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Palladium-Catalyzed Double Carbonylation Using Near Stoichiometric Carbon Monoxide: Expedient Access to Substituted $^{13}C_2$-Labeled Phenethylamines

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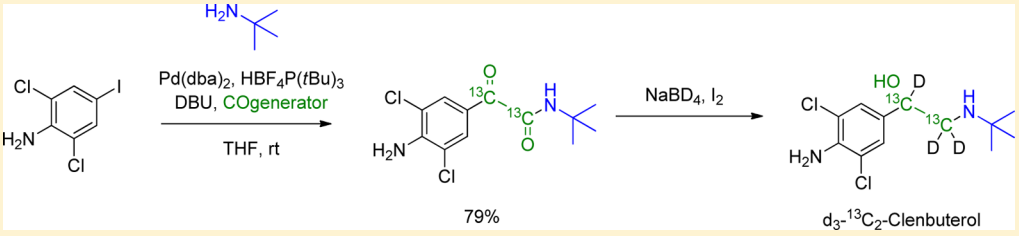
Supporting Information



ABSTRACT: A novel and general approach for $^{13}C_2$- and ^{2}H-labeled phenethylamine derivatives has been developed, based on a highly convergent single-step assembly of the carbon skeleton. The efficient incorporation of two carbon-13 isotopes into phenethylamines was accomplished using a palladium-catalyzed double carbonylation of aryl iodides with near stoichiometric carbon monoxide.

INTRODUCTION

Phenethylamine is a monoamine alkaloid, which is found naturally in living organisms and many foods, for example, chocolate.[1] Substituted phenethylamines constitute an important class of compounds whereof many are involved in regulating neurotransmission, and the phenethylamine backbone is present in a variety of endogenous neuromodulators, designer drugs, and therapeutic agents (Figure 1).[2] These compounds can be categorized into (a) the phenethylamines, including tyramine (a peripheral sympathomimetic compound produced from tyrosine in the fermentation of foods),[3] mescaline (a natural psychotropic agent),[4] and compounds from the 2C family of synthetic psychedelic and hallucinogenic drugs,[5] and (b) the amphetamines, for example, methamphetamine, Bromo-DragonFLY (a synthetic psychedelic and hallucinogenic compound with a potency comparable to LSD),[6] the anti-Parkinsonian drug, Selegiline, the naturally occurring sympathomimetic amine, ephedrine, and cathinone (active compound in the illicit drug khat). Catecholamines represent a special class of phenethylamines, which encompasses dopamine and the "fight-or-flight" hormones epinephrine and norepinephrine.[7] The endogenous monoamine neuromodulators histamine and tryptamine are heterocyclic equivalents of phenethylamine, and, in particular, the tryptamine backbone is present in a plethora of biologically active compounds, such as LSD (natural psychotropic agent), serotonin (neurotransmitter), and melatonin (hormone involved in the circadian cycle). All of the above compound classes can assume a +1 or +2 oxidation state on the α-carbon (e.g., epinephrine and cathinone, respectively) and, in more rare cases, a +2 oxidation state on the β-carbon, as in small molecule HIV-1 inhibitors reported by Bristol-Myers Squibb whereby an α-ketoamide motif is displayed.[8]

Phenethylamine derivatives pose an increasing societal problem as the their use and abuse is widespread as recreational drugs,[2,5] performance-enhancing drugs[9] in sports, and as growth-promoting agents[10] in animal production. Therefore, there is a constant search for analytical methods for the detection of phenethylamine derivatives aiming for sensitive and specific detection. In this respect, isotope dilution mass spectrometry (IDMS) is far superior to more traditional techniques for trace analysis, such as external calibration and standard addition. In IDMS trace analysis of organic compounds, a difference of at least three mass units is required between the analyte and the standard to avoid spectral overlap, which would result in nonlinear calibration curves.[11] Extensive isotope labeling can result in different physicochemical properties of the standard compared with the analyte, and notably, deuterated compounds have been reported to exhibit deviating elution properties resulting in altered retention times in, for example, GC and LC separations.[12] Minimal ^{13}C-labeling has been proposed as a viable solution to this problem.[13] Because of the widespread importance of phenethylamine derivatives, new methods for their synthesis and isotopic labeling are highly sought after. ^{13}C-labeling of phenethyl-

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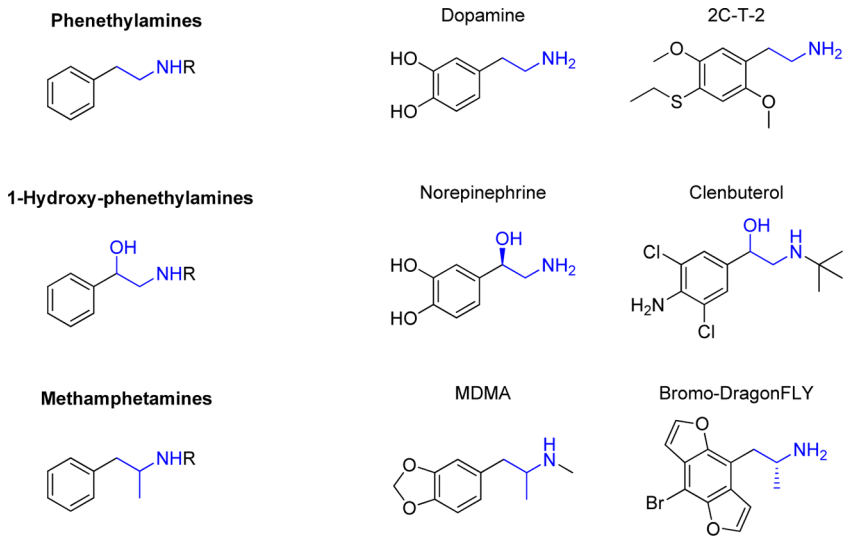
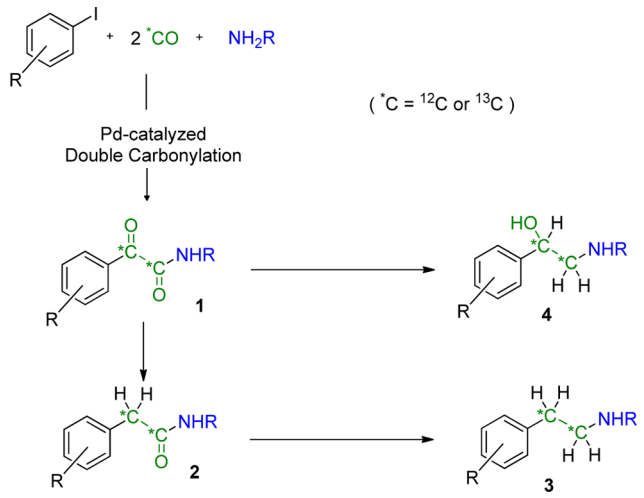


Figure 1. Selected examples of bioactive compounds representing the three most important structural classes of phenethylamines.

amines is typically achieved via lengthy syntheses from, for example, ^{13}C-labeled aryl precursors.[14] To the best of our knowledge, no general procedure for $^{13}C_2$-labeling of the omnipresent ethyl moiety of phenethylamines exists.

To achieve this goal, we considered applying the palladium-catalyzed double carbonylation of aryl halides in the presence of carbon monoxide (CO) and an amine for accessing α-ketoamides **1** as possible precursors to phenethylamines, as illustrated in Scheme 1. Upon use of ^{13}C-labeled CO, this

Scheme 1. Proposed Strategy for the Synthesis of 1-Hydroxyphenethylamines 4 and Phenethylamines 3 from α-Ketoamide 1



method would allow for the installment of both carbon labels in the aryl side chain. Our group has recently demonstrated in a number of Pd-catalyzed carbonylative transformations that such reactions can be optimized to operate with near stoichiometric quantities of CO in a two-chamber reactor. This technique has also been applied as a highly valuable method for the introduction of ^{13}C-carbon-labeled carbonyl groups.[15] It was, therefore, our goal to examine in more detail the usefulness of this carbonylation technique as a general route to α-ketoamides. Numerous protocols are present in the literature dealing with the reduction of the ketone group in α-ketoamides to the corresponding benzylic alcohol.[16] Furthermore, there are sporadic reports on the complete reduction of this carbonyl group to yield 2-aryl acetamides **2**,[17] which can be reduced to the phenethylamines **3**, and on the global reduction of α-ketoamides to yield β-amino alcohols **4**.[18]

Hence, in this paper, we wish to report our studies on the successful application of the Pd-catalyzed double carbonylation protocol with aryl halides and an amine with stoichiometric CO as a key step in the preparation of α-ketoamides, which can be applied as a common entry to a variety of phenethylamines. More importantly, this synthesis route and technique is adaptable for $^{13}C_2$-labeling of this important class of neurotransmission regulators.

RESULTS AND DISCUSSION

The palladium-catalyzed double carbonylation of aryl halides in the presence of amines was discovered in 1982 by Yamamoto and Tanaka et al.[19] However, catalytic protocols for accessing the α-ketoamide products from aryl halides have, until recently, been plagued by a narrow substrate scope and the necessity for a high pressure of CO. Extensive mechanistic studies by Yamamoto et al. has suggested that a bis(acyl)-type palladium complex is an important intermediate in the formation of α-ketoamides. The selectivity for formation of α-ketoamide over amide was found to be highly dependent on the applied pressure of CO, and decent selectivities required the application of at least 10 atm.[20] Miura et al. have demonstrated that, by adding CuI as a cocatalyst, the uptake of CO could be promoted, thereby allowing for the selective formation of α-ketoamide even at atmospheric pressures of CO.[21] However, a more general method was disclosed by Uozomi et al. in 2001,[22] choosing DABCO as a base, which proved important for the selectivity. In 2006, Kondo and co-workers reported that using P(tBu)$_3$ as a ligand resulted in almost complete selectivity for the α-ketoamide at room temperature and atmospheric pressures of CO in THF.[23] Moreover, this altered protocol gave access to double carbonylation of electron-deficient aryl iodides. Curiously, with this phosphine ligand, DABCO promoted amide formation, while using DBU as the base completely restored the selectivity for α-ketoamide.[23]

In 2011, we reported the use of 9-methylfluorenecarbonyl chloride (COgen) as a solid source of carbon monoxide for

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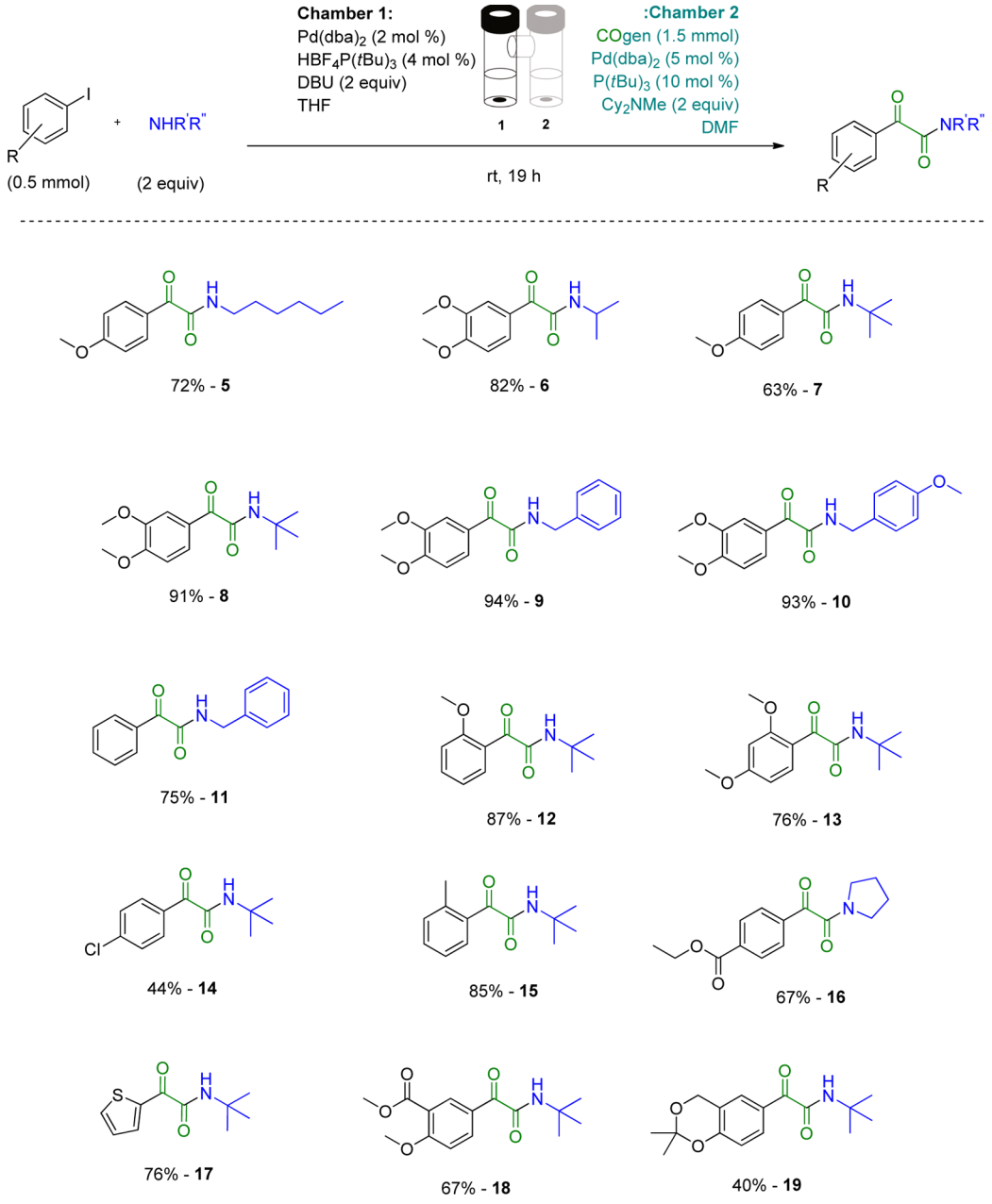
Scheme 2. Palladium-Catalyzed Double Carbonylation of Aryl Iodides with Amine Nucleophiles



external delivery of CO in a sealed two-chamber glass reactor (COware).[15a] COgen was observed to release carbon monoxide even at room temperature upon exposure to a Pd source, $(t\text{Bu})_3\text{P}$, and DIPEA or TEA in THF. This ability to release CO at ambient temperature was exploited in a double carbonylation of iodoanisole with hexylamine as a nucleophile to provide the corresponding α-ketoamide in a 68% isolated yield along with 7% of the monocarbonylated amide product. However, it was observed that the CO release in this protocol occurred only slowly from an inhomogeneous mixture, and attempting to apply it on a broader scope of aryl iodides resulted in poor conversions and a lack of reproducibility. To increase the versatility and reliability of a protocol for carbonylation at room temperature using COgen, we, therefore, turned our attention toward the CO-releasing reaction. By measuring the rate of CO evolution using gas volumetric measurements, it was found that CO was released substantially faster at room temperature by changing the solvent to DMF and exploiting the free phosphine ligand rather than its HBF_4 salt. However, it was observed that the yield of the CO-generating reaction decreased considerably under these conditions, as determined by volume expansion measurements. This was solved by utilizing Cy_2NMe[24] in place of DIPEA as a base, whereby the volumetric yield reached 60% within 45 min.[25] With a reliable source of carbon monoxide at hand, we set out to test the generality of the CO-delivery system in the Pd-catalyzed double carbonylation of aryl iodides.

Upon subjecting an aryl iodide to 2 equiv of an amine nucleophile, $Pd(dba)_2$, $P(t\text{Bu})_3$, DBU, and 3 equiv of carbon monoxide generated from COgen in COware (V_{total} = 16 mL) with THF as a solvent at 20 °C, we found that the desired α-ketoamide could be isolated in excellent yields (Scheme 2). To some surprise, the selectivity for the α-ketoamide over the simple amide appeared to parallel the observations previously reported by Kondo, despite the application of only 1 equiv of

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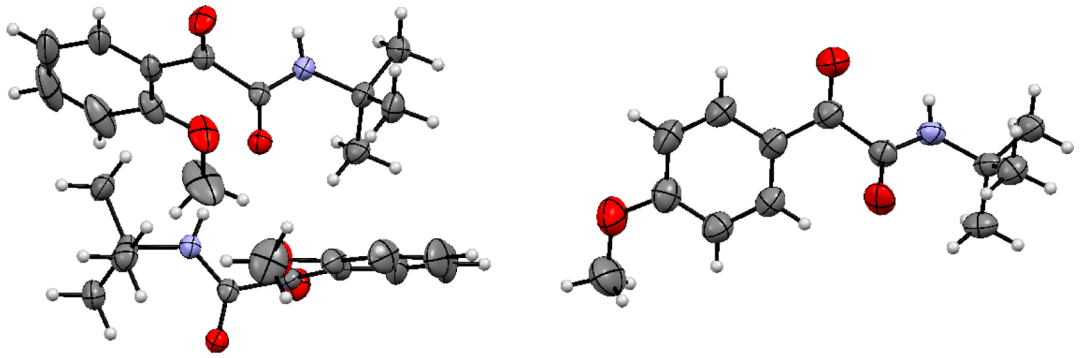
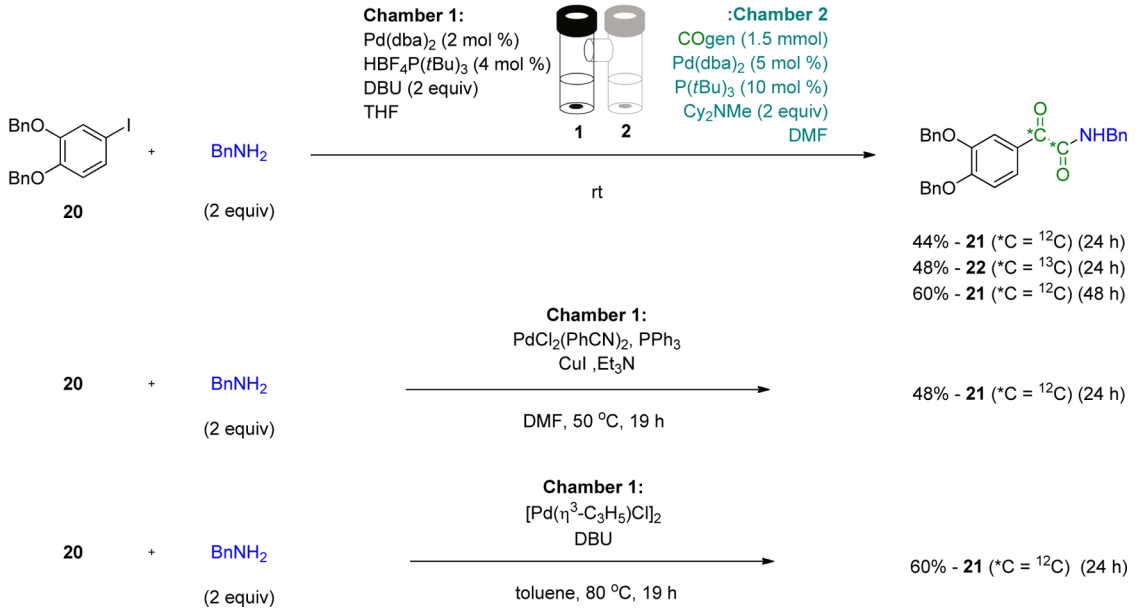


Figure 2. ORTEP diagram of *N*-(*tert*-butyl)-2-(2-methoxyphenyl)-2-oxoacetamide **12** (left) and *N*-(*tert*-butyl)-2-(4-methoxyphenyl)-2-oxoacetamide **7** (right).

Scheme 3. Comparing Protocols for the Double Carbonylation with Amine Nucleophiles



excess CO. In good accordance with previous protocols for the double carbonylation, electron-rich aryl iodides performed best, providing the α-ketoamides **5**−**10**, **12**, and **13** in a 63−94% isolated yield. More electron-deprived aryl iodides, such as *p*-iodochlorobenzene, reacted poorly and resulted in a 44% isolated yield of **14**. Nevertheless, esters were tolerated either when combined with a strongly nucleophilic amine, such as pyrrolidine, or when the ring was further substituted with electron-donating substituents to afford both **16** and **18** in a 67% isolated yield. *Ortho* substitution, including a methoxy and methyl group, as in **12** and **13**, and **15**, respectively, did not affect the yields, resulting in good coupling yields of 87% and 76%, and 85%, respectively

Curiously, we found that, with **12**, the chemical shift of the *o*-hydrogen was considerably more upfield shifted (7.63 ppm) compared with what is normally found for the double carbonylated products, as observed for **7** (8.36 ppm) and **15** (8.36 ppm). It has previously been reported for acylated anilines that the proximity of the carbonyl oxygen to the *o*-hydrogen results in a significant downfield shift of this proton.[26] In an attempt to visualize this interaction and verify the structure of the *o*-methoxy **12**, we obtained crystal structures of both **7** and **12** (Figure 2). However, analysis of these structures did not reveal any significant difference in the environment for these *ortho*-hydrogens.

To our astonishment a complete reversal in selectivity was observed when *o*-iodochlorobenzene was used, whereby the monocarbonylated amide product could be isolated in an 85% yield. On the other hand, a 2-iodothiophene was applied successfully to this coupling protocol, providing the α-ketoamide **17** in a 76% yield. Carbonylative coupling of *t*-butylamine, benzylamine, or *p*-methoxybenzylamine with 4-iodoveratrole furnished the corresponding *N*-*t*-butyl-, *N*-benzyl- and *N*-PMB-protected α-ketoamides **8**, **9**, and **10**, respectively, in excellent isolated yields of over 90%.

During the preparation of this article, Castillón and co-workers published a phosphine-free protocol for the double carbonylation of aryl iodides,[27] and hence, we decided to compare this work with the literature protocols for double carbonylation at atmospheric pressures of carbon monoxide directly using our developed CO-generator. The bis-benzyl-protected iodocatechol **20**, which could prove a valuable entry point toward the $^{13}C_2$-labeled catecholamines, turned out to participate only slowly in the double carbonylation with benzylamine, leading to a 61% conversion in 24 h, and the α-ketoamide **21** in a 44% isolated yield (Scheme 3). However, it was observed that prolonged reaction times led to a perceptible

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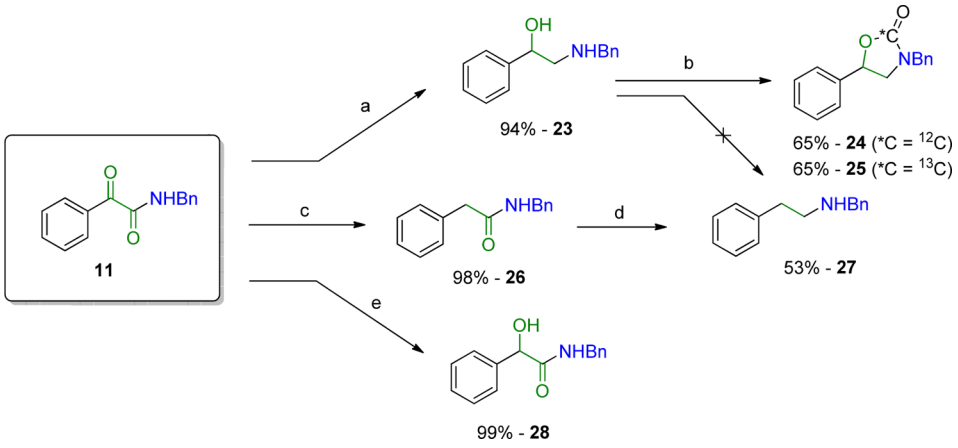
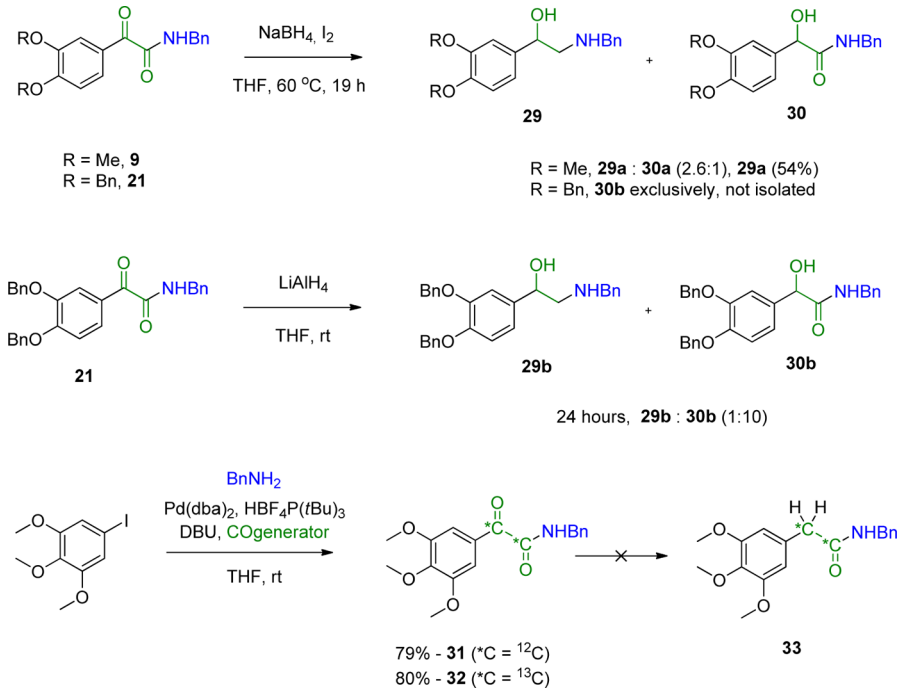
Scheme 4. Modification of α-Ketoamides to a Range of Biologically Relevant Motifs[a]



[a](a) $NaBH_4$, I_2, THF, 60 °C, overnight. (b) COware: (1) Chamber 1: **23**, Se(s), Et_3N, DMF, rt, 19 h. Chamber 2: [12C]- or [13C]-COgen, $Pd(dba)_2$, $P(tBu)_3$, Cy_2NMe, DMF. (2) O_2, overnight. (c) $Pd(OH)_2$, H_2, H_2SO_4, EtOH, 50 °C, overnight. (d) BH_3, THF, rt, overnight. (e) $Pd(OH)_2$, H_2, EtOAc, rt, overnight.

Scheme 5. Attempted Synthesis of Protected Norepinephrine from the α-Ketoamides 9 and 21 and *N*-Benzyl-Protected $^{13}C_2$-Mescaline via $^{13}C_2$-α-Ketoamide 33



increase in yields to 60%, and surprisingly, the monocarbonylation product was not observed under these conditions. Applying cocatalytic CuI led to full conversion within 24 h, yet only produced a 48% isolated yield of **21**. Using the phosphine-free protocol identified by Castillón also provided full conversion within the same time span, yielding the desired product **21** in a 60% yield. Simply exchanging COgen for [^{13}C]-COgen in the original protocol, the $^{13}C_2$-labeled **22** could be isolated in an equivalent 48% yield.

Having established a reliable method for conducting the double carbonylation of aryl iodides with near stoichiometric carbon monoxide, we proceeded to investigate potential viable routes to access a diverse set of substituted phenethylamines. Reduction of α-ketoamide **11** to the corresponding β-amino alcohol **23** was effectuated smoothly using 10 equiv of BH_3 in THF in a 66% isolated yield. It was found that, by applying in situ generated BH_3 from $NaBH_4/I_2$, the reduction could be brought to a satisfying 94% isolated yield of **23** (Scheme 4); 3.6 equiv of $NaBH_4$ (1.5 equiv of I_2) was found to be of importance for a successful reduction, as less $NaBH_4/I_2$ resulted in an incomplete reduction to yield a mixture of the starting α-ketoamide, α-hydroxy amide **28**, and the desired β-amino alcohol **23**, whereas increasing the amount of $NaBH_4/I_2$ resulted in considerable amounts of an unidentified byproduct along with the desired product.

Importantly, $NaBD_4$ is a cheap and easily accessible source of deuteride, allowing us to access substituted $^2H_3$- and $^2H_3{}^{13}C_2$-labeled phenethylamines as M+3 and M+5 internal standards for mass spectrometry. An effective synthesis of the β-amino alcohols also provided a useful entry to 2-oxazolidinones.

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Selenium-mediated carbonylation of **23** using the COgenerator as a source of CO, afforded 5-phenyl-2-oxazolidinone **24** in a 65% isolated yield, and the corresponding ^{13}C-labeled oxazolidinone **25** in an equivalent 65% yield by changing to [^{13}C]-COgen.

Extensive efforts to deoxygenate the β-amino alcohol **23** to the corresponding phenethylamine **27** unfortunately were not successful. However, the phenethylamine could be accessed by first deoxygenating the keto functionality of **11** under hydrogenative conditions using Pearlman's catalyst in EtOH/H_2SO_4 to afford **26** in an excellent 98% isolated yield. By excluding the addition of acids to the hydrogenative protocol, reduction of the ketone could be achieved to afford the α-hydroxyamide **28** in an excellent 99% isolated yield. Reduction of the *N*-benzylamide **26** failed in our hands using the $NaBH_4$/I_2 protocol, but was ultimately effectuated with BH_3 in THF to give the desired protected phenethylamine **27** in a 53% yield.

With the above results in hand, we next turned our attention to the $^{13}C_2$-labeling of norepinephrine. Subjecting **9** to $NaBH_4$/I_2 resulted in a crude mixture of the β-aminoalcohol **29a** and the α-hydroxy amide **30a** in a 2.6-to-1 ratio, from which **29a** could be isolated in a 54% yield (Scheme 5). Unfortunately, demethylation with BBr_3 to liberate the catechol was unsuccessful. Subjecting the bis-benzyl-protected α-ketoamide **21** to $NaBH_4/I_2$ resulted exclusively in the reduction of the aromatic ketone. The reduction of **21** was subsequently attempted with $LiAlH_4$ at ambient temperature in THF, which furnished the benzyl-protected norepinephrine **29b** in a 1:10 ratio with the α-hydroxy amide **30b**. Prolonged reaction times did not affect the ratio, and increasing the reaction temperature to 66 °C only resulted in decomposition of the material. Attempting to isolate the benzyl-protected norepinephrine **29b** from the crude mixture proved unfruitful.

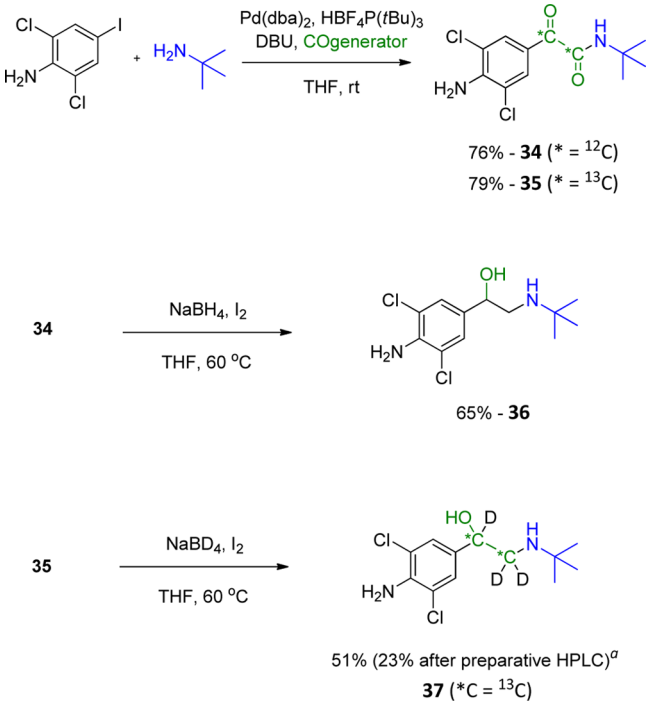
The α-ketoamide **31** and $^{13}C_2$-α-ketoamide **32** (Scheme 5) were synthesized in an excellent 79% and 80% isolated yield, respectively. Deoxygenation of the aryl ketone, followed by borane reduction of the resulting amide, was envisioned to generate the *N*-benzyl-protected $^{13}C_2$-mescaline, as outlined in Scheme 4. Subjecting **31** to Pearlman's catalyst in EtOH/H_2SO_4 under an atmosphere of hydrogen at 50 °C unfortunately resulted in a low conversion to the corresponding α-hydroxy amide alone.

Finally, 2,6-dichloro-4-iodoaniline was subjected to the conditions for double carbonylation with *t*-butylamine as the nucleophile, resulting in a 76% isolated yield after column chromatography of the α-ketoamide **34** (Scheme 6). When **34** was treated with $NaBH_4/I_2$, clenbuterol (**36**) could be obtained in a 65% isolated yield. Exchanging COgen for [^{13}C]-COgen provided the corresponding $^{13}C_2$-labeled α-ketoamide **35** in a 79% isolated yield. Treating **35** with $NaBD_4/I_2$ gave d_3-$^{13}C_2$-clenbuterol **37** in a 51% yield after column chromatography and 23% after preparative HPLC. Notably, this provides M+5 labeled clenbuterol as a potential internal standard for IDMS in only two synthetic steps.

CONCLUSION

The palladium-catalyzed double carbonylation of aryl iodides with amine nucleophiles has been demonstrated to operate in good yields with an excellent selectivity for the double carbonylated product over the insertion of only one carbon monoxide with very low loading of this diatomic gas. The double carbonylation protocol has been presented as a new approach to $^{13}C_2$-phenethylamine derivatives, such as β-amino alcohols, phenethylamines, 2-oxazolidinones, etc. Specifically, ^{13}C-isotope labeling of norepinephrine, mescaline, and clenbuterol has been studied. By substituting the hydrogen source with a deuterium-enriched variant in the reductive deoxygenation protocols studied, we were able to synthesize d_3-$^{13}C_2$-clenbuterol in only two synthetic steps. The synthesis of d_3-$^{13}C_2$-clenbuterol points to the strengths of this approach as an approach to the synthesis of useful internal standards of substituted phenethylamines for isotope dilution mass spectrometry (IDMS).

Scheme 6. Synthesis of d_3-$^{13}C_2$-Clenbuterol 37 in Two Synthetic Steps from 2,6-Dichloro-4-iodoaniline[a]



[a]Purification by preparative HPLC to obtain 9.8 mg of **37**.

EXPERIMENTAL PROCEDURES

General Methods. Solvents were dried according to standard procedures. Flash chromatography was performed on silica gel 60 (230−400 mesh). The ^{1}H NMR, ^{13}C NMR, and ^{19}F NMR spectra were recorded at 400, 100, and 367 MHz, respectively. The chemical shifts of the NMR spectra are reported in parts per million (ppm) relative to the solvent residual peak.[28] NMR spectra are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintuplet, m = multiplet, b = broad. MS and HRMS spectra were recorded on an LC TOF (ES) apparatus. Semipreparative HPLC (C18-column, 250 × 10.0 mm, 10 μm, 100 Å) was used for purification. All purchased chemicals were used as received without further purification.

***N*-Hexyl-2-(4-methoxyphenyl)-2-oxoacetamide (5).[15a] General Procedure for the Double Carbonylation of Aryl Iodides.** Chamber 2: In a glovebox under argon, to chamber 2 of the two-chamber system was added COgen (9-methyl-9*H*-fluorene-9-carbonyl chloride) (364 mg, 1.50 mmol), P(*t*Bu)$_3$ (30 mg, 0.15 mmol), Pd(dba)$_2$ (43 mg, 0.075 mmol), and DMF (3 mL and Cy_2NMe (642 μL, 3.0 mmol)) in that order. The chamber was sealed with a screwcap fitted with a Teflon seal. Chamber 1: In a glovebox under argon, to chamber 1 of the two-chamber system was added 1-iodo-4-methoxybenzene (117 mg, 0.500 mmol), Pd(dba)$_2$ (5.8 mg, 0.01 mmol), $HBF_4P(tBu)_3$ (5.8 mg, 0.02 mmol), *n*-hexylamine (132 μL, 1.00 mmol), DBU (150 μL, 1.00 mmol), and toluene (5 mL) in that

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order. The chamber was sealed with a screwcap fitted with a Teflon seal. The loaded two-chamber system was removed from the glovebox and left at room temperature for 20 h. The title compound was obtained after flash chromatography (10% EtOAc in pentane) as a light yellow solid (94.0 mg, 0.36 mmol, 72%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H ppm 8.42 (d, J = 8.3 Hz, 2H), 7.13 (bs, 1H), 6.94 (d, J = 9.1 Hz, 2H), 3.88 (s, 3H), 3.36 (q, J = 7.2 Hz, 2H), 1.59 (quin, J = 7.6 Hz, 2H), 1.40−1.31 (m, 6H), 0.89 (t, J = 6.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C ppm 185.8, 164.6, 162.2, 133.9 (2C), 126.5, 113.8 (2C), 55.5, 39.4, 31.4, 29.3, 26.6, 22.5, 14.0. GCMS $C_{15}H_{21}O_3N$ [M] Calcd: 263.15. Found: 263 (19%), 135 (100%), 92 (13%), 77 (16%).

2-(3,4-Dimethyoxyphenyl)-*N*-isopropyl-2-oxoactamide (6). The same procedure as for **5** using 4-iodo-(1,2)-dimethoxybenzene (132.0 mg, 0.50 mmol) and isopropylamine (82 μL, 1.0 mmol). The title compound was obtained after flash chromatography (30% EtOAc in pentane) as a light yellow solid (103.0 mg, 0.41 mmol, 82%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H ppm 8.25 (dd, J = 8.5 Hz, 1.9 Hz, 1H), 7.90 (d, J = 2.0 Hz, 1H), 6.97 (bs, 1H), 6.91 (d, J = 8.5 Hz, 1H), 4.14 (sep, J = 6.7 Hz, 1H), 3.96 (s, 3H), 3.94 (s, 3H), 1.26 (d, J = 6.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C ppm 185.7, 161.4, 154.6, 148.7, 127.3, 126.5, 112.7, 110.2, 56.1, 56.0, 41.6, 22.4 (2C). HRMS $C_{13}H_{17}O_4N$ [M + Na^+] Calcd: 274.1055. Found: 274.1051. mp 100−102 °C.

***N*-(*tert*-Butyl)-2-(4-methoxyphenyl)-2-oxoacetamide (7).**[27] The same procedure as for **5** using 4-iodoanisole (117.0 mg, 0.50 mmol) and *tert*-butylamine (106 μL, 1.00 mmol). The title compound was obtained after flash chromatography (10% EtOAc in pentane) as a light yellow solid (74.1 mg, 0.32 mmol, 63%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H ppm 8.36 (d, J = 9.1 Hz, 2H), 6.97 (bs, 1H), 6.91 (d, J = 9.1 Hz, 2H), 3.85 (s, 3H), 1.43 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C ppm 186.5, 164.5, 161.7, 133.9 (2C), 126.4, 113.7 (2C), 55.5, 51.5, 28.4 (3C). GCMS $C_{13}H_{17}O_3N$ [M] Calcd: 235.12. Found: 235 (13%), 135 (100%), 107 (16%), 92 (19%), 77 (20%).

***N*-(*tert*-Butyl)-2-(3,4-dimethoxyphenyl)-2-oxoacetamide (8).** The same procedure as for **5** using 4-iodo-(1,2)-dimethoxybenzene (132.0 mg, 0.50 mmol) and *tert*-butylamine (106 μL, 1.00 mmol). The title compound was obtained after flash chromatography (20% EtOAc in pentane) as a light yellow solid (120.6 mg, 0.45 mmol, 91%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H ppm 8.22 (dd, J = 8.5 Hz, 2.0 Hz, 1H), 7.86 (d, J = 2.0 Hz, 1H), 6.97 (bs, 1H), 6.90 (d, J = 8.6 Hz, 1H), 3.96 (s, 3H), 3.94 (s, 3H), 1.45 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C ppm 186.4, 161.7, 154.5, 148.7, 127.3, 126.4, 112.7, 110.1, 107.9, 56.1, 56.0, 51.5, 28.4 (3C). HRMS $C_{14}H_{19}O_4N$ [M + K^+] Calcd: 304.0946. Found: 304.0948.

***N*-Benzyl-2-(3,4-dimethoxyphenyl)-2-oxoacetamide (9).** The same procedure as for **5** using 4-iodo-(1,2)-dimethoxybenzene (132.0 mg, 0.50 mmol) and benzylamine (110 μL, 1.00 mmol). The title compound was obtained after flash chromatography (20% EtOAc in pentane) as a light yellow solid (140.6 mg, 0.47 mmol, 94%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H ppm 8.29 (d, J = 8.5 Hz, 1H), 7.89 (s, 1H), 7.46 (bs, 1H), 7.38−7.30 (m, 4H), 6.92 (d, J = 8.6 Hz, 1H), 4.56 (d, J = 6.0 Hz, 2H), 3.97 (s, 3H), 3.94 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C ppm 185.2, 162.0, 154.7, 148.8, 137.2, 128.8 (2C), 127.8 (2C), 127.7, 127.4, 126.4, 112.7, 110.2, 56.1, 56.0, 43.4. HRMS $C_{17}H_{17}O_4N$ [M + Na^+] Calcd: 322.1050. Found: 322.1053. mp 82−84 °C.

2-(3,4-Dimethoxyphenyl)-*N*-(4-methoxybenzyl)-2-oxoacetamide (10). The same procedure as for **5** using 4-iodo-(1,2)-dimethoxybenzene (132.0 mg, 0.50 mmol) and (4-methoxyphenyl)-methanamine (131 μL, 1.00 mmol). The title compound was obtained after flash chromatography (30% EtOAc in pentane) as a light yellow solid (153.8 mg, 0.47 mmol, 93%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H ppm 8.25 (dd, J = 8.5 Hz, 1.9 Hz, 1H), 7.88 (d, J = 1.8 Hz, 1H), 7.41 (bs, 1H), 7.24 (s, 1H), 6.92−6.86 (m, 3H), 4.48 (d, J = 10.0 Hz, 2H), 3.96 (s, 3H), 3.93 (s, 3H), 3.79 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C ppm 185.4, 162.0, 159.2, 154.7, 148.8, 129.2 (2C), 127.4, 126.4, 114.7 (2C), 112.6, 110.2, 56.1, 56.0, 55.3, 42.9. HRMS $C_{18}H_{19}O_5N$ [M + Na^+] Calcd: 352.1161. Found: 352.1155. mp 128−130 °C.

***N*-Benzyl-2-oxo-2-phenylacetamide (11).**[29] The same procedure as for **5** using iodobenzene (102.0 mg, 0.50 mmol) and benzylamine (110 μL, 1.00 mmol). The title compound was obtained after flash chromatography (20% EtOAc in pentane) as a colorless solid (88.6 mg, 0.37 mmol, 74%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H ppm 8.37 (d, J = 7.2 Hz, 2H), 7.64 (t, J = 7.4 Hz, 1H), 7.49 (t, J = 8.0 Hz, 2H), 7.40−7.30 (m, 5H), 4.58 (d, J = 6.08 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C ppm 187.5, 161.5, 137.1, 134.4, 133.3, 131.2 (2C), 128.9 (2C), 128.5 (2C), 127.9 (2C), 127.8, 43.5. GCMS $C_{15}H_{13}O_2N$ [M] Calcd: 239.09. Found: 239 (4%), 105 (100%), 91 (54%), 77 (46%).

***N*-(*tert*-Butyl)-2-(2-methoxyphenyl)-2-oxoacetamide (12).**[30] The same procedure as for **5** using 2-iodoanisole (65 μL, 0.50 mmol) and *tert*-butylamine (106 μL, 1.00 mmol). The title compound was obtained after flash chromatography (10% EtOAc in pentane) as a light yellow solid (102.3 mg, 0.44 mmol, 87%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H ppm 7.63 (dd, J = 7.6 Hz, 1.7 Hz, 1H), 7.48 (td, J = 7.5 Hz, 5.0 Hz, 1H), 7.01 (t, J = 7.5 Hz, 1H), 6.96 (d, J = 8.0 Hz, 1H), 6.46 (bs, 1H), 3.83 (s, 3H), 1.44 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C ppm 192.3, 162.4, 159.4, 134.3, 131.0, 124.7, 120.6, 111.9, 56.0, 51.5, 28.4 (3C). GCMS $C_{13}H_{17}O_3N$ [M] Calcd: 235.12. Found: 235 (6%), 135 (100%), 77 (13%).

***N*-(*tert*-Butyl)-2-(2,4-dimethoxyphenyl)-2-oxoacetamide (13).** The same procedure as for **5** using 1-iodo-2,4-dimethoxybenzene (132.0 mg, 0.50 mmol) and *tert*-butylamine (106 μL, 1.00 mmol). The title compound was obtained after flash chromatography (30% EtOAc in pentane) as a light yellow solid (100.5 mg, 0.38 mmol, 76%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H ppm 7.74 (d, J = 8.6 Hz, 1H), 6.48 (dd, J = 8.7 Hz, 2.3 Hz, 1H), 6.40 (d, J = 1.8 Hz, 1H), 6.38 (bs, 1H), 3.80 (s, 3H), 3.78 (s, 3H), 1.40 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C ppm 190.0, 165.3, 163.7, 161.8, 133.7, 117.2, 105.5, 98.6, 55.8, 55.5, 51.4, 28.4 (3C). HRMS $C_{14}H_{19}O_4N$ [M + Na^+] Calcd: 288.1206. Found: 288.1209. mp 130−133 °C.

***N*-(*tert*-Butyl)-2-(4-chlorophenyl)-2-oxoacetamide (14).**[29] The same procedure as for **5** using 1-chloro-4-iodobenzene (119.2 mg, 0.50 mmol) and *tert*-butylamine (106 μL, 1.00 mmol). The title compound was obtained after flash chromatography (10% EtOAc in pentane) as a light yellow solid (52.1 mg, 0.22 mmol, 44%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H ppm 8.28 (d, J = 8.4 Hz, 2H), 7.41 (d, J = 8.5 Hz, 2H), 6.96 (bs, 1H), 1.44 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C ppm 187.1, 160.7, 140.9, 132.7 (2C), 131.7, 128.7 (2C), 51.7, 28.3 (3C). GCMS $C_{12}H_{14}O_2NCl$ [M] Calcd: 239.07. Found: 239 (13%), 139 (100%), 111 (25%), 57 (28%).

***N*-(*tert*-Butyl)-2-oxo-2-(*o*-tolyl)acetamide (15).**[29] The same procedure as for **5** using 2-iodotoluene (109.0 mg, 0.50 mmol) and *tert*-butylamine (106 μL, 1.00 mmol). The title compound was obtained after flash chromatography (10% EtOAc in pentane) as a light yellow solid (93.7 mg, 0.43 mmol, 85%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H ppm 8.36 (d, J = 8.0 Hz, 1H), 7.40 (td, J = 7.5 Hz, 1.4 Hz, 1H), 7.27−7.23 (m, 2H), 6.92 (bs, 1H), 2.46 (s, 3H), 1.44 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C ppm 192.3, 161.3, 139.7, 133.0, 132.4, 131.7, 125.2, 51.6, 28.3 (3C), 20.7. GCMS $C_{13}H_{17}O_2N$ [M] Calcd: 219.13. Found: 219 (19%), 119 (100%), 91 (38%), 57 (22%).

Ethyl 4-(2-Oxo-2-(pyrrolidin-1-yl)acetyl)benzoate (16).[15f] The same procedure as for **5** using ethyl 4-iodobenzoate. Flash column chromatography using 30% diethyl ether in pentane as eluent resulted in 92.5 mg (67% yield) of the title product as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H ppm 8.11 (d, J = 8.4 Hz, 2H), 8.02 (d, J = 8.2 Hz, 2H), 4.37 (q, J = 7.2 Hz, 2H), 3.62 (t, J = 7.0 Hz, 2H), 3.40 (t, J = 6.6 Hz, 2H), 1.93−1.91 (m, 4H), 1.37 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C ppm 190.6, 165.4, 164.1, 136.1, 135.4, 129.9 (2 C), 129.7 (2 C), 61.5, 46.7, 45.4, 25.9, 23.9, 14.2. HRMS $C_{15}H_{17}NO_4$ [M + Na^+] Calcd: 298.1055. Found: 298.1055.

***N*-(*tert*-Butyl)-2-oxo-2-(thiophen-2-yl)acetamide (17).** The same procedure as for **5** using 2-iodothiophene (105.0 mg, 0.50 mmol) and *tert*-butylamine (106 μL, 1.00 mmol). The title compound was obtained after flash chromatography (2% ethyl acetate in pentane → 5% ethyl acetate in pentane) as a light yellow solid (80.3 mg, 0.38 mmol, 76%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H ppm 8.33 (d, J = 5.1 Hz, 1H), 7.78 (d, J = 6.1 Hz, 1H), 7.18 (bs, 1H), 7.14 (t, J = 4.0 Hz,

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1H), 1.43 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C ppm 179.2, 160.0, 138.6, 137.9, 136.2, 127.9, 51.5, 28.3 (3C). HRMS $C_{10}H_{13}O_2NS$ [M + Na^+] Calcd: 234.0559. Found: 234.0558. mp 43−45 °C.

Methyl 5-(2-(*tert*-Butylamino)-2-oxoacetyl)-2-methoxybenzoate (18). The same procedure as for **5** using methyl 5-iodo-2-methoxybenzoate (146.0 mg, 0.50 mmol) and *tert*-butylamine (106 μL, 1.00 mmol). The title compound was obtained after flash chromatography (20% EtOAc in pentane) as a light yellow solid (98.8 mg, 0.34 mmol, 67%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H ppm 8.82 (d, J = 2.3 Hz, 1H), 8.58 (dd, J = 8.9 Hz, 2.28 Hz, 1H), 7.01 (d, J = 8.9 Hz, 1H), 3.98 (s, 3H), 3.90 (s, 3H), 1.44 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C ppm 185.7, 165.6, 163.3, 161.0, 137.3, 135.5, 125.8, 120.2, 111.4, 56.3, 52.2, 51.6, 28.4 (3C). HRMS $C_{15}H_{19}O_5N$ [M + Na^+] Calcd: 316.1155. Found: 316.1155. mp 82−84 °C.

***N*-(*tert*-Butyl)-2-(2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-6-yl)-2-oxoacetamide (19).** The same procedure as for **5** using 6-iodo-2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxine. Flash column chromatography using 4% ethyl acetate in pentane as eluent resulted in 58.8 mg (40% yield) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H ppm 8.20 (s, 1H), 8.16 (dd, J = 2.1, 8.7 Hz, 1H), 7.00 (bs, 1H), 6.84 (d, J = 8.7 Hz, 1H), 4.87 (s, 2H), 1.55 (s, 3H), 1.43 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C ppm 186.3, 161.5, 156.8, 131.9, 129.4, 125.8, 118.9, 117.2, 100.7, 60.7, 51.5, 28.4 (3C), 24.8 (2C). HRMS $C_{16}H_{21}NO_4$ [M + Na^+] Calcd: 314.1363. Found: 314.1365.

***N*-Benzyl-2-(3,4-bis(benzyloxy)phenyl)-2-oxoacetamide (21).** The same procedure as for **5** using (((4-iodo-1,2-phenylene)-bis(oxy))bis(methylene))dibenzene. Flash column chromatography using 10% ethyl acetate in pentane → 25% ethyl acetate as eluent resulted in 98.9 mg (44% yield) as a greenish solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H ppm 8.20 (dd, J = 2.0 Hz, 8.6 Hz, 1H), 8.02 (d, J = 1.9 Hz, 1H), 7.48−7.31 (m, 15H), 6.96 (d, J = 8.6 Hz, 1H), 5.26 (s, 2H), 5.21 (s, 2H), 4.55 (d, J = 6.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C ppm 185.2, 162.0, 154.6, 148.4, 137.2, 136.7, 136.2, 128.8 (2C), 128.6 (2C), 128.5 (2C), 128.1, 127.0, 127.8 (2C), 127.8, 127.5, 127.4 (2C), 127.1 (2C), 126.6, 116.0, 112.8, 71.0, 70.7, 43.4. HRMS $C_{29}H_{25}NO_4$ [M + Na^+] Calcd: 474.1676. Found: 474.1665. mp 119−120 °C.

[$^{13}C_2$]-*N*-Benzyl-2-(3,4-bis(benzyloxy)phenyl)-2-oxoacetamide (22). The same procedure as for **5** using (^{13}C)(((4-iodo-1,2-phenylene)bis(oxy))bis(methylene))dibenzene in chamber 1 and [^{13}C]COgen (365.6 mg, 1.500 mmol) in chamber 2. Flash column chromatography using 10% ethyl acetate in pentane → 25% ethyl acetate as eluent resulted in 108.4 mg (48% yield) as a greenish solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H ppm 8.21 (ddd, J = 2.0, 3.7, 8.6 Hz, 1H), 8.01 (dd, J = 2.0, 3.8 Hz, 1H), 7.45−7.30 (m, 15H), 6.96 (dd, J = 0.7, 8.6 Hz, 1H), 5.26 (s, 2H), 5.21 (s, 2H), 5.55 (dd, J = 3.2, 6.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C ppm 185.3 (d, J = 60.4 Hz, ^{13}C-enriched), 162.1 (d, J = 60.4 Hz, ^{13}C-enriched), 154.6, 148.4 (d, J = 4.7 Hz, 1C), 137.2 (d, J = 1.2 Hz, 1C), 136.5 (d, J = 46.8 Hz, 1C), 128.8 (4C), 128.6 (4C), 128.5 (2C), 128.1, 128.0, 127.8 (2C), 127.8, 127.5 (2C), 127.1, 71.0, 70.7, 43.3 (d, J = 1.5 Hz, 1C). HRMS $^{13}C_2C_{27}H_{25}NO_4$ [M + Na^+] Calcd: 476.1743. Found: 476.1733. mp 117−118 °C.

***N*-Benzyl-2-oxo-2-(3,4,5-trimethoxyphenyl)acetamide (31).** The same procedure as for **5** using 5-iodo-1,2,3-trimethoxybenzene (147.0 mg, 0.50 mmol) and benzylamine (110 μL, 1.00 mmol). The title compound was obtained after flash chromatography (30% EtOAc in pentane) as a light yellow solid (131.2 mg, 0.39 mmol, 79%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H ppm 7.79 (s, 2H), 7.45 (bs, 1H), 7.39−7.29 (m, 5H), 4.57 (d, J = 6.0 Hz, 2H), 3.96 (s, 3H), 3.92 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C ppm 185.5, 161.7, 152.8, 144.1, 137.0, 128.9 (2C), 128.2, 127.8 (2C), 108.9 (2C), 61.0, 56.3 (2C), 43.5. GCMS $C_{18}H_{19}O_5N$ [M] Calcd: 329.13. Found: 329 (17%), 195 (100%), 91 (14%). mp 98−99 °C.

[$^{13}C_2$]-*N*-Benzyl-2-oxo-2-(3,4,5-trimethoxyphenyl)acetamide (32). The same procedure as for **5** using 5-iodo-1,2,3-trimethoxybenzene in chamber 1 and [^{13}C]COgen (365.6 mg, 1.500 mmol) in chamber 2. Flash column chromatography using 30% ethyl acetate in pentane as eluent resulted in 132.5 mg (0.400 mmol, 80% yield) of the title compound as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H ppm 7.79 (d, J = 4.1 Hz, 2H), 7.45 (bs, 1H), 7.35 (m, 5H), 4.57 (dd, J = 3.0, 6.0 Hz, 2H), 3.96 (s, 3H), 3.92 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C ppm 185.5 (d, J = 60.0 Hz, ^{13}C-enriched), 161.7 (d, J = 61.0 Hz, ^{13}C-enriched), 152.8 (d, J = 5.8 Hz, 1C), 144.3, 137.0, 129.0 (2C), 128.4 (d, J = 58.7 Hz, 1C), 128.0 (3C) 109.0 (d, J = 2.9 Hz, 2C), 61.0, 56.3 (2C), 43.5. ^{13}C impurity at 159.6 ppm arising from the corresponding amide (3% based on the ^{13}C-enriched peak at 161.7 ppm). HRMS $^{13}C_2C_{16}H_{19}NO_5$ [M + Na^+] Calcd: 354.1223. Found: 354.1234.

2-(4-Amino-3,5-dichlorophenyl)-*N*-(*tert*-butyl)-2-oxoacetamide (34). The same procedure as for **5** using 2,6-dichloro-4-iodoaniline (143.4 mg, 0.50 mmol) and *tert*-butylamine (106 μL, 1.00 mmol). The title compound was obtained after flash chromatography (5% EtOAc in pentane) as a colorless solid (109.8 mg, 0.38 mmol, 76%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H ppm 8.36 (s, 1H), 7.02 (bs, 1H), 5.10 (bs, 2H), 1.43 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C ppm 183.8, 161.1, 145.2, 131.7 (2C), 123.4, 118.4 (2C), 51.6, 28.3 (3C). GCMS $C_{12}H_{14}O_2N_2Cl_2$ [M] Calcd: 288.04. Found: 288 (21%), 187 (71%), 188 (100%), 124 (21%), 57 (21%).

[$^{13}C_2$]-2-(4-Amino-3,5-dichlorophenyl)-*N*-(*tert*-butyl)-2-oxoacetamide (35). The same procedure as for **5** using 2,6-dichloro-4-iodoaniline (143.4 mg, 0.50 mmol) and *tert*-butylamine (106 μL, 1.00 mmol) in chamber 1, and [^{13}C]COgen (367.7 mg, 1.50 mmol) in chamber 2.The title compound was obtained after flash chromatography (5% EtOAc in pentane) as a colorless solid (114.7 mg, 0.39 mmol, 79%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H ppm 8.36 (s, 1H), 7.02 (bs, 1H), 5.11 (bs, 2H), 1.42 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C ppm 183.8 (d, J = 59.9 Hz, ^{13}C-enriched), 161.1 (d, J = 59.9 Hz, ^{13}C-enriched), 145.3, 131.7 (d, J = 2.9 Hz), 128.6 (d, J = 57.3 Hz), 123.4 (dd, J = 60.0 Hz, 15.6 Hz), 118.4 (d, J = 5.7 Hz), 51.6, 28.3 (3C). HRMS $^{13}C_2C_{10}H_{14}O_2N_2Cl_2$ [M + Na^+] Calcd: 313.0392. Found: 313.0394. mp 166−168 °C.

2-(Benzylamino)-1-phenylethanol (23).[31] To a solution of $NaBH_4$ (600 mg, 15.9 mmol) in THF (5 mL) under argon was added *N*-benzyl-2-oxo-2-phenylacetamide (**11**) (1.06 g, 4.41 mmol) in THF (10 mL) and I_2 (1.68 g, 6.61 mmol) in THF (10 mL) in that order at room temperature. The temperature was then raised to 60 °C, and the reaction mixture stood for 16 h. The reaction was quenched with 6 M HCl (10 mL) and neutralized with 2 M NaOH. The compound was worked up by extraction with Et_2O (3×) and dried over Na_2SO_4, followed by removal of solvents in vacuo. Flash column chromatography using 3% MeOH in CH_2Cl_2 as eluent resulted in 941 mg (94% yield) of the title product as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H ppm 7.32 (m, 10H), 4.76 (dd, J = 3.5, 8.9 Hz, 1H), 3.86 (d, J = 13.3 Hz, 1H), 3.81 (d, J = 13.2 Hz, 1H), 2.93 (dd, J = 3.6, 12.2 Hz, 1H), 2.85 (bs, 2H), 2.76 (dd, J = 9.0, 12.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C ppm 142.5, 139.5, 128.5 (2C), 128.4 (2C), 128.2 (2C), 127.5, 127.2, 125.8 (2C), 71.8, 56.4, 53.5. GCMS $C_{15}H_{17}NO$ Calcd: 227.1330. Found: 209 (69%), 118 (78%), 91 (100%).

3-Benzyl-5-phenyloxazolidin-2-one (24).[32] Chamber 2: In a glovebox under argon, to chamber 2 of the two-chamber system was added P(*t*Bu)$_3$ (22.3 mg, 0.110 mmol), Pd(dba)$_2$ (31.6 mg, 0.0550 mmol), COgen (267 mg, 1.10 mmol), Cy_2NMe (471 μL, 2.2 mmol), and DMF (3 mL) in that order. The chamber was sealed with a Teflon seal. Chamber 1: In a glovebox under argon, to chamber 1 of the two-chamber system was added 2-(benzylamino)-1-phenylethanol (**23**) (100 mg, 0.440 mmol), Se (104 mg, 1.32 mmol), Et_3N (184 μL, 1.32 mmol), and DMF (3 mL) in that order. The chamber was sealed with a screwcap fitted with a Teflon seal. The loaded two-chamber system was stirred at room temperature for 24 h, followed by removal of the screwcaps and additional stirring at room temperature for 24 h. The crude mixture from chamber 1 was transferred with CH_2Cl_2 (10 mL) and extracted with Et_2O (100 mL). The combined organic phase was washed with water (5×) and brine (1×) and dried over $MgSO_4$. Solvents were removed in vacuo. The title compound was obtained after flash chromatography (10% EtOAc/pentane−20% EtOAc/pentane−30% EtOAc/pentane) as a colorless solid (72.8 mg, 0.287 mmol, 65%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H ppm 7.35−7.28 (m, 10H), 5.46 (t, J = 8.0 Hz, 1H), 4.48 (d, J = 70.8 Hz, 1H), 4.48 (d, J =

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41.1 Hz, 1H), 3.77 (t, J = 8.8 Hz, 1H), 3.30 (dd, J = 7.5 Hz, J = 8.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C ppm 157.9, 138.6, 135.6, 128.9 (2C), 128.8 (2C), 128.2 (2C), 128.0 (2C), 125.5 (2C), 74.5, 51.5, 48.4. GCMS $C_{16}H_{15}NO_2$ [M] Calcd: 253.30. Found: 253 (19.3%), 104 (100%), 91 (63.2%).

[^{13}C]-3-Benzyl-5-phenyloxazolidin-2-one (25). Chamber 2: In a glovebox under argon, to chamber 2 of the two-chamber system was added P(tBu)$_3$ (22.3 mg, 0.110 mmol), Pd(dba)$_2$ (31.6 mg, 0.0550 mmol), [^{13}C]COgen (268 mg, 1.10 mmol), Cy_2NMe (471 μL, 2.2 mmol), and DMF (3 mL) in that order. The chamber was sealed with a Teflon seal. Chamber 1: In a glovebox under argon, to chamber 1 of the two-chamber system was added 2-(benzylamino)-1-phenylethanol (**23**) (100 mg, 0.440 mmol), Se (104 mg, 1.32 mmol), Et_3N (184 μL, 1.32 mmol), and DMF (3 mL) in that order. The chamber was sealed with a screwcap fitted with a Teflon seal.The loaded two-chamber system was stirred at room temperature for 24 h, followed by removal of the screwcaps and additional stirring at room temperature for 24 h. The crude mixture from chamber 1 was transferred with CH_2Cl_2 (10 mL) and extracted with Et_2O (100 mL). The combined organic phase was washed with water (5×) and brine (1×) and dried over $MgSO_4$. Solvents were removed in vacuo. The title compound was obtained after flash chromatography (10% EtOAc/pentane−20% EtOAc/pentane−30% EtOAc/pentane) as a colorless solid (72.7 mg, 0.286 mmol, 65%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H ppm 7.37−7.30 (m, 10H), 5.46 (dt, J = 1.7 Hz, J = 9.0 Hz, 1H), 4.47 (dd, J = 3.4 Hz, J = 69.2 Hz, 1H), 4.47 (dd, J = 3.4 Hz, J = 39.6 Hz, 1H), 3.76 (dt, J = 3.4 Hz, J = 8.8 Hz, 1H), 3.30 (ddd, J = 2.2 Hz, J = 8.8 Hz, J = 11.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C ppm 157.9 (^{13}C-enriched), 138.6 (d, J = 1.5 Hz), 135.6, 128.9 (2C), 128.8 (2C), 128.2 (2C), 128.0 (2C), 125.5, 74.5, 51.5 (d, J = 5.2 Hz), 48.4 (d, J = 1.9 Hz). HRMS $C_{16}H_{15}NO_2$ [M + Na$^+$] Calcd: 277.1029. Found: 277.1033. mp 67−68 °C.

***N*-Benzyl-2-phenylacetamide (26).**[33] *N*-Benzyl-2-oxo-2-phenylacetamide (**11**) (100 mg, 0.418 mmol) was dissolved in ethanol (99.9%, 2 mL), and H_2SO_4 (100 μL) was added. The flask was purged with hydrogen, heated to 50 °C, and left stirring under an atmosphere of hydrogen from a balloon for 5 h. The reaction mixture was diluted with H_2O and extracted with Et_2O. The organic phase was washed with brine, dried over Na_2SO_4, and evaporated to dryness in vauo, resulting in a white solid (92.0 mg, 0.408 mmol, 98%), which was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H ppm 7.37−7.22 (m, 8H), 7.19−7.15 (m, 2H), 5.75 (bs, 1H), 4.41 (d, J = 6.0 Hz, 2H), 3.62 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C ppm 171.0, 138.3, 135.0, 129.6 (2C), 129.2 (2C), 128.8 (2C), 127.7 (2C), 127.6, 127.6, 44.0, 43.8. HRMS $C_{15}H_{15}NO$ [M + H$^+$] Calcd: 226.1226. Found: 226.1227.

***N*-Benzyl-2-phenylethanamine (27).**[34] *N*-Benzyl-2-phenylacetamide (**26**) (100 mg, 0.443 mmol) was dissolved in 5 mL of anhydrous THF under argon at room temperature. BH_3·THF (1 M) (1.33 mL, 1.33 mmol) was slowly added to the solution. The mixture was refluxed at 100 °C for 17 h. The solution was quenched with 12 M HCl (1 mL), and the pH was adjusted to 9 with 2 M NaOH. The mixture was extracted with Et_2O (3×) and dried over $MgSO_4$ and concentrated in vacuo. The crude product was dissolved in Et_2O (10 mL), and 1 M HCl in Et_2O (1.33 mL, 1.33 mmol, 3 equiv) was added dropwise to the solution. The mixture was extracted with Na_2CO_3 and Et_2O (3×), dried over $MgSO_4$, and dried in vacuo. The title compound was obtained as a colorless solid (48.5 mg, 0.223 mmol, 53%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H ppm 7.34−7.22 (m, 10H), 3.83 (s, 2H), 2.95−2.92 (m, 2H), 2.87−2.84 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C ppm 140.3, 140.1, 128.7, 128.5, 128.4, 128.1, 126.9, 126.2, 53.9, 50.6, 36.4. HRMS $C_{15}H_{17}N$ [M + H$^+$] Calcd: 212.1439. Found: 212.1441.

***N*-Benzyl-2-hydroxy-2-phenylacetamide (28).**[35] Pd(OH)$_2$/C (20 w/w %, 20 mg, 0.028 mmol) was added to *N*-benzyl-2-oxo-2-phenylacetamide (**11**) (100 mg, 0.418 mmol) in EtOAc (8 mL) and left stirring at room temperature under an atmosphere of hydrogen (balloon) for 24 h. The reaction mixture was filtered over a silica plug, which was washed with EtOAc. Solvents were evaporated in vacuo to afford the title compound as a colorless solid (102.2 mg, 0.423 mmol, 101%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H ppm 7.43−7.24 (m, 8H), 7.20−7.16 (m, 2H), 6.42 (bs, 1H), 5.09 (s, 1H), 4.84 (dd, J = 6.0 Hz, J = 14.8 Hz, 1H), 4.42 (dd, J = 6.0 Hz, 15.2 Hz), 3.55 (bs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C ppm 172.3, 139.6, 137.9, 129.1 (2C), 128.9 (2C), 128.9, 127.8, 127.8 (2C), 127.0 (2C), 74.4, 43.7. HRMS $C_{15}H_{15}NO_2$ [M + Na$^+$] Calcd: 264.0995. Found: 264.0995.

2-(Benzylamino)-1-(3,4-dimethoxyphenyl)ethanol (29a). To a solution of $NaBH_4$ (54.6 mg, 1.44 mmol) in THF (1 mL) under argon was added *N*-benzyl-2-(3,4-dimethoxyphenyl)-2-oxoacetamide (**9**) (120 mg, 0.401 mmol) in THF (2 mL) and I_2 (152.7 mg, 0.602 mmol) in THF (2 mL) in that order at room temperature. The temperature was then raised to 60 °C, and the reaction mixture stood for 16 h. The reaction was quenched with 6 M HCl (0.5 mL) and neutralized with 2 M NaOH. The compound was worked up by extraction with Et_2O (3×) and dried over Na_2SO_4, followed by removal of solvents in vacuo. Flash column chromatography using 5% MeOH in CH_2Cl_2 as eluent resulted in 59.0 mg (54%) of a colorless waxy solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H ppm 7.33−7.26 (m, 5 H), 6.92−6.81 (m, 3 H), 4.71 (dd, J = 3.6 Hz, 1 H), 3.87−3.84 (m, 8 H), 2.91 (dd, J = 3.6, 12.1 Hz, 1 H), 2.78 (d, J = 12.1 Hz, 1 H), 2.75 (d, J = 9.0 Hz, 1 H), 2.67 (bs, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C ppm 149.0, 148.4, 139.3, 135.0, 128.5 (2 C), 128.2 (2 C), 127.3, 118.0, 111.0, 109.0, 71.5, 56.4, 55.9, 55.8, 53.4. HRMS $C_{17}H_{21}NO_3$ [M + H$^+$] Calcd: 288.1594. Found: 288.1594.

1-(4-Amino-3,5-dichlorophenyl)-2-(*tert*-butylamino)ethanol (36).[36] To a solution of $NaBH_4$ (28.3 mg, 0.747 mmol) in THF (2 mL) under argon was added 2-(4-amino-3,5-dichlorophenyl)-*N*-(*tert*-butyl)-2-oxoacetamide (**34**) (60 mg, 0.208 mmol) in THF (3 mL) and I_2 (78 mg, 0.311 mmol) in THF (3 mL) in that order at room temperature. The temperature was then raised to 60 °C, and the reaction mixture stood for 16 h. The reaction was quenched with 6 M HCl (0.5 mL) and neutralized with 2 M NaOH. The compound was worked up by extraction with Et_2O (3×) and dried over Na_2SO_4, followed by removal of solvents in vacuo. The compound was isolated by flash column chromatography (1% MeOH in CH_2Cl_2 → 5% MeOH in CH_2Cl_2 → 10% MeOH in CH_2Cl_2) as a colorless solid (57.5 mg, 0,207 mmol, 65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm 7.26 (s, 2H), 5.15 (d, J = 10.0 ppm, 1H), 3.10 (dd, J = 2.2 Hz, J = 12.1 Hz, 1H), 2.86 (dd, J = 10.3 Hz, J = 12.0 Hz, 1H), 1.44 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C ppm 139.7, 130.7, 125.3 (2C), 119.6 (2C), 68.0, 56.8, 49.9, 26.3 (3C).

[$^{13}C_2d_3$]1-(4-Amino-3,5-dichlorophenyl)-2-(*tert*-butylamino)-ethanol (37). To a solution of $NaDH_4$ (22.4 mg, 0.535 mmol) in THF (2 mL) under argon was added [$^{13}C_2$]-2-(4-amino-3,5-dichlorophenyl)-*N*-(*tert*-butyl)-2-oxoacetamide (**35**) (43.3 mg, 0.149 mmol) in THF (3 mL) and I_2 (56.5 mg, 0.223 mmol) in THF (3 mL) in that order at room temperature. The temperature was then raised to 60 °C, and the reaction mixture stood for 16 h. The reaction was quenched with 6 M HCl (0.4 mL) and neutralized with 2 M NaOH. The compound was worked up by extraction with EtOAc (3×), washed with brine (1×), and dried over Na_2SO_4, followed by removal of solvents in vacuo. The compound was isolated by flash column chromatography (1% MeOH in CH_2Cl_2 → 5% MeOH in CH_2Cl_2 → 10% MeOH in CH_2Cl_2) as a colorless solid (27.2 mg, 0.0751 mmol, 51%), which was subjected to preparative HPLC using 15% → 60% CH_3CN/H_2O (0.1% TFA) to afford a colorless solid (9.8 mg, 0.035 mmol, 23%). ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ_H ppm 7.25 (s, 2H), 6.04 (bs, 2H), 4.43 (s, 2H), 1.42 (s, 9H). ^{13}C NMR (100 MHz, $(CD_3)_2SO$): δ_C ppm 139.7, 125.3, 119.6 (d, J = 5.4 ppm, 2C), 110.0 (2C), 67.8 (m, 1C, ^{13}C-enriched), 56.7, 49.3 (m, 1C, ^{13}C-enriched), 26.3 (3C). HRMS $^{13}C_2C_{12}D_3H_{15}Cl_2N_2O$ [M + H$^+$] Calcd: 282.1124. Found: 282.1122. mp 77−78 °C.

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H NMR and ^{13}C NMR spectra for all of the coupling products. This material is available free of charge via the Internet at http://pubs.acs.org. CCDC 880674 and 880675 contains the supplementary crystallographic data for this paper.

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These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, U.K.; Fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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