Tetrahedron 66 (2010) 5692–5700

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Pd(II)-catalyzed synthesis of indoles from α-aryloxime *O*-pentafluorobenzoates via intramolecular aromatic C–H amination

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ARTICLE INFO

Article history:
Received 2 March 2010
Received in revised form 22 April 2010
Accepted 10 May 2010
Available online 15 May 2010

Keywords:
Indoles
Oximes
C–H amination
Vinyl nitrene
Palladium catalysts

ABSTRACT

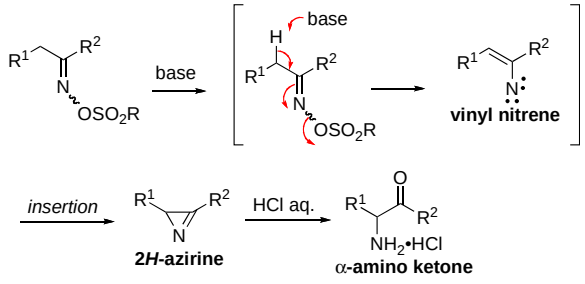
α-Aryl-α-aminocarbonyloxime *O*-pentafluorobenzoates are found to be promising precursors for synthesis of 2,3-disubstituted indole derivatives catalyzed by $PdCl_2(MeCN)_2$ in the presence of MgO as a base. The reaction is supposed to proceed via intramolecular aromatic C–H amination of a vinyl nitrene–palladium intermediate.

1. Introduction

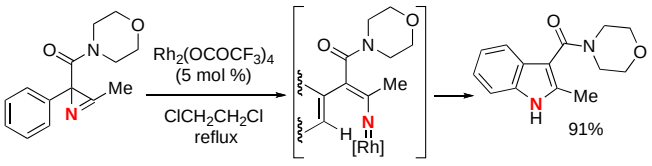
Indole is one of the most ubiquitous heterocyclic compounds, being present as a basic core in natural products[1] and potent pharmaceutical compounds.[2] Despite numerous diverse approaches toward the synthesis of indoles developed so far,[3,4] it is still challenging to develop synthetic methodologies of indoles bearing various substituents from readily available starting materials.

Our recent attention has been drawn to the reaction course of the Neber reaction of *O*-sulfonyloximes, which has been utilized as one of the preparative methods for α-amino ketones via 2*H*-azirines as an intermediate (Scheme 1).[5] One of the plausible reaction pathways of the formation of 2*H*-azirines from *O*-sulfonyloximes involves initial removal of an α-proton followed by loss of the sulfonate to afford vinyl nitrenes, which are converted into 2*H*-azirines via insertion onto the C–C double bond.[6]

Based on the mechanistic insight of the Neber reaction, we recently disclosed a $Rh_2(OCOCF_3)_4$-catalyzed isomerization reaction of 2-aryl-2*H*-azirines to 2,3-disubstituted indoles (Scheme 2), where transient vinyl nitrene-rhodium intermediates might undergo intramolecular aromatic C–H amination.[7a] However, most of 2*H*-azirines were difficult to prepare and handle due to their instability.



Scheme 1.



Scheme 2.

Thus we have strived to develop general and efficient methods to prepare indoles utilizing *O*-acyloxime derivatives, which are readily available from the corresponding ketones and rather stable to utilize. It was expected that coordination of the nitrogen atom of *O*-acyloximes **I** to appropriate transition metal [M] followed by

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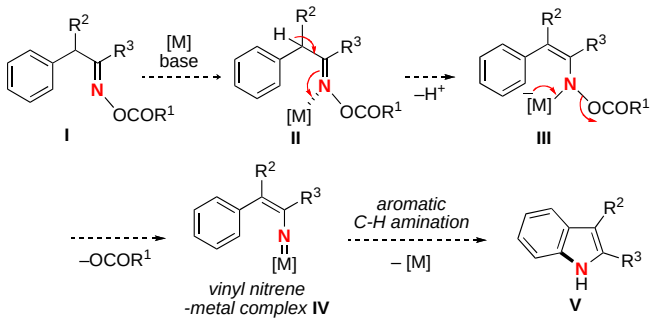
doi:10.1016/j.tet.2010.05.029

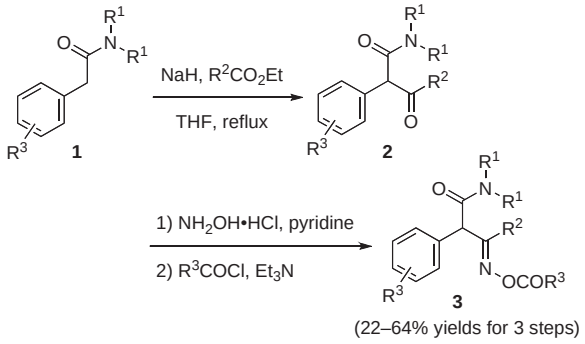
deprotonation would afford metal–nitrenoid **III**. α-Elimination of carboxylate from nitrenoid **III** would give metal-nitrene intermediate **IV**, subsequent aromatic C–H amination[4n,7] of which would provide the corresponding indoles (Scheme 3). Herein, we wish to report Pd(II)-catalyzed indole formation from α-aryl-α-aminocarbonyloxime *O*-pentafluorobenzoates via aromatic C–H amination.



Scheme 3.

2. Results and discussion

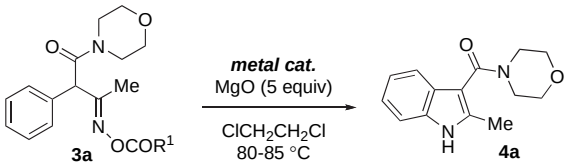
A synthetic scheme of α-aryl-α-aminocarbonyloxime derivatives **3** is depicted in Scheme 4. Treatment of α-arylamide **1** with esters in the presence of NaH provided α-acylated product **2**, which were converted into *O*-acyloximes **3** via a reaction with hydroxylamine followed by acylation.



Scheme 4.

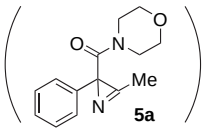
At first, we carried out extensive investigations to identify the best reaction conditions using 2-aminocarbonyl-2-phenylacetone oxime *O*-pentafluorobenzoate **3aa**,[8] benzoate **3ab**, and acetate **3ac** with some transition metal catalysts in the presence of MgO (5 equiv) as a base in 1,2-dichloroethane, and Table 1 listed representative results. Although the reaction of *O*-pentafluorobenzoate **3aa** with $Rh_2(OCOCF_3)_4$ (10 mol %) afford only 15% yield of desired indole **4a** with 34% recovery of **3aa** (entry 1), more electron-deficient $Rh_2(OCOC_3F_7)_4$ provided indole **4a** in 58% yield along with 40% recovery of **3a** (entry 2). When $PdCl_2(MeCN)_2$ (15 mol %) was used instead of Rh(II) dicarboxylates, the yield of indole **4a** was improved to 71% (entry 3). Higher catalytic loading of $PdCl_2(MeCN)_2$ (25 mol %) accelerated the reaction, providing indole **4a** in 82% yield (entry 4). Other Pd(II) catalysts like $Pd(OAc)_2$, $Pd(OTf)_2$, and $PdBr_2$ (entry 5) were ineffective as well as the other transition metals, such as $Cu(OTf)_2$, $NiBr_2$, AuCl, and $ReCl(CO)_5$. To lower catalytic loading, utilization of $PhI(OAc)_2$ and O_2 were examined as an additional oxidant with $PdCl_2(MeCN)_2$ (10 mol %), however, the reactions proceeded slowly, providing indole **4a** in 47 and 55% yields, respectively (entries 6 and 7). Treatment of **3aa** with MgO in the absence of the catalyst provided only 2*H*-azirine **5a** after 12 h (entry 8). Although the indole formation from both benzoate **3ab** and acetate **3ac** was observed using $PdCl_2(MeCN)_2$, the yield of **4a** was not satisfactory (entries 9 and 10).

Table 1
Optimization of reaction conditions



Entry	R^1	Metal catalysts	Time/h	Yield/%[a]
1	**3aa**–C_6F_5	$Rh_2(OCOCF_3)_4$ (10 mol %)	23	15 (34)[b]
2	**3aa**–C_6F_5	$Rh_2(OCOC_3F_7)_4$ (10 mol %)	12	58 (40)[b]
3	**3aa**–C_6F_5	$PdCl_2(MeCN)_2$ (15 mol %)	9	71
4	**3aa**–C_6F_5	$PdCl_2(MeCN)_2$ (25 mol %)	3	82
5	**3aa**–C_6F_5	$PdBr_2$ (25 mol %)	8	60
6	**3aa**–C_6F_5	$PdCl_2(MeCN)_2$ (10 mol %)	23	47[c]
7	**3aa**–C_6F_5	$PdCl_2(MeCN)_2$ (10 mol %)	22	55[d]
8	**3aa**–C_6F_5	—	12	0[e]
9	**3ab**–C_6H_5	$PdCl_2(MeCN)_2$ (25 mol %)	9	58
10	**3ac**–Me	$PdCl_2(MeCN)_2$ (25 mol %)	3	47

[a] Isolated yields.
[b] Recovery of starting material **1**.
[c] $PhI(OAc)_2$ (0.5 equiv) was added to the reaction.
[d] The reaction was run under an O_2 atmosphere.
[e] 2*H*-Azirine **5a** was obtained in 78% yield.



With the identification of the optimized conditions in hand, we next examined the generality of this method for synthesis of substituted indoles **4** using *O*-pentafluorobenzoyl oximes **3** (Table 2). Substrates bearing halogen substituents, such as Cl, Br, and F atoms on the benzene ring were converted into the corresponding indoles with keeping the C–halogen bond intact (entries 1–5), although the yield of 5,7-dibromoindole was moderate (entry 4). In the case of *meta*-chloro substituted substrate **3f**, two regioisomeric indoles **4f** and **4f′** were formed in the ratio of 3:2 (entry 5). Methyl and phenyl groups could be installed on the benzene ring of indoles (entries 6 and 7). The reaction of α-2-naphtyl oxime **3h** formed C–N bond only with C(1), providing indole **4h** in 87% yield (entry 8). Some alkyl groups on C(2) of indoles **4** were incorporated in good yields (entries 9–12), while 2-aryl indole **3n** was obtained in moderate yield (49%) with formation of the corresponding 2*H*-azirine **5n** (entry 13).[9] Along with a morpholino carbonyl motif, *N*,*N*′-dimethylamino-, and piperidino carbonyl parts could be introduced at the C(3) position of indoles (entries 14 and 15).

Finally, a reaction of deuterium-labeled oxime **3o–d** was examined to elucidate the mechanism of the C–H amination process, namely a concerted σ-bond methathesis or a stepwise electrophilic aromatic substitution (Scheme 5).[10,11] The product isotope effect of obtained indole **4o–d** was 1.0 (100% conversion, 49% yield), which would support an electrophilic aromatic substitution for the C–H amination process, not σ-bond methathesis.[4n,12]

3. Conclusion

In summary, we have developed a concise approach to substituted indoles using readily available and rather stable *O*-acyloximes via Pd(II)-catalyzed aromatic C–H amination. Further application of this method for synthesis of various azaheterocycles are currently underway.

Table 2
Synthesis of indoles[a]

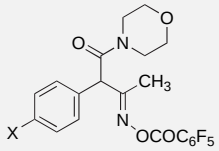
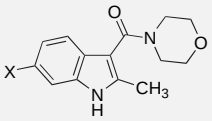
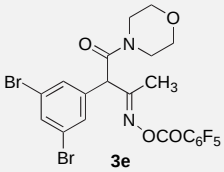
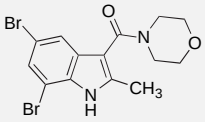
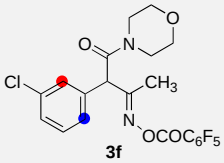
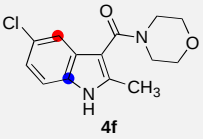
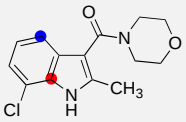
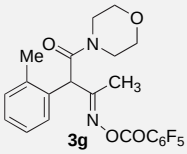
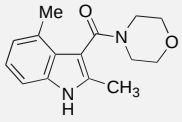
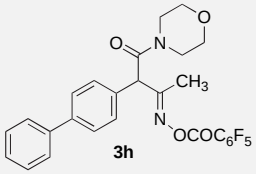
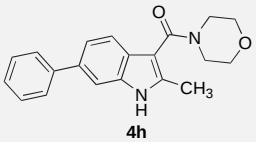
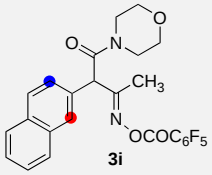
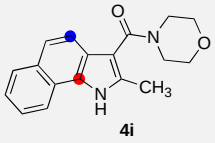
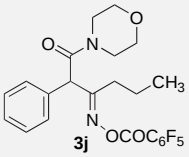
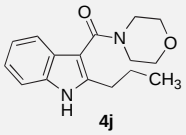
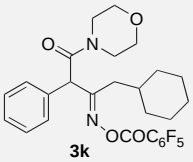
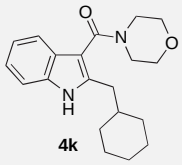
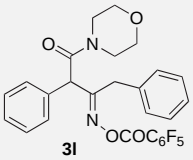
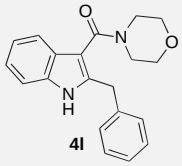
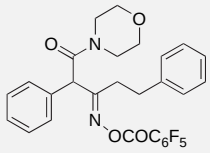
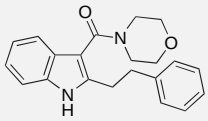
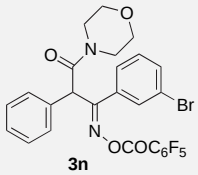
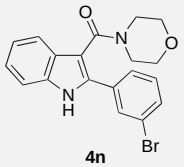
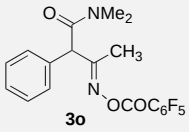
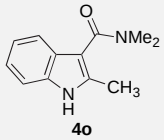
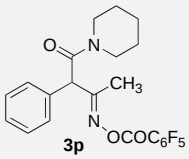
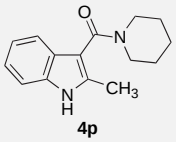
Entry	Oximes **3**	Indoles **4**	Time, yield[b]
			
1	**3b**: X=Cl	**4b**	4 h, 70%
2	**3c**: X=Br	**4c**	6 h, 75%
3	**3d**: X=F	**4d**	4 h, 70%
4	 **3e**	 **4e**	10 h, 33%
5	 **3f**	 **4f**	6 h, 59%
		 **4f'**	40%
6	 **3g**	 **4g**	6 h, 46%
7	 **3h**	 **4h**	3.5 h, 72%
8	 **3i**	 **4i**	5 h, 87%
9	 **3j**	 **4j**	12 h, 51%
10	 **3k**	 **4k**	9 h, 91%
11	 **3l**	 **4l**	9 h, 63%

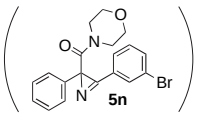
Table 2 (*continued*)

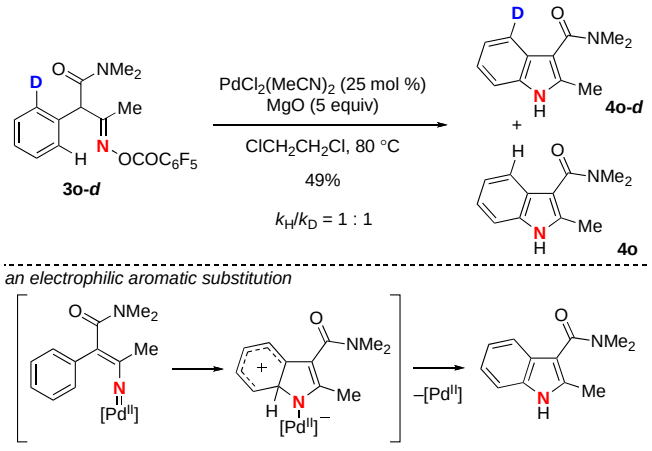
Entry	Oximes **3**	Indoles **4**	Time, yield[b]
12	 **3m**	 **4m**	9 h, 55%
13[c]	 **3n**	 **4n**	10 h, 49%
14	 **3o**	 **4o**	5 h, 68%
15	 **3p**	 **4p**	5 h, 73%

[a] The reaction was conducted by treatment of oximes **3** with 25 mol% of $PdCl_2(MeCN)_2$ and 5 equiv of MgO in 1,2-dichloroethane at 80 °C

[b] Isolated yields by flash column chromatography on silica gel.

[c] Yield (32%) of 2*H*-azirine **5n** was isolated from the reaction.


5n



Scheme 5.

4. Experimental section

4.1. General

^{1}H NMR (300 MHz) spectra were recorded on a Bruker Avance 300 spectrometers, ^{1}H NMR (400 MHz) spectra were recorded on a Bruker Avance 400 spectrometers, and ^{1}H NMR (500 MHz) spectra were recorded on a Bruker Avance 500 spectrometers in $CDCl_3$ [using $CHCl_3$ (for ^{1}H, δ=7.26) or $(CH_3)_4Si$ (for ^{1}H, δ=0.00) as internal standard] or in DMSO-d_6 [using DMSO (for ^{1}H, δ=2.49) or $(CH_3)_4Si$ (for ^{1}H, δ=0.00) as internal standard]. ^{13}C NMR (75 MHz) spectra on a Bruker Avance 300 spectrometers and ^{13}C NMR (100 MHz) spectra on a Bruker Avance 400 spectrometers in $CDCl_3$ [using $CHCl_3$ (for ^{13}C, δ=77.0) as internal standard] or in DMSO-d_6 [using DMSO (for ^{13}C, δ=39.5) as internal standard]. The following abbreviations were used to explain the multiplicities: s=singlet, d=doublet, t=triplet, m=multiplet, br=broad. IR spectra were recorded on a Shimazu IR Prestige-21 FT-IR Spectrometer. High-resolution mass spectra were obtained with a Finnigan MAT 95 XP mass spectrometer (Thermo Electron Corporation). Melting points were uncorrected and were recorded on a Buchi B-54 melting point apparatus.

Flash column chromatography was performed using Merck silica gel 60 with distilled solvents. Toluene, tetrahydrofuran (THF), and dichloromethane (CH_2Cl_2) were taken from a solvent purification system (PS-400-5, innovative technology Inc.). *N*,*N*-Dimethylformamide (DMF) was distilled from CaH_2 and stored over MS 4A. 1,2-Dichloroethane ($ClCH_2CH_2Cl$) was distilled from CaH_2.

4.2. Synthesis of amide derivatives 1

*4.2.1. 1-Morpholino-2-phenylethanone (**1a**)[13] (method A).* To a solution of 2-phenylacetyl chloride (8.55 mL, 64.5 mmol) in CH_2Cl_2 (92 mL) was added morpholine (14.1 mL, 162 mmol), and the mixture was stirred for 30 min. After that, the mixture was filtered through Celite and washed with CH_2Cl_2. The organic materials were extracted with CH_2Cl_2 for three times. The combined extracts were washed with water and brine, dried over $MgSO_4$, and

filtered. The solvents were removed in vacuo. The crude materials were purified by recrystallization from hexane–ethyl acetate to give **1a** (9.92 g, 48.3 mmol) in 75% yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.44–3.64 (8H, m), 3.74 (2H, s), 7.23–7.35 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 40.9, 42.2, 46.5, 66.5, 66.8, 126.9, 128.5, 128.8, 134.8, 169.9.

*4.2.2. 2-(4-Chlorophenyl)-1-morpholinoethanone (**1b**).* Yield 89%; white crystal; mp 107.0–108.0 °C; FTIR (KBr) 2966, 2840, 1650, 1499, 1452, 1272, 1112, 1034, 818, 782 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.43 (2H, t, J=4.5 Hz), 3.53 (2H, t, J=4.4 Hz), 3.65 (4H, s), 3.69 (2H, s), 7.18 (2H, d, J=8.4 Hz), 7.30 (2H, d, J=8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 39.8, 42.1, 46.3, 66.3, 66.7, 128.8, 139.9, 132.7, 133.2, 169.0; ESIMS: found: m/z 240.0790. Calcd for $C_{12}H_{15}NO_2Cl$: $(M+H)^+$ 240.0791.

*4.2.3. 2-(4-Fluorophenyl)-1-morpholinoethanone (**1d**)[14].* Yield 88%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.43 (2H, t, J=4.4 Hz), 3.52 (2H, t, J=4.6 Hz), 3.63 (4H, s), 3.68 (2H, s), 6.99 (1H, d, J=8.4 Hz), 7.01 (1H, d, J=8.8 Hz), 7.19 (1H, d, J=8.4 Hz), 7.20 (1H, d, J=8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 39.7, 42.1, 46.4, 66.4, 66.7, 115.5 (d, J=21.4 Hz), 130.1 (d, J=7.9 Hz), 130.4 (d, J=3.4 Hz), 161.8 (d, J=243.8 Hz), 169.4.

*4.2.4. N,N-Dimethyl-2-phenylacetamide (**1o**)[15].* Yield 85%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.95 (3H, s), 2.98 (3H, s), 3.71 (2H, s), 7.20–7.33 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 35.5, 37.6, 40.9, 126.5, 128.5, 128.6, 135.0, 170.9.

*4.2.5. 2-Phenyl-1-(piperidin-1-yl)ethanone (**1p**)[16].* Yield quant; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33–1.38 (2H, m), 1.51–1.60 (4H, m), 3.37 (2H, t, J=5.6 Hz), 3.57 (2H, t, J=5.3 Hz), 3.73 (2H, s), 7.23–7.34 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.4, 25.4, 26.2, 41.1, 42.9, 47.2, 126.6, 128.5, 128.6, 135.4, 169.2.

*4.2.6. 2-(3-chlorophenyl)-1-morpholinoethanone (**1f**) (method B).* To a solution of 2-(3-chlorophenyl)acetic acid (2.87 g, 16.8 mmol) in CH_2Cl_2 (17 mL) was added $(COCl)_2$ (1.6 mL, 18.5 mmol). A drop of DMF was added, gas bubbles CO and CO_2 started to form. The solution was stirred until no more gas bubbles were observed. A solution of morpholine (3.40 mL, 38.6 mmol) was added into the mixture at 0 °C. After stirring for 1 h, the mixture was quenched with water and extracted with CH_2Cl_2. The organic layer was then washed with saturated $NaHCO_3$ solution and brine. The extract was dried over $MgSO_4$ and filtered. The solvents were removed in vacuo. The crude materials were purified by recrystallization from hexane–ethyl acetate to give **1f** (3.04 g, 12.6 mmol) in 75% yield.

Yield 75%; white crystal; mp 59.0–60.7 °C; FTIR (KBr) 2976, 2851, 1649, 1609, 1602, 1575, 830, 750 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.44 (2H, t, J=4.6 Hz), 3.54 (2H, t, J=4.8 Hz), 3.65 (4H, s), 3.70 (2H, s), 7.13 (1H, d, J=6.4 Hz), 7.23–7.29 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 40.1, 42.2, 46.4, 66.4, 66.8, 126.8, 127.2, 128.8, 129.9, 134.5, 136.7, 168.8; ESIMS: found: m/z 240.0791. Calcd for $C_{12}H_{15}ClNO_2$: $(M+H)^+$ 240.0791.

*4.2.7. 2-(4-Bromophenyl)-1-morpholinoethanone (**1c**).* Yield 92%; colorless oil; FTIR (KBr) 2966, 2840, 1650, 1499, 1452, 1272, 1112, 1034, 816, 775 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.43 (2H, t, J=4.6 Hz), 3.53 (2H, t, J=4.6 Hz), 3.67 (2H, s), 7.11 (2H, d, J=8.4 Hz), 7.45 (2H, d, J=8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 40.0, 42.2, 46.4, 66.4, 66.8, 120.9, 130.4, 131.8, 133.7, 169.0; ESIMS: found: m/z 284.0287. Calcd for $C_{12}H_{15}NO_2Br$: $(M+H)^+$ 284.0286.

*4.2.8. 2-(3,5-Dibromophenyl)-1-morpholinoethanone (**1e**).* Yield 87%; Yellow oil; FTIR (KBr) 2930, 2855, 1628, 1584, 1553, 1458, 1112, 1036, 845, 740 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) 3.42–3.64 (10H, m), δ 7.31 (2H, s), 7.54 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 39.3, 42.1, 46.3, 66.3, 66.6, 122.9, 130.7, 132.6, 138.5, 168.0; ESIMS: found: m/z 363.9375. Calcd for $C_{12}H_{14}NO_2Br_2$: $(M+H)^+$ 363.9371.

*4.2.9. 1-Morpholino-2-o-tolylethanone (**1g**)[13].* Yield 88%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.28 (3H, s), 3.39 (2H, t, J=4.6 Hz), 3.55 (2H, t, J=4.4 Hz), 3.67 (2H, s), 3.68 (4H, s), 7.12–7.17 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.6, 38.2, 42.0, 46.3, 66.4, 66.8, 126.2, 127.0, 128.5, 130.3, 133.3, 136.1, 169.6.

*4.2.10. 2-(Biphenyl-4-yl)-1-morpholinoethanone (**1h**)[13].* Yield 91%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.48 (2H, t, J=4.2 Hz), 2.51 (2H, t, J=4.2 Hz), 3.66 (4H, s), 3.76 (2H, s), 7.30–7.36 (3H, m), 7.41–7.46 (2H, m), 7.55–7.60 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 40.3, 42.1, 46.5, 66.5, 66.8, 127.0, 127.3, 127.4, 128.7, 129.0, 133.8, 139.8, 140.6, 169.5.

*4.2.11. 1-Morpholino-2-(naphthalen-2-yl)ethanone (**1i**).* Yield 88%; white crystal; mp 226.0–227.1 °C; FTIR (KBr) 2919, 2857, 1633, 1436, 1273, 1229, 1111, 1037, 797, 744 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.46–3.66 (8H, m), 4.00 (2H, s), 7.38 (1H, dd, J=1.6, 8.4 Hz), 7.48–7.51 (2H, m), 7.68 (1H, s), 7.80–7.85 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 41.0, 42.1, 46.5, 66.4, 66.8, 125.8, 126.3, 126.7, 127.0, 127.5, 127.6, 128.5, 132.2, 132.3, 133.5, 169.5; ESIMS: found: m/z 256.1337. Calcd for $C_{16}H_{18}NO_2$: $(M+H)^+$ 256.1338.

4.3. Synthesis of *O*-pentafluorobenzoyl oximes 3

*4.3.1. 1-morpholino-3-(perfluorobenzoyloxyimino)-2-phenylbutan-1-one (**3aa**) (a typical procedure).* To an ice cold solution of 1-morpholino-2-phenylethanone (2.00 g, 9.74 mmol) in THF (30.0 mL) was added NaH (60% dispersion in paraffin liquid, 896 mg, 22.4 mmol), and the mixture was stirred at room temperature for 30 min. After the mixture was cooled to 0 °C, ethyl acetate (1.44 mL, 14.6 mmol) was added and the mixture was stirred at reflux overnight. The mixture was then cooled to 0 °C and quenched with slow addition of aqueous 1 M HCl. The organic layer was extracted using ethyl acetate three times and then washed with brine. The combined extracts were dried over $MgSO_4$ and filtered. The solvents were removed in vacuo, and the resulting crude mixture was used for next step without purification.

To an ice cold solution of crude materials in EtOH (12.0 mL) was added pyridine (2.42 mL, 30.0 mmol) and hydroxylamine hydrochloride (1.04 g, 15.0 mmol). The mixture was then stirred at room temperature for 1 h. The reaction was quenched with water and the organic layer was extracted with ethyl acetate three times. The combined extracts were washed with aqueous 1 M HCl then with brine. The extracts were dried over $MgSO_4$ and filtered. The solvents were removed in vacuo, and the resulting crude mixture was used for next step without any purification.

To an ice cold solution of crude oxime obtained above in CH_2Cl_2 (49.0 mL) was added triethylamine (Et_3N) (3.40 mL, 24.4 mmol) and 2,3,4,5,6-pentafluoro-benzoyl chloride (1.48 mL, 10.7 mmol) slowly. The mixture was stirred at 0 °C for 30 min and at room temperature for another 30 min. The reaction was quenched with water and the organic layer was extracted with ethyl acetate three times. The extract was dried over $MgSO_4$ and filtered. The solvents were removed in vacuo. The crude material was purified by flash column chromatography with hexane–ethyl acetate=6:4 to give the 1-morpholino-3-(perfluorobenzoyloxyimino)-2-phenylbutan-1-one (2.58 g, 5.65 mmol) in 58% yield for three steps. Further purification was done by recrystallization from a hexane–ethyl acetate solvent system.

White crystal; mp 113.6–114.7 °C; FTIR (KBr) 3008, 2859, 1761, 1651, 1525, 1497, 1437, 1328, 1194, 1004, 754, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.04 (3H, s), 3.12–3.75 (8H, m), 5.06 (1H, s), 7.31

(2H, d, J=7.2 Hz), 7.38–7.42 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.4, 42.0, 46.2, 54.3, 66.0, 66.6, 106.7 (m), 128.4, 128.5, 129.5, 133.5, 137.7 (dm, J=243 Hz), 144.4 (dm, J=267 Hz), 145.5 (dm, J=250 Hz), 166.5, 167.8, 168.3; ESIMS: found: m/z 457.1187. Calcd for $C_{21}H_{18}F_5N_2O_4$: $(M+H)^+$ 457.1187.

*4.3.2. 2-(4-Chlorophenyl)-1-morpholino-3-(perfluorobenzoyloxyimino) butan-1-one (**3b**).* Yield 36%; brown viscous oil; FTIR (KBr) 2924, 2859, 1761, 1651, 1524, 1497, 1435, 1327, 1192, 1115, 1092, 1003,758 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.05 (3H, s), 3.13–3.75 (8H, m), 5.04 (1H, s), 7.26–7.28 (2H, d, J=8.0 Hz), 7.40 (2H, d, J=8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.4, 42.1, 46.2, 53.6, 66.1, 66.6, 106.6 (m), 129.7, 129.8, 132.0, 134.7, 137.7 (dm, J=245 Hz), 143.4 (dm, J=256 Hz), 145.6 (dm, J=255 Hz), 156.4, 167.5, 167.8; ESIMS: found: m/z 491.0785. Calcd for $C_{21}H_{17}ClF_5N_2O_4$: $(M+H)^+$ 491.0797.

*4.3.3. 2-(4-Bromophenyl)-1-morpholino-3-(perfluorobenzoyloxyimino)-butan-1-one (**3c**).* Yield 35%; white solid; mp 91.3–92.7 °C; FTIR (KBr) 2851, 1751, 1646, 1525, 1497, 1437, 1327, 1192, 1003, 748 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.04 (3H, s), 3.12–3.74 (8H, m), 5.01 (1H, s), 7.21 (2H, d, J=8.4 Hz), 7.55 (2H, d, J=8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.4, 42.1, 46.2, 53.7, 66.1, 66.6, 106.6 (m), 122.8, 130.1, 132.6, 132.7, 137.8 (dm, J=250 Hz), 143.6 (dm, J=259 Hz), 145.5 (dm, J=263 Hz), 156.4, 167.4, 167.8; ESIMS: found: m/z 535.0292. Calcd for $C_{21}H_{17}BrF_5N_2O_4$: $(M+H)^+$ 535.0292.

*4.3.4. 2-(4-Fluorophenyl)-1-morpholino-3-(perfluorobenzoyloxyimino)-butan-1-one (**3d**).* Yield 63%; white solid; mp 46.5–51.1 °C; FTIR (KBr) 2960, 2860, 1764, 1652, 1525, 1506, 1437, 1328, 1228, 1193, 1116, 1004, 757 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.03 (3H, s), 3.12–3.73 (8H, m), 5.03 (1H, s), 7.08–7.13 (2H, m), 7.26–7.31 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.3, 42.1, 46.2, 53.5, 66.1, 66.6, 106.7 (m), 116.5 (d, J=21.6 Hz), 129.3 (d, J=3.5 Hz), 130.2 (d, J=8.2 Hz), 137.7 (dm, J=247 Hz), 143.5 (dm, J=264 Hz), 144.5 (dm, J=263 Hz), 156.5, 162.6 (d, J=247 Hz), 167.7, 168.0; ESIMS: found: m/z 475.1084. Calcd for $C_{21}H_{17}F_6N_2O_4$: $(M+H)^+$ 475.1093.

*4.3.5. 2-(3,5-Dibromophenyl)-1-morpholino-3-(perfluorobenzoyl-oxyimino)butan-1-one (**3e**).* Yield 21%; yellow oil; FTIR (KBr) 2870, 1760, 1652, 1555, 1528, 1332, 1189, 1001, 758 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.07 (3H, s), 3.16–3.75 (8H, m), 4.98 (1H, s), 7.43 (2H, s), 7.69 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.4, 42.3, 46.4, 53.3, 66.1, 66.6, 106.7 (m), 124.0, 130.2, 134.5, 137.9 (dm, J=265 Hz), 137.4, 142.4 (dm, J=244 Hz), 144.6 (dm, J=383 Hz), 156.4, 166.5, 167.1; ESIMS: found: m/z 612.9358. Calcd for $C_{25}H_{20}F_5N_2O_4$: $(M+H)^+$ 612.9397.

*4.3.6. 2-(3-Chlorophenyl)-1-morpholino-3-(perfluorobenzoyloxyimino) butan-1-one (**3f**).* Yield 48%; white solid; mp 53.5–55.5 °C; FTIR (KBr) 2975, 2859, 1762, 1653, 1525, 1506, 1499, 1437, 1328, 1192, 1116, 1004, 701 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.06 (3H, s), 3.13–3.78 (8H, m), 5.03 (1H, s), 7.21–7.24 (1H, m), 7.33 (1H, s), 7.35–7.37 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.4, 42.2, 46.3, 53.8, 66.1, 66.6, 106.8 (m), 126.6, 128.6, 128.9, 130.7, 135.5, 135.6, 137.7 (dm, J=249 Hz), 143.5 (dm, J=254 Hz), 145.6 (dm, J=256 Hz), 156.4, 167.2, 167.7; ESIMS: found: m/z 491.0788. Calcd for $C_{21}H_{17}ClF_5N_2O_4$: $(M+H)^+$ 491.0797.

*4.3.7. 1-Morpholino-3-(perfluorobenzoyloxyimino)-2-o-tolylbutan-1-one (**3g**).* Yield 21%; brown oil; FTIR (KBr) 2973, 2859, 1762, 1652, 1525, 1506, 1496, 1437, 1328, 1259, 1228, 1193, 1116, 1004, 757 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.02 (3H, s), 2.38 (3H, s), 2.93–3.81 (8H, m), 5.08 (1H, s), 7.23–7.29 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.5, 19.5, 42.0, 45.9, 51.9, 65.9, 66.6, 106.9 (m), 126.8, 128.3, 128.7, 131.4, 131.6, 137.6 (dm, J=255 Hz), 136.8, 143.4 (dm, J=254 Hz), 145.5 (dm, J=272 Hz), 156.5, 167.2, 168.8; ESIMS: found: m/z 471.1342. Calcd for $C_{22}H_{20}F_5N_2O_4$: $(M+H)^+$ 471.1243.

*4.3.8. 2-(Biphenyl-4-yl)-1-morpholino-3-(perfluorobenzoyloxyimino) butan-1-one (**3h**).* Yield 61%; white solid; mp 80.0–81.7 °C; FTIR (KBr) 2919, 2860, 1757, 1653, 1525, 1507, 1496, 1437, 1327, 1192, 1116, 1004, 750, 699 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.09 (3H, s), 3.18–3.78 (8H, m), 5.10 (1H, s), 7.37–7.40 (3H, m), 7.46 (2H, dd, J=7.6, 7.2 Hz), 7.59 (2H, d, J=7.6 Hz), 7.65 (2H, d, J=7.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.4, 42.1, 46.3, 54.0, 66.1, 66.6, 106.8 (m), 127.0, 127.8, 128.1, 128.8, 128.9, 132.4, 139.8, 137.8 (dm, J=250 Hz), 141.4, 143.5 (dm, J=259 Hz), 145.5 (dm, J=252 Hz), 156.5, 167.9, 168.3; ESIMS: found: m/z 533.1490. Calcd for $C_{27}H_{22}F_5N_2O_4$: $(M+H)^+$ 533.1500.

*4.3.9. 1-Morpholino-2-(naphthalen-2-yl)-3-(perfluorobenzoyloxyimino)-butan-1-one (**3i**).* Yield 41%; white solid; mp 159.2–160.0 °C; FTIR (KBr) 3037, 2858, 1761, 1652, 1525, 1506, 1327, 1260, 1192, 1116, 1092, 1003 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.07 (3H, s), 3.19–3.74 (8H, m), 5.22 (1H, s), 7.40 (1H, dd, J=1.6, 8.5 Hz), 7.54–7.56 (2H, m), 7.79 (1H, s), 7.83–7.91 (3H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.5, 42.1, 46.2, 54.4, 66.1, 66.6, 106.8 (m), 125.6, 126.9, 127.0, 127.6, 127.8, 127.9, 129.5, 130.9, 132.9, 133.4, 137.7 (dm, J=255 Hz), 143.5 (dm, J=259 Hz), 145.5 (dm, J=259 Hz), 156.6, 168.0, 168.3; ESIMS: found: m/z 507.1329. Calcd for $C_{25}H_{20}F_5N_2O_4$: $(M+H)^+$ 507.1343.

*4.3.10. 1-Morpholino-3-(perfluorobenzoyloxyimino)-2-phenylhexan-1-one (**3j**).* Yield 47%; white crystal; mp 108.0–109.0 °C; FTIR (KBr) 2967,2858, 1759, 1651, 1524, 1497, 1435, 1327, 1184, 1115, 1005, 756, 702 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.53–0.63 (1H, m), 0.67 (3H, t, J=6.9 Hz), 1.28–1.40 (2H, m), 2.35 (1H, dt, J=11.9 Hz, 5.0 Hz), 2.68 (1H, dt, J=11.9, 5.0 Hz), 3.17–3.74 (8H, m), 5.01 (1H, s), 7.32–7.41 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.4, 20.0, 32.4, 42.1, 46.2, 54.3, 66.0, 66.6, 106.9 (m), 128.6 (overlapped), 129.4, 133.3, 137.8 (dm, J=232 Hz), 143.5 (dm, J=245 Hz), 145.4 (dm, J=260 Hz), 156.7, 168.1, 171.0; ESIMS: found: m/z 485.1504. Calcd for $C_{23}H_{22}F_5N_2O_4$: $(M+H)^+$ 485.1500.

*4.3.11. 4-Cyclohexyl-1-morpholino-3-(perfluorobenzoyloxyimino)-2-phenylbutan-1-one (**3k**).* Yield 23%; white powder; mp 135.0–135.5 °C; FTIR (KBr) 2926, 2854, 1762, 1653, 1521, 1496, 1452, 1434, 1326, 1240, 1201, 1115, 1036, 1003, 702 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.45–1.60 (11H, m), 2.47 (1H, dd, J=13.2 Hz, 7.0 Hz), 2.62 (1H, dd, J=13.2 Hz, 7.0 Hz), 3.15–3.77 (8H, m), 4.97 (1H, s), 7.29–7.39 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.8, 26.0, 26.1, 32.9, 33.1, 36.0, 37.5, 42.2, 46.3, 54.6, 66.0, 66.6, 107.2 (m), 128.4, 128.8, 129.2, 133.7, 137.8 (dm, J=265 Hz), 143.3 (dm, J=258 Hz), 145.0 (dm, J=272 Hz), 157.0, 168.1, 169.5; ESIMS: found: m/z 539.1959. Calcd for $C_{27}H_{28}F_5N_2O_4$: $(M+H)^+$ 539.1969.

*4.3.12. 1-Morpholino-3-(perfluorobenzoyloxyimino)-2,4-diphenylbutan-1-one (**3l**).* Yield 20%; yellow viscous oil; FTIR (KBr) 3105, 2860, 1762, 1646, 1525, 1496, 1454, 1437, 1327, 1231, 1198, 1116, 1003, 754, 703 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.03–3.86 (8H, m), 3.84 (1H, d, J=15.3 Hz), 4.12 (1H, d, J=15.3 Hz), 4.91 (1H, s), 6.83–7.30 (10H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 36.0, 42.2, 46.0, 53.7, 65.9, 66.5, 106.9 (m), 126.6, 128.3, 128.4, 128.6, 129.0, 129.1, 132.8, 134.7, 137.5 (dm, J=244 Hz), 143.2 (dm, J=258 Hz), 144.9 (dm, J=249 Hz), 156.9, 167.7, 168.2; ESIMS: found: m/z 533.1494. Calcd for $C_{27}H_{22}F_5N_2O_4$: $(M+H)^+$ 533.1500.

*4.3.13. 1-Morpholino-3-(perfluorobenzoyloxyimino)-2,5-diphenylpentan-1-one (**3m**).* Yield 44%; white solid; mp 54.0–56.7 °C; FTIR (KBr) 3040, 2859, 1761, 1647, 1524, 1497, 1456, 1327, 1192, 1115, 1003, 754, 702 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.79–3.76 (12H, m), 4.98 (1H, s), 6.84 (2H, d, J=7.3 Hz), 7.15–7.46 (8H, m); ^{13}C NMR

(100 MHz, $CDCl_3$) δ 32.3, 32.4, 42.1, 46.1, 54.5, 66.0, 66.6, 106.8 (m), 126.2, 128.0, 128.4, 128.7 (overlapped), 129.5, 133.2, 137.7 (dm, J=251 Hz), 140.5, 143.5 (dm, J=265 Hz), 145.4 (dm, J=263 Hz), 156.6, 168.0, 169.9; ESIMS: found: m/z 547.1647. Calcd for $C_{28}H_{24}F_5N_2O_4$: $(M+H)^+$ 547.1656.

*4.3.14. 3-(3-Bromophenyl)-1-morpholino-3-(perfluorobenzoyloxyimino)-2-phenylpropan-1-one (**3n**).* Yield 44%; white solid; mp 134.1–135.9 °C; FTIR (KBr) 2858, 1763, 1651, 1524, 1499, 1535, 1327, 1190, 1005, 756, 714 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.13–3.76 (8H, m), 5.33 (1H, s), 6.96 (1H, d, J=7.6 Hz), 7.07–7.11 (2H, m), 7.16–7.18 (2H, m), 7.32–7.34 (3H, m), 7.39 (1H, d, J=8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 42.3, 46.4, 55.8, 65.9, 66.5, 106.4 (m), 121.4, 126.7, 128.6, 129.0, 129.1, 129.2, 130.6, 132.0, 132.8, 133.3, 137.5 (dm, J=254 Hz), 143.5 (dm, J=259 Hz), 145.1 (dm, J=262 Hz), 156.6, 166.8, 167.7; ESIMS: found: m/z 597.0438. Calcd for $C_{26}H_{19}BrF_5N_2O_4$: $(M+H)^+$ 597.0448.

*4.3.15. N,N-Dimethyl-3-(perfluorobenzoyloxyimino)-2-phenylbutanamide (**3o**).* Yield 47%; white crystal; mp 104.5–115.8 °C; FTIR (KBr) 3019, 1762, 1657, 1526, 1420, 1332, 1218, 1007, 777 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.05 (3H, s), 2.84 (3H, s), 3.02 (3H, s), 5.09 (1H, s), 7.30–7.40 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.3, 35.6, 37.3, 54.4, 106.8 (m), 128.3, 128.4, 129.3, 133.7, 137.7 (dm, J=251 Hz), 143.4 (dm, J=259 Hz), 145.5 (dm, J=251 Hz), 156.5, 168.7, 169.2; ESIMS: found: m/z 415.1080. Calcd for $C_{19}H_{16}F_5N_2O_3$: $(M+H)^+$ 415.1081.

*4.3.16. 3-(Perfluorobenzoyloxyimino)-2-phenyl-1-(piperidin-1-yl) butan-1-one (**3p**).* Yield 33%; yellow oil; FTIR (KBr) 2941, 2859, 1762, 1642, 1523, 1497, 1444, 1328, 1004, 755, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.11–1.68 (6H, m), 2.04 (3H, s), 3.13–3.75 (4H, m), 5.09 (1H, s), 7.27–7.42 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.5, 24.2, 25.4, 25.7, 42.8, 46.9, 54.5, 106.9 (m), 128.2, 128.5, 129.3, 134.1, 136.4 (dm, J=248 Hz), 142.1 (dm, J=263 Hz), 144.2 (dm, J=257 Hz), 156.6, 167.5, 168.8; ESIMS: found: m/z 455.1395. Calcd for $C_{22}H_{20}F_5N_2O_3$: $(M+H)^+$ 455.1394.

*4.3.17. 3-(Benzoyloxyimino)-1-morpholino-2-phenylbutan-1-one (**3ab**).* Yield 70%; white crystal; mp 133.5–134.5 °C; FTIR (KBr) 3010, 1737, 1643, 1523, 1435, 1215, 1062, 752, 669 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.12 (3H, s), 3.16–3.77 (8H, m), 5.13 (1H, s), 7.33–7.61 (8H, m), 8.07 (2H, d, J=8.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.1, 42.0, 46.2, 54.5, 66.1, 66.6, 128.3, 128.4, 128.5, 128.9, 129.4, 129.6, 133.3, 134.1, 163.9, 166.5, 168.3; ESIMS: found: m/z 367.1659. Calcd for $C_{21}H_{23}N_2O_4$: $(M+H)^+$ 367.1658.

*4.3.18. 3-(Acetoxyimino)-1-morpholino-2-phenylbutan-1-one (**3ac**).* Yield 74%; colorless oil; FTIR (KBr) 3018, 1759, 1643, 1435, 1367, 1215, 1114, 1001, 756, 669 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.97 (3H, s), 2.16 (3H, s), 3.09–3.77 (8H, m), 5.01 (1H, s), 7.28–7.42 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.8, 19.4, 41.9, 46.1, 54.3, 65.9, 66.5, 128.1, 128.2, 129.3, 134.0, 165.6, 168.2, 168.3; ESIMS: found: m/z 305.1503. Calcd for $C_{16}H_{21}N_2O_4$: $(M+H)^+$ 305.1501.

4.4. Synthesis of indoles

*4.4.1. (2-Methyl-1H-indol-3-yl)(morpholino)methanone (**4a**)[7a] (a typical procedure).* To a solution of 1-morpholino-3-(perfluorobenzoyloxyimino)-2-phenylbutan-1-one (105 mg, 0.230 mmol) in $ClCH_2CH_2Cl$ (3.80 mL) were added $PdCl_2(MeCN)_2$ (15.0 mg, 0.057 mmol) and MgO (46.3 mg, 1.15 mmol). The mixture was stirred at reflux for 3 h. After the reaction has finished, most of the solvent was removed by vacuo. The crude material was then purified by column chromatography. The silica gel was treated with hexane and Et_3N solution (hexane–Et_3N=99:1). The eluent (Ethyl acetate–Et_3N=99:1) was used to purify to give indole product, (2-Methyl-1*H*-indol-3-yl) (morpholino)methanone (45.8 mg, 0.187 mmol) in 82% yield. Further purification was done by recrystallization method.

Yield 82%; ^1H NMR (300 MHz, $CDCl_3$) δ 2.37 (3H, s), 3.67–3.72 (8H, m), 7.12–7.14 (2H, m), 7.20–7.21 (1H, m), 7.45–7.47 (1H, m), 8.80 (1H, br); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.6, 67.3 (overlapped), 107.9, 110.8, 118.8, 120.7, 121.8, 126.1, 134.7, 137.8, 167.7.

*4.4.2. (6-Chloro-2-methyl-1H-indol-3-yl)(morpholino)methanone (**4b**).* Yield 70%; viscous oil; FTIR (KBr) 3019, 2890, 1593, 1566, 1470, 1427, 1117, 1022, 756 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 2.41 (3H, s), 3.46–3.60 (8H, m), 7.05 (1H, dd, J=1.6, 8.4 Hz), 7.36 (1H, d, J=1.6 Hz), 7.40 (1H, d, J=8.4 Hz), 11.58 (1H, br); ^{13}C NMR (100 MHz, DMSO-d_6) δ 12.5, 66.4 (overlapped), 107.2, 110.7, 119.8, 120.1, 124.8, 125.6, 135.1, 138.8, 166.0; ESIMS: found: m/z 279.0905. Calcd for $C_{14}H_{16}ClN_2O_2$: $(M+H)^+$ 279.0900.

*4.4.3. (6-Bromo-2-methyl-1H-indol-3-yl)(morpholino)methanone (**4c**).* Yield 75%; brown solid; mp >250 °C; FTIR (KBr) 3020, 2895, 1653, 1590, 1560, 1542, 1474, 1430, 1116, 1023, 753 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 2.38 (3H, s), 3.44–3.57 (8H, m), 7.14 (1H, dd, J=1.7, 8.5 Hz), 7.32 (1H, d, J=8.5 Hz), 7.47 (1H, d, J=1.7 Hz), 11.56 (1H, br); ^{13}C NMR (75 MHz, DMSO-d_6) δ 12.4, 66.4 (overlapped), 107.3, 113.5, 113.6, 120.2, 122.7, 125.0, 135.5, 138.8, 165.9; ESIMS: found: m/z 323.0393. Calcd for $C_{14}H_{16}BrN_2O_2$: $(M+H)^+$ 323.0395.

*4.4.4. (6-Fluoro-2-methyl-1H-indol-3-yl)(morpholino)methanone (**4d**).* Yield 70%; yellow solid; mp >250 °C; FTIR (KBr) 3020, 1653, 1559, 1539, 1506, 1465, 1419, 1114, 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.32 (3H, s), 3.66–3.71 (8H, m), 6.87–6.92 (2H, m), 7.35–7.39 (1H, m), 8.86 (1H, br); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.6, 67.2 (overlapped), 97.4 (d, J=26 Hz), 107.9, 109.3 (d, J=23 Hz), 119.5 (d, J=9.8 Hz), 122.6, 134.7 (d, J=12.4 Hz), 137.7 (d, J=3.1 Hz), 159.6 (d, J=237 Hz), 167.3; ESIMS: found: m/z 263.1195. Calcd for $C_{14}H_{16}FN_2O_2$: $(M+H)^+$ 263.1196.

*4.4.5. (5,7-Dibromo-2-methyl-1H-indol-3-yl)(morpholino)methanone (**4e**).* Yield 33%; yellow oil; FTIR (KBr) 2960, 2980, 1624, 1567, 1479, 1441, 1429, 1186, 1113, 1019, 752 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 2.56 (3H, s), 3.64–3.72 (8H, m), 7,45 (1H, s), 7.58 (1H, s), 8.42 (1H, br); ^{13}C NMR (100 MHz, DMSO-d_6) δ 12.9, 67.2 (overlapped), 104.6, 109.3, 114.0, 120.9, 126.7, 128.3, 132.3, 139.0, 166.1; ESIMS: found: m/z 402.9481. Calcd for $C_{14}H_{15}N_2O_2Br_2$: $(M+H)^+$ 402.9480.

*4.4.6. (5-Chloro-2-methyl-1H-indol-3-yl)(morpholino)methanone (**4f**).* Yield 59%; white solid; mp 165.0–166.0 °C; FTIR (KBr) 2900, 2810, 1639, 1461, 1436, 1421, 1263, 1215, 1116, 1022, 758 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.06 (3H, s), 3.65–3.71 (8H, m), 7.01 (2H, s), 7.40 (1H, s), 9.86 (1H, br); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.2, 67.2 (overlapped), 107.0, 112.1, 117.8, 122.0, 126.3, 126.9, 133.2, 139.3, 167.5; ESIMS: found: m/z 279.0880. Calcd for $C_{14}H_{16}ClN_2O_2$: $(M+H)^+$ 279.0900.

*4.4.7. (7-Chloro-2-methyl-1H-indol-3-yl)(morpholino)methanone (**4f**).* Yield 40%; light yellow viscous oil; FTIR (KBr) 3268, 2900, 2854, 1626, 1609, 1468, 1447, 1426, 1119, 1115, 1019, 749 cm^{-1}; ^1H NMR (400 MHz, CDCl3) δ 2.55 (3H, s), 3.65–3.71 (8H, br), 7.08 (1H, dd, J=7.6, 7.6 Hz), 7.15 (1H, d, J=7.6 Hz), 7.38 (1H, d, J=7.6 Hz), 8.60 (1H, s); ^{13}C NMR (100 MHz, CDCl3) δ 12.8, 67.2 (overlapped), 109.3, 116.2, 117.6, 121.3, 121.6, 127.5, 131.9, 138.2, 166.8; ESIMS: found: m/z 279.0880. Calcd for $C_{14}H_{16}ClN_2O_2$: $(M+H)^+$ 279.0900.

*4.4.8. (2,4-Dimethyl-1H-indol-3-yl)(morpholino)methanone (**4g**).* Yield 46%; brown viscous oil; FTIR (KBr) 3249, 2859, 1639, 1604, 1477, 1438, 1420, 1359, 1230, 1116, 1022, 752 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.40 (3H, s), 2.49 (3H, s), 3.38–3.91 (8H, m), 6.88 (1H, d,

J=7.2 Hz), 7.04 (1H, dd, J=8.0, 7.2 Hz), 7.12 (1H, d, J=8.0 Hz), 8.06 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.8, 19.1, 42.3, 47.7, 67.0, 108.0, 108.4, 121.4, 121.9, 125.3, 129.1, 132.7, 135.3, 168.6; ESIMS: found: m/z 259.1443. Calcd for $C_{15}H_{19}N_2O_2$: $(M+H)^+$ 259.1447.

*4.4.9. (2-Methyl-6-phenyl-1H-indol-3-yl)(morpholino)methanone (**4h**).* Yield 72%; brown solid; mp >250 °C; FTIR (KBr) 2963, 2856, 1653, 1601, 1559, 1507, 1467, 1433, 1264, 1115, 1008, 698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.30 (3H, s), 3.72 (8H, br), 7.26, (1H, s), 7.30 (1H, d, J=7.1 Hz), 7.37–7.40 (4H, m), 7.40–7.52 (3H, m), 9.25 (1H, br); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.6, 67.3 (overlapped), 107.6, 109.4, 118.9, 120.5, 125.4, 126.7, 127.2, 128.7, 135.3, 135.4, 138.7, 141.8, 167.8; ESIMS: found: m/z 321.1603. Calcd for $C_{20}H_{21}N_2O_2$: $(M+H)^+$ 321.1603.

*4.4.10. (2-Methyl-1H-benzo[g]indol-3-yl)(morpholino)methanone (**4i**).* Yield 87%; yellow solid; mp 205.4–206.5 °C; FTIR (KBr) 3185, 3020, 1589, 1560, 1539, 1507, 1490, 1465, 1437, 1109, 1021, 756, 669 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.50 (3H, s), 3.53–3.63 (8H, m), 7.39–8.33 (6H, m), 9.28 (1H, br); ^{13}C NMR (100 MHz, DMSO-d_6) δ 12.5, 66.4 (overlapped), 108.9, 119.0, 120.4, 120.5, 121.4, 121.7, 123.6, 125.6, 128.3, 128.9, 129.3, 135.2, 166.5; ESIMS: found: m/z 295.1440. Calcd for $C_{18}H_{19}N_2O_2$: $(M+H)^+$ 295.1447.

*4.4.11. Morpholino(2-propyl-1H-indol-3-yl)methanone (**4j**).* Yield 51%; yellow viscous liquid; FTIR (KBr) 3273, 3017, 2862, 1605, 1460, 1443, 1115, 1016, 756 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (3H, t, J=7.2 Hz), 1.65 (2H, m), 2.74 (2H, br), 3.67–3.72 (8H, br), 7.11–7.12 (2H, m), 7.24–7.25 (1H, m), 7.43 (1H, dd, J=5.6, 2.8 Hz), 8.87 (1H, br); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.7, 22.8, 28.7, 67.3 (overlapped), 107.7, 111.0, 118.8, 120.6, 121.7, 125.8, 134.5, 142.2, 167.7; ESIMS: found: m/z 273.1595. Calcd for $C_{16}H_{21}N_2O_2$: $(M+H)^+$ 273.1603.

*4.4.12. (2-(Cyclohexylmethyl)-1H-indol-3-yl)(morpholino)methanone (**4k**).* Yield 91%; white solid; mp >250 °C; FTIR (KBr) 3017, 2926, 1653, 1558, 1539, 1507, 1457, 1437, 1419, 1112, 1020, 754 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.89–1.70 (11H, m), 2.72 (2H, d, J=7.2 Hz), 3.49–3.66 (8H, m), 7.01–7.10 (2H, m), 7.32–7.39 (2H, m), 11.37 (1H, br); ^{13}C NMR (100 MHz, DMSO-d_6) δ25.6, 25.9, 32.5, 33.6, 37.8, 66.4 (overlapped), 107.5, 111.2, 118.3, 119.9, 120.9, 125.3, 134.4, 141.1, 166.5; ESIMS: found: m/z 327.2072. Calcd for $C_{20}H_{27}N_2O_2$: $(M+H)^+$ 327.2073.

*4.4.13. (2-Benzyl-1H-indol-3-yl)(morpholino)methanone (**4l**).* Yield 62%; brown solid; mp >250 °C; FTIR (KBr) 3017, 2925, 1605, 1499, 1460, 1443, 1272, 1115, 1016, 1003, 750 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.45 (8H, m), 4.16 (2H, s), 7.06–7.29 (7H, m), 7.34 (2H, d, J=8.4 Hz), 7.39 (1H, d, J=7.2 Hz), 11.52 (1H, br); ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.1, 66.3 (overlapped), 107.4, 111.5, 118.5, 120.1, 121.1, 125.2, 126.2, 128.3, 128.5, 134.5, 139.3, 140.8, 166.3; ESIMS: found: m/z 321.1606. Calcd for $C_{20}H_{21}N_2O_2$: $(M+H)^+$ 321.1603.

*4.4.14. Morpholino(2-phenethyl-1H-indol-3-yl)methanone (**4m**).* Yield 55%; Yellow solid; mp >250 °C; FTIR (KBr) 3240, 2922, 1601, 1495, 1462, 1331, 1271, 1115, 1020, 748 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.87 (2H, t, J=7.0 Hz), 2.99 (2H, br), 3.63 (8H, br), 7.02 (2H, d, J=6.9 Hz), 7.09–7.11 (2H, m), 7.17–7.22 (4H, m), 7.40 (1H, d, J=7.1 Hz), 9.16 (1H, br); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.3, 35.5, 67.2 (overlapped), 107.9, 111.1, 118.7, 120.6, 121.8, 125.5, 126.2, 128.3, 128.4, 134.6, 140.7, 141.5, 167.7; ESIMS: found: m/z 335.1757. Calcd for $C_{21}H_{23}N_2O_2$: $(M+H)^+$ 335.1760.

*4.4.15. (2-(3-Bromophenyl)-1H-indol-3-yl)(morpholino)methanone (**4n**).* Yield 49%; white solid; mp 217.6–218.0 °C; FTIR (KBr) 3261, 2973, 2919, 2864, 1606, 1482, 1480, 1359, 1226, 1113, 1002, 749 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.11–3.90 (8H, m), 7.12–7.28 (4H, m), 7.36 (1H, d, J=7.6 Hz), 7.42 (1H, d, J=9.2 Hz), 7.59 (1H, d, J=8.4 Hz), 7,68 (1H, s), 9.12 (1H, br); ^{13}C NMR (75 MHz, $CDCl_3$) δ 66.7 (overlapped), 108.7, 111.4, 119.7, 121.2, 122.9, 123.5, 125.9, 127.2, 130.1, 130.5, 131.5, 133.3, 134.5, 135.8, 168.7; ESIMS: found: m/z 385.0548. Calcd for $C_{19}H_{18}BrN_2O_2$: $(M+H)^+$ 385.0552.

*4.4.16. (3-(3-Bromophenyl)-2-phenyl-2H-azirin-2-yl)(morpholino)methanone (**5n**).* Yield 32%; yellow viscous liquid; FTIR (KBr) 2973, 2913, 2857, 1741, 1637, 1564, 1497, 1438, 1114, 749 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.55–3.95 (8H, m), 7.19–7.44 (7H, m), 7.72 (1H, d, J=8.7 Hz), 7.98 (1H, d, J=7.8 Hz), 8.17 (1H, br); ^{13}C NMR (75 MHz, $CDCl_3$) δ 42.1, 46.7, 66.6, 66.8, 123.2, 124.5, 125.1, 127.8, 128.8, 129.1, 130.8, 133.1, 136.6, 137.3, 162.3, 168.0; ESIMS: found: m/z 385.0555. Calcd for $C_{19}H_{18}BrN_2O_2$: $(M+H)^+$ 385.0552.

*4.4.17. N,N,2-Trimethyl-1H-indole-3-carboxamide (**4o**).* Yield 68%; white solid; mp 225.4–226.1 °C; FTIR (KBr) 3019, 1653, 1601, 1576, 1507, 1215, 1064, 668 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.45 (3H, s), 3.10 (6H, s), 7.11–7.27 (3H, m), 7.45 (1H, m), 8.37 (1H, br); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.7 (overlapped), 109.1, 110.6, 119.4, 120.5, 121.6, 126.5, 134.7, 136.8, 168.6; ESIMS: found: m/z 203.07. Calcd for $C_{12}H_{15}N_2O$: $(M+H)^+$ 203.12.

*4.4.18. (2-Methyl-1H-indol-3-yl)(piperidin-1-yl)methanone (**4p**).* Yield 73%; brown oil; FTIR (KBr) 3380, 3020, 1653, 1601, 1576, 1507, 1459, 1426, 1395, 1179, 1065, 749 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.58–1.65 (6H, m), 1.98 (3H, s), 3.58 (4H, m), 6.99–7.06 (3H, m), 7.43 (1H, d, J=7.6 Hz), 10.00 (1H, br); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.0, 24.6 (overlapped), 26.4, 107.9, 111.1, 118.4, 119.9, 121.1, 126.2, 134.9, 137.4, 168.0; ESIMS: found: m/z 243.1494. Calcd for $C_{15}H_{19}N_2O$: $(M+H)^+$ 243.1497.

4.5. A reaction of deuterium-labeled oxime 3o–d

*4.5.1. Synthesis of amide **1o–d**[17].* To an ice cold stirred solution of 2-deuteriobenzaldehyde (**6**)[18] (1.28 g, 11.9 mmol) and CBr_4 (5.90 g, 18.0 mmol) in dry CH_2Cl_2 (95 mL) was added PPh_3 (9.40 g, 36.0 mmol) in CH_2Cl_2 (90 mL) with a dropping funnel for 10 min. After the reaction was completed, the reaction mixture was concentrated under reduced pressure and then $CHCl_3$ (20 mL) was added to the residue. The suspended mixture was filtered to remove triphenylphosphine oxide that was washed with $CHCl_3$. The combined filtrates were concentrated under reduced pressure and the resulting crude mixture of dibromoalkene **7** was used for next step without any purification.

To a solution of dimethylamine (50.0 mL, 40% in water) was added dibromoalkene **7** prepared above at room temperature. After stirring for 3 h, the resulting mixture was concentrated under reduced pressure to remove excess amine. Aqueous HCl (3 N, 20 mL) solution was added to the residue, and the resulting mixture was extracted with $CHCl_3$. The combined organic layers were washed with a saturated aqueous $NaHCO_3$ solution and then, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified with column chromatography to give the pure product, labeled *N,N*-dimethyl-2-phenylacetamide (**1o–d**) (1.06 g, 6.45 mmol) in 54% yield.

White viscous liquid; FTIR (KBr) 3018, 1648, 1633, 1477, 1480, 767 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.94 (6H, s), 3.70 (2H, s), 7.22–7.30 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.5, 37.4, 40.7, 126.4, 128.2, 128.3, 128.5, 134.8, 170.7; ESIMS: found: m/z 165.1134. Calcd for $C_{10}H_{13}DNO$: $(M+H)^+$ 165.1138.

*4.5.2. Synthesis of oxime **3o–d**.* The same procedures with as in Section 4.3.1 was applied starting from amide **1o–d** (0.636 g, 3.87 mmol) to afford **3o–d** (0.559 g, 1.35 mmol) in 35% yield.

Yield 35%; white crystal; mp 104.6–115.7 °C; FTIR (KBr) 3015, 2935, 1747, 1642, 1579, 1540, 1500, 1324, 989, 758, 711 cm^{-1}; ^{1}H

NMR (300 MHz, $CDCl_3$) δ 2.04 (3H, s), 2.83 (3H, s), 3.01 (3H, s), 5.08 (1H, s), 7.30–7.40 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.4, 35.6, 37.4, 54.4, 109.9 (m), 128.3, 128.4, 129.3, 129.4, 133.6, 137.7 (dm, J=248 Hz), 143.5 (dm, J=277 Hz), 145.6 (dm, J=259 Hz), 156.6, 168.7, 169.3; ESIMS: found: m/z 416.1132. Calcd for $C_{19}H_{15}DN_2O_3F_5$: $(M+H)^+$ 416.1144.

4.5.3. Indole formation using oxime ***3o–d*** *(Scheme 4).* The same procedures with as in Section 4.4.1 was applied starting from oxime **3o–d** (95.0 mg, 0.228 mmol) to afford **4o–d** and **4o** (22.7 mg, 0.111 mmol) in 49% yield.

Yield 49%; white solid; mp 225.4–226.0 °C; FTIR (KBr) 3019, 1642, 1602, 1504, 1422, 1215, 743, 666 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 2.37 (3H, s), 2.95 (6H, s), 7.00–7.31 (3.5H, m), 11.3 (1H, br); ^{13}C NMR (75 MHz, DMSO-d_6) δ 12.5 (overlapped), 110.9, 118.8, 119.5, 119.6, 120.7, 134.6, 136.9, 167.2; ESIMS: found: m/z 204.1243. Calcd for $C_{12}H_{14}DN_2O$: $(M+H)^+$ 204.1247.

Acknowledgements

This work was supported by funding from Nanyang Technological University, Singapore Ministry of Education, and Science & Engineering Research Council (A*STAR grant No. 082 101 0019). We thank Dr. Yongxin Li (Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University) for assistance in X-ray crystallographic analysis.

Supplementary data

Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.05.029.

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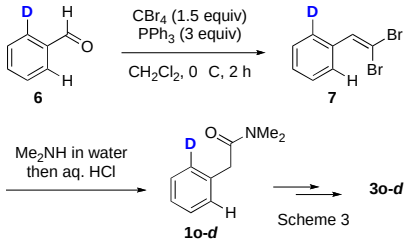
8. The stereochemistry of oxime **3aa** was determined by X-ray crystallographic analysis. CCDC-767809 contains the supplementary crystallographic data. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/conts/retrieving.html.
9. The stereochemistry of oxime **3n** was determined by X-ray crystallographic analysis. CCDC-767810 contains the supplementary crystallographic data. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/conts/retrieving.html.
10. Deuterium-labeled oxime **3o–d** was prepared by the following scheme.



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