Triphenylphosphine Catalyzed Michael Addition of Oximes onto Activated Olefins[1]

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Dedicated to the employees of Dr Reddys.

Abstract: A new reaction condition for Michael addition of oximes onto activated olefins has been discovered using a catalytic amount of triphenylphosphine. This is a first and milder alternative to classical base (hydroxide, alkoxide) catalyzed Michael addition of oximes. Various aldoximes **1a**–**h** and ketoximes **2a**–**c** (Figure 1) were reacted with different Michael acceptors such as ethyl acrylate, acrylonitrile, phenyl vinyl sulfone, methyl vinyl ketone, and 1-nitrocyclohex-1-ene to obtain the corresponding Michael adducts. About 35 different examples were attempted (Table 1 and Scheme 1); except in six cases where reactions did not produce desired products, yields varied from good to excellent. Reactions without triphenylphosphine did not proceed. A plausible mechanism of catalytic action in the present reactions is proposed (Figure 2).

Key words: Michael additions, oximes, alkenes, phosphorus, catalysis

Michael addition of a heteroatom-centered nucleophile[2] is a convenient way to introduce heteroatom-based functionality to a β-carbon attached to an electron-withdrawing group. Following this strategy, very recently various nitrogen,[3] oxygen,[4] sulfur[5] and phosphorus[6] linked functionalized Michael adducts have been synthesized.

Classical base-catalyzed Michael addition of oximes having oxygen as a nucleophilic center is known in the literature. For example, Mukaiyama et al. have reported the Michael reaction of benzaldoxime with acrylonitrile facilitated by KOH or $BnNMe_3OH$ under heating.[7] Similarly, strong bases like NaOMe has also been used to promote these reactions.[8] There are also reports of a series of β-aminoxypropanoates being synthesized from various oximes and ethyl acrylate, following a KOH catalyzed Michael addition strategy, which was used in medicinal chemistry.[9] However, a generalized method of Michael addition of oximes onto various common electron-deficient olefins, preferably using milder reaction conditions, is still due.

Recently, while working on the synthesis of oxime based compounds[10] of interest, we felt the need for developing milder conditions for Michael addition of oximes. From the literature,[3] we knew that on some occasions Michael addition of amines proceeds without any requirement for an external catalyst, owing to the basicity of amines themselves to drive the 1,4-addition. Hence we wanted to see the potency of classical organic non-nucleophilic bases, and to our surprise we noticed that triphenylphosphine, which is well known as an oxophilic neutral species, nicely catalyzes Michael addition of oximes.[11,12]

Initially we chose a model reaction: addition of 4-nitrobenzaldehyde oxime (**1a**) to ethyl acrylate. We scanned mild to moderate organic bases e.g. DABCO, DBU, triethylamine, ethyldiisopropylamine, DMAP, and incidentally triphenylphosphine. For each base five different solvents e.g. DMF, MeCN, THF, dichloromethane, and 1,2-dichloroethane were considered to test the reaction of an equimolar mixture of the starting materials. Reactions were done at room temperature, with stirring up to 3 days. We concluded that a combination of 15–20 mol% of triphenylphosphine in any of the solvents MeCN, DMF, dichloromethane, or 1,2-dichloroethane, having 2.0 M substrate concentration was required to yield ethyl β-(4-nitrobenzylideneamioxy)propanoate in 50–60% isolated yield after 3 days. All the other bases in all studied solvents failed to yield more than 10% of the required product leaving the unreacted oxime. After choosing MeCN as an optimized solvent, we next observed that under heating condition (65 °C) that the reaction was faster, yielding 85% of the desired product after 2 hours when 20 mol% of the catalyst was used. There was no reaction when triphenyphosphine was absent from the reaction mixture.

Once the reaction conditions were optimized, we wanted to see the generality of this methodology. For that, a series of aldoximes **1a**–**h**, and ketoximes **2a**–**c** were synthesized (Figure 1).[13] Structural diversity in the oximes **1** and **2**, bearing aromatic, hetero-aromatic, aliphatic, and cinnamyl groups, were deliberately chosen to test the potential generality of this methodology. Each of the oximes **1** and **2** were independently reacted with the Michael acceptors, namely ethyl acrylate, acrylonitrile, and phenyl vinyl sulfone in MeCN following the optimized reaction condition to obtain the corresponding Michael adducts **3** and **4**, respectively. Results are presented in Table 1.

We observed very good to excellent reactivity of phenyl vinyl sulfone towards all the tested aldoximes and ketoximes (Table 1). Aldoximes of aromatic and heteroaromatic aldehydes were more reactive, yielding 65–85% of

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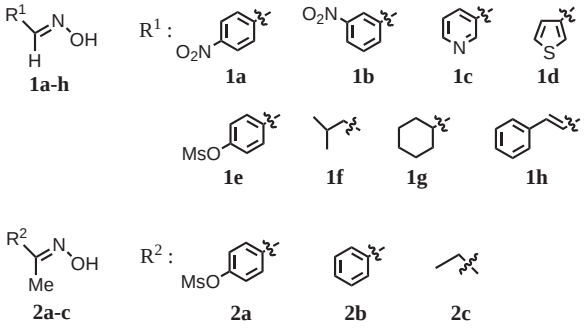


Figure 1

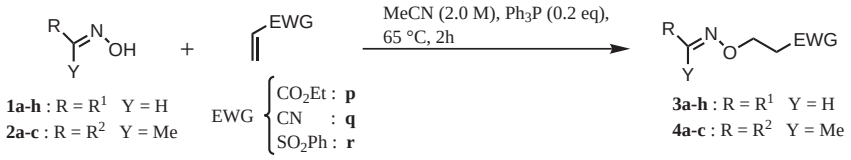
Michael adducts with ethyl acrylate and acrylonitrile, than the tested aryl methyl ketoximes **2a**,**b** for which yields were in the range of mediocre to good (30–62%). These mediocre yields were further improved to a range of 65–85% when 3 equivalents of Michael acceptors were used with respect to oximes (see entries 22, 23, 25, 26) in addition to increasing the reaction time from 2 to 16 hours.

Aliphatic aldoximes **1f**,**g** and ketoxime **2c**, though reacting smoothly with phenyl vinyl sulfone, were found to be poor Michael donors towards ethyl acrylate and acrylonitrile. Even when excess amounts of Michael acceptors were used and the reaction mixtures were heated at 65 °C for 1 day, the aldoximes **1f** (entries 15, 16) and **1g** (results not shown in the Table) remained unchanged, whereas for **2c** undesired reactions took place in both cases (entries 28 and 29) leaving mainly unreacted starting material.

Interestingly cinnamaldehyde oxime **1h** was good enough to produce the desired Michael adducts **3hp**, **3hq**, and **3hr** in good to excellent yields (62–90%) with the three tested Michael acceptors.

In all the cases, the presence of triphenylphosphine was found to be essential to promote these reactions. Though all the reactions reported in Table 1 were carried out in MeCN solvent, most of the reactions gave similar results when 1,2-dichloroethane was substituted as the solvent.

Table 1 Triphenylphosphine Catalyzed Michael Addition of Oximes onto Activated Olefins



Entry	Oxime	EWG	Michael adduct	Yield[a]	Entry	Oxime	EWG	Michael adduct	Yield[a]
1	**1a**	CO_2Et	**3ap**	85	16	**1f**	CN		[b]
2	**1a**	CN	**3aq**	80	17	**1f**	SO_2Ph	**3fr**	89
3	**1a**	SO_2Ph	**3ar**	90	18	**1g**[c]	SO_2Ph	**3gr**	88[c]
4	**1b**	CO_2Et	**3bp**	80	19	**1h**	CO_2Et	**3hp**	71
5	**1b**	CN	**3bq**	80	20	**1h**	CN	**3hq**	62
6	**1b**	SO_2Ph	**3br**	95	21	**1h**	SO_2Ph	**3hr**	90
7	**1c**	CO_2Et	**3cp**	70	22	**2a**	CO_2Et	**4ap**	30 (65)
8	**1c**	CN	**3cq**	65	23	**2a**	CN	**4aq**	40 (78)
9	**1c**	SO_2Ph	**3cr**	88	24	**2a**	SO_2Ph	**4ar**	84
10	**1d**	CO_2Et	**3dp**	66	25	**2b**	CO_2Et	**4bp**	50 (75)
11	**1d**	CN	**3dq**	76	26	**2b**	CN	**4bq**	62 (85)
12	**1d**	SO_2Ph	**3dr**	92	27	**2b**	SO_2Ph	**4br**	87
13	**1e**	CN	**3eq**	85	28	**2c**	CO_2Et		[d]
14	**1e**	SO_2Ph	**3er**	96	29	**2c**	CN		[d]
15	**1f**	CO_2Et		[b]	30	**2c**	SO_2Ph	**4cr**	84

[a] Yields of isolated products after column chromatography, which were characterized by routine spectroscopy (^1H, ^{13}C NMR, mass, IR). Unless otherwise mentioned, all the reactions were carried out following the typical procedure described in the experimental section for **3ar**. Yields in parentheses were realized when the reactions were carried out for 16 h using 3 equiv of Michael acceptors with respect to oximes.
[b] Starting material remained mainly unreacted, even after 24 h of reaction.
[c] Oxime was a mixture of *cis* and *trans* isomers in 1:4 ratio. The same ratio was reflected in isolated product.
[d] Undesired reaction occurred in each case.

Methyl vinyl ketone is probably the simplest Michael acceptor. However, because of its volatility, we had to evolve a slightly different reaction condition for this Michael acceptor. To illustrate we present the results with two oximes, **1b** and **2b**. When the reactions were done in MeCN or 1,2-dichloroethane at room temperature using 2–3 equivalents of methyl vinyl ketone with respect to oxime and 0.2 equivalents of triphenylphosphine as catalyst in a closed reaction flask, the desired products **5** and **6** were obtained in very good yield (Scheme 1).

The generality of this methodology was further demonstrated by carrying out the Michael addition of **1b** onto 1-nitrocyclohex-1-ene. A good yield of the desired Michael adduct **7** was obtained when the reaction was done at room temperature for 24 hours. However, the product was found to be a mixture of *cis* and *trans* (70:30) isomers based on ^{1}H NMR (400 MHz) and ^{13}C NMR (50 MHz) analysis of column purified **7**. Here also both MeCN and 1,2-dichloroethane gave similar results. When the same reactions were carried out under heating condition, 1-nitrocyclohexene tends to decompose quickly leading to a lower yield of **7** but with nice selectivity for *trans* geometry (Scheme 1).

The catalytic action of triphenylphosphine in the present oxa-Michael addition reactions may be viewed as in Figure 2 in light of the proposition of Echavarren and coworkers.[11] Thus a zwitterionic species **8a** is most likely formed initially from triphenylphosphine and the activated olefins. As soon it forms, **8a** is expected to capture a proton from oxime **1** or **2** to produce the corresponding oxime anion **8b**. Intermediate **8b** initiates the catalytic cycle by reacting with the Michael acceptor to form the adduct **8c** bearing an anion on the α-carbon. This anion **8c** again captures a proton from another molecule of oxime to become neutral **3** or **4**, thereby producing another molecule of deprotonated oxime **8b** to initiate another cycle. The poor reactivity of aliphatic oximes towards these Michael reactions is well explained from the proposed mechanism. Thus, the deprotonation of **1** or **2** into the anionic intermediate **8b**, which is crucial to initiate as well as to progress the catalytic cycle, is more facile when the R group is aromatic or cinnamyl over aliphatic. This is due to extensive delocalization of the anion in the presence of an aromatic or cinnamyl group. However, the relatively higher basicity of **8a** or **8c** when the EWG is a benzenesulfonyl group may overcome the lower reactivity of aliphatic oximes, and hence these oximes reacted smoothly with phenyl vinyl sulfone.

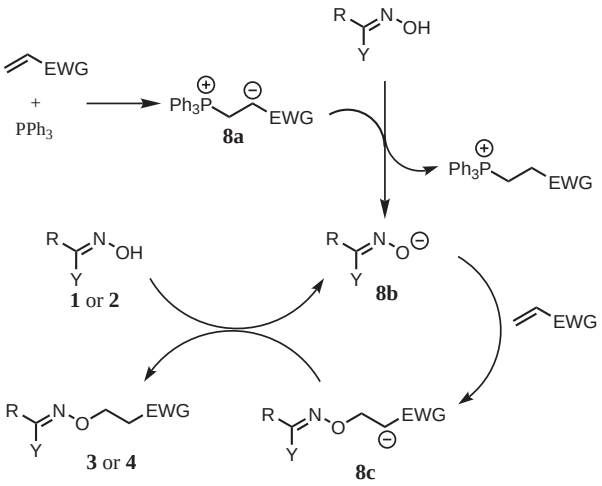
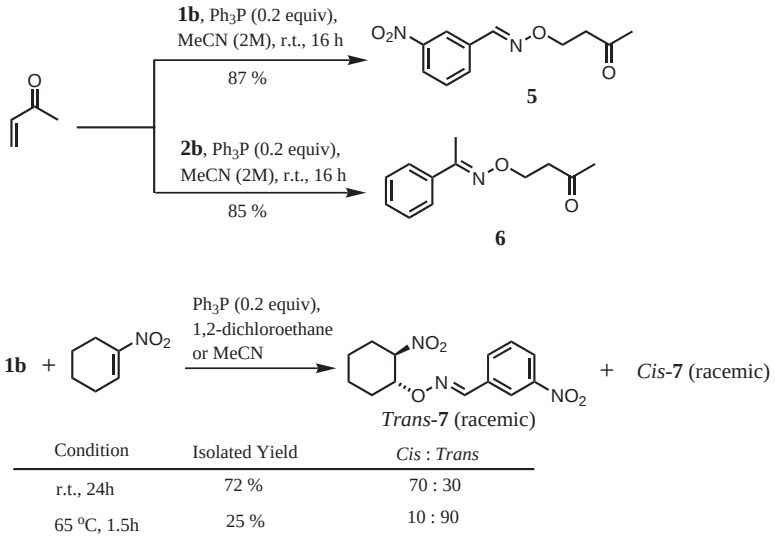


Figure 2

In conclusion, this is the first report where triphenylphosphine has been found to be a catalyst for the Michael addition of various oximes,[11,12] including both aldoximes and ketoximes, with activated olefins e.g. ethyl acrylate, acrylonitrile, phenyl vinyl sulfone, methyl vinyl ketone, and 1-nitrocyclohex-1-ene. Phenyl vinyl sulfone was found to be the most reactive Michael acceptor towards all the studied aldoximes and ketoximes. This is a milder alternative to the earlier reported procedures,[7–9] where more



Condition	Isolated Yield	*Cis* : *Trans*
r.t., 24h	72 %	70 : 30
65 °C, 1.5h	25 %	10 : 90

Scheme 1

basic KOH, $BnN(Me)_3OH$ or NaOMe reagents and harsher conditions have been used, and hence the present method may be of choice when base sensitive substrates are desired to react. A plausible mechanism of the catalytic cycle for these reactions has been described based on a literature report[11] of triphenylphosphine catalyzed Michael addition of a carbon nucleophile.

The mps were uncorrected. ^1H and ^{13}C NMR spectra were recorded on Mercury Plus (Varian 400 MHz), Unity Inova (Varian 500 MHz), and Gemini-2000 (Varian 200 MHz) spectrometer in $CDCl_3$ with TMS as internal standard: chemical shifts are quoted in ppm and *J* values are given in Hz. IR spectra were recorded on an FT-IR spectrophotometer from the Perkin–Elmer 1600 series. Mass spectra were recorded on a Hewlett Packard 5989A LC-mass spectrometer using isobutene as chemical ionizer gas (source temp. 250 °C and quadruple temp. 100 °C). Elemental analyses were done on a Perkin–Elmer II series.

Phenyl 2-(4-Nitrobenzylideneaminoxy)ethyl Sulfone (3ar); Typical Procedure

A typical procedure for the synthesis of **3** and **4** via triphenylphosphine catalyzed Michael addition reaction is as follows.

A mixture of 4-nitrobenzaldehyde oxime **1a** (100 mg, 0.6 mmol, 1 equiv), phenyl vinyl sulfone (100.8 mg, 0.6 mmol, 1 equiv), and Ph_3P (32 mg, 0.12 mmol, 0.2 equiv) in MeCN (300 μL) was heated at 65 °C while stirring for 2 h. Being guided by TLC, the reaction mixture was stopped and the solvent was removed. No work-up was required. The residue thus obtained was purified by flash chromatography to obtain the desired Michael adduct **3ar**.

Yield: 180 mg (90%); solid mass; mp 87–88 °C; purity (HPLC) 99.7%.

IR (neat): 2928, 1589, 1520, 1347, 1145 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 3.58 (t, *J* = 6 Hz, 2 H), 4.56 (t, *J* = 6 Hz, 2 H), 7.52 (t, *J* = 7.6 Hz, 2 H), 7.58–7.62 (aromatic, 3 H), 7.74 (s, 1 H), 7.92 (d, *J* = 8.8 Hz, 2 H), 8.18 (d, *J* = 8.8 Hz, 2 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 55.33, 67.60, 123.73 (2 C), 127.53 (2 C), 127.93 (2 C), 128.98 (2 C), 133.54, 137.38, 139.61, 147.44, 148.25.

LC-MS (CI): *m*/*z* = 335 (M + 1, 100%).

Anal. Calcd For $C_{15}H_{14}N_2O_5S$: C, 53.88; H, 4.22; N, 8.38. Found C, 54.07; H, 4.29; N, 8.24.

Ethyl 3-(4-Nitrobenzylideneaminoxy)propanoate (3ap)

Mp 51–52 °C.

IR (neat): 2984, 1735, 1589, 1522, 1347, 1189 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 1.26 (t, *J* = 7 Hz, 3 H), 2.74 (t, *J* = 6.3 Hz, 2 H), 4.17 (q, *J* = 7 Hz, 2 H), 4.49 (t, *J* = 6.3 Hz, 2 H), 7.70 (d, *J* = 8.8 Hz, 2 H), 8.09 (s, 1 H), 8.20 (d, *J* = 8.8 Hz, 2 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 14.14, 34.50, 60.64, 70.16, 123.91 (2 C), 127.56 (2 C), 138.20, 146.79, 148.31, 171.07.

LC-MS (CI): *m*/*z* = 267 (M + 1, 100%).

Anal. Calcd for $C_{12}H_{14}N_2O_5$: C, 54.11; H, 5.30; N, 10.52. Found C, 54.19; H, 5.39; N, 10.49.

2-(4-Nitrobenzylideneaminoxy)ethylcyanide (3aq)

Mp 91–93 °C.

IR (neat): 2955, 2251, 1588, 1517, 1349, 1043 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 2.80 (t, *J* = 6 Hz, 2 H), 4.42 (t, *J* = 6 Hz, 2 H), 7.74 (d, *J* = 8.8 Hz, 2 H), 8.17 (s, 1 H), 8.23 (d, *J* = 8.8 Hz, 2 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 18.39, 68.80, 117.27, 123.98 (2 C), 127.82 (2 C), 137.55, 148.12, 148.30.

LC-MS (CI): *m*/*z* = 220 (M + 1, 100%).

Anal. Calcd for $C_{10}H_9N_3O_3$: C, 54.77; H, 4.14; N, 19.17. Found C, 54.73; H, 4.28; N, 18.92.

Ethyl 3-(3-Nitrobenzylideneaminoxy)propanoate (3bp)

Purity (HPLC): 96%.

IR (neat): 2984, 1735, 1534, 1354, 1188 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 1.27 (t, *J* = 7 Hz, 3 H), 2.74 (t, *J* = 6.3 Hz, 2 H), 4.18 (q, *J* = 7 Hz, 2 H), 4.48 (t, *J* = 6.3 Hz, 2 H), 7.53 (t, *J* = 8.1 Hz, 1 H), 7.86 (d, *J* = 7.8 Hz, 1 H), 8.10 (s, 1 H), 8.18 (dt, *J* = 8.2, 1.5 Hz, 1 H), 8.40 (t, *J* = 1.5 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 14.09, 34.50, 60.57, 69.97, 121.49, 124.10, 129.62, 132.48, 133.91, 146.59, 148.44, 171.10.

LC-MS (CI): *m*/*z* = 267 (M +1, 100%).

2-(3-Nitrobenzylideneaminoxy)ethylcyanide (3bq)

Mp 76–78 °C.

IR (neat): 2937, 2252, 1532, 1354, 1051 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 2.80 (t, *J* = 6.2 Hz, 2 H), 4.40 (t, *J* = 6.2 Hz, 2 H), 7.56 (t, *J* = 8.1 Hz, 1 H), 7.88 (d, *J* = 7.8 Hz, 1 H), 8.18 (s, 1 H), 8.22 (dt, *J* = 8.2, 1.5 Hz, 1 H), 8.42 (t, *J* = 1.5 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 18.31, 68.65, 117.33, 121.66, 124.52, 129.79, 132.73, 133.28, 147.93, 148.40.

LC-MS (CI): *m*/*z* = 220 (M + 1, 100%).

Anal. Calcd for $C_{10}H_9N_3O_3$: C, 54.77; H, 4.14; N, 19.17. Found C, 54.68; H, 4.17; N, 18.80.

Phenyl 2-(3-Nitrobenzylideneaminoxy)ethyl Sulfone (3br)

Mp 93–94 °C.

IR (neat): 2929, 1531, 1354, 1319, 1145 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 3.58 (t, *J* = 6.1 Hz, 2 H), 4.55 (t, *J* = 6.1 Hz, 2 H), 7.50–7.61 (aromatic, 4 H), 7.73–7.76 (aromatic, 2 H), 7.92 (d, *J* = 8.0 Hz, 2 H), 8.17-8.20 (aromatic, 1 H), 8.27 (t, *J* = 1.5 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 55.37, 67.52, 121.42, 124.34, 127.99 (2 C), 129.01 (2 C), 129.66, 132.53, 133.16, 133.58, 139.66, 147.35, 148.27.

LC-MS (CI): *m*/*z* = 335 (M + 1, 100%).

Ethyl 3-(Pyridin-3-ylmethylideneaminoxy)propanoate (3cp)

Purity (HPLC) 99%.

IR (neat): 2983, 1736, 1189, 1049 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 1.28 (t, *J* = 7.3 Hz, 3 H), 2.75 (t, *J* = 6.3 Hz, 2 H), 4.19 (q, *J* = 7.3 Hz, 2 H), 4.48 (t, *J* = 6.3 Hz, 2 H), 7.29 (dd, *J* = 7.8, 4.9 Hz, 1 H), 7.93 (dt, *J* = 7.8, 1.9 Hz, 1 H), 8.07 (s, 1 H), 8.59 (dd, *J* = 4.9, 1.9 Hz, 1 H), 8.72 (d, *J* = 1.9 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 13.76, 34.13, 60.11, 69.41, 123.16, 127.78, 132.95, 145.66, 148.26, 150.26, 170.71.

LC-MS (CI): *m*/*z* = 223 (M + 1, 100%).

2-(Pyridin-3-ylmethylideneaminoxy)ethylcyanide (3cq)

IR (neat): 2948, 2252, 1417, 1054 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 2.78 (t, *J* = 6.3 Hz, 2 H), 4.38 (t, *J* = 6.3 Hz, 2 H), 7.31 (dd, *J* = 7.8, 4.9 Hz, 1 H), 7.93 (dt, *J* = 7.8,

1.9 Hz, 1 H), 8.13 (s, 1 H), 8.60 (dd, *J* = 4.9, 1.9 Hz, 1 H), 8.72 (d, *J* = 1.9 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 18.02, 68.24, 117.25, 123.41, 127.38, 133.40, 147.05, 148.36, 150.64.

LC-MS (CI): *m*/*z* = 176 (M + 1, 100%).

Phenyl 2-(Pyridin-3-ylmethylideneaminoxy)ethyl Sulfone (3cr)
Purity (HPLC) 96%.

IR (neat): 2927, 1316, 1146 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.57 (t, *J* = 6.1 Hz, 2 H), 4.52 (t, *J* = 6.1 Hz, 2 H), 7.26 (dd, *J* = 8.2, 4.9 Hz, 1 H), 7.51 (t, *J* = 7.8, Hz, 2 H), 7.57–7.62 (aromatics, 1 H), 7.64 (s, 1 H), 7.79 (dt, *J* = 7.8, 1.9 Hz, 1 H), 7.91 (d, *J* = 8.2 Hz, 2 H), 8.56 (d, *J* = 1.9 Hz, 1 H), 8.58 (d, *J* = 1.9 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 55.19, 67.17, 123.32, 127.26, 127.80 (2 C), 128.79 (2 C), 133.20, 133.34, 139.54, 146.54, 148.25, 150.60.

LC-MS (CI): *m*/*z* = 291 (M + 1, 100%).

Ethyl 3-(Thiophen-3-ylmethylideneaminoxy)propanoate (3dp)
Purity (HPLC) 97%.

IR (neat): 3103, 2982, 1735, 1186, 1046 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.26 (t, *J* = 7 Hz, 3 H), 2.72 (t, *J* = 6.3 Hz, 2 H), 4.17 (q, *J* = 7 Hz, 2 H), 4.41 (t, *J* = 6.3 Hz, 2 H), 7.31 (dd, *J* = 5, 3 Hz, 1 H), 7.39 (dd, *J* = 5, 1 Hz, 1 H), 7.42 (dd, *J* = 3, 1 Hz, 1 H), 8.10 (s, 1 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 14.08, 34.52, 60.44, 69.28, 124.75, 126.27, 126.50, 134.40, 144.25, 171.28.

LC-MS (CI): *m*/*z* = 228 (M + 1, 100%).

2-(Thiophen-3-ylmethylideneaminoxy)ethylcyanide (3dq)
Purity (HPLC) 98%.

IR (neat): 3103, 2942, 2252, 1054 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.77 (t, *J* = 6.4 Hz, 2 H), 4.33 (t, *J* = 6.4 Hz, 2 H), 7.33 (dd, *J* = 5.2, 2.8 Hz, 1 H), 7.39 (dd, *J* = 5.2, 1 Hz, 1 H), 7.48 (dd, *J* = 2.8, 1 Hz, 1 H), 8.16 (s, 1 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 18.18, 67.99, 117.50, 124.64, 126.74, 127.09, 133.76, 145.43.

LC-MS (CI): *m*/*z* = 181 (M + 1, 100%).

Phenyl 2-(Thiophen-3-ylmethylideneaminoxy)ethyl Sulfone (3dr)
Purity (HPLC) 98%.

IR (neat): 3102, 2928, 1607, 1315, 1146 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.57 (t, *J* = 6.1 Hz, 2 H), 4.47 (t, *J* = 6.1 Hz, 2 H), 7.27–7.35 (aromatic, 3 H), 7.53 (t, *J* = 7.6 Hz, 2 H), 7.61 (d, *J* = 7.5 Hz, 1 H), 7.68 (s, 1 H), 7.93 (d, *J* = 7.5 Hz, 2 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 55.21, 66.74, 124.35, 126.51, 126.74, 127.78 (2 C), 128.79 (2 C), 133.33, 133.53, 139.53, 144.76.

LC-MS (CI): *m*/*z* = 296 (M + 1, 100%).

2-(4-Methanesulfonyloxybenzylideneaminoxy)ethylcyanide (3eq)
IR (neat): 2931, 2252, 1388, 1153 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.78 (t, *J* = 6.2 Hz, 2 H), 3.16 (s, 3 H), 4.37 (t, *J* = 6.2 Hz, 2 H), 7.31 (d, *J* = 8.8 Hz, 2 H), 7.65 (d, *J* = 8.8 Hz, 2 H), 8.12 (s, 1 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 18.32, 29.60, 37.56, 68.37, 117.42, 122.40 (2 C), 128.77 (2 C), 130.81, 148.73, 150.22.

LC-MS (CI): *m*/*z* = 269 (M + 1, 100%).

Phenyl 2-(4-Methanesulfonyloxybenzylideneaminoxy)ethyl Sulfone (3er)
Mp 89–90 °C.

IR (neat): 2939, 1500, 1365, 1154 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 3.16 (s, 3 H), 3.57 (t, *J* = 5.8 Hz, 2 H), 4.52 (t, *J* = 5.8 Hz, 2 H), 7.27 (d, *J* = 8.8 Hz, 2 H), 7.49–7.55 (aromatic, 4 H), 7.62 (t, *J* = 7.3 Hz, 1 H), 7.66 (s, 1 H), 7.93 (d, *J* = 8.8 Hz, 2 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 37.54, 55.47, 67.27, 122.31 (2 C), 128.05 (2 C), 128.56 (2 C), 129.04 (2 C), 130.70, 133.58, 139.75, 148.16, 150.07.

LC-MS (CI): *m*/*z* = 384 (M + 1, 100%).

Anal. Calcd for $C_{16}H_{17}NO_6S_2$: C, 50.12; H, 4.47; N, 3.65. Found C, 50.37; H, 4.79; N, 3.61.

Phenyl 2-(3-Methybutylideneaminoxy)ethyl Sulfone (3fr)
Purity (HPLC) 99.4%.

IR (neat): 2959, 1320, 1145 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 0.87 (d, *J* = 6.7 Hz, 6 H), 1.60–1.80 (m, 1 H), 1.92 (t, *J* = 6.6 Hz, 2 H), 3.50 (t, *J* = 6.1 Hz, 2 H), 4.35 (t, *J* = 6.1 Hz, 2 H), 6.99 (t, *J* = 6.6 Hz, 1 H), 7.50–7.70 (aromatic, 3 H), 7.92 (d, *J* = 7.2 Hz, 2 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 22.05, 26.27, 37.81, 55.43, 66.27, 128.03 (2 C), 128.90 (2 C), 133.44, 139.78, 151.50.

LC-MS (CI): *m*/*z* = 270 (M + 1, 100%).

Phenyl 2-(Cyclohexylmethylideneaminoxy)ethyl Sulfone (3gr)
Isolated as mixture of *cis* and *trans* (1:4 by HPLC and ^{13}C NMR)) isomers. This is because the starting oxime itself was a mixture of *cis* and *trans* isomers. NMR data are given for the *trans* isomer only for simplicity.

IR (neat): 2929, 2855, 1449, 1320, 1146 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.00–1.32 (m, 6 H), 1.60–1.75 (m, 4 H), 2.00–2.10 (m, 1 H), 3.49 (t, *J* = 6.2 Hz, 2 H), 4.33 (t, *J* = 6.2 Hz, 2 H), 6.87 (d, *J* = 6.4 Hz, 1 H), 7.54 (t, *J* = 7.5 Hz, 2 H), 7.63 (t, *J* = 7.5 Hz, 1 H), 7.92 (d, *J* = 7.5 Hz, 2 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 25.11, 25.55, 29.97, 38.16, 55.38, 66.26, 128.03 (2 C), 128.88 (2 C), 133.41, 139.84, 155.95.

LC-MS (CI): *m*/*z* = 296 (M + 1, 100%).

Ethyl 3-(3-Phenylprop-2-enylideneaminoxy)propanoate (3hp)
Purity (HPLC) 98%.

IR (neat): 2983, 1736, 1187, 1037 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.26 (t, *J* = 7 Hz, 3 H), 2.70 (t, *J* = 6.4 Hz, 2 H), 4.17 (q, *J* = 7 Hz, 2 H), 4.37 (t, *J* = 6.4 Hz, 2 H), 6.78–6.80 (m, 2 H), 7.26–7.36 (aromatic, 3 H), 7.41–7.44 (aromatic, 2 H), 7.86 (dd, *J* = 6.7, 1.6 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 14.16, 34.50, 60.55, 69.43, 121.79, 126.86 (2 C), 128.75 (2 C), 128.79, 135.91, 138.65, 150.98, 171.28.

LC-MS (CI): *m*/*z* = 248 (M + 1, 100%).

2-(3-Phenylprop-2-enylideneaminoxy)ethylcyanide (3hq)
IR (neat): 2937, 2252, 1049 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.75 (t, *J* = 6.5 Hz, 2 H), 4.29 (t, *J* = 6.5 Hz, 2 H), 6.75–6.87 (m, 2 H), 7.29–7.38 (aromatic, 3 H), 7.45 (d, *J* = 7.6 Hz, 2 H), 7.93 (d, *J* = 8.6 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 18.20, 68.11, 117.43, 121.14, 126.97 (2 C), 128.79 (2 C), 129.05, 135.65, 139.75, 152.16.

LC-MS (CI): *m*/*z* = 201 (M + 1, 100%).

Phenyl 2-(3-Phenylprop-2-enylideneaminoxy)ethyl Sulfone (3hr)
Purity (HPLC) 99.2%.

IR (neat): 2926, 1447, 1319, 1144 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.54 (t, *J* = 6.1 Hz, 2 H), 4.43 (t, *J* = 6.1 Hz, 2 H), 6.59–6.69 (aromatic, 2 H), 7.26–7.35 (aromatic, 3 H), 7.38–7.43 (aromatic, 3 H), 7.51–7.55 (aromatic, 2 H), 7.59–7.64 (aromatic, 1 H), 7.90–7.92 (aromatic, 2 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 55.39, 66.98, 121.02, 126.80, 128.03, 128.69, 128.92, 128.97, 133.49, 135.51, 139.30, 139.75, 151.48.

LC-MS (CI): *m*/*z* = 316 (M + 1, 100%).

Ethyl 3-[1-(4-Methanesulfonyloxyphenyl)ethylideneaminoxy]propanoate (4ap)
IR (neat): 2938, 1732, 1611, 1503, 1370 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.26 (t, *J* = 7.1 Hz, 3 H), 2.20 (s, 3 H), 2.73 (t, *J* = 6.4 Hz, 2 H), 3.14 (s, 3 H), 4.16 (q, *J* = 7.1 Hz, 2 H), 4.46 (t, *J* = 6.4 Hz, 2 H), 7.27 (d, *J* = 8.7 Hz, 2 H), 7.69 (d, *J* = 8.7 Hz, 2 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 12.44, 14.08, 34.78, 37.27, 60.41, 69.49, 121.80 (2 C), 127.59 (2 C), 135.65, 149.57, 153.65, 171.37.

LC-MS (CI): *m*/*z* = 330 (M + 1, 100%).

2-[1-(4-Methanesulfonyloxyphenyl)ethylideneaminoxy]ethylcyanide (4aq)
Mp 84–85 °C.

IR (neat): 2944, 2249, 1373, 1157 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.26 (s, 3 H), 2.78 (t, *J* = 6.3 Hz, 2 H), 3.15 (s, 3 H), 4.39 (t, *J* = 6.3 Hz, 2 H), 7.29 (d, *J* = 8.7 Hz, 2 H), 7.70 (d, *J* = 8.7 Hz, 2 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 12.67, 18.42, 37.36, 68.17, 117.63, 121.90 (2 C), 127.74 (2 C), 135.13, 149.78, 155.14.

LC-MS (CI): *m*/*z* = 283 (M + 1, 100%).

Phenyl 2-[1-(4-Methanesulfonyloxyphenyl)ethylideneaminoxy]ethyl Sulfone (4ar)
Mp 108–109 °C.

IR (neat): 2927, 1599, 1368, 1147 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.90 (s, 3 H), 3.14 (s, 3 H), 3.59 (t, *J* = 6.3 Hz, 2 H), 4.53 (t, *J* = 6.3 Hz, 2 H), 7.24 (d, *J* = 8.7 Hz, 2 H), 7.51 (t, *J* = 7.8 Hz, 2 H), 7.56 (d, *J* = 8.7 Hz, 2 H), 7.61 (t, *J* = 7.3 Hz, 1 H), 7.91 (d, *J* = 8.7 Hz, 2 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 12.43, 37.47, 55.65, 67.26, 121.91 (2 C), 127.63 (2 C), 128.01 (2 C), 129.13 (2 C), 133.58, 135.11, 139.86, 149.72, 154.65.

LC-MS (CI): *m*/*z* = 398 (M + 1, 100%).

Ethyl 3-(1-Phenylylethylideneaminoxy)propanoate (4bp)
Purity (HPLC) 99.4%.

IR (neat): 2932, 1738, 1592 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.25 (t, *J* = 7.1 Hz, 3 H), 2.21 (s, 3 H), 2.74 (t, *J* = 6.6 Hz, 2 H), 4.16 (q, *J* = 7.1 Hz, 2 H), 4.46 (t, *J* = 6.6 Hz, 2 H), 7.34–7.36 (aromatic, 3 H), 7.61–7.64 (aromatic, 2 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 12.63, 14.16, 34.93, 60.43, 69.37, 125.99 (2 C), 128.30 (2 C), 129.03, 136.50, 155.08, 171.53.

LC-MS (CI): *m*/*z* = 236 (M + 1, 100%).

2-(1-Phenylethylideneaminoxy)ethylcyanide (4bq)
IR (neat): 2936, 2252, 1379, 1051 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.27 (s, 3 H), 2.79 (t, *J* = 6.3 Hz, 2 H), 4.39 (t, *J* = 6.3 Hz, 2 H), 7.38–7.39 (aromatic, 3 H), 7.64–7.66 (aromatic, 2 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 12.78, 18.42, 68.04, 117.62, 126.04 (2 C), 128.36 (2 C), 129.35, 135.95, 156.54.

LC-MS (CI): *m*/*z* = 189 (M + 1, 100%).

Phenyl 2-(1-Phenylylethylideneaminoxy)ethyl Sulfone (4br)
Mp 53–55 °C.

IR (neat): 2928, 1587, 1316, 1145 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.92 (s, 3 H), 3.63 (t, *J* = 6.2 Hz, 2 H), 4.54 (t, *J* = 6.2 Hz, 2 H), 7.33–7.36 (aromatic, 3 H), 7.49–7.55 (aromatic, 4 H), 7.59–7.63 (aromatic, 1 H), 7.92–7.95 (aromatic, 2 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 12.34, 55.52, 66.95, 125.79 (2 C), 127.84 (2 C), 128.18 (2 C), 128.94 (2 C), 129.16, 133.38, 135.72, 139.76, 155.78.

LC-MS (CI): *m*/*z* = 304 (M + 1, 100%).

Anal. Calcd for $C_{16}H_{17}NO_3S$: C, 63.34; H, 5.65; N, 4.62. Found C, 63.24; H, 5.68; N, 4.66.

Phenyl 2-(2-Butylideneaminoxy)ethyl Sulfone (4cr)
IR (neat): 2926, 1319, 1144 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.98 (t, *J* = 7.5 Hz, 3 H), 1.51 (s, 3 H), 2.06 (q, *J* = 7.5 Hz, 2 H), 3.53 (t, *J* = 6.1 Hz, 2 H), 4.35 (t, *J* = 6.1 Hz, 2 H), 7.54 (t, *J* = 7.6 Hz, 2 H), 7.63 (t, *J* = 7.4 Hz, 1 H), 7.92 (d, *J* = 7.8 Hz, 2 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 10.45, 13.18, 28.56, 55.25, 65.97, 127.65 (2 C), 128.74 (2 C), 133.18, 139.70, 159.62.

LC-MS (CI): *m*/*z* = 256 (M + 1, 100%).

2-(3-Nitrobenzylideneaminoxy)ethyl Methyl Ketone (5); Typical Procedure
A typical procedure for the synthesis of **5** and **6** via Ph_3P catalyzed Michael addition onto methyl vinyl ketone is as follows.

A mixture of aldoxime **1b** (100 mg, 0.6 mmol, 1.0 equiv), methyl vinyl ketone (100 μL, 1.2 mmol, 2.0 equiv) and Ph_3P (32 mg, 0.12 mmol, 0.2 equiv) in MeCN (300 μL) was stirred at r.t. for 16 h. The reaction mixture was concentrated and the residue was triturated with hexane. The remaining crude product was purified by flash chromatography ($CHCl_3$) to obtain the desired product **5**.

Yield: 123 mg (87%); thick oil.

IR (neat): 2926, 1716, 1533, 1356, 1053 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.22 (s, 3 H), 2.86 (t, *J* = 6.1 Hz, 2 H), 4.47 (t, *J* = 6.1 Hz, 2 H), 7.54 (t, *J* = 7.9 Hz, 1 H), 7.87 (t, *J* = 7.4, 1.3 Hz, 1 H), 8.09 (s, 1 H), 8.20 (ddd, *J* = 8.3, 2.3, 1.0 Hz, 1 H), 8.40 (t, *J* = 1.5 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 30.34, 42.93, 69.53, 121.58, 124.17, 129.68, 132.48, 133.94, 146.56, 148.55, 206.36.

LC-MS (CI): *m*/*z* = 237 (M + 1, 100%).

2-(1-Phenylethylideneaminoxy)ethyl Methyl Ketone (6)
IR (neat): 2927, 1715, 1384, 1055 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 2.20 (s, 3 H), 2.22 (s, 3 H), 2.85 (t, *J* = 6.3 Hz, 2 H), 4.46 (t, *J* = 6.3 Hz, 2 H), 7.35–7.37(aromatic, 3 H), 7.61–7.64 (aromatic, 2 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 12.62, 30.35, 43.46, 69.06, 125.96 (2 C), 128.32 (2 C), 129.05, 136.44, 154.99, 207.09.

LC-MS (CI): *m*/*z* = 206 (M + 1, 100%).

2-(3-Nitrobenzylideneaminoxy)-1-nitrocyclohexane (7)
Characterized as a mixture of *cis*–*trans* isomers (70:30).

^1H NMR ($CDCl_3$, 400 MHz): δ = 1.30–1.70 (m, 4 H), 1.85–2.40 (m, 4 H), 4.53 (ddd, *J* = 11.3, 4.3, 3 Hz, 0.7 H, C^1-H, from *cis* isomer), 4.62–4.73 (m, 0.6 H, C^1-H and C^2-H, from *trans* isomer), 5.07–5.13 (m, 0.7 H, C^2-H, from *cis* isomer), 7.55 (t, *J* = 7.8 Hz, 1 H), 7.85 (dt, *J* = 7.8, 1 Hz, 1 H), 8.09 (s, 0.3 H, from *trans* isomer), 8.13 (s, 0.7 H, from *cis* isomer), 8.21 (dt, *J* = 7.8, 1.3 Hz, 1 H), 8.39 (t, *J* = 1.2 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 19.33 (*cis* isomer), 22.99 (*cis* isomer), 23.22, 23.54, 24.42 (*cis* isomer), 28.85 (*cis* isomer), 29.89, 30.74, 79.17 (*cis* isomer), 81.87, 84.59 (*cis* isomer), 88.07, 121.66, 121.73 (*cis* isomer), 124.33 (not separated), 129.72 (not separated), 132.62 (*cis* isomer), 132.66, 133.61 (not separated), 147.25, 147.29 (*cis* isomer), 148.45 (not separated).

LC-MS (CI): *m*/*z* = 294 (M + 1, 100%).

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