1H), 7.12 (d, J = 1.0 Hz, 1H), 6.72 (d, J = 1.0 Hz, 1H), 4.25 (d, J = 18.2 Hz, 1H), 3.92 (d, J

= 13.3 Hz, 1H), 3.76 (d, J = 14.3 Hz, 1H), 3.72-3.63 (m, 3H), 3.69 (s, 3H), 3.48 (ABq, Δv = 70.7, J = 12.6 Hz, 2H), 3.46 (s, 3H); $^{13}C\{^1H\}$ NMR (400 MHz, $CDCl_3$): δ 173.3, 170.1, 168.0, 145.1, 140.0, 137.3, 133.1, 131.0, 129.0, 128.95, 128.4, 128.1, 127.4, 127.2, 126.5, 122.9, 92.2, 66.9, 61.0, 57.9, 53.2, 52.8, 47.5, 44.9; HRMS (+APCI) m/z: $[M + H]^+$ Calcd. for $C_{32}H_{31}N_4O_4$ 535.2346; Found 535.2337.

ASSOCIATED CONTENT

Supporting Information

^1H and ^{13}C spectra and an HPLC trace of racemate **16a** are provided in the supporting information.

The Supporting Information is available free of charge on the ACS Publications website.

FAIR Data is available as Supporting Information for publication which includes the primary NMR FID files for compounds: **13b**, **15**, **17**, **14a**, **i**, **ii**, **14b**, **14c**, **14d**, **14e**, **14f**, **14g**, **14h**, **14i**, **14j**, **14k**, **14l**, **16a**, **16b**, **16c**, **16d**, **16e**, **16f**, **16g**, **16h**, **16i**, **16j**, **16k**, and **22**.

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The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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