JOC The Journal of Organic Chemistry

Note

pubs.acs.org/joc

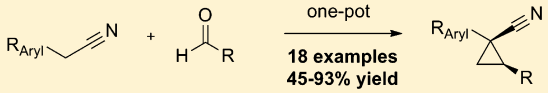
Diastereoselective One-Pot Knoevenagel Condensation/Corey–Chaykovsky Cyclopropanation

Jeremy J. Clemens,* Juliana L. Asgian, Brett B. Busch, Timothy Coon, Justin Ernst, Leonard Kaljevic, Paul J. Krenitsky, Timothy D. Neubert, Edwin J. Schweiger,† Andreas Termin, and Dean Stamos

Department of Drug Innovation, Vertex Pharmaceuticals, 11010 Torreyana Road, San Diego, California 92121, United States

Supporting Information

ABSTRACT: Efforts to substitute the cyclopropane ring in a series of aryl cyclopropylnitriles led to the discovery of an operationally simple one-pot method for Knoevenagel condensation and subsequent Corey–Chaykovsky cyclopropanation giving diastereomerically pure products as a racemic mixture of enantiomers. Method development and results for variably substituted aryl acetonitriles and aldehydes in the reaction are reported. A concise synthesis of (±)-bicifadine in two steps is provided to demonstrate the utility of the method.



Trisubstituted aryl cyclopropylnitriles have found utility in organic synthesis as precursors to a wide variety of natural products,[1,2] biologically active compounds,[3,4] and important materials.[5,6] Current methodology to rapidly assemble these compounds primarily relies on addition/cyclization reactions between aryl acetonitriles and epihalohydrins[7,8] or 1,4-additions of aryl acetonitriles in anionic[9−12] or ylide[13−15] forms to Michael acceptors followed by a cyclization step. Additional approaches to access trisubstituted aryl cyclopropylnitriles include carbenoid chemistry[16−18] or the treatment of acrylonitriles with sulfur/sulfoxonium ylides[19,20] or photochemical conditions.[21] A rapid method for the introduction of a wider variety of groups on the cyclopropyl ring directly from aryl acetonitriles in one step is, however, lacking. Dimethylsulfoxonium methylide, or "the Corey ylide," has proven to be an excellent tool in the synthesis of a wide variety of functional groups including epoxides, aziridines, and cyclopropanes since its inception nearly five decades ago. In one embodiment of use, the ylide is known to readily cyclopropanate α,β-unsaturated nitriles to give the corresponding cyclopropylnitriles in excellent yields.[22,23]

Here, we wish to report a one-pot procedure in which the basic conditions utilized to generate the Corey ylide in situ combine to catalyze a Knoevenagel condensation between aryl acetonitriles and aldehydes with the intermediate α,β-unsaturated nitriles undergoing cyclopropanation to give tri- and tetrasubstituted aryl cyclopropylnitriles diastereoselectively as a racemic mixture of two enantiomers. The reported reaction represents the transformation of a methylene group into an all-carbon quaternary center in one pot. Method development, scope, and an example of the utility of this facile transformation are reported.

Arising from our desire to diastereoselectively substitute the cyclopropyl ring of a geminal aryl/nitrile cyclopropane with functionality *syn* with respect to the nitrile, we envisioned a two-step process involving Knoevenagel condensation of aryl acetonitriles with aldehydes followed by cyclopropanation of the resulting olefin. In the case of phenylacetonitrile **1a** and benzyloxyacetaldehyde **2a** the method was found to proceed favorably by utilizing catalytic cesium carbonate as the base in *N*-methylpyrrolidinone (NMP) to give a mixture of aldol adduct **3** and desired olefin **4** in a 4:1 ratio and 79% combined yield (Scheme 1). The products are separated, and compound **3** is dehydrated by treatment with methanesulfonyl chloride and pyridine to give additional **4** in 73% yield. The resulting acrylonitrile was then subjected to a Corey–Chaykovsky cyclopropanation using potassium *tert*-butoxide in DMSO giving compound **5** in 66% yield and 41% overall yield for the three-step process.

The observation that both the condensation and cyclopropanation reactions take place under basic conditions in polar solvent led to the hypothesis that the reactions could be performed in tandem in one pot. To this end, compounds **1a** and **2a** (1 equiv each) were combined in DMSO followed by the addition of trimethylsulfoxonium iodide and potassium *tert*-butoxide (1.1 equiv each). The mixture was stirred for 30 min at room temperature giving product **5** in 40% yield as a single diastereomer after workup and purification (racemic mixture of enantiomers; relative stereochemistry proven by NOE after reduction of the nitrile; see Supporting Information). Manipulating the stoichiometry of the reaction resulted in an optimized 62% yield using 2 equiv of activated methylene compound, trimethylsulfoxonium iodide, and potassium *tert*-butoxide accompanied with 1 equiv of aldehyde (Table 1).

In a scan of reaction conditions, lithium, sodium, and potassium bis(trimethylsilyl)amide as well as potassium *tert*-butoxide were found to be suitable bases. The utilization of cesium carbonate, 1,8-diazabicyclo[5.4.0]undec-7-ene, or sodium *tert*-butoxide suppressed the yield of the reaction. Both DMSO and THF were found to be suitable solvents. Manipulating the order of addition, temperature, concentration, and duration and attempting to preform the Corey ylide did not improve the yield. In summary, optimal yields were

Received: November 13, 2012
Published: December 19, 2012

Scheme 1. Three-Step Synthesis of Compound 5

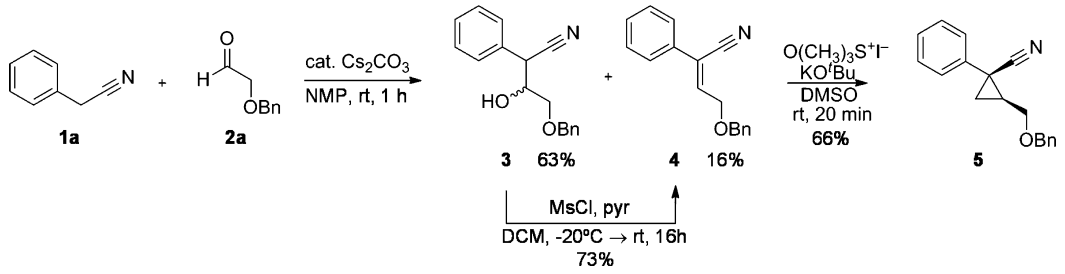
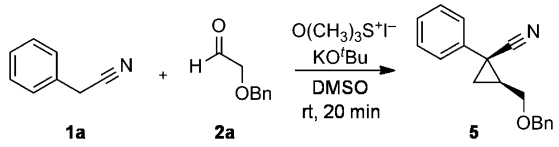


Table 1. Optimization of Reaction Stoichiometry



equivalents				
1a	2a	$O(CH_3)_3S^+I^-$	KO^tBu	yield (%)[a]
1	1	1.1	1.1	40
1	1	1.5	1.5	40
1	1	1.1	2	42
1	1	2	1.1	40
1	2	2	2	26
2	1	2	2	62

[a]Reactions run at 0.25 mmol scale, 1 M in DMSO, quenched by addition of saturated aqueous ammonium chloride.

obtained by adding 2 equiv of potassium *tert*-butoxide to a stirring solution of activated methylene compound (2 equiv), aldehyde (1 equiv), and trimethylsulfoxonium iodide (2 equiv) in DMSO at room temperature followed by stirring for 20 min and quenching with saturated aqueous ammonium chloride.

With reaction conditions determined, the reactivity of a set of seven aryl acetonitriles with benzyloxyacetaldehyde as well as nine benzaldehydes with phenylacetonitrile was assessed, the results of which are included in Table 2. Yields in the transformation fell generally in the ~50−75% range.

In all cases, analysis of crude reaction mixtures by LCMS showed the formation of diastereomerically pure products (racemic mixture of enantiomers). The cyclopropyl substitution arising from the aldehyde bears a *syn* relationship to the nitrile group in the case of phenylacetonitrile and benzyloxyacetaldehyde (proven by NOE after reduction of the nitrile of **5**; see Scheme 2 and Supporting Information). This observation can be rationalized by increased steric repulsion imparted by the aryl ring (relative to the nitrile) on the aldehyde derived side chain during 1,3-elimination of dimethylsulfoxide in the cyclopropanation of the intermediate acrylonitrile. This effect has previously been reported in the construction of similar cyclopropanes from cyanohydrins.[1,8]

Construction of the pyrrolidine ring of (±)-bicifadine as described below also demonstrates the *syn* relationship between the nitrile group and aldehyde derived functionality. Minimal byproducts were observed in the crude reaction mixtures, with the mass balance of the low yielding reactions comprised of unreacted starting materials or degradation to unidentifiable products. Occasionally a small amount of byproduct **12** (0−20% by UV detection in LCMS at 254 nm) presumably arising from nucleophilic 1,4-addition of deprotonated aryl nitrile to the Knoevenagel adduct intermediate of aryl nitrile to aldehyde was observed in the crude mixture (Scheme 3).

In order to demonstrate the utility of the method, the synthesis of bicifadine was targeted in an attempt to produce this biologically interesting serotonin/norepinephrine reuptake inhibitor in racemic form rapidly.[24,25] To this end, 4-methylphenylacetonitrile **13** and benzyloxyacetaldehyde **2a** were subjected to the cyclopropanation method giving compound **14** in 55% yield (Scheme 4). Compound **14** was next heated to 175 °C by microwave irradiation in the presence of lithium aluminum hydride in an effort to effectively reduce the nitrile. On inspection of the reaction, however, the displacement of the benzyloxy anion by the newly produced amine had occurred giving (±)-bicifadine as the HCl salt after purification in 66% yield.

In summary we have reported a novel, one-pot Knoevenagel condensation/Corey−Chaykovsky cyclopropanation sequence between activated methylenes and aldehydes to produce differentially substituted and diastereomerically pure cyclopropanes. An optimized method is provided along with results for variably substituted aryl acetonitriles and benzaldehydes in the reaction. Additionally the method was applied to a concise synthesis of (±)-bicifadine in two steps and 36% overall yield.

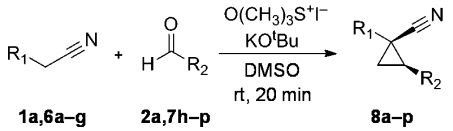
■ EXPERIMENTAL SECTION

General. Reactions were performed in sealed glass vials under an air atmosphere. Commercially available reagents and solvents were used without further purification. 1D-NMR spectra were recorded using a 400 or 500 MHz spectrometer with TMS as the internal standard. 2D-NMR was recorded on a 500 MHz spectrometer. Chemical shifts (δ) are given in parts per million (ppm) and coupling constants (J) are reported in Hertz (Hz). Column chromatography was performed on normal phase silica gel (230−400 mesh, 35−70 μm). Reversed-phase preparatory HPLC was performed on a 5 μm C18 column. HRMS analysis was performed on an ESI-TOF mass spectrometer or Orbitrap mass spectrometer. A 2 mg/mL solution of sodium iodide in isopropanol was infused through a reference channel and used as a lock mass for correction calculations. Mass accuracy errors were obtained using the formula: [[(observed mass) − (exact mass)]/exact mass − 1] * 1000000 = error (ppm).

General Procedure for the One-Pot Knoevenagel Condensation/Corey−Chaykovsky Cyclopropanation. *General Procedure A.* To a stirring solution of activated methylene compound (2 mmol) and aldehyde (1 mmol) in 1 mL of DMSO was added trimethylsulfoxonium iodide (2 mmol) followed by potassium *tert*-butoxide (2 mmol), and the suspension was stirred at room temperature for 20 min. Saturated aqueous ammonium chloride (5 mL) was added, and the mixture was extracted with diethyl ether (3 × 5 mL). The organic phases were combined, dried (magnesium sulfate), filtered, concentrated, and purified as indicated below. Compounds purified by reversed-phase HPLC used a gradient from 1 to 99% mobile phase B (mobile phase A = 0.1% HCl in water, mobile phase B = 0.1% HCl in CH_3CN). Compounds purified by silica gel

dx.doi.org/10.1021/jo302443k | J. Org. Chem. 2013, 78, 780−785

Table 2. Synthesis of 8a–p by the One-Pot Knoevenagel Condensation/Corey–Chaykovsky Cyclopropanation Reaction

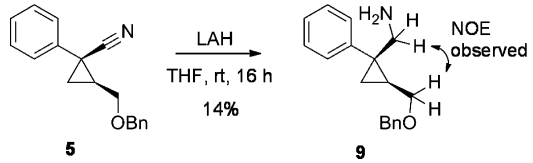


1a,6a–g 2a,7h–p 8a–p

Nitrile	Aldehyde	Product	Yield (%)
6a	2a	8a	69
6b	2a	8b	74
6c	2a	8c	57
6d	2a	8d	45
6e	2a	8e	51
6f	2a	8f	61
6g	2a	8g	48
1a	7h	8h	60
1a	7i	8i	64
1a	7j	8j	73
1a	7k	8k	58
1a	7l	8l	93
1a	7m	8m	61
1a	7n	8n	61
1a	7o	8o	63
1a	7p	8p	53

[a]Isolated yields. Reactions run at 1 mmol scale, 1 M in DMSO, quenched by addition of saturated aqueous ammonium chloride.

Scheme 2. Reduction of 5 and Determination of Relative Stereochemistry of Cyclopropane Ring



5 9

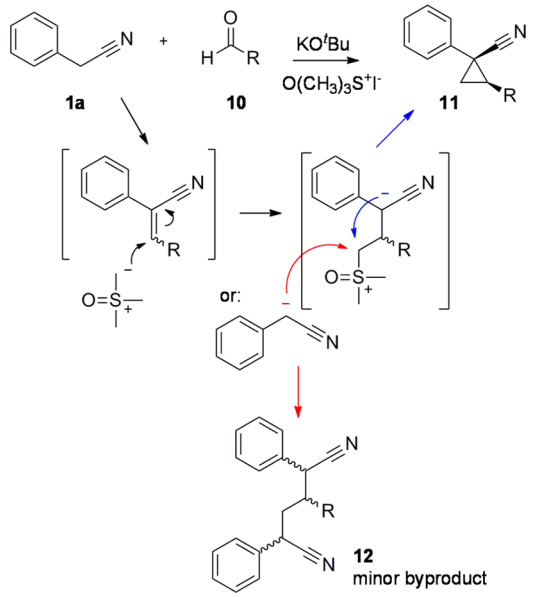
chromatography used a gradient from 100% hexanes to 100% ethyl acetate unless otherwise noted.

2-(Benzyloxymethyl)-1-phenylcyclopropanecarbonitrile (5). Prepared in 62% yield (163.3 mg) from phenylacetonitrile and benzyloxyacetaldehyde using General Procedure A. Purification by reversed-phase preparatory HPLC gave **5** as a tan oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44–7.16 (m, 10H), 4.64 (d, J = 11.8 Hz, 1H), 4.59 (d, J = 11.8 Hz, 1H), 3.86 (dd, J = 5.7, 10.7 Hz, 1H), 3.70 (dd, J = 7.9, 10.7 Hz, 1H), 2.03–1.84 (m, 1H), 1.67–1.53 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.0, 136.0, 129.1, 128.7, 128.1, 128.02, 127.96, 126.2, 120.7, 73.6, 70.6, 29.5, 21.8, 19.7. HRMS calculated for $[M + H]^+$ ($C_{18}H_{17}NOH^+$) 264.1388, found 264.1396.

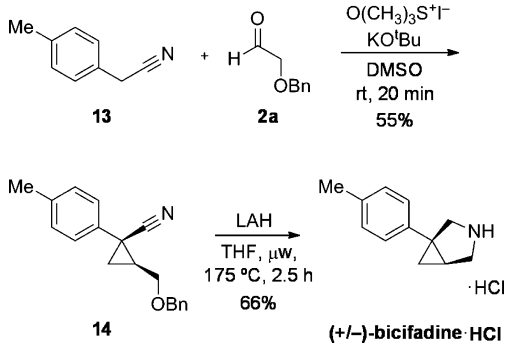
2-(Benzyloxymethyl)-1-(pyridin-2-yl)cyclopropanecarbonitrile (8a). Prepared in 69% yield (182.4 mg) from 2-(pyridin-2-yl)acetonitrile and benzyloxyacetaldehyde using General Procedure A. Purification by silica gel column chromatography gave **8a** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46–8.39 (m, 1H), 7.73–7.68 (m, 1H), 7.68–7.61 (m, 1H), 7.41–7.29 (m, 4H), 7.29–7.23 (m, 1H), 7.16–7.10 (m, 1H), 4.62 (d, J = 11.8 Hz, 1H), 4.58 (d, J = 11.8 Hz, 1H), 3.91 (dd, J = 5.3, 10.8 Hz, 1H), 3.65 (dd, J = 8.3, 10.8 Hz, 1H), 2.43–2.31 (m, 1H), 2.02 (dd, J = 4.6, 8.9 Hz, 1H), 1.58 (dd, J = 4.6, 7.4 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.1, 149.5, 137.8, 136.6, 128.4, 127.83, 127.75, 122.0, 120.9, 120.0, 73.3, 70.1, 30.8, 23.3, 21.0. HRMS calculated for $[M + H]^+$ ($C_{17}H_{16}N_2OH^+$) 265.1341, found 265.1340.

dx.doi.org/10.1021/jo302443k | J. Org. Chem. 2013, 78, 780–785

Scheme 3. Proposed Mechanism for the Formation of Product 11 and Minor Byproduct 12



Scheme 4. Two-Step Synthesis of (±)-Bicifadine Utilizing the One-Pot Knoevenagel Condensation/Corey–Chaykovsky Cyclopropanation Reaction



2-(Benzyloxymethyl)-1-(pyridin-3-yl)cyclopropanecarbonitrile (8b). Prepared in 74% yield (195.5 mg) from 2-(pyridin-3-yl)acetonitrile and benzyloxyacetaldehyde using General Procedure A. Purification by reversed-phase preparatory HPLC gave **8b** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.87 (d, J = 1.7 Hz, 1H), 8.80 (d, J = 5.3 Hz, 1H), 8.52 (d, J = 8.1 Hz, 1H), 7.94 (dd, J = 5.6, 8.1 Hz, 1H), 7.40–7.31 (m, 4H), 7.31–7.25 (m, 1H), 4.63 (d, J = 11.8 Hz, 1H), 4.59 (d, J = 11.8 Hz, 1H), 4.04 (dd, J = 4.3, 10.9 Hz, 1H), 3.58 (dd, J = 8.6, 10.9 Hz, 1H), 2.29–2.18 (m, 1H), 2.08 (dd, J = 6.4, 9.1 Hz, 1H), 1.91 (dd, J = 6.6, 7.4 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.7, 140.0, 138.5, 138.1, 137.6, 128.7, 128.23, 128.16, 127.1, 117.9, 73.9, 69.6, 32.6, 23.3, 18.2. HRMS calculated for $[M + H]^+$ ($C_{17}H_{16}N_2OH^+$) 265.1341, found 265.1328

2-(Benzyloxymethyl)-1-(pyridin-4-yl)cyclopropanecarbonitrile (8c). Prepared in 57% yield (150.6 mg) from 2-(pyridin-4-yl)acetonitrile and benzyloxyacetaldehyde using General Procedure A. Purification by reversed-phase preparatory HPLC gave **8c** as an orange oil after addition of aqueous sodium bicarbonate and extraction with ethyl acetate. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (d, J = 5.5 Hz, 2H), 7.40–7.32 (m, 4H), 7.32–7.27 (m, 1H), 7.20–7.15 (m, 2H), 4.63 (d, J = 11.8 Hz, 1H), 4.58 (d, J = 11.8 Hz, 1H), 3.90 (dd, J = 5.3, 10.7 Hz, 1H), 3.68 (dd, J = 7.9, 10.7 Hz, 1H), 2.07–1.96 (m, 1H), 1.73 (two overlapping doublet of doublets, J = 5.9, 11.2, 6.0, 12.7 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.3, 145.7, 137.7, 128.7, 128.2, 128.1, 120.0, 119.0, 73.8, 70.1, 31.5, 23.4, 19.3. HRMS calculated for $[M + H]^+$ ($C_{17}H_{16}N_2OH+$) 265.1341, found 265.1353.

2-(Benzyloxymethyl)-1-(thiophen-2-yl)cyclopropanecarbonitrile (8d). Prepared in 45% yield (121.2 mg) from 2-(thiophen-2-yl)acetonitrile and benzyloxyacetaldehyde using General Procedure A. Purification by silica gel column chromatography using a gradient from 100% hexanes to 30% ethyl acetate/hexanes gave **8d** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44–7.33 (m, 4H), 7.33–7.26 (m, 1H), 7.18 (dd, J = 1.2, 5.2 Hz, 1H), 7.06 (dd, J = 1.2, 3.6 Hz, 1H), 6.93 (dd, J = 3.6, 5.2 Hz, 1H), 4.64 (d, J = 11.8 Hz, 1H), 4.59 (d, J = 11.8 Hz, 1H), 3.83 (dd, J = 5.6, 10.8 Hz, 1H), 3.66 (dd, J = 7.9, 10.8 Hz, 1H), 2.04–1.92 (m, 1H), 1.62 (two overlapping doublet of doublets, J = 5.6, 8.0, 6.1, 7.7 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.2, 137.9, 128.7, 128.0 (2C), 127.4, 126.2, 125.0, 119.9, 73.6, 70.1, 30.8, 23.3, 15.8. HRMS calculated for $[M + H]^+$ ($C_{16}H_{15}NOSH^+$) 270.0952, found 270.0944.

2-(Benzyloxymethyl)-1-(4-chlorophenyl)cyclopropanecarbonitrile (8e). Prepared in 51% yield (152.0 mg) from 4-chlorophenylacetonitrile and benzyloxyacetaldehyde using General Procedure A. Purification by reversed-phase preparatory HPLC gave **8e** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.26 (m, 7H), 7.26–7.19 (m, 2H), 4.63 (d, J = 11.8 Hz, 1H), 4.59 (d, J = 11.8 Hz, 1H), 3.87 (dd, J = 5.5, 10.7 Hz, 1H), 3.65 (dd, J = 8.0, 10.7 Hz, 1H), 1.93–1.82 (m, 1H), 1.58 (two overlapping doublet of doublets, J = 5.8, 8.2, 6.0, 7.7 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.9, 134.7, 133.9, 129.3, 128.7, 128.0 (2C), 127.7, 120.3, 73.7, 70.4, 29.7, 21.7, 19.2. HRMS calculated for $[M + H]^+$ ($C_{18}H_{16}ClNOH^+$) 298.0998, found 298.0989.

2-(Benzyloxymethyl)-1-(4-bromophenyl)cyclopropanecarbonitrile (8f). Prepared in 61% yield (208.7 mg) from 4-bromophenylacetonitrile and benzyloxyacetaldehyde using General Procedure A. Purification by reversed-phase preparatory HPLC gave **8f** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50–7.43 (m, 2H), 7.40–7.32 (m, 4H), 7.32–7.26 (m, 1H), 7.20–7.13 (m, 2H), 4.64 (d, J = 11.8 Hz, 1H), 4.59 (d, J = 11.8 Hz, 1H), 3.86 (dd, J = 5.5, 10.7 Hz, 1H), 3.65 (dd, J = 8.0, 10.7 Hz, 1H), 1.95–1.82 (m, 1H), 1.58 (two overlapping doublet of doublets, J = 5.8, 7.7, 6.5, 7.8 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.9, 135.2, 132.3, 128.7, 128.09, 128.08, 128.0, 122.0, 120.2, 73.7, 70.4, 29.7, 21.8, 19.3. HRMS calculated for $[M + H]^+$ ($C_{18}H_{16}BrNOH^+$) 342.0493, found 342.0509.

2-(Benzyloxymethyl)-1-(4-iodophenyl)cyclopropanecarbonitrile (8g). Prepared in 48% yield (187.2 mg) from 4-iodophenylacetonitrile and benzyloxyacetaldehyde using General Procedure A. Purification by reversed-phase preparatory HPLC gave **8g** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71–7.63 (m, 2H), 7.41–7.32 (m, 4H), 7.32–7.27 (m, 1H), 7.07–7.00 (m, 2H), 4.64 (d, J = 11.8 Hz, 1H), 4.59 (d, J = 11.8 Hz, 1H), 3.86 (dd, J = 5.5, 10.7 Hz, 1H), 3.66 (dd, J = 8.0, 10.7 Hz, 1H), 1.95–1.83 (m, 1H), 1.60 (two overlapping doublet of doublets, J = 5.8, 6.7, 5.8, 6.3 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.2, 137.9, 136.0, 128.7, 128.12, 128.09, 128.07, 120.2, 93.3, 73.7, 70.4, 29.8, 21.9, 19.4. HRMS calculated for $[M + H]^+$ ($C_{18}H_{16}INOH^+$) 390.0355, found 390.0364.

1,2-Diphenylcyclopropanecarbonitrile (8h). Prepared in 60% yield (131.6 mg) from phenylacetonitrile and benzaldehyde using General Procedure A. Purification by reversed-phase preparatory HPLC gave **8h** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46–7.36 (m, 6H), 7.36–7.28 (m, 4H), 2.79 (dd, J = 8.4 Hz, 1H), 2.20 (dd, J = 6.2, 7.8 Hz, 1H), 2.01 (dd, J = 7.6, 16.5 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.4, 135.1, 129.2, 128.9, 128.3, 128.1, 128.0, 125.9, 120.1, 35.6, 24.0, 22.0. HRMS calculated for $[M + H]^+$ ($C_{16}H_{13}NH^+$) 220.1121, found m/z 220.1122.

2-(Naphthalen-2-yl)-1-phenylcyclopropanecarbonitrile (8i). Prepared in 64% yield (172.9 mg) from phenylacetonitrile and 2-naphthaldehyde using General Procedure A. Purification by silica gel column chromatography gave **8i** as a slightly off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90–7.81 (m, 3H), 7.80–7.75 (m, 1H), 7.53–7.29 (m, 8H), 2.96 (t, J = 8.4 Hz, 1H), 2.35 (dd, J = 6.2, 7.8 Hz, 1H), 2.09 (dd, J = 6.2, 8.9 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.4, 133.5, 133.2, 132.7, 129.3, 128.7, 128.1, 128.03, 127.95, 127.2, 126.6,

dx.doi.org/10.1021/jo302443k | J. Org. Chem. 2013, 78, 780–785

126.4, 126.3, 125.9, 120.1, 35.9, 24.2, 22.2. HRMS calculated for $[M + H]^+$ ($C_{20}H_{15}NH^+$) 270.1282, found 270.1295.

2-(4-(Dimethylamino)phenyl)-1-phenylcyclopropanecarbonitrile (8j). Prepared in 73% yield (192.1 mg) from phenylacetonitrile and 4-(dimethylamino)benzaldehyde using General Procedure A with the exception that saturated aqueous sodium bicarbonate was used to quench and ethyl acetate was used in extraction. Purification by silica gel column chromatography gave **8j** as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42−7.34 (m, 4H), 7.34−7.27 (m, 1H), 7.23−7.16 (m, 2H), 6.79−6.69 (m, 2H), 2.96 (s, 6H), 2.72 (t, J = 8.4 Hz, 1H), 2.15 (dd, J = 6.1, 7.9 Hz, 1H), 1.95 (dd, J = 6.1, 9.0 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.7, 136.8, 129.1, 129.0, 127.7, 125.7, 122.5, 120.6, 112.7, 40.7, 35.8, 23.9, 22.2. HRMS calculated for $[M + H]^+$ ($C_{18}H_{18}N_2H^+$) 263.1548, found 263.1559.

2-(3-(Dimethylamino)phenyl)-1-phenylcyclopropanecarbonitrile (8k). Prepared in 58% yield (152.7 mg) from phenylacetonitrile and 3-(dimethylamino)benzaldehyde using General Procedure A. Purification by reversed-phase preparatory HPLC gave **8k** as a yellow oil after addition of saturated aqueous sodium bicarbonate and extraction with ethyl acetate. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.35 (m, 4H), 7.34−7.27 (m, 1H), 7.27−7.20 (m, 1H), 6.70−6.64 (m, 3H), 2.95 (s, 6H), 2.74 (t, J = 8.4 Hz, 1H), 2.17 (dd, J = 6.1, 7.9 Hz, 1H), 1.95 (dd, J = 6.1, 9.0 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.9, 136.7, 135.8, 129.4, 129.1, 127.8, 125.8, 120.2, 116.1, 112.4, 112.3, 40.7, 36.3, 23.8, 22.3. HRMS calculated for $[M + H]^+$ ($C_{18}H_{18}N_2H^+$) 263.1548, found 263.1537.

2-(4-Methoxyphenyl)-1-phenylcyclopropanecarbonitrile (8l). Prepared in 93% yield (232.6 mg) from phenylacetonitrile and 4-methoxybenzaldehyde using General Procedure A. Purification by silica gel column chromatography gave **8l** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42−7.34 (m, 4H), 7.34−7.28 (m, 1H), 7.28−7.22 (m, 2H), 6.96−6.88 (m, 2H), 3.81 (s, 3H), 2.75 (t, J = 8.4 Hz, 1H), 2.15 (dd, J = 6.1, 7.8 Hz, 1H), 1.98 (dd, J = 6.1, 9.0 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.5, 136.5, 129.5, 129.2, 127.8, 127.2, 125.7, 120.3, 114.3, 55.5, 35.3, 23.9, 22.2. HRMS calculated for $[M + H]^+$ ($C_{17}H_{15}NOH^+$) 250.1232, found 250.1223.

2-(3-Methoxyphenyl)-1-phenylcyclopropanecarbonitrile (8m). Prepared in 61% yield (152.6 mg) from phenylacetonitrile and 3-methoxybenzaldehyde using General Procedure A. The crude product was purified by reversed-phase preparatory HPLC giving **8m** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43−7.36 (m, 4H), 7.36−7.28 (m, 2H), 6.95−6.90 (m, 1H), 6.89−6.84 (m, 2H), 3.82 (s, 3H), 2.77 (t, J = 8.4 Hz, 1H), 2.19 (dd, J = 6.2, 7.8 Hz, 1H), 2.00 (dd, J = 6.1, 8.9 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.0, 136.7, 136.4, 129.9, 129.2, 128.0, 125.9, 120.5, 120.1, 114.2, 113.5, 55.5, 35.7, 24.0, 22.1. HRMS calculated for $[M + H]^+$ ($C_{17}H_{15}NOH^+$) 250.1232, found 250.1227.

2-(2-Methoxyphenyl)-1-phenylcyclopropanecarbonitrile (8n). Prepared in 61% yield (152.6 mg) from phenylacetonitrile and 2-methoxybenzaldehyde using General Procedure A. Purification by reversed-phase preparatory HPLC gave **8n** as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53−7.47 (m, 2H), 7.43−7.36 (m, 2H), 7.36−7.29 (m, 2H), 7.21−7.15 (m, 1H), 7.02−6.93 (m, 2H), 3.90 (s, 3H), 2.82 (t, J = 8.3 Hz, 1H), 2.10 (dd, J = 5.8, 7.9 Hz, 1H), 1.91 (dd, J = 5.8, 8.7 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.3, 137.0, 129.4, 129.0, 128.5, 127.9, 127.0, 124.3, 120.8, 120.7, 110.6, 55.7, 30.2, 22.8, 20.9. HRMS calculated for $[M + H]^+$ ($C_{17}H_{15}NOH^+$) 250.1232, found 250.1228.

2-(3,4-Dimethoxyphenyl)-1-phenylcyclopropanecarbonitrile (8o). Prepared in 63% yield (176.5 mg) from phenylacetonitrile and 3,4-dimethoxybenzaldehyde using General Procedure A. Purification by reversed-phase preparatory HPLC gave **8o** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44−7.35 (m, 4H), 7.35−7.29 (m, 1H), 6.89−6.87 (m, 2H), 6.86−6.82 (m, 1H), 3.91 (s, 3H), 3.89 (s, 3H), 2.76 (t, J = 8.2 Hz, 1H), 2.17 (dd, J = 6.2, 7.8 Hz, 1H), 1.99 (dd, J = 6.1, 9.0 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.2, 149.0, 136.5, 129.2, 127.9, 127.6, 125.6, 120.3, 120.3, 111.7, 111.4, 56.1, 56.1, 35.7, 24.0, 22.4. HRMS calculated for $[M + H]^+$ ($C_{18}H_{17}NO_2H^+$) 280.1337, found 280.1328.

2-(3,5-Dimethoxyphenyl)-1-phenylcyclopropanecarbonitrile (8p). Prepared in 53% yield (148.5 mg) from phenylacetonitrile and 3,5-dimethoxybenzaldehyde using General Procedure A. Purification by reversed-phase preparatory HPLC gave **8p** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43−7.35 (m, 4H), 7.35−7.29 (m, 1H), 6.47 (d, J = 2.2 Hz, 2H), 6.42 (t, J = 2.2 Hz, 1H), 3.80 (s, 6H), 2.73 (t, J = 8.4 Hz, 1H), 2.16 (dd, J = 6.2, 7.8 Hz, 1H), 1.97 (dd, J = 6.2, 8.9 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.1, 137.4, 136.4, 129.2, 128.0, 125.9, 120.0, 106.5, 100.1, 55.6, 35.8, 23.9, 22.2. HRMS calculated for $[M + H]^+$ ($C_{18}H_{17}NO_2H^+$) 280.1337, found 280.1346.

(2-(Benzyloxymethyl)-1-phenylcyclopropyl)methanamine (9). To a stirring solution of **3** (35.7 mg, 0.1356 mmol) in 0.5 mL of THF under a nitrogen atmosphere lithium aluminum hydride (2.5 M in THF, 54.2 μL, 0.1356 mmol) was added dropwise. The solution was warmed to room temperature, stirred 16 h, filtered, and washed with MeOH and the filtrate was concentrated and purified by reversed-phase preparatory HPLC using a gradient from 1 to 99% mobile phase B (mobile phase A = 0.1% HCl in water, mobile phase B = 0.1% HCl in CH_3CN) giving 5.0 mg of **9** as a colorless oil in 14% yield (5.0 mg). ^{1}H NMR (400 MHz, DMSO) δ 7.84 (bs, 2H), 7.38 (d, J = 4.4 Hz, 4H), 7.36 (d, J = 4.3 Hz, 4H), 7.32 (dd, J = 4.3, 8.3 Hz, 1H), 7.28 (dd, J = 4.3, 8.7 Hz, 1H), 4.58 (d, J = 12.0 Hz, 1H), 4.53 (d, J = 12.0 Hz, 1H), 3.82 (dd, J = 5.9, 10.9 Hz, 1H), 3.55 (dd, J = 9.1, 10.8 Hz, 1H), 3.37 (dd, J = 7.0, 14.0 Hz, 1H), 3.02 (d, J = 13.7 Hz, 1H), 1.51−1.39 (m, 1H), 1.25 (dd, J = 5.1, 8.8 Hz, 1H), 1.13−1.02 (m, 1H). ^{13}C NMR (126 MHz, DMSO) δ 144.5, 138.6, 129.0, 128.3, 128.1, 127.5, 127.4, 126.1, 71.8, 69.8, 46.2, 23.7, 16.1.

2-(Benzyloxymethyl)-1-*p*-tolylcyclopropanecarbonitrile (14). Prepared in 55% yield (153.0 mg) from 4-methylphenylacetonitrile (6.658 mmol) and benzyloxyacetaldehyde (3.329 mmol) using General Procedure A. Purification by silica gel column chromatography gave **14** as a pale orange oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41−7.31 (m, 4H), 7.31−7.25 (m, 1H), 7.21−7.16 (m, 2H), 7.16−7.09 (m, 2H), 4.63 (d, J = 11.8 Hz, 1H), 4.58 (d, J = 11.8 Hz, 1H), 3.84 (dd, J = 5.7, 10.7 Hz, 1H), 3.68 (dd, J = 7.9, 10.7 Hz, 1H), 2.32 (s, 3H), 1.92−1.81 (m, 1H), 1.57 (dd, J = 5.6, 8.7 Hz, 1H), 1.51 (dd, J = 5.6, 7.2 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.0, 137.8, 133.0, 129.7, 128.6, 128.0, 127.9, 126.2, 120.8, 73.5, 70.6, 29.2, 21.5, 21.1, 19.3. HRMS calculated for $[M + H]^+$ ($C_{19}H_{19}NOH^+$) 278.1545, found 278.1555.

1-*p*-Tolyl-3-azabicyclo[3.1.0]hexane·HCl ((±)-Bicifadine·HCl). To a stirring solution of **14** (300 mg, 1.082 mmol) in THF (10.85 mL) under a nitrogen atmosphere at 0 °C lithium aluminum hydride (2.5 M in THF, 2.705 mL, 5.410 mmol) was added dropwise. The solution was warmed to room temperature, capped, and heated under microwave irradiation to 175 °C for 2.5 h. The reaction was quenched with water followed by 5 N NaOH (3 mL) and diluted with saturated aqueous potassium sodium tartrate (100 mL). This solution was extracted with dichloromethane (3 × 75 mL), and the organic fractions were combined, dried ($MgSO_4$), filtered, and concentrated to a clear oil which was purified by reversed-phase preparatory HPLC using a gradient from 1 to 99% mobile phase B (mobile phase A = 0.05% HCl in water, mobile phase B = 0.05% HCl in CH_3CN) giving **(±)-bicifadine•HCl** as a white solid in 66% yield (149 mg). ^{1}H NMR (400 MHz, DMSO) δ 9.53 (bs, 2H), 7.17−7.11 (m, 4H), 3.65 (d, J = 11.2 Hz, 1H), 3.47 (dd, J = 3.8, 11.2 Hz, 1H), 3.40 (d, 1H), 3.35 (d, 1H), 2.27 (s, 3H), 2.10−2.01 (m, 1H), 1.31 (t, J = 6.5 Hz, 1H), 1.03 (t, J = 7.2 Hz, 1H). ^{13}C NMR (101 MHz, DMSO) δ 136.2, 135.7, 129.0, 126.5, 49.5, 46.9, 30.1, 23.0, 20.6, 15.3. HRMS calculated for $[M + H]^+$ ($C_{12}H_{15}NH^+$) 174.1282, found 174.1283.

■ ASSOCIATED CONTENT

Supporting Information

NMR spectra, compiled HRMS data, and LCMS traces. This material is available free of charge via the Internet at http://pubs.acs.org.

dx.doi.org/10.1021/jo302443k | J. Org. Chem. 2013, 78, 780−785

AUTHOR INFORMATION

Corresponding Author

*E-mail: jeremy_clemens@sd.vrtx.com.

Present Address

[†]DART NeuroScience LLC, 10420 Wateridge Ct., San Diego, CA 92121.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We are grateful to Khisal Alvi and Xiaoli Wang for analytical support. We thank Professors Michael E. Jung and Brian M. Stoltz for useful discussions as well as Dr. John Saunders for research support. Dedicated to Professor Michael E. Jung on the occasion of his 65th birthday.

REFERENCES

(1) Katagiri, T.; Irie, M.; Uneyama, K. *Org. Lett.* **2000**, *2*, 2423.
(2) Bryson, T.; Koen, J., Jr.; Roth, G. *Synlett* **1992**, 723.
(3) Epstein, J.; Brabander, H.; Fanshawe, W.; Hofmann, C.; McKenzie, T.; Safir, S.; Osterberg, A.; Cosulich, D.; Lovell, F. *J. Med. Chem.* **1981**, *24*, 481.
(4) Vervisch, K.; D'hooghe, M.; Törnroos, K.; De Kimpe, N. *Org. Biomol. Chem.* **2009**, *7*, 3271.
(5) Kusumoto, T.; Nakayama, A.; Sato, K.; Hiyama, T.; Takehara, S.; Osawa, M.; Nakamura, K. *Chem. Lett.* **1992**, 2047.
(6) Kusumoto, T.; Nakayama, A.; Sato, K.; Hiyama, T.; Takehara, S.; Shoji, T.; Osawa, M.; Kuriyama, T.; Nakamura, K.; Fujisawa, T. *Tetrahedron Lett.* **1991**, *32*, 939.
(7) Albrecht, U.; Freifeld, I.; Reinke, H.; Langer, P. *Tetrahedron* **2006**, *62*, 5775.
(8) Langer, P.; Freifeld, I. *Org. Lett.* **2001**, *3*, 3903.
(9) Nishiyama, K.; Oda, J.; Inoue, Y. *Bull. Inst. Chem. Res., Kyoto Univ.* **1974**, *52*, 499.
(10) Agawa, T.; Yoshida, Y.; Komatsu, M.; Oshiro, Y. *J. Chem. Soc., Perkin Trans. 1* **1981**, 751.
(11) Ericsson, A.; Plobeck, N.; Bäckvall, J. *Acta Chem. Scand.* **1994**, *48*, 252.
(12) Marini, F.; Sternativo, S.; Del Verme, F.; Testaferri, L.; Tiecco, M. *Adv. Synth. Catal.* **2009**, *351*, 1801.
(13) Yoneda, R.; Santo, K.; Harusawa, S.; Kurihara, T. *Synth. Commun.* **1987**, *17*, 921.
(14) Hori, M.; Kataoka, T.; Shimizu, H.; Tsutsumi, K.; Yoshimatsu, M. *J. Org. Chem.* **1990**, *55*, 2458.
(15) Jończyk, A.; Konarska, A. *Synlett* **1999**, 1085.
(16) Moss, R.; Kmiecik-Lawrynowicz, G.; Cox, D. *Synth. Commun.* **1984**, *14*, 21.
(17) Denton, J.; Cheng, K.; Davies, H. *Chem. Commun.* **2008**, 1238.
(18) Nowlan, D., III; Gregg, T.; Davies, H.; Singleton, D. *J. Am. Chem. Soc.* **2003**, *125*, 15902.
(19) Wu, W.; Burnett, D.; Caplen, M.; Domalski, M.; Bennett, C.; Greenlee, W.; Hawes, B.; O'Neill, K.; Weig, B.; Weston, D.; Spar, B.; Kowalski, T. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3674.
(20) Li, A.; Dai, L. *Chem. Rev.* **1997**, *97*, 2341.
(21) Kumagai, T.; Segawa, T.; Endo, Z.; Mukai, T. *Tetrahedron Lett.* **1986**, *27*, 6225.
(22) Gololobov, Y.; Nesmeyanov, A.; Lysenko, V.; Boldeskul, I. *Tetrahedron* **1987**, *43*, 2609.
(23) Aggarwal, V.; Winn, C. *Acc. Chem. Res.* **2004**, *37*, 611.
(24) Xu, F.; Murry, J.; Simmons, B.; Corley, E.; Fitch, K.; Karady, S.; Tschaen, D. *Org. Lett.* **2006**, *8*, 3885.
(25) Chen, Z.; Yang, J.; Little, G.; Keats, A. *J. Label Compd. Radiopharm.* **2007**, *50*, 97.