Organic & Biomolecular Chemistry

PAPER

View Article Online
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Cite this: *Org. Biomol. Chem.*, 2016, **14**, 97

# Investigation of benzoyloximes as benzoylating reagents: benzoyl-Oxyma as a selective benzoylating reagent†

Satvika Burugupalli, Sayali Shah, Phillip L. van der Peet, Seep Arora, Jonathan M. White and Spencer J. Williams*

Received 9th October 2015,
Accepted 28th October 2015

DOI: 10.1039/c5ob02092a

www.rsc.org/obc

Hydroxybenzotriazole (HOBt) and HOBt-derived reagents have been classified as Class I explosives, with restrictions on their transportation and storage. We explored a range of benzoylated oxime-based reagents as alternatives to benzoyloxybenzotriazole (BBTZ) for the selective benzoylation of carbohydrate polyols. Benzoylated oximes derived from 2-hydroximino-malononitrile, ethyl 2-hydroximino-2-cyano-acetate (Oxyma), and *tert*-butyl 2-hydroximino-2-cyanoacetate were most effective for benzoylation of a simple primary alcohol, with yields approaching that obtained for BBTZ. When applied to carbohydrate diols, the most effective reagent was identified as benzoyl-Oxyma. Benzoyl-Oxyma is a highly crystalline, readily prepared alternative to BBTZ, useful in the selective benzoylation of carbohydrate polyols.

## Introduction

Benzoic acid esters are widely used hydroxyl protecting groups for polyhydroxylated substrates such as nucleosides, sugars, and inositols owing to their ease of introduction and removal, and their stability to a wide range of reaction conditions.[1,2] In the context of carbohydrate chemistry, benzoates can be used to alter stereoselectivity of glycosylations by providing anchimeric assistance,[3] and to attenuate reactivity according to the armed/disarmed principle.[4] The selective benzoylation of a polyol[5] can be achieved by careful control of reaction conditions[6] and through use of a range of selective benzoylating reagents including benzoyl cyanide,[7,8] *N*-benzoyltetrazole,[9–11] *N*-benzoylimidazole,[9,10,12] Mitsunobu conditions,[13] benzoyl chloride/collidine,[14] and BzCl in combination with organotin reagents.[15] However, depending on the substrate or reagent, various problems emerge including poor solubility for many polyol substrates at the low temperatures sometimes required, high toxicity, poor reactivity, and/or poor regioselectivity. Among the most reliable and widely-used selective benzoylating reagent is the hydroxybenzotriazole (HOBt; **1**) derived benzoyloxybenzotriazole (BBTZ, **2**), first introduced for this purpose by Kim and co-workers (Fig. 1).[16] BBTZ reacts under mild conditions with outstanding regio- and chemoselectivity that surpasses that of most other benzoylating reagents.[17] The intrinsically high regioselectivity of benzoylation with BBTZ has been harnessed in the use of BzOH with the HOBt-derived ammonium salt TBTU (**3**),[18] which ostensibly proceeds through a BBTZ intermediate.

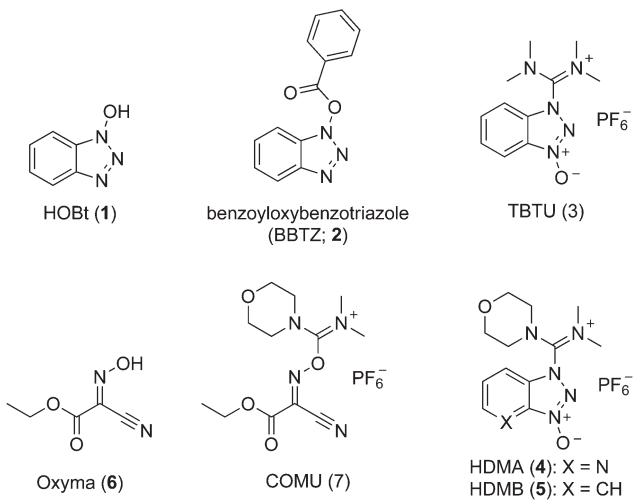



**Fig. 1** Benzotriazole- and Oxyma-based reagents.

In recent years, the safety of HOBt has been called into question. HOBt and its monohydrate are classified as Class 1 explosives, with significant limitations on their transport and storage.[19] Safety concerns extend to HOBt-derivatives such as TBTU (**3**),[19] HDMA (**4**)[20] and HDMB (**5**) (Fig. 1).[20] Against this backdrop, various oxime-based alternatives have emerged as

*School of Chemistry and Bio21 Molecular Science and Biotechnology Institute, University of Melbourne, Parkville, Victoria, Australia 3010.*
*E-mail: sjwill@unimelb.edu.au*

†Electronic supplementary information (ESI) available. CCDC 1406156 and 1406157. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c5ob02092a

viable alternatives to HOBt as nucleophilic catalysts in peptide couplings. In particular ethyl 2-hydroximino-2-cyanoacetate (Oxyma, OxymaPure, **6**) has been identified as a viable alternative to HOBt,[21] and has been elaborated to the uronium-type coupling reagent COMU (**7**),[20,22] which is effective for both peptide couplings[20] and esterifications.[18,23] Both Oxyma and COMU show a better safety profile than HOBt and HOBt-based reagents, including a lower heatflow associated with smaller increases in temperature and lower released pressures, equating to a lower risk of runaway thermal explosions.[20,21] In this work we report the synthesis of a range of benzoylated oximes and investigation of their ability to act as selective benzoylating reagents. Benzoyl-Oxyma is identified as a readily synthesized, highly crystalline and storable alternative for BBTZ in the regio- and chemoselective acylation of carbohydrate alcohols.

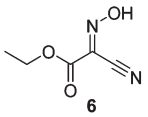
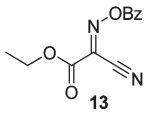
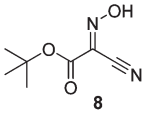
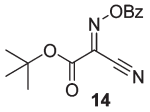
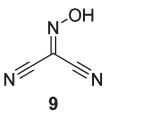
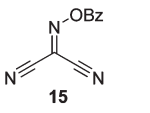
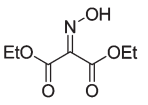
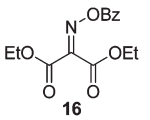
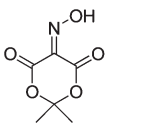
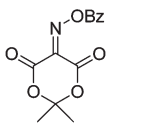
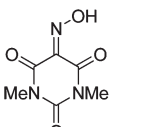
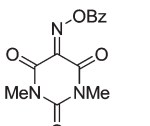
## Results and discussion

### Design and synthesis of oxime-based benzoylating reagents

Initially we sought to explore a range of benzoylated oxime-based reagents varying in the nature of the electron-withdrawing groups adjacent to the oxime. It has been found that Oxyma (**6**) can undergo side-reactions at the ethoxylcarbonyl group.[21,24] Therefore we also studied the *tert*-butyl ester **8** (derived from *tert*-butyl cyanoacetate)[25] and the bis-nitrile **9** (derived from malonitrile)[26] (Table 1). In order to complete the series we included the bis-ethoxycarbonyl derivative **10** (derived from diethyl malonate).[27] Several analogues of COMU have been reported to provide improved peptide couplings, most notably based on oximes **11** (derived from Meldrum's acid)[28] and **12** (derived from dimethylbarbituric acid),[29] which were also included in our studies. Oximes **6**, **10–12** or the corresponding silver salts of **8** and **9**, were converted to benzoylated derivatives **13**, **14**, **15**,[26] **16**,[30] **17** and **18** by treatment with benzoic anhydride ($Bz_2O$) in ether, or using BzCl and pyridine or $Et_3N$. Among these examples, we highlight the exceptionally simple preparation of benzoyl-Oxyma (**13**): addition of $Bz_2O$ to a 0.3 M solution of Oxyma in $Et_2O$ resulted in the formation of a precipitate within 1 min. Filtration and drying provided the pure reagent. This result stands in contrast with the preparation of BBTZ (**2**): commercial HOBt containing 20% water can either be dried under vacuum (caution: explosion risk) or alternatively stirred with activated molecular sieves, prior to reaction with BzCl and $Et_3N$.[16] Following aqueous workup, the reagent may, with some difficulty, be crystallized from EtOAc/petrol, with the crystallization likely complicated by the known interconversion of *O*- and *N*-acyl isomers.[31] In the case of the esters **13** and **14** derived from unsymmetrical oximes, the stereochemistry about the oxime double bond was defined as *Z* by single crystal X-ray diffraction analysis (Fig. 2).

While simple oximes possess p$K_a$ values of 8.3–11.8,[33] Oxyma (**6**) is characterized by the presence of strongly electron-withdrawing cyano and ethoxycarbonyl groups. The p$K_a$ value of Oxyma is reported to be 4.6,[34] matching that reported for HOBt (**1**).[35] In order to understand the leaving group ability of various oximes we initially sought to extract p$K_a$ data from the literature; however, owing to the range of different solvents used for these studies we were unable to directly compare the various oximes. Consequently, we measured the p$K_a$ values for the series of compounds by spectrophotometric titration of the oximes in a solution in 95% MeCN in water.[32] As revealed in Table 1, the p$K_a$ values for the series of oximes fell within the

**Table 1** Oximes and their benzylated derivatives. p$K_a$ values and preparation

| Oxime | p$K_a$ value | Benzoyl-oxime | Method[a] | Yield (%) |
|---|---|---|---|---|
|  **6** | 4.32 |  **13** | A | 90 |
|  **8** | 4.39 |  **14** | C | 65 |
|  **9** | 4.09[32] |  **15** | C | 64 |
|  **10** | 4.32 |  **16** | D | 78 |
|  **11** | 3.96 |  **17** | D | 80 |
|  **12** | 4.46 |  **18** | B | 83 |

[a] Method A: $Bz_2O$, $Et_3N$, $Et_2O$; method B: $Bz_2O$, $Et_3N$, $CH_2Cl_2$; method C: BzCl, pyr, $CH_2Cl_2$; method D: BzCl, $Et_3N$, $CH_2Cl_2$.

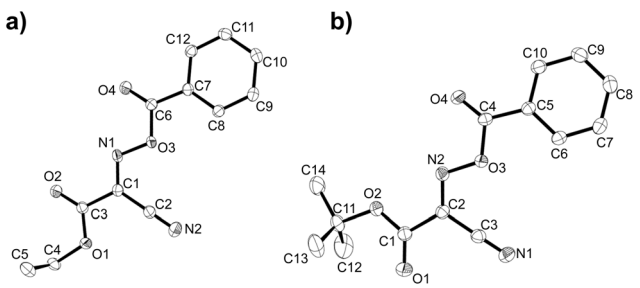
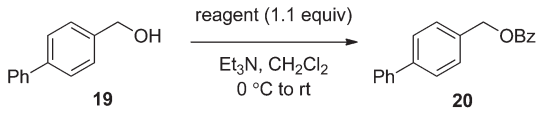



**Fig. 2** ORTEP representations of the molecular structures of benzoylated oximes (a) **13** and (b) **14**, determined by single-crystal X-ray crystallography. Ellipsoids are at the 50% probability level.

**Table 2** Comparison of benzoylation of 4-phenylbenzyl alcohol (**19**) by BBTZ and various benzoyl oximes




19 20

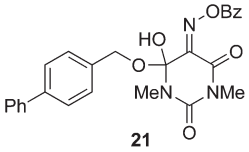
| Entry | Reagent | Yield[a] (%) |
|---|---|---|
| 1 | BBTZ (**2**) | 100 |
| 2 | Benzoyl-Oxyma (**13**) | 80 (95)[b] |
| 3 | **14** | 98 |
| 4 | **15** | 95 |
| 5 | **16** | 50[c] |
| 6 | **17** | 2 |
| 7 | **18** | 15 |

[a] Reactions performed using $Et_3N$ as received. [b] Reaction using $Et_3N$ dried by distillation over $CaH_2$. [c] Yield after 5 days. At this time the reaction still contained unreacted **4** and **19**.

range 3.96–4.39, and under these conditions the p$K_a$ value of HOBt was determined to be 4.25; based on their p$K_a$ values, the series of oximes possess similar intrinsic leaving group ability.

### Investigation of the benzoylation of a simple primary alcohol

The effectiveness of the benzoylated oximes as benzoylating agents was investigated by studying their reaction with a simple alcohol, 4-phenylbenzyl alcohol **19** (Table 2). This substrate was chosen as it is crystalline, easily dried and readily detected owing to the presence of a chromaphore. Treatment of **19** with 1.1 equiv. of BBTZ (**2**) and $Et_3N$ at 0 °C and warming to room temperature overnight afforded the benzoate **20** in quantitative yield (entry 1), highlighting the impressive benzoylating ability of this reagent. Treatment with 1.1 equiv. of the nitrile-containing reagents **13–15** gave yields of 95–98% (entries 2–4). Significantly, we found that for optimal yields using benzoyl-Oxyma **13**, use of dry $Et_3N$ was critical, as using undried $Et_3N$ only afforded an 80% yield. This sensitivity to trace moisture appears to be unique to the Oxyma-derived reagent as close to quantitative yields were obtained with the *t*-butyl ester **14**, dicyanooxime **15** and BBTZ using undried $Et_3N$, results that suggest that the carbonyl group of the Oxyma-derived **13** may be a site of unwanted reactivity. On the other hand the malonate-derived reagents **10–12** gave much poorer yields. The diethyl malonate derivative **10** provided just 50% after 5 d, with tlc evidence of both unreacted **10** and **19** (entry 5); the Meldrum's acid derivative **11** delivering only 2% (entry 6), accompanied by degradation of the reagent to materials that could not be identified; and the barbiturate **12** providing only a 15% yield (entry 7). In the last case, the major by-product was tentatively assigned as the addition product **21**. Overall, these results reveal that despite similarity in the p$K_a$ value of the conjugate acid of the leaving group, significant differences in reactivity occur across the series.



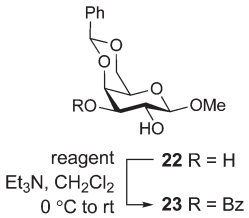

21

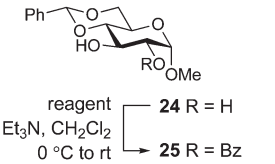
Securing exclusive nucleophilic attack at the carbonyl of the oxime-ester for these reagents, which contain multiple electrophilic sites at the oxime imino group and the adjacent nitrile/ester positions, is critical for high-yielding benzoylation. The isolation of the adduct **21** provides an indication of one of the alternative modes of reactivity. Despite considerable effort, we were unable to convincingly identify any by-products derived from reaction at the ethoxycarbonyl group of **13**. El-Fahem, Albericio and coworkers demonstrated that Oxyma undergoes reaction at the imino and ethoxycarbonyl groups when used as an additive in peptide coupling.[21] In the case of the Meldrum's acid derived **17**, tlc analysis revealed rapid consumption of the reagent yet little product formation, and it appears likely that nucleophilic attack at the dioxanedione carbonyl groups results in fragmentation of the reagent. The poor reactivity of **16** is at odds with the p$K_a$ value of the conjugate acid of the leaving group; however, we highlight that this reagent is the only non-crystalline compound of the series and we speculate that the two ethoxycarbonyl groups α to the oxime cause steric distortion of the system, affecting its conjugation and attenuating its reactivity.

### Selective benzoylation of carbohydrate alcohols

Having identified the nitrile-containing oximes **13–15** as the most effective benzoylating reagents for a simple alcohol, we next turned our attention to the selective acylation of carbohydrate diols. Typically, good acylation selectivity is observed for diols when one hydroxyl group has a *cis*-disposed vicinal

**Table 3** Comparison of benzoylation of galactoside **22** (to the 3-benzoate **23**) and glucoside **24** (to the 2-benzoate **25**) by BBTZ and benzoyl oximes **13–15**

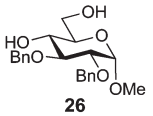
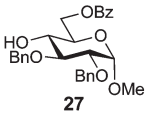
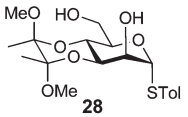
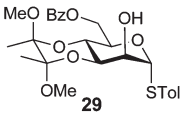
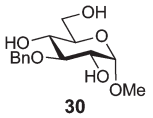
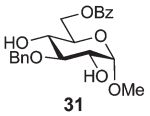
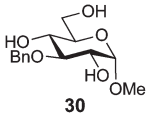
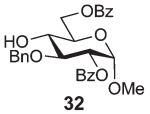
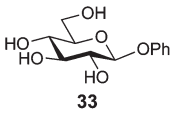
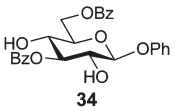



| Entry | Substrate | Reagent | Yield[a] (%) |
|---|---|---|---|
| 1 | **22** | BBTZ | 100 |
| 2 | **22** | Benzoyl-Oxyma (**13**) | 90 (100)[b] |
| 3 | **22** | **14** | 90 (100)[b] |
| 4 | **22** | **15** | 72 (90)[b] |
| 5 | **24** | BBTZ (**1**) | 87 |
| 6 | **24** | Benzoyl-Oxyma (**13**) | 83 (89)[b] |
| 7 | **24** | **14** | 75 (93)[b] |
| 8 | **24** | **15** | 80 (93)[b] |

[a] Reactions were performed using 1.1 equivalent of reagent, 1.2 equiv. dry $Et_3N$ in dry $CH_2Cl_2$, 0 °C to rt overnight. [b] Yield for reaction performed using 1.4 equiv. of benzoyl-Oxyma.

Table 4 Selective benzoylation of carbohydrate alcohols using benzoyl–Oxyma (**13**)

| Entry | Substrate | Product | Equivalents of benzoyl–Oxyma | Yield[a] (%) |
|---|---|---|---|---|
| 1 |  **26** |  **27** | 1.4 | 86 |
| 2 |  **28** |  **29** | 1.4 | 50 |
| 3 |  **30** |  **31** | 1.4 | 93 |
| 4 |  **30** |  **32** | 2.8 | 41 |
| 5 |  **33** |  **34** | 2.2 | 55 |

[a] Reactions were performed using the indicated equivalent of reagent, 1.2-fold of dry $Et_3N$ in dry $CH_2Cl_2$, 0 °C to rt overnight.

oxygen, which is believed to result from the presence of an intramolecular hydrogen bond that enhances the reactivity of the hydroxyl group. Using the optimum protocol identified from Table 2, the benzoylation of galactoside **22** was studied (Table 3). Consistent with literature yields[36] treatment of galactoside **22** with BBTZ provided a quantitative yield of the 3-benzoate **23** (entry 1). Among the three nitrile-based reagents, the best yield of **23** was obtained for the Oxyma-derived reagent **13** (90%, entry 2), which could be improved to a quantitative yield by using 1.4 equivalents of the reagent. We next explored acylation of the glucoside **24**. BBTZ afforded **25** in an 87% yield (entry 5). The three nitrile-containing oximes **13–15** gave marginally lower yields, with the best result obtained for the Oxyma-derived reagent (83%, entry 6). Increasing the amount of the Oxyma-derived reagent to 1.4 equivalents provided **25** in an 89% yield, commensurate with that obtained using 1.1 equivalents of BBTZ. We therefore conclude that the nitrile-based reagents are effective for selective acylation of diols, with the Oxyma-derived reagent **13** the most promising. Although these reagents are slightly less effective than BBTZ, use of 1.4 equiv. of **13** provides similar yields to that obtained using 1.1 equiv. BBTZ.

In view of the importance of selective hydroxyl functionalization in carbohydrate chemistry, we explored several additional examples using benzoyl-Oxyma (**13**) (Table 4). Selectivity for a primary *versus* a secondary alcohol was demonstrated through the benzoylation of the 4,6-diol **26** to afford the 6-benzoate **27** in 86% yield (entry 1), the 2,6-diol **28** to afford the 6-benzoate **29** in 50% yield (entry 2), and the 2,4,6-triol **30** to afford the 6-benzoate **31** in 93% yield (entry 3), in each case using 1.4 equiv. of **13**. Two additional transformations are noteworthy. Treatment of 2,4,6-triol **30** with 2.8 equivalents of **13** afforded 2,6-dibenzoate **31** in 41%, with the greater reactivity of the 2-position relative to the 4-position a result of the *cis*-relationship with the anomeric oxygen. Finally, treatment of tetraol **33** with 2.2 equiv. of **13** directly provided the 3,6-dibenzoate **34** in 55% yield.

## Conclusions

The classification of HOBt and related reagents as Class I explosives has provided an impetus for the development of new reagents that allow similar transformations with a lower risk of explosion. Oxime-based reagents, particularly those based on Oxyma, have emerged as effective alternatives for HOBt and have formed the basis of the development of COMU as a replacement for HBTU and HDMB. In this work we have explored a range of oxime-based alternatives to the selective acylating reagent BBTZ, leading to the identification of the nitrile-based benzoates **13–15** as the most promising representatives. In particular, benzoyl–Oxyma (**13**) can be considered a viable alternative to BBTZ, featuring a facile preparation, yields that approach those of BBTZ in various model reactions and a broad utility in the selective benzoylation of various carbohydrates.

## Experimental

### General

Proton nuclear magnetic resonance spectra ($^1$H NMR) and proton decoupled carbon nuclear magnetic resonance spectra

($^{13}$C NMR) were obtained in deuterated chloroform, methanol-$d_4$ ($CD_3OD$) and DMSO-$d_6$ with residual protonated solvent as internal standard. Abbreviations for multiplicity are s, singlet; d, doublet; t, triplet; q, quartet; p, pentet. Flash chromatography was carried out on silica gel 60 according to the procedure of Still *et al.*[37] IR spectra were obtained as thin films or solids on a Fourier-transform attenuated total reflectance infrared spectrophotometer equipped with a diamond-coated zinc selenide sample accessory. Analytical thin layer chromatography (t.l.c.) was conducted on aluminium-backed 2 mm thick silica gel 60 $GF_{254}$ and chromatograms were visualized with ceric ammonium molybdate (Hanessian's stain) or orcinol/$FeCl_3$ (Bial's reagent). High resolution mass spectra (HRMS) were obtained by ionizing samples using electro-spray ionization (ESI) and a time-of-flight mass analyzer. Dry DMF was obtained by drying over 4 Å molecular sieves. Hexanes refers to petroleum ether, boiling range 40–60 °C. $CH_2Cl_2$ and THF were dried over alumina according to the method of Pangborn *et al.*[38] Oxyma (ethyl 2-hydroximino-2-cyanoacetate, **6**) was purchased from Sigma-Aldrich. The synthesis of various oximes and oxime benzoates has been reported previously: **8**,[25] **9**,[26] **10**,[27] **11**,[28] **12**,[29] **15**,[26] and **16**.[30]

### Ethyl 2-benzoyloximino-2-cyanoacetate (benzoyl-Oxyma, 13)

A mixture of benzoic anhydride (2.21 g, 8.44 mmol) and Oxyma (**6**) (1.00 g, 7.04 mmol) in dry diethyl ether (25 mL) was stirred at room temperature for 1 min. The resulting precipitate was filtered and washed with cold petroleum ether to afford **13** as a white crystalline powder (1.50 g, 90%), m.p. 99.3 °C (lit.[39] 100 °C); $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 1.43 (3 H, t, $J$ 7.1 Hz, $CH_3$), 4.50 (2 H, q, $J$ 7.1 Hz, $CH_2$), 7.54–8.21 (5 H, m, Ph); $^{13}$C NMR ($CDCl_3$, 100 MHz) 14.1 ($CH_3$), 64.6 ($CH_2$), 107.1 (C═N), 125.8 (C≡N), 129.2, 130.6, 131.7, 135.2 (Ph), 157.0 (C═O), 160.7 (C═O); IR $\nu$ 2988.1, 2200.2, 1776.1, 1752.3, 1599.1, 1583.7, 1451.9, 1368.7, 1297.3, 1233.3, 1179.0, 1146.7, 1110.4, 1077.1, 1031.0, 996.2, 904.4, 837.5, 801.6, 764.9, 709.2, 666.5 cm$^{-1}$; HRMS [M + Na]$^+$ calcd for $C_{12}H_{10}N_2O_4Na$ $m/z$ 269.0533, found 269.0532.

### *t*-Butyl 2-benzoyloximino-2-cyanoacetate (14)

A solution of sodium nitrite (2.93 g, 42.5 mmol) in water (13 mL) was added to a solution of *t*-butyl cyanoacetate (2.00 g, 14.1 mmol) in acetic acid (6 mL) and water (6 mL) at 0 °C. The solution was stirred at room temperature for 12 h in the dark. A solution of $AgNO_3$ (2.40 g, 14.1 mmol) in water (13 mL) was added and stirred for 30 min. The resulting yellow precipitate was collected by filtration, washed with cold petroleum ether, and dried under vacuum (3.57 g, 70%). BzCl (0.554 g, 3.94 mmol) was added to a stirred solution of the yellow precipitate (1.00 g, 3.58 mmol) in toluene (7.5 mL). A drop of pyridine was added to the solution resulting in the rapid formation of a white precipitate. Stirring was continued for another 30 min and then the precipitate was collected by filtration. The filtrate was concentrated and the residue recrystallized to afford **14** as a white crystalline solid (0.62 g, 65%), m.p. 72.5–73.5 °C (ether/petroleum ether); $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 1.63 (9 H, s), 7.55–8.21 (5 H, m, Ph); $^{13}$C NMR ($CDCl_3$, 100 MHz) 27.0, 87.4, 107.4, 125.7, 128.9, 130.3, 132.6, 134.8, 155.2, 160.6; IR $\nu$ 3679.5, 2984.8, 2938.9, 2844.3, 2238.0, 1978.2, 1928.0, 1841.7, 1778.1, 1730.8, 1598.1, 1449.1, 1347.5, 1259.5, 1224.9, 1175.7, 1141.2, 1028.8, 989.8, 901.6, 843.0, 701.9, 665.7 cm$^{-1}$; HRMS [M + Na]$^+$ calcd for $C_{14}H_{14}N_2O_4Na$ $m/z$ 297.0846, found 297.0847.

### Benzoate ester of isonitroso Meldrum's acid (17)

Isonitroso Meldrum's acid **11**[28] (0.500 g, 2.89 mmol) was dissolved in $CH_2Cl_2$ (7 mL) and $Et_3N$ (0.44 mL, 3.16 mmol) was added, followed by addition of BzCl (0.34 mL, 2.9 mmol). The solution was stirred for 1 h, then diluted with $CH_2Cl_2$ (35 mL) and stirred for another 5 min. The solution was washed with water (2 × 20 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Flash chromatography (5–10% EtOAc/petroleum ether) afforded **17** as a brown solid (1.50 g, 70%), m.p. 108.5–109 °C; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 1.87 (6 H, s, $CH_3$), 7.55–8.27 (5 H, m, Ph); $^{13}$C NMR ($CDCl_3$, 100 MHz) 28.4, 46.0, 106.8, 126.2, 129.0, 129.2, 130.7, 131.0, 134.6, 135.1, 139.2, 150.9, 155.7, 161.3, 162.5; IR $\nu$ 3750.7, 2943.4, 1778.5, 1749.4, 1589.9, 1556.2, 1493.8, 1453.1, 1396.4, 1384.2, 1293.3, 1264.7, 1230.0, 1198.3, 1181.8, 1159.3, 1055.4, 1032.0, 1011.9, 982.3, 969.9, 949.0, 930.9, 891.0, 864.9, 798.8, 739.0, 701.8, 677.7, 667.1 cm$^{-1}$; HRMS [M + Na]$^+$ calcd for $C_{13}H_{11}NO_6Na$ $m/z$ 300.0479, found 297.0478.

### Benzoate ester of isonitroso dimethylbarbituric acid (18)

Benzoic anhydride (0.70 g, 2.97 mmol) was added to a solution of isonitroso dimethylbarbituric acid **12**[29] (0.500 g, 2.70 mmol) in dry $Et_2O$ (12.5 mL) and the solution was stirred overnight at room temperature. The resulting precipitate was filtered and washed with cold petroleum ether. The product was obtained as a green solid (0.65 g, 83%), m.p. 218.5–219 °C; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 3.45 (3 H, s, $CH_3$), 3.47 (3 H, s, $CH_3$), 7.54–8.33 (5 H, m, Ph); $^{13}$C NMR ($CDCl_3$, 100 MHz) 29.0, 29.5, 31.0, 126.5, 129.1, 130.9, 134.9, 161.7; IR $\nu$ 3000.1, 1949.2, 1773.7, 1686.0, 1447.8, 1367.7, 1283.3, 1234.9, 1070.9, 1014.7, 994.2, 970.3, 924.2, 866.2, 793.4, 746.3, 716.5 cm$^{-1}$; HRMS [M + Na]$^+$ calcd for $C_{13}H_{11}N_3O_5Na$ $m/z$ 312.0591, found 312.0595.

### Protocol for benzoylation of 4-phenylbenzyl alcohol (19)

A mixture of 4-phenylbenzyl alcohol (**19**) (0.100 g, 0.542 mmol), 1.1 equivalents of the benzoylating reagent and $Et_3N$ (0.091 mL, 0.650 mmol) in dry $CH_2Cl_2$ (3.0 mL) at 0 °C was stirred overnight. The solution was diluted with $CH_2Cl_2$, washed with water (2 × 20 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (10–15% EtOAc/petroleum ether) to afford 4-phenylbenzyl benzoate **20** as a white solid, m.p. 62–63 °C (lit.[40] 61.5–62.5 °C); $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 5.42 (2 H, s, $CH_2$), 7.34–8.12 (15 H, m, Ph); $^{13}$C NMR ($CDCl_3$, 100 MHz) 66.6 ($CH_2$), 127.2, 127.5, 127.6, 128.5, 128.9, 129.8, 130.2, 133.2, 135.1, 140.8, 141.3 (Ph), 166.6 (C═O); HRMS [M + Na]$^+$ calcd for $C_{20}H_{16}O_2Na$ $m/z$ 311.1043, found 311.1042.

**Characterization data for adduct of benzoate ester of isonitroso dimethylbarbituric acid and 4-phenylbenzyl alcohol, compound (21)**

$^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 3.01 (3 H, s, Me), 3.05 (3 H, s, Me), 5.29 (1 H, d, $J$ 12 Hz, $CH_2$), 5.41 (1 H, d, $J$ 12 Hz, $CH_2$), 7.42–7.85 (14 H, m, 2 × Ph, $C_6H_4$); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 25.54, 26.15, 69.32, 82.3, 126.4, 127.2, 127.3, 127.4, 127.6, 127.7, 128.5, 128.8, 128.9, 129.0, 129.4, 129.2, 129.4, 132.8, 134.1, 140.4, 142.2, 155.9, 162.3, 164.8, 166.3; HRMS $[M + H]^+$ calcd for $C_{26}H_{23}N_3O_6$ $m/z$ 474.1620, found 474.1659.

**Methyl 3-*O*-benzoyl 4,6-*O*-benzylidene-β-D-galactopyranoside (23)**

A mixture of methyl 4,6-*O*-benzylidene-β-D-galactopyranoside (**22**) (0.100 g, 0.354 mmol), benzoylating reagent (1.1 equivalent), and $Et_3N$ (0.060 mL, 0.42 mmol) in dry $CH_2Cl_2$ (3.0 mL) at 0 °C was stirred overnight. The solution was diluted with $CH_2Cl_2$, washed with water (2 × 20 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Flash chromatography (75–85% EtOAc/petroleum ether) of the residue afforded the 3-benzoate **23** as a white solid, m.p. 163–164 °C (lit.[36] m.p. 166–167 °C); $[\alpha]_D$ +94 ($c$ 1.0, $CHCl_3$; lit.[36] $[\alpha]_D$ +95); $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 2.34 (1 H, d, $J$ 2.4 Hz, OH), 3.60–3.62 (4 H, m, H5, $CH_3$), 4.11 (1 H, dd, $J$ 12.5, 1.7 Hz, H6), 4.18 (1 H, ddd, $J$ 10.1, 7.8, 2.5 Hz, H2), 4.41–4.36 (2 H, m, H1,6), 4.51 (1 H, d, $J$ 3.6 Hz, H4), 5.15 (1 H, dd, $J$ 10.1, 3.7 Hz, H3), 5.53 (1 H, s, PhC**H**), 7.29–8.12 (10 H, m, Ph) $^{13}$C NMR ($CDCl_3$, 100 MHz) 57.4 ($CH_3$), 66.7, 68.9, 69.1, 73.7, 74.3, 100.9, 104.2 (C1), 126.2, 128.1, 128.5, 128.9, 129.8, 130.0, 133.4, 137.7 (Ph), 166.6 (C═O); HRMS $[M + H]^+$ calcd for $C_{21}H_{22}O_7Na$ $m/z$ 409.1254, found 409.1254.

**Methyl 2-*O*-benzoyl 4,6-*O*-benzylidene-α-D-glucopyranoside (25)**

A mixture of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (**24**) (0.100 g, 0.354 mmol), 1.4 equivalents of the benzoylating reagent and $Et_3N$ (0.060 mL, 0.415 mmol) in dry $CH_2Cl_2$ (3.0 mL) at 0 °C was stirred overnight. The solution was diluted with $CH_2Cl_2$, washed with water (2 × 20 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Flash chromatography (25–35% EtOAc/petroleum ether) of the residue afforded the 2-benzoate **25** as a white solid, m.p. 169–170 °C (169–170 °C); $[\alpha]_D$ +108 ($c$ 1.0, $CHCl_3$; lit.[16] $[\alpha]_D$ +107); $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 2.57 (1 H, s, OH), 3.40 (3 H, s, $CH_3$), 3.63 (1 H, t, $J$ 9.4 Hz, H6), 3.80 (1 H, t, $J$ 10.3 Hz, H6), 3.91 (1 H, ddd, $J$ 9.8, 9.8, 4.7 Hz, H5), 4.34 (2 H, m, H3,4), 5.04 (1 H, dd, $J$ 9.5, 3.8 Hz, H2), 5.08 (1 H, d, $J$ 3.8 Hz, H1), 5.58 (1 H, s, PhC**H**), 7.36–8.13 (10 H, m, Ph); $^{13}$C NMR ($CDCl_3$, 100 MHz) 55.7 ($CH_3$), 62.2, 69.0, 69.1, 74.2, 81.6, 97.9, 102.2 (C1), 126.4, 128.5, 128.6, 129.4, 130.1, 133.5, 137.1 (Ph), 166.3 (C═O); HRMS $[M + H]^+$ calcd for $C_{21}H_{22}O_7Na$ $m/z$ 409.1257, found 409.1260.

**Methyl 2,3-di-*O*-benzyl-6-*O*-benzoyl-α-D-glucopyranoside (27)**

A mixture of benzoyl-Oxyma **13** (0.092 g, 0.374 mmol), methyl 2,3-di-*O*-benzyl-α-D-glucopyranoside **26**[41] (0.100 g, 0.267 mmol) and $Et_3N$ (0.050 mL, 0.32 mmol) in dry $CH_2Cl_2$ (3.0 mL) at 0 °C was stirred overnight. The solution was diluted with $CH_2Cl_2$, washed with water (2 × 20 mL), dried over ($MgSO_4$), filtered and concentrated under reduced pressure. Flash chromatography (30–40% EtOAc/petroleum ether) of the residue afforded **27** (0.11 g, 86%), m.p. 77–79 °C (lit.[42] 75–77 °C); $[\alpha]_D$ +35 ($c$ 0.25, $CHCl_3$; lit.[42] $[\alpha]_D$ +25); $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 2.53 (1 H, d, $J$ 2.9 Hz, OH), 3.40 (3 H, s, $CH_3$), 3.53 (2 H, m, H4,5), 3.87 (2 H, m, H2,3), 4.51 (1 H, dd, $J$ 12.1, 2.1 Hz, H6), 4.59–4.68 (3 H, m, H1,6,C**H**$_2$), 4.77 (2 H, dd, $J$ 11.6, 10.3 Hz, C**H**$_2$Ph), 5.01 (1 H, d, $J$ 11.3, C**H**$_2$Ph), 7.28–8.02 (15 H, m, Ph); $^{13}$C NMR ($CDCl_3$, 100 MHz) 55.3, 63.8, 69.5, 70.2, 73.3, 75.7, 79.7, 81.3, 98.2 (C1), 128.0, 128.1, 128.2, 128.4, 128.6, 128.7, 129.8, 133.2, 138.0, 138.7 (Ph), 166.8 (C═O); HRMS $[M + Na]^+$ calcd for $C_{28}H_{30}O_7Na$ $m/z$ 501.1884, found 501.1886.

**4-Methylphenyl 3,4-*O*-(2′,3′-dimethoxybutan-2′,3′-diyl)-6-*O*-benzoyl-1-thio-α-D-mannopyranoside (29)**

A mixture of benzoyl-Oxyma **13** (0.036 g, 0.146 mmol), 3,4-di-*O*-(2,3-dimethoxybutane-2,3-diyl)-α-D-mannopyranoside **28**[43] (0.042 g, 0.105 mmol), and $Et_3N$ (0.020 mL, 0.126 mmol) in dry $CH_2Cl_2$ (3.0 mL) at 0 °C was stirred overnight. The solution was diluted with $CH_2Cl_2$, washed with water (2 × 20 mL), dried over ($MgSO_4$), filtered and concentrated under reduced pressure. Flash chromatography (50–70% EtOAc/petroleum ether) of the residue afforded **29** as a syrup (0.030 g, 50%), $[\alpha]_D$ +167.8 ($c$ 0.25, $CHCl_3$); $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 1.30 (3 H, s, $CH_3$), 1.34 (3 H, s, $CH_3$), 2.27 (3 H, s, $CH_3$Ar), 3.17 (3 H, s, $OCH_3$), 3.32 (3 H, s, $OCH_3$), 4.07 (1 H, dd, $J$ 9.1, 3.0 Hz, H2), 4.18–4.22 (2 H, m, H3,6), 4.49 (1 H, ddd, $J$ 11.9, 6.1 Hz, H6), 4.55–4.65 (2 H, m, H4,5), 5.52 (1 H, s, H1), 6.98–8.01 (10 H, m, Ph); $^{13}$C NMR ($CDCl_3$, 100 MHz) 14.1 ($CH_3$), 17.7 ($CH_3$), 17.8, 21.2, 29.8, 48.1, 48.3, 63.0, 64.1, 64.7, 67.1, 69.7, 72.7, 87.1, 100.2, 100.5, 107.1, 125.8, 128.4, 128.54, 129.2, 129.7, 129.8, 130.0, 130.0, 130.7, 132.7, 133.1, 133.3, 135.3, 138.2, 157.1 (Ph), 160.7, 165.9, 166.4 (C═O); HRMS $[M + H]^+$ calcd for $C_{26}H_{32}O_8SNa$ $m/z$ 527.1701 found 527.1705.

**Methyl 3-*O*-benzyl-6-*O*-benzoyl-α-D-glucopyranoside (31)**

A mixture of benzoyl-Oxyma **13** (0.121 g, 0.491 mmol), methyl 3-*O*-benzyl-α-D-glucopyranoside **30**[44] (0.100 g, 0.351 mmol) and $Et_3N$ (0.060 mL, 0.421 mmol) in dry $CH_2Cl_2$ (3.0 mL) at 0 °C was stirred overnight. The solution was diluted with $CH_2Cl_2$ washed with water (2 × 20 mL), dried over ($MgSO_4$), filtered and concentrated under reduced pressure. Flash chromatography (40–50% EtOAc/petroleum ether) of the residue afforded **31** as a white solid (0.13 g, 55%), m.p. 70–71 °C; $[\alpha]_D$ +88.0 ($c$ 1.0, $CHCl_3$); $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 2.27 (1 H, d, $J$ 8.3 Hz, OH), 2.83 (1 H, d, $J$ 3.2 Hz, OH), 3.45 (3 H, s, $CH_3$), 3.54 (1 H, ddd, $J$ 9.1, 9.1, 2.3 Hz, H4), 3.63 (1 H, dd, $J$ 8.4, 8.4 Hz, H3), 3.69 (1 H, ddd, $J$ 9.1, 3.8 Hz, H2), 3.87 (1 H, ddd, $J$ 9.8, 4.7, 2.2 Hz, H5), 4.52 (1 H, dd, $J$ 12.1, 2.2 Hz, H6), 4.67 (1 H, dd, $J$ 12.1, 4.7 Hz, H6), 4.77–4.83 (2 H, m, H1, C**H**$_2$), 4.98 (1 H, d, $J$ 11.4, C**H**$_2$), 7.29–8.08 (10 H, m, Ph); $^{13}$C NMR ($CDCl_3$, 100 MHz) 55.4 ($CH_3$), 63.7, 69.9, 69.9, 72.7, 75.3, 82.5, 99.6 (C1), 120.3, 128.1, 128.5, 128.7, 129.8, 129.8, 133.3, 138.5 (Ph),

167.0 (C═O); HRMS $[M + H]^+$ calcd for $C_{21}H_{24}O_7$ Na *m*/*z* 411.1414, found 411.1412.

### Methyl 3-*O*-benzyl-2,6-di-*O*-benzoyl-α-D-glucopyranoside (32)

A mixture of benzoyl-Oxyma **13** (0.194 g, 0.787 mmol), of methyl 3-*O*-benzyl-α-D-glucopyranoside **30**[44] (0.080 g, 0.281 mmol) and $Et_3N$ (0.05 mL, 0.337 mmol) in dry $CH_2Cl_2$ (3.0 mL) at 0 °C was stirred overnight. The solution was diluted with $CH_2Cl_2$, washed with water (2 × 20 mL), dried over ($MgSO_4$), filtered and concentrated under reduced pressure. Flash chromatography (30–40% EtOAc/petroleum ether) of the residue afforded **32** as a syrup (0.0600 g, 41%), $[\alpha]_D$ +100.4 (*c* 0.5, $CHCl_3$); $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 3.42 (3 H, s, $CH_3$), 3.72 (1 H, t, *J* 9.1 Hz, H4), 3.98 (1 H, ddd, *J* 10.1, 4.4, 2.2 Hz, H5), 4.08 (1 H, t, *J* 9.0 Hz, H3), 4.56 (1 H, dd, *J* 12.1, 2.2 Hz, H6), 4.73–4.79 (2 H, m, H2,6), 4.88 (1 H, d, *J* 11.3 Hz, C**H**$_2$Ph), 5.07–5.12 (2 H, m, H1,C**H**$_2$Ph), 7.48–8.12 (10 H, m, Ph); $^{13}$C NMR ($CDCl_3$, 100 MHz) 55.4 ($CH_3$), 63.6, 69.7, 70.4, 73.9, 75.5, 79.6, 82.5, 97.5, 99.6 (C1), 128.0, 128.1, 128.5, 128.6, 128.7, 129.7, 129.8, 129.9, 129.9, 130.2, 133.3, 133.4, 133.5, 138.1 (Ph), 160.0, 167.1 (C═O); HRMS $[M + H]^+$ calcd for $C_{28}H_{28}O_8Na$ *m*/*z* 515.1676 found 515.1668.

### Phenyl 3,6-di-*O*-benzoyl-β-D-glucopyranoside (34)

A mixture of benzoyl-Oxyma **13** (0.210 g, 0.853 mmol), phenyl β-D-glucopyranoside **33** (0.100 g, 0.390 mmol) and $Et_3N$ (0.060 mL, 0.468 mmol) in dry $CH_2Cl_2$ (3.0 mL) at 0 °C was stirred overnight. The solution was diluted with $CH_2Cl_2$, washed with water (2 × 20 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Flash chromatography (2–5% acetone/$CH_2Cl_2$) of the residue afforded **34** as a white solid (0.11 g, 55%), m.p. 144 °C; $[\alpha]_D$ +2.7 (*c* 0.5, $CHCl_3$); $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 2.81 (1 H, s, OH), 3.49 (1 H, s, OH), 3.83 (1 H, t, *J* 9.3 Hz, H4), 3.90 (1 H, ddd, *J* 9.7, 6.1, 2.3 Hz, H5), 4.00 (1 H, dd, *J* 9.1, 8.0 Hz, H2), 4.63 (1 H, dd, *J* 12.0, 6.1 Hz, H6), 4.74 (1 H, dd, *J* 12.0, 2.3 Hz, H6), 5.07 (1 H, d, *J* 7.7 Hz, H1), 5.33 (1 H, t, *J* 9.1 Hz, H3), 7.07–8.08 (15 H, m, Ph); $^{13}$C NMR ($CDCl_3$, 100 MHz) 63.0, 69.7, 72.2, 74.6, 78.6 (C2,3,4,5), 101.0 (C1), 117.0, 123.2, 128.5, 128.6, 129.3, 129.6, 129.7, 129.9, 130.1, 133.4, 133.7, 157.0 (Ph), 166.9, 167.6 (C═O); HRMS $[M + H]^+$ calcd for $C_{26}H_{24}O_8Na$ *m*/*z* 487.1363, found 487.1361.

### X-ray crystallography

Crystals of **13** and **14** were mounted in low temperature oil then flash cooled using an Oxford low temperature device. Intensity data were collected at 130 K on an Oxford SuperNova X-ray diffractometer with CCD detector using Cu-Kα ($\alpha$ = 1.54184 Å) radiation. Data were reduced and corrected for absorption. The structures were solved by direct methods and difference Fourier synthesis using the SHELX suite of programs[45] as implemented within the WINGX software.[46] Thermal ellipsoid plots were generated using the program ORTEP-3.

Crystal data for **13**: $C_{12}H_{10}N_2O_4$ $M$ = 246.22, $T$ = 130.0(1) K, $\lambda$ = 1.54184, monoclinic, space group $P2_1/n$, $a$ = 11.8867(1), $b$ = 8.0556(1), $c$ = 12.3853(1) Å, $\beta$ = 99.064(1), $V$ = 1171.14(2) Å$^3$, $Z$ = 4, $D_c$ = 1.396 g cm$^{-3}$, $\mu$(Cu-Kα) 0.904 mm$^{-1}$, $F$(000) = 512, crystal size 0.49 × 0.44 × 0.32 mm. 8000 reflections measured, 2434 independent reflections ($R_{int}$ = 0.0170), the final $R$ was 0.0342 [$I > 2\sigma(I)$ 2347 data] and w$R(F^2)$ (all data) was 0.0966. CCDC deposition: 1406156.

Crystal data for **14**: $C_{14}H_{14}N_2O_4$ $M$ = 274.27, $T$ = 130.0(1) K, $\lambda$ = 1.54184 Å, monoclinic, space group $P2_1/n$, $a$ = 5.9020(1), $b$ = 21.5230(3), $c$ = 11.2041(2) Å, $\beta$ = 102.073(2)°, $V$ = 1391.76(4) Å$^3$, $Z$ = 4, $D_c$ = 1.309 g cm$^{-3}$, $\mu$(Cu-Kα) 0.813 mm$^{-1}$, $F$(000) = 576, crystal size 0.50 × 0.15 × 0.06 mm. 9619 reflections measured, 2897 independent reflections ($R_{int}$ = 0.0299), the final $R$ was 0.0392 [$I > 2\sigma(I)$ 2605 data] and w$R(F^2)$ (all data) was 0.1018. CCDC deposition: 1406157.

### Spectrophotometric titrations

Dissociation constants (p$K_a$ values) of the oximes or HOBt were measured spectrophotometrically using a Cary-50 Bio UV/Vis spectrophotometer in 95% (v/v) MeCN-water at wavelengths of 220–315 nm. Buffer solutions across the pH range of 2–10 were prepared by adding 0.2 M NaOH to a mixture of 0.04 M phosphoric acid, acetic acid, and boric acid. HOBt or oximes at 0.1 mM concentration were prepared in the buffer solutions and the absorbance measured. Each cuvette contained 50 μl of 1 mM stock solution of oxime or HOBt in MeCN, 100 μl of 40 mM buffer, and 1.85 mL of MeCN were used to obtain a final concentration of 0.025 mM of the reagent. Absorbances were measured at the wavelength where the difference between the absorbance of the oxime or HOBt, and its conjugate base was maximized. Titration curves are provided in the ESI.†

## Acknowledgements

We thank the Australian Research Council (ARC) for financial support. SJW is an ARC-funded Future Fellow. SS thanks the Department of State Development, Business and Innovation of Victoria for a Victoria-India Doctoral Scholarship and the Australia India Institute.

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