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Carboxylate Salt Bridge Mediated Enamine Catalysis: Expanded Michael Reaction Substrate Scope and Facile Access to Antidepressant (R)-Pristiq

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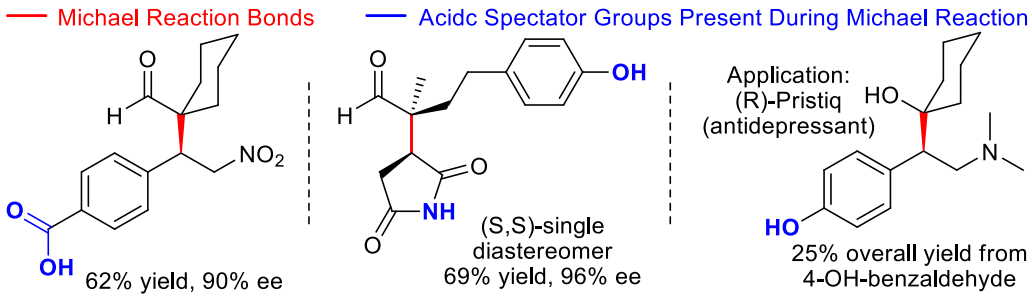
KEY WORDS: organocatalysis, carboxylate salt bridge, Michael reaction, nitroalkene, maleimide, peracetic acid

Graphical Content



Abstract: We report broad guidance on how to catalyze enantioselective aldehyde additions to nitroalkene or maleimide Michael electrophiles in the presence of unprotected acidic spectator groups, *e.g.*, carboxylic acids, acetamides, phenols, catechols, and maleimide NH groups. Remarkably, these L-threonine and L-serine potassium salt catalyzed reactions proceed even when the nucleophilic and electrophilic Michael partners simultaneously contain acidic spectator groups. These findings begin to address the historical non-compatibility of enantioselective catalytic reactions in the presence of acidic moieties and simultaneously encroach on the reaction capabilities normally associated with cellular

environments. A carboxylate salt bridge, from the catalyst enabled enamine to the Michael electrophile, is thought to facilitate the expanded Michael substrate profile. A practical outcome of these endeavors is a new synthetic route to (R)-Pristiq, (-)-O-desmethylvenlafaxine, an antidepressant, in the highest yield known to date because no protecting groups are required.

Michael reactions embody many different nucleophile/electrophile pairings making them good proving grounds for probing and applying new catalytic methods. An exhaustively examined example is the enantioselective addition of aldehydes to *ortho*-, *meta*-, or *para*-substituted-β-nitrostyrenes (Scheme 1).[1] A large array of electron rich and poor aromatic substituents are compatible and excellent yield and *ee* are noted. However, when a weakly acidic functional group (pK_a= 0 to 12) is present, high level achievement is restricted to β-nitrostyrene substrates containing an *ortho*-OH or *ortho*-NHAc substituent.[2,3] A substrate based *ortho*-directing effect, in the transition state, has been offered as a plausible explanation.[2g] In short, despite the comprehensive study of aldehydic Michael additions to β-nitrostyrenes, only three examples are known with a coexisting acidic spectator group when an *ortho*-OH or *ortho*-NHAc substituent is lacking. Those examples are restricted to *meta*- or *para*-based phenolic alcohol substrates and involve the addition of acetaldehyde,[4] propanal,[5] or isobutyraldehyde.[6]

Carboxylate salt based enamine catalysis is known but not widely employed,[7,8] and we speculated that its application could overcome the non-compatibility of acidic spectator functional groups during enantioselective catalysis, in particular for the Michael reaction. Here we show that threonine or serine potassium salt catalysis: (i) far surpasses the lone catalysis examples employing 3- or 4-hydroxy-β-nitrostyrenes;[4-6] (ii) is applicable to unreported and more acidic spectator groups, *e.g.*, 3,4-catechols, 3- or 4-positioned acetamide or carboxylic acid moieties; and (iii) allows both the Michael electrophile and nucleophile to simultaneously contain an acidic spectator group. In total, these results bear out the hypothesis that potassium salts of amino acids have broadened the substrate breadth for enantioselective enamine catalysis and we propose that these expanded reaction capabilities are due to a carboxylate salt bridge that assembles the starting materials.

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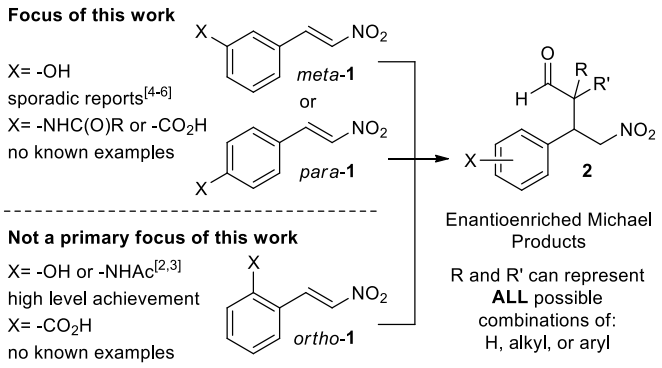

Scheme 1. Enantioselective aldehyde additions to β-nitrostyrenes containing acidic moieties.

Ignoring, temporarily, the challenge of coexisting acidic spectator groups, it is noteworthy that a smaller number of reports show the addition of α-branched aldehydes,[7-9] as opposed to linear aldehydes, to β-nitrostyrenes.[1] We have consequently focused on α-branched aldehyde additions here, which lead to the more difficult to form quaternary carbon based Michael products. Our initial investigations (Table 1) focused on adding isobutyraldehyde, the benchmark α-branched aldehyde substrate, and cyclohexanecarboxaldehyde, documented as difficult to add.[7a-c,9a,b,e,f]

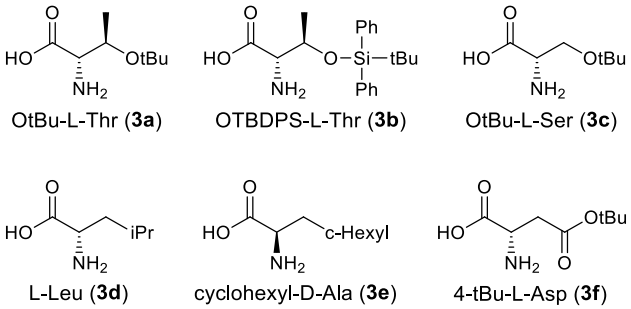

Figure 1. The potassium salts of threonine, serine, leucine, alanine, and aspartic acid derivatives were screened.

We have previously shown that OtBu-L-Thr (Figure 1) is capable of adding isobutyraldehyde (**4**) to β-nitrostyrenes,[7c,e] and modified conditions there from have now permitted us to readily add isobutyraldehyde to β-nitrostyrenes with *meta*- or *para*-positioned carboxylic acid, acetamide, catechol units, or phenolic OH moieties in good yield (70-86%) and excellent ee (94-97%), see structures **2a**, **b**, **d**,

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f, **g**, **l**, **j** of Table 1. For cyclohexanecarboxaldehyde additions, OtBu-L-Ser proved to, always, be the optimal amino acid from those shown in Figure 1. For example when a carboxylic acid, acetamide, catechol, or phenolic OH spectator group was present (Table 1, see products **2c**, **2e**, **2j**, **2l**), both the yields (62-86%) and *ees* (90-95%) were dramatically higher under OtBu-L-Ser catalysis. For perspective, cyclohexanecarboxaldehyde (**5**) has never been added in the presence of an acidic spectator group, and excluding our earlier study[7c] and this one, its addition to simple β-nitrostyrene (no acid groups present) always required a ≥20 mol%[7a,b,9 a,b,e,f] catalyst loading and, in the best outcome, resulted in 51% yield (80% *ee*) for the Michael product.[9e]

These initial results were rounded out by adding cyclopentanecarboxaldehyde, Table 1 product **2h**, albeit optimally with a silyl protected threonine catalyst: OTBDPS-L-Thr (Figure 1).[10] Except for compounds **2f** and **2i**, all Table 1 products are new and have been fully characterized (Supporting Information). For the formation of product **2i** (*para*-OH) and **2f** (*ortho*-OH), our starting material stoichiometry and catalyst loading far exceed the previous findings.[2e,6,11]

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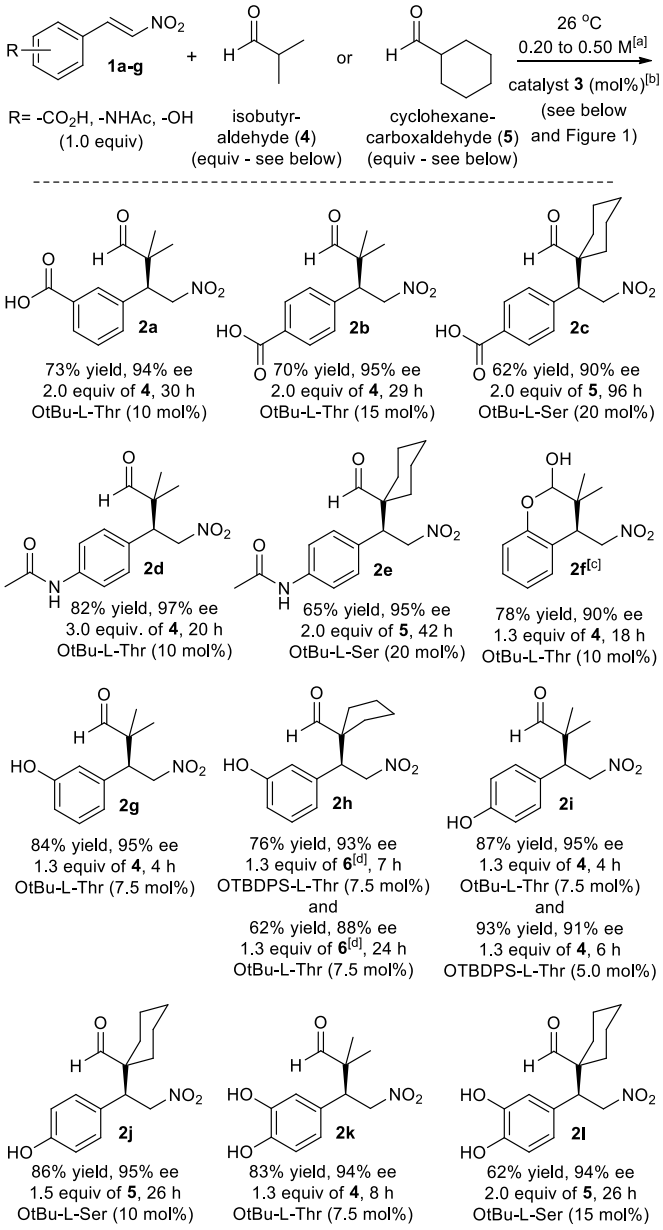
Table 1. Quaternary carbon Michael product formation in the presence of acidic spectator functionality.[a,b]



[a] For representative solvents, see the Experimental Section of the manuscript [b] The potassium salt of the shown amino acid was used. [c] The ee was determined for the corresponding lactone. [d] Cyclopentanecarboxaldehyde (**6**) used.

The Table 1 Michael products (**2**) establish the broad applicability of enantioselective aldehyde addition to β-nitrostyrenes in the presence of mildly acidic functional groups. *Of further importance, the first examples*

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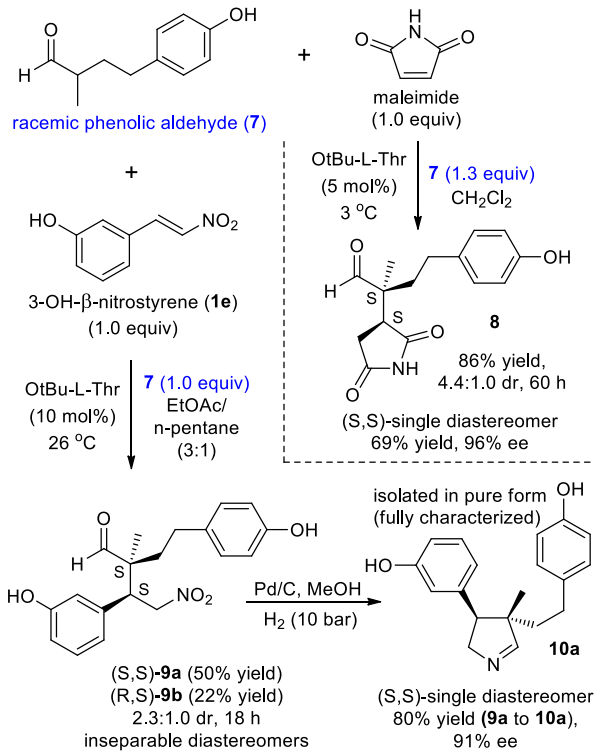
*of aldehyde addition to a β-nitrostyrene substituted by a carboxylic acid, see products **2a**-**c**, were realized; and no racemic examples of the same reactions exist.* Those results led us to pursue a higher level challenge: *the first Michael reaction in which both the electrophile and the nucleophile contain an acidic moiety.* To test this possibility and simultaneously examine stereogenic quaternary carbon formation, we added a phenol containing nonsymmetrical α-branched aldehyde (**7**) to 3-OH-β-nitrostyrene and separately to maleimide[12,13] (Scheme 2). The produced Michael products (**8** and **9**) contain vicinal quaternary-tertiary stereogenic centers and were obtained in high *ee* and good yield under remarkably practical starting material stoichiometries and reasonable catalyst loadings (Scheme 2). Motivated by our inability to separate diastereomers **9a**/**9b** and the further application potential of these products, we converted them into the separable dihydropyrroles **10a**/**10b** and fully characterized them.



Scheme 2. Stereogenic quaternary carbon formation when both the nucleophile and electrophile contain an acidic moiety. Formation of adjacent stereogenic centers.

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In total (Schemes 1 and 2), these results are significant due to the lack of examples of enantioselective catalytic reactions that tolerate the co-existence of acidic functional groups. In short, the demonstrated acidic spectator groups are reminiscent of those allowed within cellular reaction environments, but not chemical ones.

(±)-Venlafaxine (Scheme 3) is a widely prescribed anti-depressant whose HCl salt is marketed as Effexor. The cytochrome P-450 metabolite thereof, (±)-O-desmethylvenlafaxine or Pristiq, has largely replaced the sale of Venlafaxine because of its improved half-life and inhibitor potency (norepinephrine and dopamine uptake).[14] (R)-Pristiq (Scheme 3) is known to be a more active antidepressant than racemic Pristiq and is patent protected for that indication.[15] In aggregate, this family of compounds has a rich synthetic history which is now briefly summarized before elaborating on how the application of the above outlined methodology has allowed the highest yielding synthesis of (R)-Pristiq to date.

Enantioselective syntheses are not known for (R)-Pristiq but are known for Venlafaxine,[16] the best among them in 25% overall yield.[16a] However none are industrially used. All syntheses of (R)-Pristiq rely on a common strategy in which a starting material with a protected phenolic OH group is advanced to (±)-Venlafaxine, resolved to (R)-Venlafaxine, and finally O-demethylated[17] to reveal the phenolic OH of (R)-Pristiq. A resolution allows a maximum 50% yield and the best resolution of (±)-Venlafaxine employs di-*p*-toluoyl-D-tartaric acid, providing (R)-Venlafaxine in 24% yield.[14c,15] The best available O-demethylation procedures are high yielding (>80%) but require high energy reagents or high temperature, as exemplified by treatment with: nBuLi/diphenylphosphine,[15] or thiolate, *e.g.* anhydrous sodium sulfide, at ≥145 ^{o}C,[18] making their industrial application feasible but of lower economic value. Finally, in 2009 a three step synthesis of (±)-Pristiq from 4-methoxyphenylacetonitrile was reported in 26% overall yield,[19] but to date no one has described a method allowing the resolution of racemic Pristiq to (R)- or (S)-Pristiq. In short, no synthesis of (R)-Pristiq is able to circumvent the yield inefficient phenolic OH protect/deprotection and resolution steps. What follows is our protection group free enantioselective synthesis of (R)-Pristiq which holds potential as a scalable industrial synthesis.

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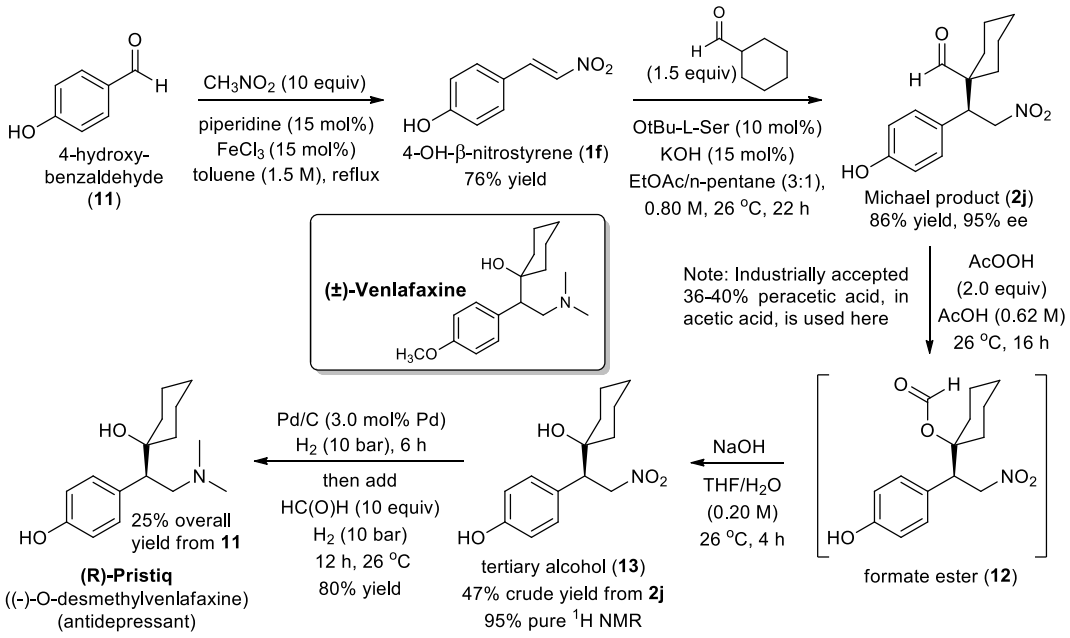

Scheme 3. The first enantioselective synthesis of (R)-Pristiq.

Inexpensive 4-hydroxybenzaldehyde (**11**) was converted to 4-OH-β-nitrostyrene (**1f**) using catalytic $FeCl_3$ in 76% yield (Scheme 3).[20] The next reaction step, enantioselective Michael addition of cyclohexanecarboxaldehyde, required non-trivial catalyst, solvent, and molarity screening beyond our initial phenolic substrate optimizations. For example, the potassium salt of OtBu-L-Thr provided excellent yield and ee when adding isobutyraldehyde to *ortho*-, *meta*-, and *para*-OH-β-nitrostyrenes, but attempts to broaden the aldehyde substrate scope to a vastly more hindered α-branched aldehyde, specifically cyclohexanecarboxaldehyde, resulted in non-practical outcomes. Emblematic of those challenges was the addition of cyclohexanecarboxaldehyde to *para*-OH-β-nitrostyrene, which resulted in the Prisitq Michael product (**2j**) in 71% yield and 79% ee under catalysis with the potassium salt of OtBu-L-Thr.

We reasoned that this mediocre result originated from the increased steric congestion encountered in the transition state when adding sterically hindered cyclohexanecarboxaldehyde *vs* isobutyraldehyde, and by extension we speculated that reducing the steric bulk of the catalyst might overcome this problem. After considering the likely enamine and transition state factors, Scheme 4, we noted that the OtBu-L-Ser enamine would have a reduced energetic penalty for rotation about its C2-C3 bond *vs* the OtBu-L-Thr

enamine (Scheme 4, right panel), and this, in turn, would reduce the steric interaction of the -OtBu group, of the catalyst, with the cyclohexane ring of cyclohexanecarboxaldehyde, while still enforcing high enamine facial selectivity. These presumptions appear to be borne out in the final product profile for product **2j**, 86% yield with 95% ee, under OtBu-L-Ser catalysis (10 mol%). These optimized conditions additionally proceed with a practical 1.0 to 1.5 stoichiometry for the starting materials: 4-OH-β-nitrostyrene/cyclohexanecarboxaldehyde.

The next challenge was selective conversion of aldehyde **2j** to the corresponding formate ester **12**. Excellent comprehensive reviews of Baeyer-Villiger oxidation are available,[21] but trends for the migratory aptitude of non-aromatic aldehydes are not explicitly discussed. Fortunately, literature examples published after those seminal reviews do show that secondary and tertiary carbon migration can be favored over hydrogen migration for aliphatic aldehydes when using mCPBA.[22] With that precedent, we converted aldehyde **2j** into formate ester **12** in the presence of mCPBA, but the corresponding hydrolysis product, alcohol **13**, was always noted in ~10% yield. Accompanying the mCPBA with a phosphate based salt did not change the reaction outcome. Of greater detriment was our inability to removal the m-chlorobenzoic acid by product from alcohol **13** via chromatography or the application of aqueous acid-base work-up procedures. These considerations and the fact that mCPBA is not used on an industrial scale prompted our investigation of industrially acceptable 36-40% peracetic acid in acetic acid,[23] which is commercially available. In the event, we again noted formate ester **12** and alcohol **13** formation. After considerable investigation we found it of operational convenience and beneficial (no loss in yield, see methods A versus B in the Supporting Information, Section 9) to use the crude Baeyer-Villiger product for the subsequent hydrolysis step. Employing this two-step method, aldehyde **2j** was consistently converted to alcohol **13** in no less than 47% overall yield. The two-step overall yield did not improve when using mCPBA.

Transformation of alcohol **13** directly into (R)-Pristiq was trivial. After nitro group reduction with Pd/C and H_2, and without work-up or further modification, excess aqueous formaldehyde was added and the reaction re-pressurized under hydrogen. This one-pot procedure allowed an 80% yield of (R)-Pristiq after

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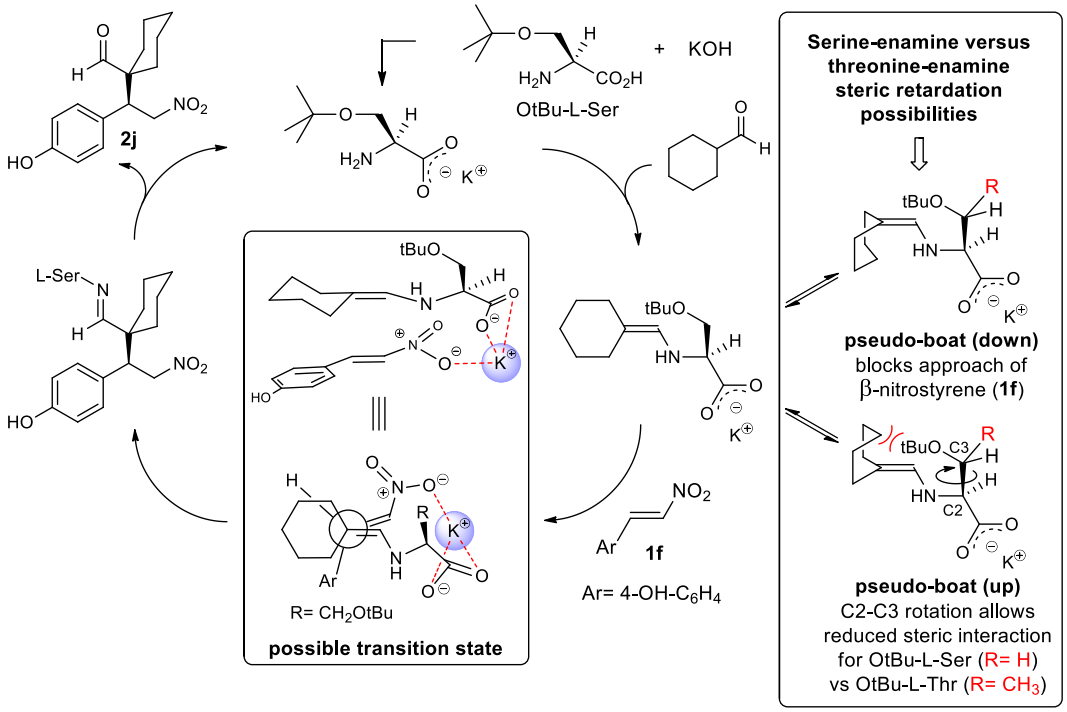
chromatographic purification. Despite the obvious nature of this sequence, we were surprised to find no other examples in which a nitro group has been converted directly to a dimethylamine when using hydrogen as the main reductant. In total, this synthesis represents: (i) the first enantioselective synthesis and (ii) at 25% overall yield, from 4-hydroxybenaldehyde, the highest overall yield to date for (R)-Pristiq (Scheme 3).

Regarding critical points within the catalytic cycle of the developed Michael reaction, the enamine transition state conformation and the assembled salt-bridge, carboxylate to potassium cation to nitro group (see transition state in Scheme 4), have been previously elaborated on via earlier DFT studies within an earlier manuscript of ours, albeit for a maleimide electrophile.[7e] Among other cations, *e.g.*, lithium, sodium, rubidium, and cesium, the potassium cation is critical for high yield and selectivity. The importance of the potassium cation was further underscored when the reaction of **1f** to **2j** (Scheme 3) resulted a in 15% yield of **2j**, after 30 h, in the presence of equal molar quantities of 18-C-6 (10 mol% - same as the catalyst loading). It should be further noted that catalysis with only OtBu-L-Ser, *i.e.*, without KOH, resulted in no reaction after 48 h.



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Scheme 4. Probable OtBu-L-Ser potassium salt catalytic cycle for cyclohexanecarboxaldehyde addition to 4-OH-β-nitrostyrene (**1f**) to give Pristiq Michael product **2j**, also see Scheme 3. Right panel: OtBu-L-Ser *versus* OtBu-L-Thr enamine steric considerations.

Based on the available information, one conclusion is that the shown substrates were not previously viable because the acidic spectator groups negatively impacted vital proton exchange equilibriums required within the catalytic cycle and/or these substrates were not sufficiently electrophilic enough to react. It is important to note that enamine based Michael reactions have been exhaustively examined and are overwhelmingly reported with steric based aminocatalysts and less frequently with amino acids (albeit with no base added). By contrast, performing these reactions with the carboxylate salt of an amino acid catalyst allows the catalyst enabled enamine and the Michael electrophile to assemble. This forces the reacting carbon centers within bonding distance proximity with much greater frequency. This point alone is likely the most influential one, and what separates these findings from the earlier ones. If correct, it is remarkable that the catalyst's carboxylate moiety can achieve productive equilibriums of the suggested transition state assemblies despite the presence of stoichiometric quantities of acidic spectator groups which will participate in non-productive protonation/deprotonation equilibriums.

Conclusion:

Carboxylate salt mediated enamine catalysis has resulted in a dramatic broadening of the acceptable Michael reaction nucleophiles and electrophiles to those containing an acidic spectator group. The demonstrated reaction capabilities expand chemical reactions into those formerly reserved for cellular environments. This advance is potentially explainable through a carboxylate salt hinge that facilitates highly congested and ordered transition states to reliably assemble despite the presence of competing acidic spectator groups, and the findings should be extendable to other reaction types. Regarding the product breadth, the method is tolerant of sterically hindered aldehyde additions and stereogenic quaternary carbon based Michael products can be formed. Finally, this opening report will likely spur the investigation of a broader number of amino acid catalysts, e.g., cysteine analogs, and perhaps more

importantly optimization of the amino acid protecting groups from O-t-Bu to, among others, pivaloyl or benzoyl based esters, etc.

Experimental Section:

179 pages of experimental descriptions and characterization data are available in the Supporting Information.

Generic Michael reaction procedure: To a screw cap vial was added KOH (10-60 mol%), catalyst (5.0-20.0 mol%), and then a solvent/cosolvent (see next paragraph). This was stirred for 2-3 min before adding the aldehyde (1.3-3.0 equiv). The reaction vessel was stirred for no more than 5 min and then a β-nitrostyrene derivative or maleimide (1.00 equiv) was added. Please refer to individual compound description for the specific starting material stoichiometries, solvents, and reaction times. All reactions were performed at 26 °C.

Solvents: It is important to note that each β-nitrostyrene category (phenol versus acetamide versus carboxylic acid substituents) required a solvent optimization, which more often than not was related to the solubility of the β-nitrostyrene. Examination of single solvents revealed either incomplete reactions (low conversion) or low ee. These deficits were overcome by screening for synergistic combinations of those same solvents. Solvent/cosolvent screening from MeOH, EtOH, acetone, THF, EtOAc, CH_3CN, CH_2Cl_2, *t*BuOMe, toluene, and n-pentane allowed the optimal binary solvent combination to be determined. Representative examples follow for products **2a**, **2d**, **2j**, **8**. See the Supporting Information for even greater detail.

(*S*)-3-(3,3-dimethyl-1-nitro-4-oxobutan-2-yl)benzoic acid (2a)
Reaction time= 30 h, KOH (MW= 56.11, 60.0 mol%, 0.31 mmol, 17.39 mg), O-^{t}Bu-L-threonine (MW= 175.23, 10.0 mol%, 0.05 mmol, 8.8 mg), *t*BuOMe/MeOH (8.5:1.5 vol ratio, 2.0 mL, 0.26 M), isobutyraldehyde (MW= 72.11, 2.0 equiv, 1.04 mmol, 75.00 mg, 94.9 µL), (*E*)-3-(2-nitrovinyl)benzoic acid (MW= 193.16, 1.00 equiv, 0.52 mmol, 100.4 mg). R_f **=** 0.41 (EtOAc/petroleum, 3:7) containing 3-4 drops of acetic acid. Silica gel chromatography provided the pure product as a white sticky solid (MW= 265.26, 101 mg, 0.38 mmol, 73% yield).
95% ee: Chiralcel OD-H chiral HPLC column, *i*PrOH/n-heptane (20:80), the n-heptane was a 0.30 vol% AcOH solution of n-heptane (vol/vol), flow rate = 0.8 mL/min, λ = 254 nm, t_{major}= 22.5 min, t_{minor}= 20.6 min.
^{1}H NMR (400 MHz, DMSO-d_6) (ppm): 0.88 (s, 3H), 1.04 (s, 3H), 3.97 (dd, *J* = 11.7, 3.6 Hz, 1H), 5.00 (dd, *J* = 13.7, 3.9 Hz, 1H), 5.24 (t, *J* = 13.2 Hz, 1H), 7.46 (t, *J* = 7.6 Hz, 1H), 7.61 (d, *J* = 7.6 Hz, 1H), 13.08 (bs, 1H), 7.85 (m, 2H), 9.58 (s, 1H). **^{13}C NMR (100 MHz, DMSO-d_6) (ppm):** 18.7, 20.1, 47.3, 48.0, 75.9, 128.5, 128.6, 129.9, 130.9, 133.4, 137.1, 167.2, 205.0. **IR (ATR mode):**V_{max} = 2964, 2918, 2854, 1689, 1554, 1376, 1294. **MS (EI, negative ion mode), *m/z* (relative intensity):** 158 (100%). **HRMS (ESI-TOF) m/z:** $[M - H^+]^-$ Calculated for $C_{13}H_{14}NO_5$:264.0877; Found: 264.0880.

(*S*)-*N*-(4-(3,3-dimethyl-1-nitro-4-oxobutan-2-yl)phenyl)acetamide (2d)
Reaction time= 20 h, T= 26 ºC, KOH (MW= 56.11, 13.0 mol%, 0.05 mmol, 2.80 mg), O-^{t}Bu-L-threonine (MW= 175.23,10.0 mol%, 0.04 mmol, 7.00 mg), EtOAc/acetone 3.5:1.5 (2.0 mL, 0.20 M), isobutyraldehyde (MW= 72.11, 3.00 equiv, 0.80 mmol, 57.68 mg, 73.00 µL), (*E*)-*N*-(4-(2-nitrovinyl)phenyl)acetamide (MW= 206.20, 1.00 equiv, 0.40 mmol, 82.0 mg). Note, this is the only reaction for which the equiv of isobutyraldehyde were not optimized. R_f = 0.31 (MeOH/CH_2Cl_2, 02:98). Silica gel chromatography provided the pure product as a pale yellow sticky solid (MW = 278.30, 91 mg, 0.33 mmol, 83% yield).
97% ee: Chiralcel OD-H chiral HPLC column, iPrOH/n-heptane (15:85), flow rate = 1.0 mL/min, λ = 254 nm, t_{major}= 46.8 min, t_{minor}= 25.3 min.
^{1}H NMR (400 MHz, $CDCl_3$) (ppm): 0.96 (s, 3H), 1.09 (s, 3H), 2.10 (s, 3H), 3.73 (dd, *J* = 4.1 Hz, 11.5 Hz, 1H), 4.66 (dd, *J* = 4.2, 13.0 Hz, 1H), 4.82 (dd, *J* = 11.6, 12.9 Hz, 1H), 7.10 (d, *J* = 8.5 Hz, 2H), 7.45 (d, *J* =

8.5 Hz, 2H), 8.07 (s, 1H), 9.48 (s, 1H). **^{13}C NMR (100 MHz, $CDCl_3$) (ppm):** 18.9, 21.6, 24.4, 48.0, 48.4, 76.4, 120.0, 129.6, 130.9, 138.1, 169.0, 204.5. **IR (ATR mode):** V_{max}= 1721, 2720, 1668, 3191, 3119, 1516 cm^{-1}. **MS (EI, positive ion mode), *m/z* (relative intensity):** 160 (100%). **HRMS (ESI-TOF) m/z:** [M + H^+]$^+$ Calculated for $C_{14}H_{19}N_2O_4$: 279.1339; Found: 279.1337.

(S)-1-(1-(4-hydroxyphenyl)-2-nitroethyl)cyclohexanecarbaldehyde (2j)
Reaction time= 22 h, T= 26 °C, KOH (MW= 56.11, 0.15 equiv, 0.545 mmol, 30.6 mg), O-^{t}Bu-L-serine (MW= 161.20, 10 mol%, 0.363 mmol, 58.6 mg), EtOAc/n-pentane (3:1 volume ratio, 4.5 mL, 0.8 M), cyclohexanecarboxaldehyde (MW= 112.17, 1.50 equiv, 5.45 mmol, 611 mg), 4-hydroxy-β-nitrostyrene (MW= 165.15, 1.00 equiv, 3.63 mmol, 600 mg). R_f= 0.27 (EtOAc/petroleum ether, 15:85). Silica gel chromatography provided the pure product as a light yellow viscous oil which sometimes solidifies (MW= 277.32 MW, 3.14 mmol, 871 mg, 86% yield).
95% ee: Chiralcel OD-H chiral HPLC column, *i*-PrOH/Heptane (15:85), flow rate = 0.8 mL/min, λ = 254 nm, t_{minor}= 15.6 min and t_{major}= 29.8 min.
^{1}H NMR (400 MHz, **$CDCl_3$) (ppm)**: δ 1.05-1.27 (m, 4H), 1.37 (dt, J= 12.6, 3.7, 1H), 1.55-1.71 (m, 3H), 1.88 (m, 1H), 2.06 (m, 1H), 3.48 (dd, J= 11.0, 4.8 Hz, 1H), 4.70 (dd, J= 13.0, 4.8 Hz, 1H), 4.76 (dd, J= 12.9, 11.1 Hz, 1H), 5.29 (bs, 1H), 6.74 (d, J= 8.6 Hz, 2H), 6.98 (d, J= 8.6 Hz, 2H), 9.53 (s, 1H). **^{13}C NMR (100 MHz**, **$CDCl_3$) (ppm)**: δ 22.7, 22.8, 25.2, 29.9, 31.1, 49.9, 51.6, 76.4, 115.7, 126.8, 130.4, 155.6, 207.9. **IR (ATR mode):** V_{max}= 3400, 2924, 2854, 1716. **(ESI-TOF)-MS m/z**: [M-H^+]$^-$ Calcd for $C_{15}H_{19}NO_4$ 276.1235; Found 276.1241. **MS (EI), *m/z* (relative intensity):** 107.96, 133.93, 121.01, 163.84, 169.88.

(S)-2-((S)-2,5-dioxopyrrolidin-3-yl)-4-(4-hydroxyphenyl)-2-methylbutanal (8)
Reaction time= 60 h, T= 3 °C, KOH (MW= 56.11, 8.0 mol%, 0.04 mmol, 2.2 mg), O-tBu-L-threonine (MW= 175.23, 5.0 mol%, 0.025 mmol, 4.4 mg), CH_2Cl_2 (0.5 mL, 1.0 M). 4-(4-hydroxyphenyl)-2-methylbutanal (**7**) (MW= 178.23, 1.3 equiv, 0.650 mmol, 115.8 mg), maleimide (MW= 97.1, 1.0 equiv, 0.50 mmol, 48.5 mg). R_f(major)= 0.31, R_f(minor)= 0.35 (EtOAc/petroleum ether, 1:1). Careful silica gel chromatography provided the major diastereomer as a white solid (MW= 275.30, 95.1 mg, 0.345 mmol, 69% yield).
96% ee: Chiralpak IA chiral HPLC column, EtOAc/n-heptane (50:50), flow rate = 1.0 mL/min, λ = 254 nm, t_{major}= 12.9 min and t_{minor}= 17.5 min.
^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm): 0.98 (s, 3H), 1.56-1.80 (m, 2H), 2.21 (dt, J= 4.56, 12.77 Hz, 1H), 2.37 (dt, J= 5.24, 12.80 Hz, 1H), 2.62 (dd, J = 5.80, 18.21 Hz, 1H), 2.75 (dd, J = 9.29 Hz, 18.17 Hz, 1H), 3.48 (dd, J = 5.89, 9.06 Hz, 1H), 6.65 (d, J = 8.26, 2H), 6.96 (d, J = 8.27 Hz, 2H), 9.60 (s, 1H). **^{13}C NMR (DMSO-d_6, 100 MHz)** δ (ppm): 13.5, 28.5, 31.2, 36.5, 45.6, 50.1, 115.1, 129.1, 131.5, 155.5, 177.8, 179.9, 204.4. **IR (ATR, cm^{-1}): v=** 3142, 1710, 1516. **MS (EI), *m/z* (relative intensity, negative mode):** 273.78. **HRMS (ESI-TOF) m/z: [M-H^+]$^-$** Calculated for $C_{15}H_{16}NO_4$: 274.1085; Found: 274.1073

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