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Nickel-Catalyzed Cyanation of Benzylic and Allylic Pivalate Esters

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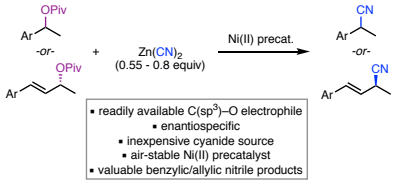
Supporting Information



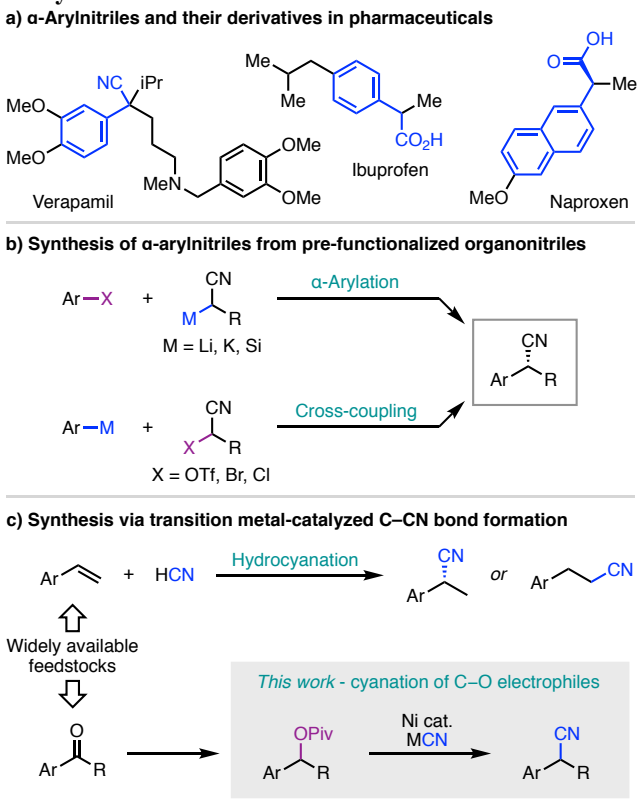
ABSTRACT: A nickel-catalyzed cyanation reaction of benzylic and allylic pivalate esters is reported using an air-stable Ni(II) precatalyst and substoichiometric quantities of $Zn(CN)_2$. Alkene additives were found to inhibit catalysis, suggesting that avoiding β-hydride elimination side-reactions are essential for productive catalysis. An enantioenriched allylic ester undergoes enantiospecific cross-coupling to produce an enantioenriched allylic nitrile. This method was applied to an efficient synthesis of (±)-naproxen from commercially available starting materials.

INTRODUCTION

The synthesis of nitrile-containing organic molecules has garnered considerable attention from the community for over a century due to their prevalence in pharmaceuticals and their versatile nature as synthetic intermediates.[1,2] The nitrile group can be readily converted into a wide variety of functional groups such as amides, carboxylic acid derivatives, ketones, aldehydes, amines and has also been involved in a number of transition-metal catalyzed transformations.[3] The synthesis of α-arylnitriles and their derivatives has been of particular interest as they are commonly found in pharmaceuticals (Scheme 1a).[1a,4] Frequently, retrosynthetic disconnections rely on the α-functionalization of organonitriles via deprotonation and subsequent alkylation. However, in addition to being limited to sterically accessible electrophiles, stereocontrol and over-alkylation are major challenges in these reactions. More recently, the α-arylation of nitriles under palladium catalysis has emerged as an effective strategy for the synthesis of α-arylnitriles (Scheme 1b),[5] and has been applied towards the synthesis of stereodefined quaternary centers.[6] However, the synthesis of enantioenriched tertiary nitriles using this strategy remains a challenge, in part due to base-mediated epimerization of the products. To this end, methods based on an inversion of polarity of the two coupling partners have been developed for producing enantioenriched products. In these transformations, α-cyanohydrin derived electrophiles are used as coupling partners (Scheme 1b).[7]

While the above-mentioned methods rely on the α-functionalization of nitrile-containing building blocks, direct incorporation of cyanide to generate the C(sp^3)–CN bond is an attractive strategy as it avoids the necessity to prepare a functionalized organonitrile intermediate.[8,9] This results in a more streamlined synthetic strategy from widely available chemical feedstocks (Scheme 1c). For example, Lewis acids, in combination with TMSCN, have been applied to the cyanation of benzylic alcohols via substitution

Scheme 1. Transition Metal-Catalyzed Synthesis of α-Arylnitriles

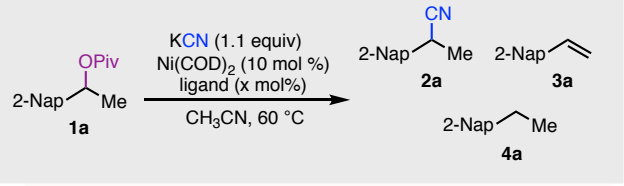


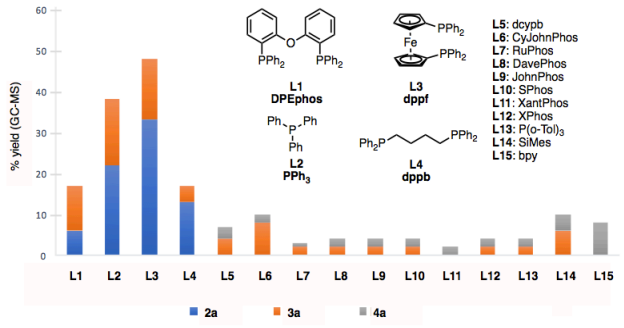
pathways.[10] α-Arylnitriles can also be prepared from styrene derivatives via nickel-catalyzed hydrocyanation reactions. Challenges in this field such as regio-[11] and stereoselectivity[12] as well as the toxicity of hydrogen cyanide[13] have been ad-

dressed. Other recent methods to access α-arylnitriles involve decarboxylation,[14] hydrogen atom transfer,[15] or dehydration[16] using copper catalysis.

Inspired by recent work using C(sp^3)–OR electrophiles in nickel-catalyzed cross-coupling reactions,[17,18] we wondered if α-arylnitriles could be prepared from benzylic esters. Recent reports have demonstrated that enantioenriched α -arylethers or esters are suitable electrophiles for enantiospecific Kumada-Tamao-Corriu, Negishi, and Suzuki-Miyaura reactions.[19] The relative ease in preparing enantioenriched alcohol derivatives is a clear advantage of these methods. While these previous reports have all involved organometallic reagents for C–C bond formation,[17,19,20] we hypothesized that a cyanation protocol could be developed in a similar fashion using inexpensive, readily available, and relatively (compared to HCN) non-toxic cyanide salts (Scheme 1c).[21] Herein, we describe the development of a nickel-catalyzed cyanation of benzylic and allylic pivalate esters using $Zn(CN)_2$ as a source of cyanide.

Scheme 2. Effect of the Ligand on Product Distribution

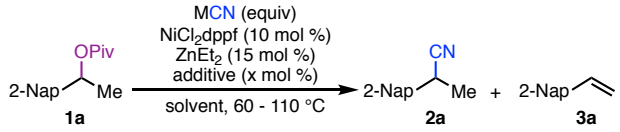




RESULTS AND DISCUSSION

We initiated our study by using pivalate derivative **1a** as the model substrate and investigating reaction conditions similar to those previously reported in Ni-catalyzed cyanation of phenol derivatives.[18a] An evaluation of various ligands revealed that bidentate phosphines were best for this transformation (Scheme 2). Only a small number of ligands (**L1**-**L4**), afforded the desired nitrile **2a**, where the main side product was alkene **3a** arising from β-hydride elimination. Based on these results, dppf (**L3**) was selected for further optimization. A combination of KCN, $Ni(COD)_2$, and dppf in acetonitrile at 60 °C afforded **2a** in 35% yield (Table 1, entry 1). An air-stable Ni(II) precatalyst, $NiCl_2$dppf, in combination with $ZnEt_2$ as a reductant, could be used instead of air-sensitive $Ni(COD)_2$ and afforded **2a** in a comparable yield (Table 1, entry 2). The amount of cyanide and concentration of the reaction were found to be very important, likely due to the propensity for cyanide anions to bind to and deactivate metal catalysts.[22] Minor deviations in solvent combinations of acetonitrile and DMF provided **2a** in increased, yet irreproducible yields (Table 1, entry 3).

Table 1. Optimization of Reaction Conditions[a]

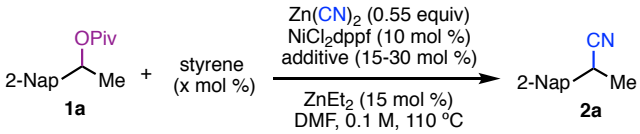


entry	MCN (equiv)	additive[b] (mol %)	solvent(s) (M)	yield (%)[c] 2a	3a
1[d,e]	KCN (1.1)	-	CH_3CN (1.0)	35	19
2[f]	KCN (1.0)	-	CH_3CN (1.0)	37	27
3[f]	KCN (1.0)	-	3:1 CH_3CN:DMF (1.0)	35 - 80	20 - 25
4[f]	$Zn(CN)_2$ (0.55)	-	1:2 CH_3CN:DMF (1.0)	78	7
5[f]	$Zn(CN)_2$ (0.55)	**A** (15)	DMF (1.0)	89 (77)	<5
6[g]	$Zn(CN)_2$ (0.55)	**A** (15)	DMF (0.1)	97 (86)	<5
7[g]	$Zn(CN)_2$ (0.55)	**B** (30)	DMF (0.1)	99 (94)	<5
8[g,h]	$Zn(CN)_2$ (0.55)	**A** (15)	DMF (0.1)	0	0
9[d,g]	$Zn(CN)_2$ (0.55)	**B** (30)	DMF (0.1)	61	<5

[a]Reactions were performed using pivalate **1a** (0.2 mmol, 1.0 equiv), MCN (0.55-1.1 equiv), Ni catalyst (10 mol %), K_3PO_4 (30 mol %, if added) or $Zn_5(CO_3)_2(OH)_6$ (15 mol %, if added), and $ZnEt_2$ (15 mol %) in CH_3CN and/or DMF (0.1-1.0 M) at 60-110 °C for 16 hours. [b]Additive **A** = $Zn_5(CO_3)_2(OH)_6$, **B** = K_3PO_4. [c]Calibrated yields determined by GC-MS using dodecane as an internal standard. Parentheses denote isolated yields. [d]Reaction with $Ni(COD)_2$ (10 mol %) and dppf (10 mol %). No $ZnEt_2$ was added. [e]Reaction at 60 °C. [f]Reaction at 80 °C. [g]Reaction at 110 °C. [h]Reaction in the absence of $NiCl_2$dppf.

Interestingly, while the amount of **2a** varied quite substantially (35-80%), the amount of **3a** remained relatively constant (20-25%) across numerous trials (*vide infra*). This problem could be circumvented by changing the cyanide source from KCN to $Zn(CN)_2$,[23,24] and increasing the solvent polarity with additional DMF (Table 1, entry 4). Adding catalytic amounts of basic zinc carbonate [$Zn_5(CO_3)_2(OH)_6$] to the reaction mixture and decreasing the concentration to 0.1 M afforded **2a** in 86% isolated yield (Table 1, entries 5-6). While the precise role of this complex salt is unclear, it minimizes the formation of the linear isomer byproduct (**2a'**), which arises via competitive β-hydride elimination and subsequent migratory insertion. Potassium phosphate had a similar effect, providing **2a** in 94% isolated yield (Table 1, entry 7). A control reaction indicated that the Ni catalyst was essential, as no **2a** or **3a** were observed in its absence (Table 1, entry 8).

Table 2. Effect of a Styrene Additive on Catalysis[a]

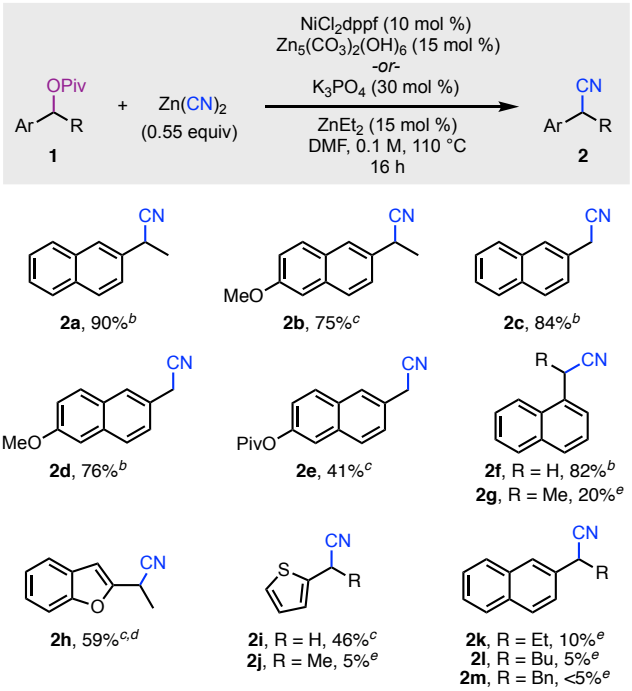


entry	additive (mol %)	styrene mol %	yield (%)[b] 2a
1	K_3PO_4 (30)	-	99
2	K_3PO_4 (30)	25 - 100	*trace*
3	$Zn_5(CO_3)_2(OH)_6$ (15)	-	97
4	$Zn_5(CO_3)_2(OH)_6$ (15)	25 - 100	*trace*

[a]Reactions were performed using the conditions outlined in Table 1. [b]Calibrated yields determined by GC-MS using dodecane as an internal standard.

The use of $Ni(COD)_2$ under these optimized conditions gave **2a** in only 61% yield. In fact, the COD ligand is not an innocent bystander in this Ni(0)-catalyzed transformation, as various cyclooctadiene and hydrocyanated cyclooctene isomers were observed (Table 1, entry 9). Intrigued by these observations, we found that when 25-100 mol % of styrene was added to the reaction, only trace amounts of **2a** were generated in each case (Table 2). Based on these results and the challenges with reproducibility that we faced during reaction optimization (Table 1, entry 3), we believe that once sufficient **3a** is generated in the reaction (20-25%), this byproduct effectively inhibits catalysis. This phenomenon has also been observed in a similar system,[19a] and highlights that the suppression of β-hydride elimination pathways leading to the generation of alkenes such as **3a** is essential for productive catalysis in these transformations.

Scheme 3. Reaction Scope for the Synthesis of α-Arylnitriles[a]

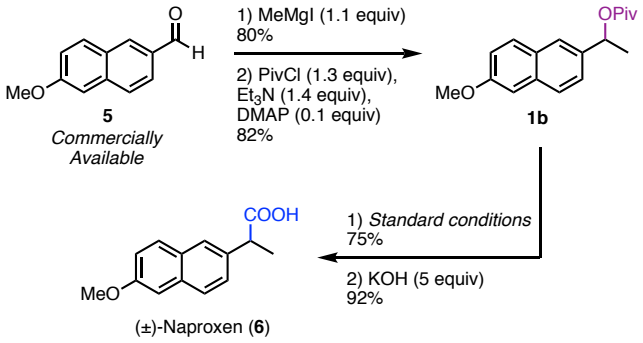


[a]Reactions were performed using pivalates **1** (0.2 mmol, 1.0 equiv), $ZnCN_2$ (0.55 equiv), $NiCl_2dppf$ (10 mol %), K_3PO_4 (30 mol %) or $Zn_5(CO_3)_2(OH)_6$ (15 mol %), and $ZnEt_2$ (15 mol %) in DMF (0.1 M) at 110 °C for 16 hours. Yields are reported as isolated yields (average of two runs). [b]K_3PO_4 (30 mol %) was added. [c]$Zn_5(CO_3)_2(OH)_6$ (15 mol %) was added. [d]20 mol% $NiCl_2dppf$ and 30 mol% $ZnEt_2$ were added. [e]Yield determined by GC-MS using dodecane as an internal standard.

Scheme 3 highlights the scope of this transformation using either potassium phosphate or basic zinc carbonate as an additive. Secondary 2-naphthyl substrates were tolerated providing **2a** and **2b** in 90% and 75% isolated yields respectively. Surprisingly, other alkyl groups such as Et, Bu, or Bn failed to undergo efficient conversion to the desired nitriles (**2k-m**). A similar unexpected substrate sensitivity has been observed in a nickel catalyzed carbocyanation reaction.[25] Greater amounts of β-hydride elimination in these reactions may have led to catalyst inhibition with these substrates, however oxidative addition also appeared to be more challenging as little to no conversion of the starting material was observed in these cases. Generally, the mass balance in these reactions consist of unreacted starting material. Primary derivatives yielded the resulting nitriles **2c** and **2d** in 84% and 76%, respectively. The reaction is selective for oxidative addition into a $C(sp^3)$–OPiv bond over a $C(sp^2)$–OPiv as demonstrated in the formation of product **2e**; competitive $C(sp^2)$–CN bond formation was not observed in this case.[18,24] 1-Naphthyl-substituted **1f** was successfully converted to the corresponding nitrile derivative **2f**, however the secondary, methyl-substituted derivative **2g** was obtained in lower yield possibly due to the increased steric bulk. Benzofuran **1h** and thiophene **1i** undergo cyanation to afford **2h** and **2i** in 57% and 48% yields, respectively. Indole, as well as other aryl substituents that lack an extended pi system such as phenyl, pyrrole, and furan were unsuccessful. The extended aromatic system is thought accelerate oxidative addition via stabilization of the transition state.[17a,19a-f]

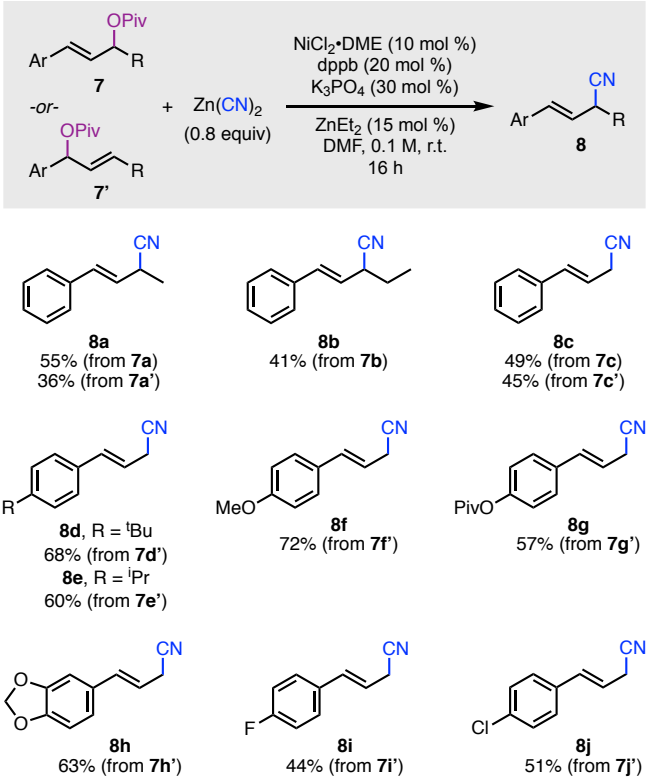
Having established a protocol for the efficient synthesis of nitrile **2b**, (±)-naproxen (**6**), a non-steroidal anti-inflamatory drug (NSAID),[26] was prepared in four steps from commercially available material (Scheme 4).

Scheme 4. Synthesis of (±)-Naproxen



Encouraged by our results for the cyanation of pivalates alpha to extended aromatic systems, we sought to extend this reaction to the synthesis of allylic nitriles from allylic pivalates (Scheme 5).[27,28] To the best of our knowledge, the nickel-catalyzed cyanation of allylic alcohol derivatives has not been reported. After a modest screen of reaction parameters, we identified dppb as the optimal ligand and potassium phosphate as an additive. An increase in the amount of zinc cyanide (0.55 to 0.8 equivalents) was necessary to avoid the formation of butadiene isomers, arising from β-hydride elimination side reactions. A 2:1 ligand to metal ratio also helped to avoid the formation of undesired side products. Notably, this reaction could be performed at room temperature. In all reactions, linear nitrile **8** was the only observed product isomer, regardless of whether allylic pivalate **7** or **7'** was used as a starting material (Scheme 5). Secondary allylic pivalates were tolerated (**8a-b**), as well as various substituents on the aromatic ring. Arenes bearing electron-neutral and electron-rich functional groups (**8d-h**) gave superior yields compared to electron deficient systems (**8i,j**). In all cases the remainder of the material was unreacted starting material. Remarkably, no $C(sp^2)$–CN bond formation was observed for either –OPiv (**8g**) or –Cl (**8j**) substituted allylic pivalates, providing handles for further derivatization of the products via other transition metal-catalyzed processes.[17,18]

Scheme 5. Reaction Scope for the Synthesis of Allylic Nitriles[a]



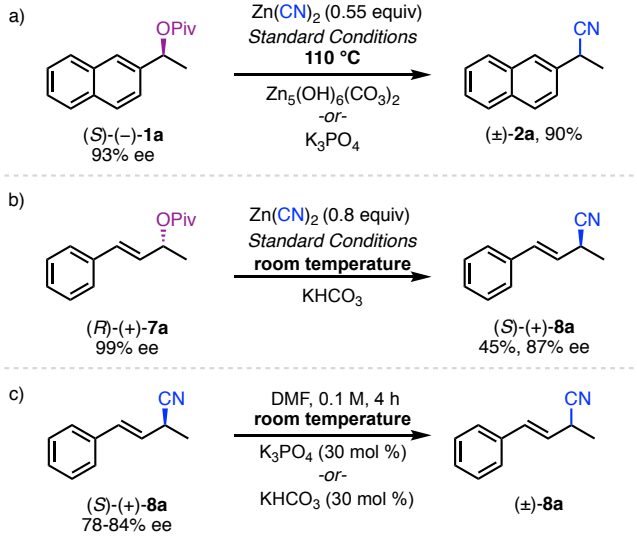
[a]Reactions were performed using pivalates **7** or **7'** (0.2 mmol, 1.0 equiv), $ZnCN_2$ (0.8 equiv), $NiCl_2$·DME (10 mol %), dppb (20 mol %), K_3PO_4 (30 mol %), and $ZnEt_2$ (15 mol %) in DMF (0.1 M) at 23 °C for 12-16 hours. Yields are reported as isolated yields (average of two runs).

When enantioenriched (*S*)-**1a** was subjected to the reaction conditions using either K_3PO_4 or $Zn_5(CO_3)_2(OH)_6$ as an additive,the resulting nitrile **2a** was obtained as a racemic mixture (Scheme 6a). This is due to the basic nature of the reaction mixture and the inherent acidity of α-arylnitriles.[29] Indeed, when an enantioenriched substrate is treated with catalytic K_3PO_4 in DMF at 110 °C, complete racemization is observed after 20 minutes. It is also possible that stereochemical information is lost prior to product formation via a bimetallic racemization pathway[19d] or a reversible β-hydride elimination/migratory insertion pathway. However, when allylic pivalate (*R*)-**7a** was subjected to the reaction conditions using $KHCO_3$ as an additive, the reaction produced (*S*)-**8a** in 87% ee and proceeded with inversion of stereochemistry (Scheme 6b).[28] We noted that when (*S*)-**8a** was simply treated with K_3PO_4 or $KHCO_3$ in DMF at room temperature, complete racemization occurred after 4 hours in both cases (Scheme 6c). Thus, it is curious that under our standard reaction conditions (12-16 hours reaction time), good stereospecificity is achieved. The mechanism by which base-mediated epimerization is avoided is not fully understood at this time and is currently under investigation in our laboratory.

CONCLUSION

In summary, we have developed a Ni-catalyzed cyanation reaction using benzylic or allylic pivalate esters as electrophiles. We found that basic additives (K_3PO_4 or $Zn_5(CO_3)_2(OH)_6$) were essential for reactivity and that undesired β-hydride elimination side reactions were involved in catalyst inhibition. Using this method, (±)-naproxen (**6**) was prepared in 4 steps from commercially available starting materials in 45% overall yield. We have also demonstrated that enantioenriched allylic nitriles can be generated via a stereospecific transformation, proceeding with inversion of stereochemistry. Further studies to develop other Ni-catalyzed cross-coupling reactions using $C(sp^3)$–OR electrophiles are currently ongoing in our laboratory.

Scheme 6. Stereospecific Cyanation Reactions[a]



[a]Standard conditions refer to the optimized conditions detailed in Schemes 3 and 5.

ASSOCIATED CONTENT

EXPERIMENTAL SECTION

Unless otherwise noted, all reactions were set up on the benchtop and run under an atmosphere of argon or nitrogen using flame-dried glassware and anhydrous solvents. Anhydrous solvents were purchased from Sigma–Aldrich in Sure/Seal bottles and were used as received. Dimethylformamide (extra-dry, over molecular sieves, Acros Organics) was degassed by sonicating under vacuum for 2 minutes before use. Diethylzinc was purchased from Sigma–Aldrich as a 1.0 M solution in hexanes and was titrated according to Knochel's protocol.[30] Potassium phosphate was dried under vacuum at 150 °C for 12 hours and stored in a desiccator before use. All other commercial reagents were used as received. Cyanation reactions were performed in 8-mL Fisherbrand threaded tubes (manufacturer no. FB7377013100; Fisher catalog no. 14-957-76A) whose ends were sealed with size-19 rubber septa and electrical tape. Compounds were purified by flash column chromatography using SiliCycle SiliCaFlash P60.

^1H and ^{13}C NMR spectra were recorded on Varian MercuryPlus 400 MHz or Bruker AvanceIII 400 MHz spectrometers. Spectra were internally referenced to the residual solvent signal ($CDCl_3$ = 7.26 ppm, DMSO-d_6 = 2.50 ppm for ^1H NMR and $CDCl_3$ = 77.16 ppm, DMSO-d_6 = 39.5 ppm for ^{13}C NMR). Data for ^1H NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet, br = broad), coupling constant (Hz), integration. IR spectra were obtained on a Perkin-Elmer Spectrum 100 instrument equipped with a single-bounce diamond/ZnSe ATR accessory as solids or thin films. Melting points were obtained on a Fisher-Johns Melting Point Apparatus. High-resolution mass spectra (HRMS) were recorded on a JEOL AccuTOF JMS-T1000LV mass spectrometer equipped with a Direct Analysis in Real Time (DART) ion source. Specific optical rotations were measured in a 50 mm cell with a Rudolph Autopol IV digital polarimeter equipped with a sodium lamp source (589 nm) and

are based on the equation $[\alpha] = 100 \cdot \alpha/(l \cdot c)$, where l is the path length in decimeters and c is the concentration expressed as g/100 mL. Specific rotations are reported as follows: $[\alpha]_D^{temp}$ (c = g/100 mL, solvent). The units (deg·mL)/(g·dm) are implicit and not included with the reported values.

General Procedures for the Synthesis of Benzylic and Allylic Pivalates. *General Procedure A: Carbonyl reductions*. The ketone or aldehyde was dissolved in anhydrous methanol (1.5 M) and cooled to 0 °C. $NaBH_4$ (0.6 equiv) was added in one portion, and the reaction mixture was slowly warmed to room temperature. When the reaction was judged to have reached completion (as determined by TLC), the solvent was removed under reduced pressure. Sat. $NaHCO_3$ was added and the crude material was extracted with EtOAc (x1). The organic phase was washed with brine (x1), dried over $MgSO_4$, and concentrated under reduced pressure. Unless otherwise noted, the crude alcohol was of sufficient purity for use in the next step.

General Procedure B: Esterification. The alcohol was dissolved in dichloromethane (0.5 M) and the solution was cooled to 0 °C. NEt_3 (1.4 equiv) was added, followed by DMAP (0.1 equiv). Trimethylacetyl chloride (1.3 equiv) was then added dropwise to the solution at 0 °C before warming slowly to room temperature. When the reaction was judged to have reached completion (as determined by TLC), sat. $NaHCO_3$ was added and the mixture was further diluted with dichloromethane. The phases were separated and the organic layer was washed with 1 M HCl (x1), brine (x1), dried over $MgSO_4$, and concentrated under reduced pressure. The crude ester was purified by column chromatography on silica gel if it was a liquid, or by recrystallization if it was a solid.

General Procedure C: Grignard Addition. To a solution of aldehyde (1.0 equiv) in THF (1.0 M) was added freshly prepared Grignard reagent (1.1 equiv). When the reaction was judged to have reached completion (as determined by TLC), sat. NH_4Cl was added slowly at 0 °C, and the mixture was extracted with EtOAc (x3). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude alcohol was purified by column chromatography on silica gel if necessary, or used without further purification.

General Procedure D: One-pot Grignard Addition and Esterification. The aldehyde (1.0 equiv) was dissolved in THF (0.5 M) and vinyl magnesium bromide (1.1 equiv) was added dropwise at room temperature. The mixture was left to stir for 1 h (or until the reaction was judged to have reached completion as determined by TLC), before trimethylacetyl chloride (1.5 equiv) was added also at room temperature. This solution was stirred for 1 h (or until the reaction was judged to have reached completion as determined by TLC) before sat. $NaHCO_3$ was added. The mixture was extracted with EtOAc (x2) and the combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude allylic ester was purified by column chromatography on silica gel. Note: Some yields appear low due to impurities present during chromatography. Only the pure material was used in the subsequent reaction, and the yields are reported as such.

1-(Naphthalen-2-yl)ethyl pivalate (1a) was prepared according to General Procedure A using 2-acetylnaphthone (17.0 g, 100 mmol, 1.00 equiv), $NaBH_4$ (2.3 g, 60 mmol, 0.60 equiv), and MeOH (160 mL, 0.63 M). The crude alcohol **(S1)** (15 g, 89% yield) was of sufficient purity for use directly in the next step according to General Procedure B using **S1** (6.9 g, 40 mmol, 1.0 equiv), triethylamine (7.8 mL, 56 mmol, 1.4 equiv), DMAP (0.49 g, 4.0 mmol, 0.10 equiv), trimethylacetyl chloride (6.4 mL, 52 mmol, 1.3 equiv) and CH_2Cl_2 (60 mL, 0.9 M). The crude product was purified by hot recrystallization in hexanes to afford 7.8 g (76% yield) of the desired product as a white solid. ^{1}**H NMR** (400 MHz, $CDCl_3$, 298 K) δ_H 7.91–7.72 (m, 4H), 7.54–7.42 (m, 3H), 6.02 (q, *J* = 6.6 Hz, 1H), 1.60 (d, *J* = 6.6 Hz, 3H), 1.23 (s, 9H); ^{13}**C NMR** (101 MHz, $CDCl_3$, 298 K) δ_C 177.8, 139.6, 133.4, 133.1, 128.5, 128.2, 127.8, 126.3, 126.1, 124.9, 124.1, 72.2, 38.9, 27.3, 22.4. The spectral data for this compound matches that reported in the literature.[19f]

1-(6-Methoxynaphthalen-2-yl)ethyl pivalate (1b) was prepared according to General Procedure C using 6-methoxy-2-naphthaldehyde (3.7 g, 20 mmol, 1.0 equiv), THF (15 mL, 1.3 M) and MeMgI (1.3 M solution in diethyl ether, 17 mL, 22 mmol, 1.1 equiv). The crude alcohol (**S2**) was purified by hot recrystallization using CH_2Cl_2 and hexanes to afford 3.2 g (80% yield) of the alcohol as an off-white solid, which was used directly in the next step according to General Procedure B using **S2** (2.0 g, 9.9 mmol, 1.0 equiv), triethylamine (1.9 mL, 14 mmol, 1.2 equiv), DMAP (0.12 g, 0.99 mmol, 0.10 equiv), trimethylacetyl chloride (1.6 mL, 13 mmol, 1.2 equiv), and dichloromethane (20 mL, 0.5 M). The crude product was purified by column chromatography on silica gel (slow gradient from 0–10% EtOAc in hexanes) to afford 2.3 g (82% yield) of the desired product as a white solid. ^{1}**H NMR** (400 MHz, $CDCl_3$, 298 K) δ_H 7.75–7.71 (m, 3H), 7.43 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.18–7.05 (m, 2H), 5.99 (q, *J* = 6.6 Hz, 1H), 3.92 (s, 3H), 1.59 (d, *J* = 6.5 Hz, 3H), 1.22 (s, 9H); ^{13}**C NMR** (101 MHz, $CDCl_3$, 298 K) δ_C 177.9, 157.9, 137.3, 134.2, 129.6, 128.8, 127.3, 124.8, 124.7, 119.1, 105.8, 72.2, 55.5, 38.9, 27.3, 22.4. The spectral data for this compound matches that reported in the literature.[19f]

Naphthalen-2-ylmethyl pivalate (1c) was prepared according to General Procedure A using 2-naphthaldehyde (3.1 g, 20 mmol, 1.0 equiv), $NaBH_4$ (0.45 g, 12 mmol, 0.60 equiv), and MeOH (35 mL, 0.57 M). The crude alcohol (**S3**) was of sufficient purity for use directly in the next step according to General Procedure B using **S3** (3.2 g, 20 mmol, 1.0 equiv), triethylamine (3.9 mL, 28 mmol, 1.4 equiv), DMAP (0.24 g, 2.0 mmol, 0.10 equiv), trimethylacetyl chloride (3.2 mL, 26 mmol, 1.3 equiv), and dichloromethane (30 mL, 0.67 M) to afford 3.96 g (82% yield over 2 steps) of the desired product as a pale yellow liquid which solidified over time to an off-white solid. ^{1}**H NMR** (400 MHz, $CDCl_3$, 298 K) δ_H 7.91–7.75 (m, 4H), 7.52–7.43 (m, 3H), 5.28 (d, *J* = 1.7 Hz, 2H), 1.25 (s, 9H); ^{13}**C NMR** (101 MHz, $CDCl_3$, 298 K) δ_C 178.5, 134.0, 133.3, 133.2, 128.5, 128.1, 127.8, 127.0, 126.4, 126.3, 125.7, 66.4, 39.0, 27.4. The spectral data for this compound matches that reported in the literature.[31]

6-Methoxynaphthalen-2-yl)methyl pivalate (1d) was prepared according to General Procedure A using 6-methoxy-2-naphthaldehyde (1.9 g, 10 mmol, 1.0 equiv), $NaBH_4$ (0.24 g, 6.3 mmol, 0.63 equiv), and MeOH (30 mL, 0.33 M). The crude alcohol (**S4**) was of sufficient purity for use directly in the next step according according to General Procedure B using **S4** (1.1 g, 5.6 mmol, 1.0 equiv), triethylamine (0.94 mL, 6.7 mmol, 1.4 equiv), DMAP (0.068 g, 0.56 mmol, 0.10 equiv), trimethylacetyl chloride (0.83 mL, 6.7 mmol, 1.3 equiv), and dichloromethane (10 mL, 0.67 M). The crude ester was purified by column chromatography on silica gel (slow gradient 2–10 % EtOAc in hexanes) to afford 0.86 g (56% yield over two steps) of the desired product as a white solid. ^{1}**H NMR** (400 MHz, $CDCl_3$, 298 K) δ_H 7.76–7.69 (m, 3H), 7.41 (dd, *J* = 8.5, 1.6 Hz, 1H), 7.19–7.12 (m, 2H), 5.23 (s, 2H), 3.93 (s, 3H), 1.24 (s, 9H); ^{13}**C NMR** (101 MHz, $CDCl_3$, 298 K) δ_C 178.6, 158.1, 134.4, 131.7, 129.6, 128.8, 127.3, 127.1, 126.5, 119.2, 105.9, 66.5, 55.5, 40.0, 27.4; **IR** (neat): 2978, 2937, 1717, 1634, 1607, 1438, 1288, 1223, 1159, 1028, 858 cm^{-1}; **m.p.:** 58–60 °C; **HRMS**

(DART-TOF+) *m/z*: $[M+NH_4]^+$ calcd for $C_{17}H_{24}NO_3$ 290.1756; found 290.1757.

6-Hydroxy-2-naphthaldehyde (S5) was prepared from 6-bromo-2-naphthol (0.50 g, 2.2 mmol, 1.0 equiv) was dissolved in anhydrous THF (27 mL, 0.08 M) and the solution was cooled to -78 °C before *n*-butyl lithium (6.2 mL, 9.9 mmol, 4.5 equiv, 1.6 M in hexanes) was added slowly. After 5 hours of stirring at -78 °C, anhydrous dimethylformamide (1.27 mL, 16.4 mmol, 7.5 equiv) was added slowly and stirring was continued for an additional 45 min. The reaction mixture was then poured into HCl/ice (pH < 1) under vigorous stirring and left to warm to room temperature overnight. The crude reaction mixture was extracted with CH_2Cl_2 (x3), and the organic layers were combined, washed with H_2O, dried with $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (30% EtOAc in hexanes) to afford 0.30 g (78% yield) of the desired aldehyde (**S5**) as a brown solid. ^{1}**H NMR** (400 MHz, DMSO-d_6, 298 K) δ = 10.34 (s, 1H), 10.05 (s, 1H), 8.44 (dd, *J* = 1.6, 0.7 Hz, 1H), 8.02 (dt, *J* = 8.5, 0.8 Hz, 1H), 7.83 (dd, *J* = 8.6, 1.6 Hz, 1H), 7.79 (dd, *J* = 8.6, 1.6 Hz, 1H), 7.25-7.21 (m, 2H) ppm. ^{13}**C NMR** (101 MHz. DMSO-d_6, 298 K) δ = 192.4, 158.4, 138.1, 134.7, 131.6, 131.3, 127.0, 126.6, 122.7, 119.8, 109.2 ppm. The spectral data for this compound matches that reported in the literature.[32]

6-((Pivaloyloxy)methyl)naphthalen-2-yl pivalate (1e) was prepared according to General Procedure A using **S5** (0.25 g, 1.5 mmol, 1.0 equiv), $NaBH_4$ (0.03 g, 0.75 mmol, 0.50 equiv), and MeOH (2.0 mL, 0.38 M). The crude alcohol (**S6**) was of sufficient purity for use directly in the next step according to General Procedure B, using **S6** (0.20 g, 1.1 mmol, 1.0 equiv), triethylamine (0.37 mL, 2.6 mmol, 2.4 equiv), DMAP (0.03 g, 0.20 mmol, 0.18 equiv), trimethylacetyl chloride (0.33 mL, 2.6 mmol, 2.4 equiv), and dichloromethane (2.0 mL, 0.55 M). The crude ester was purified by column chromatography on silica gel (20% EtOAc in hexanes) to afford 0.27 g (72% yield) of the desired product as a white solid. ^{1}**H NMR** (400 MHz, DMSO-d_6, 298 K) δ = 8.02-7.93 (m, 3H), 7.66 (d, *J* = 2.3 Hz, 1H), 7.51 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.29 (dd, *J* = 8.8, 2.4 Hz, 1H), 5.27 (s, 2H), 1.37 (s, 9H), 1.21 (s, 9H) ppm. ^{13}**C NMR** (101 MHz. DMSO-d_6, 298 K) δ = 177.2, 176.5, 148.6, 133.9, 132.9, 130.6, 129.3, 127.8, 126.3, 121.9, 118.3, 65.4, 38.6, 38.3, 26.9, 26.8 ppm.; **IR** (neat): 2975, 2934, 2873, 1449, 1727, 1611, 1478, 1278, 1142, 1123, 1106, 904 cm^{-1}; **m.p.:** 56–58 °C; **HRMS** (DART-TOF+) *m/z*: $[M+H]^+$ calcd for $C_{21}H_{29}O_4$ 342.1831; found 342.1839.

Naphthalen-1-ylmethyl pivalate (1f) was prepared according to General Procedure A, using 1-naphthaldehyde (2.3 g, 15 mmol, 1.0 equiv), $NaBH_4$ (0.67 g, 18 mmol, 1.2 equiv), and MeOH (25 mL, 0.72 M). The crude alcohol (**S7**) was of sufficient purity for use directly in the next step according to General Procedure B using **S7** (1.2 g, 7.9 mmol, 1.0 equiv), triethylamine (1.3 mL, 9.4 mmol, 1.2 equiv), DMAP (0.01 g, 0.8 mmol, 0.1 equiv), trimethylacetyl chloride (1.2 mL, 9.4 mmol, 1.2 equiv), and dichloromethane (12 mL, 0.66 M). The crude ester was isolated by column chromatography on silica gel (slow gradient of 0–10% EtOAc in hexanes) to afford 1.1 g (57% yield over two steps) of the desired product as a clear oil. ^{1}**H NMR** (400 MHz, $CDCl_3$, 298 K) δ_H 8.01 (ddd *J* = 8.4, 1.1, 1.1 Hz, 1H), 7.96–7.80 (m, 2H), 7.60–7.48 (m, 3H), 7.46 (dd, *J* = 8.2, 7.0 Hz, 1H), 5.57 (s, 2H), 1.23 (s, 9H); ^{13}**C NMR** (101 MHz, $CDCl_3$, 298 K) δ_C 178.4, 133.7, 131.9, 131.6, 129.1, 128.7, 127.0, 126.4, 125.9, 125.3, 123.6, 64.7, 39.0, 27.2. The spectral data for this compound matches that reported in the literature.[33]

1-(Benzofuran-2-yl)ethan-1-one (S8) was prepared by heating a mixture of KOH (1.1 g, 20 mmol, 1.0 equiv) and salicylaldehyde (2.1 mL, 20 mmol, 1.0 equiv) in MeOH (50 mL, 0.4 M) at reflux for 30 min, before cooling to 0 °C. Chloroacetone (2.0 mL, 24 mmol, 1.2 equiv) was then added dropwise at the same temperature and the reaction mixture was then heated at reflux once again. When the reaction was judged to have reached completion (as determined by TLC), the mixture was concentrated under reduced pressure, dissolved in dichloromethane, and washed with brine. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was recrystallized from ethanol twice to afford 0.96 g (30% yield) of the desired product as a yellow solid. ^{1}**H NMR** (400 MHz, $CDCl_3$, 298 K) δ_H 7.71 (ddd, *J* = 7.9, 1.3, 0.8 Hz, 1H), 7.63–7.56 (m, 1H), 7.53–7.45 (m, 2H), 7.32 (ddd, *J* = 8.0, 7.1, 1.0 Hz, 1H), 2.62 (s, 3H); ^{13}**C NMR** (101 MHz, $CDCl_3$, 298 K) δ_C 188.7, 155.7, 152.7, 128.3, 127.1, 123.9, 123.3, 113.1, 112.5, 26.5. This compound is commercially available (CAS = 1646-26-0, Sigma–Aldrich cat. no. = 154377)

1-(Benzofuran-2-yl)ethyl pivalate (1h) was prepared according to General Procedure A, using ketone **S8** (0.96 g, 5.9 mmol, 1.0 equiv), $NaBH_4$ (0.14 g, 3.6 mmol, 0.60 equiv), and methanol (10 mL, 0.59 M). The crude alcohol (**S9**) was of sufficient purity for use directly in the next step according to General Procedure B using **S9** (0.83 g, 5.1 mmol, 1.0 equiv), triethylamine (1.0 mL, 7.1 mmol, 1.4 equiv), DMAP (0.06 g, 0.51 mmol, 0.10 equiv), trimethylacetyl chloride (0.82 mL, 6.7 mmol, 1.3 equiv), and dichloromethane (10 mL, 0.51 M). The crude ester was purified by column chromatography on silica gel (slow gradient of 0%–15% EtOAc in hexanes) to afford 0.462 g (32% over 2 steps) of the desired product as a clear oil. ^{1}**H NMR** (400 MHz, $CDCl_3$, 298 K) δ_H 7.55 (ddd, *J* = 7.6, 1.4, 0.7 Hz, 1H), 7.47 (ddd, *J* = 8.2, 1.0, 1.0 Hz, 1H), 7.34–7.18 (m, 2H), 6.65 (dd, *J* = 0.8, 0.8 Hz, 1H), 6.06 (qd, *J* = 6.7, 0.8 Hz, 1H), 1.65 (d, *J* = 6.7 Hz, 3H), 1.22 (s, 9H); ^{13}**C NMR** (101 MHz, $CDCl_3$, 298 K) δ_C 177.7, 156.7, 155.0, 128.1, 124.5, 122.9, 121.3, 111.5, 103.8, 65.5, 39.0, 27.2, 18.6; **IR** (neat): 2973, 2935, 2873, 1716, 1455, 1152, 1142, 756 cm^{-1}; **HRMS** (DART-TOF+) *m/z*: $[M+NH_4]^+$ calcd for $C_{15}H_{22}NO_3$ 264.1600; found 264.1604.

Thiophen-2-ylmethyl pivalate (1i) was prepared according to General Procedure A, using thiophene-2-carboxaldehyde (1.7 g, 15 mmol, 1.0 equiv), $NaBH_4$ (0.02 g, 9.0 mmol, 0.60 equiv), and MeOH (15 mL, 0.60 M). The crude alcohol (**S10**) was of sufficient purity for use directly in the next step according to General Procedure B using **S10** (0.85 g, 7.5 mmol, 1.0 equiv), triethylamine (1.3 mL, 8.9 mmol, 1.2 equiv), DMAP (0.09 g, 0.75 mmol, 0.10 equiv), trimethylacetyl chloride (1.1 mL, 8.9 mmol, 1.2 equiv), and dichloromethane (12 mL, 0.63 M). The crude ester was purified by column chromatography on silica gel (slow gradient of 5–15% EtOAc in hexanes) to afford 0.85 g (70% yield) of the desired product as a yellow oil. ^{1}**H NMR** (400 MHz, $CDCl_3$, 298 K) δ_H 7.30 (dd, *J* = 5.1, 1.3 Hz, 1H), 7.06 (ddd, *J* = 3.6, 1.3, 0.7 Hz, 1H), 6.98 (dd, *J* = 5.1, 3.5 Hz, 1H), 5.26 (d, *J* = 0.8 Hz, 2H), 1.21 (s, 9H); ^{13}**C NMR** (101 MHz, $CDCl_3$, 298 K) δ_C 178.3, 138.7, 127.5, 126.8, 126.5, 60.8, 38.9, 27.2; **IR** (neat): 2972, 2908, 2873, 1727, 1441, 1279, 1134, 700 cm^{-1}; **HRMS** (DART-TOF+) *m/z*: $[M+NH_4]^+$ calcd for $C_{10}H_{18}NO_2S$ 216.1058; found 216.1062.

(*E*)-4-Phenylbut-3-en-2-yl pivalate (7a) was prepared according to General Procedure A using 4-phenyl-3-buten-2-one (7.3 g, 50 mmol, 1.0 equiv), $NaBH_4$ (1.1 g, 30 mmol, 0.6 equiv), and MeOH (75 mL, 0.67 M). The crude alcohol (**S11**) was of sufficient purity for use directly in the next step according to General Procedure B using **S11** (3.0 g, 20 mmol, 1.0 equiv), triethylamine (3.9 mL, 28 mmol, 1.4 equiv), DMAP (0.24 g, 2.0 mmol,

0.1 equiv), trimethylacetyl chloride (3.2 mL, 26 mmol, 1.3 equiv), and dichloromethane (50 mL, 0.4 M). The crude ester was purified by column chromatography on silica gel (slow gradient of 0–10 % EtOAc in hexanes) to afford 2.9 g (63% yield) of the desired product as a clear oil which solidifies over time to a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K) δ_H 7.45–7.36 (m, 2H), 7.35–7.29 (m, 2H), 7.28–7.22 (m, 1H), 6.59 (dd, *J* = 16.0, 1.1 Hz, 1H), 6.19 (dd, *J* = 16.0, 6.4 Hz, 1H), 5.51 (qdd, *J* = 6.5, 6.5, 1.3 Hz, 1H), 1.39 (d, *J* = 6.5 Hz, 3H), 1.22 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ_C 177.7, 136.5, 131.0, 129.1, 128.5, 127.8, 126.5, 70.5, 38.8, 27.1, 20.3; **IR** (neat) 2975, 2936, 2911, 2873, 1709, 1479, 1162, 1148, 753 cm^{-1}. The spectral data for this compound matches that reported in the literature.[28a]

(*E*)-1-Phenylbut-2-en-1-yl pivalate (7a') was prepared according to General Procedure C, using crotonaldehyde (predominantly trans, 0.83 mL, 10 mmol, 1.0 equiv), PhMgBr (1.0 M solution in THF, 12 mL, 12 mmol, 1.2 equiv), and THF (12 mL, 0.83 M). The crude alcohol (**S12**) was purified via column chromatography (slow gradient of 5–15% EtOAc in Hexanes) to afford 1.2 g (82% yield) of the desired product as a clear oil, which was used directly in the next step according to General Procedure B, using **S12** (1.22 g, 8.2 mmol, 1.0 equiv)), triethylamine (1.6 mL, 12 mmol, 1.4 equiv), DMAP (0.10 g, 0.82 mmol, 0.1 equiv), trimethylacetyl chloride (1.3 mL, 11 mmol, 1.3 equiv), and dichloromethane (12 mL, 0.68 M). The crude ester was purified by column chromatography (slow gradient of 0-10% EtOAc in Hexanes) to afford 1.6 g (82% yield) of the desired product as a as a clear oil (95:5 E/Z). **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K) δ_H 7.44–7.30 (m, 5H), 6.27–6.19 (m, 1H), 5.85–5.72 (m, 1H), 5.66 (ddq, *J* = 15.3, 6.7, 1.3 Hz, 1H), 1.78–1.71 (m, 3H), 1.26 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ_C 177.4, 140.2, 129.9, 129.0, 128.4, 127.7, 126.6, 75.9, 38.9, 27.2, 17.8; **IR** (neat) 2973, 2936, 2873, 1727, 1479, 1277, 1144, 962, 696 cm^{-1}. The spectral data for this compound matches that reported in the literature.[28a]

(*E*)-1-Phenylpent-1-en-3-yl pivalate (7b) was prepared according to General Procedure A, using cinnamaldehyde (1.3 mL, 10 mmol, 1.0 equiv), EtMgBr (1.7 M solution in diethyl ether, 8.8 mL, 15 mmol, 1.5 equiv), and THF (20 mL, 0.50 M). The crude alcohol (**S13**) was of sufficient purity for use directly in the next step according to General Procedure B using **S13** (1.1 g, 6.7 mmol, 1.0 equiv), triethylamine (1.3 mL, 9.4 mmol, 1.4 equiv), DMAP (0.08g, 0.67 mmol, 0.10 equiv), trimethylacetyl chloride (1.1 mL, 8.7 mmol, 1.3 equiv), and dichloromethane (12 mL, 0.56 M). The crude ester was purified by column chromatography on silica gel (slow gradient of 0-10% EtOAc in hexanes) to afford 0.98 g (59 % yield over 2 steps) of the desired product as a clear oil. **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K) δ_H 7.45–7.40 (m, 2H), 7.39–7.31 (m, 2H), 7.31–7.24 (m, 1H), 6.68–6.57 (m, 1H), 6.16 (dd, *J* = 16.0, 6.9 Hz, 1H), 5.37 (dt, *J* = 8.0, 6.3 Hz, 1H), 1.87–1.67 (m, 2H), 1.26 (s, 9H), 0.98 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ_C 177.8, 136.6, 131.9, 128.5, 127.9, 127.8, 126.5, 75.4, 38.9, 27.7, 27.2, 9.5; **IR** (neat) 2971, 2936, 2876, 1724, 1495, 1279, 1153, 936, 745, 691 cm^{-1}; **HRMS** (DART-TOF+) *m/z*: $[M]^+$ calcd for $C_{16}H_{22}O_2$ 246.1620; found 246.1630.

Cinnamyl pivalate (7c) was prepared according to General Procedure B, using cinnamyl alcohol (2.0 g, 15 mmol, 1.0 equiv), triethylamine (2.9 mL, 21 mmol, 1.4 equiv), DMAP (0.18 g, 1.5 mmol, 0.1 equiv), trimethylacetyl chloride (2.4 mL, 20 mmol, 1.3 equiv), and dichloromethane (30 mL, 0.5 M). The crude ester was purified by column chromatography on silica gel (slow gradient of 0-5% EtOAc in hexanes) to afford 1.8 g (54 % yield) of the desired product as a clear oil. **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K) δ_H 7.42–7.38 (m, 2H), 7.35–7.30 (m, 2H), 7.27 (d, *J* = 6.7 Hz, 1H), 6.70–6.60 (m, 1H), 6.29 (dt, *J* = 16.0, 6.3 Hz, 1H), 4.73 (dd, *J* = 6.3, 1.4 Hz, 2H), 1.24 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ_C 178.5, 136.5, 133.7, 128.7, 128.1, 126.7, 123.8, 65.1, 39.0, 27.4. The spectral data for this compound matches that reported in the literature.[34]

1-Phenylallyl pivalate (7c') was prepared according to General Procedure C, using benzaldehyde (1.0 mL, 10 mmol, 1.0 equiv), vinylmagnesium bromide (1.0 M solution in THF, 12 mL, 12 mmol, 1.2 equiv), and THF (10 mL, 1.0 M). The crude alcohol (**S14**) was used directly in the next step according to General Procedure B, using **S14** (1.2 g, 8.6 mmol, 1.0 equiv), triethylamine (1.7 mL, 12 mmol, 1.4 equiv), DMAP (0.11 g, 0.86 mmol, 0.1 equiv), trimethylacetyl chloride (1.4 mL, 11 mmol, 1.3 equiv), and dichloromethane (15 mL, 0.57M). The crude ester was purified by column chromatography on silica gel (slow gradient of 0-10% EtOAc in hexanes) to afford 0.83 g (38 % yield over 2 steps) of the desired product as a clear oil. **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K) δ_H 7.40–7.27 (m, 5H), 6.23 (ddd, *J* = 5.8, 1.4, 1.4 Hz, 1H), 5.99 (ddd, *J* = 17.1, 10.4, 5.8 Hz, 1H), 5.30 (ddd, *J* = 17.1, 1.4, 1.4 Hz, 1H), 5.23 (ddd, *J* = 10.4, 1.3, 1.3 Hz, 1H), 1.24 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ_C 177.4, 139.4, 136.7, 128.6, 128.1, 127.0, 116.6, 75.9, 39.0, 27.3. The spectral data for this compound matches that reported in the literature.[35]

1-(4-(*tert*-Butyl)phenyl)allyl pivalate (7d') was prepared according to General Procedure C, using 4-(tert-butyl)benzaldehyde (1.5 mL, 9.0 mmol, 1.0 equiv), vinylmagnesium bromide (1.0 M solution in THF, 10 mL, 10 mmol, 1.1 equiv), and THF (10 mL, 0.9 M). The crude alcohol (**S15**) was of sufficient purity for use directly in the next step according to General Procedure B, using **S15** (0.86 g, 4.5 mmol, 1.0 equiv), triethylamine (0.88 mL, 6.3 mmol, 1.4 equiv), DMAP (0.06 g, 0.45 mmol, 0.10 equiv), trimethylacetyl chloride (0.75 mL, 5.9 mmol, 1.3 equiv), and dichloromethane (8.0 mL, 0.56 M). The crude ester was purified by column chromatography on silica gel (slow gradient of 0-10% EtOAc in hexanes) to afford 0.86 g (35 % yield over 2 steps) of the desired product as a clear oil. **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K) δ_H 7.39–7.34 (m, 2H), 7.29–7.25 (m, 2H), 6.21 (dd, *J* = 5.9, 1.4 Hz, 1H), 5.98 (ddd, *J* = 17.2, 10.5, 5.9 Hz, 1H), 5.30 (ddd, *J* = 17.1, 1.4, 1.4 Hz, 1H), 5.21 (ddd, *J* = 10.4, 1.4, 1.4 Hz, 1H), 1.31 (s, 9H), 1.24 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ_C 177.3, 150.8, 136.7, 136.2, 126.4, 125.4, 116.2, 75.6, 38.9, 34.5, 31.3, 27.1; IR (neat) 2964, 2906, 2871, 1729, 1479, 1276, 1146, 931 cm^{-1}; **HRMS** (DART-TOF+) *m/z*: $[M+NH_4]^+$ calcd for $C_{18}H_{30}NO_2$ 292.2277; found 292.2279.

1-(4-Isopropylphenyl)allyl pivalate (7e') was prepared according to General Procedure D, using cuminaldehyde (0.76 mL, 5.0 mmol, 1.0 equiv), vinylmagnesium bromide (1.0 M solution in THF, 5.5 mL, 5.5 mmol, 1.1 equiv), THF (8.0 mL, 0.63 M), and trimethylacetyl chloride (0.92 mL, 7.5 mmol, 1.5 equiv). The crude ester was purified by column chromatography on silica gel (slow gradient of 0–10% EtOAc in hexanes) to afford 0.45 g (35% yield) of the desired product as a slightly yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K) δ_H 7.29–7.24 (m, 2H), 7.24–7.17 (m, 2H), 6.21 (ddd, *J* = 5.9, 1.4, 1.4 Hz, 1H), 5.98 (ddd, *J* = 17.2, 10.4, 5.8 Hz, 1H), 5.29 (ddd, *J* = 17.1, 1.4, 1.4 Hz, 1H), 5.21 (ddd, *J* = 10.4, 1.4, 1.4 Hz, 1H), 2.90 (hept, *J* = 6.9 Hz, 1H), 1.26 – 1.22 (m, 15H); **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ_C 177.5, 148.7, 136.9, 136.8, 126.9, 126.7, 116.4, 75.8, 39.03, 34.0, 27.3, 24.1, 24.1; **IR** (neat) 2961, 2932, 2872, 1729, 1277, 1144, 825 cm^{-1}; **HRMS** (DART-TOF+) *m/z*: $[M+NH_4]^+$ calcd for $C_{17}H_{28}NO_2$ 278.2120; found 278.2118.

1-(4-Methoxyphenyl)allyl pivalate (7f') was prepared according to General Procedure C, using p-anisaldehyde (1.1 mL, 9.0 mmol, 1.0 equiv), vinylmagnesium bromide (1.0 M solution in THF, 12 mL, 12 mmol, 1.2 equiv), and THF (10 mL, 0.90 M). The crude alcohol (**S16**) was of sufficient purity for use directly in the next step according to General Procedure B, using **S16** (1.5 g, 9.0 mmol, 1.0 equiv), triethylamine (1.8 mL, 13 mmol, 1.4 equiv), DMAP (0.11 g, 0.90 mmol, 0.10 equiv), trimethylacetyl chloride (1.4 mL, 12 mmol, 1.3 equiv), and dichloromethane (12 mL, 0.75 M). The crude ester was purified by column chromatography on silica gel (slow gradient of 2-15% EtOAc in hexanes) to afford 0.88 g (39 % yield over 2 steps) of the desired product as a clear oil. **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K) δ_H 7.27 (d, *J* = 8.5 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 6.19 (ddd, *J* = 5.6, 1.5, 1.5 Hz, 1H), 5.98 (ddd, *J* = 17.2, 10.5, 5.5 Hz, 1H), 5.27 (ddd, *J* = 17.1, 1.5, 1.5 Hz, 1H), 5.21 (ddd, *J* = 10.5, 1.4, 1.4 Hz, 1H), 3.80 (s, 3H), 1.21 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ_C 177.5, 159.5, 136.9, 131.6, 128.5, 116.2, 114.0, 75.6, 55.4, 39.0, 27.3; **IR** (neat) 2972, 2935, 2908, 2873, 2838, 1726, 1612, 1513, 1246, 1144, 1032, 927, 828 cm^{-1}; **HRMS** (DART-TOF+) *m/z*: $[M]^+$ calcd for $C_{15}H_{20}O_3$ 248.1412; found 248.1409.

4-(1-(Pivaloyloxy)allyl)phenyl pivalate (7g') was prepared according to General Procedure D, using 4-hydroxybenzaldehyde (0.61 g, 5.0 mmol, 1.0 equiv), vinylmagnesium bromide (1.0 M solution in THF, 11 mL, 11 mmol, 2.2 equiv), THF (10 mL, 0.5 M), and trimethylacetyl chloride (1.8 mL, 15 mmol, 3.0 equiv). The crude ester was purified by column chromatography on silica gel (4–12 % EtOAc in hexanes) to afford 0.31 g (20% yield) of the desired product as a clear oil. **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K) δ_H 7.35 (d, *J* = 7.6 Hz, 2H), 7.12–7.02 (m, 2H), 6.23 (ddd, *J* = 5.7, 1.5, 1.5 Hz, 1H), 5.97 (ddd, *J* = 17.2, 10.5, 5.7 Hz, 1H), 5.29 (ddd, *J* = 17.2, 1.4, 1.4 Hz, 1H), 5.23 (ddd, *J* = 10.5, 1.3, 1.3 Hz, 1H), 1.35 (s, 9H), 1.22 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ_C 177.3, 177.1, 150.9, 136.7, 136.5, 128.2, 121.7, 116.8, 75.3, 39.2, 39.0, 27.3, 27.3; **IR** (neat) 2973, 2936, 2908, 2873, 1745, 1722, 1278, 1145, 1121, 943, 899 cm^{-1}; **HRMS** (DART-TOF+) *m/z*: $[M+NH_4]^+$ calcd for $C_{19}H_{30}NO_4$ 336.2175; found 336.2184.

1-(Benzo[*d*][1,3]dioxol-5-yl)allyl pivalate (7h') was prepared according to General Procedure D, using piperonal (0.90 g, 6.0 mmol, 1.0 equiv), vinylmagnesium bromide (1.0 M solution in THF, 6.6 mL, 6.6 mmol, 1.1 equiv), THF (6.0 mL, 1.0 M), and trimethylacetyl chloride (1.1 mL, 9.0 mmol, 1.5 equiv). The crude ester was purified by successive rounds of column chromatography on silica gel (0–12 % EtOAc in hexanes) to afford 0.12 g (7 % yield) of the desired product as a clear oil. **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K) δ_H 6.87–6.72 (m, 3H), 6.13 (ddd, *J* = 5.5, 1.5, 1.5 Hz, 1H), 6.02–5.89 (m, 3H), 5.27 (ddd, *J* = 17.1, 1.4, 1.4 Hz, 1H), 5.21 (ddd, *J* = 10.5, 1.4, 1.4 Hz, 1H), 1.22 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ_C 177.4, 147.9, 147.5, 136.7, 133.3, 120.8, 116.4, 108.3, 107.6, 101.3, 75.7, 39.0, 27.3; **IR** (neat) 2974, 2935, 2906, 2875, 1726, 1488, 1443, 1238, 1145, 1036, 932, 806 cm^{-1}; **HRMS** (DART-TOF+) *m/z*: $[M]^+$ calcd for $C_{15}H_{18}O_4$ 262.1205; found 262.1208

1-(4-Fluorophenyl)allyl pivalate (7i') was prepared according to General Procedure D, using 4-fluorobenzaldehyde (0.54 mL, 5.0 mmol, 1.0 equiv), vinylmagnesium bromide (1.0 M solution in THF, 5.5 mL, 5.5 mmol, 1.1 equiv), THF (8.0 mL, 0.63 M), and trimethylacetyl chloride (0.92 mL, 7.5 mmol, 1.5 equiv). The crude ester was purified by column chromatography on silica gel (0–10 % EtOAc in hexanes) to afford 0.64 g (54% yield) of the desired product as a slight yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K) δ_H 7.36–7.28 (m, 2H), 7.09–6.99 (m, 2H), 6.20 (ddd, *J* = 5.7, 1.5, 1.5 Hz, 1H), 5.97 (ddd, *J* = 17.1, 10.5, 5.6 Hz, 1H), 5.28 (ddd, *J* = 17.2, 1.4, 1.4 Hz, 1H), 5.23 (ddd, *J* = 10.5, 1.3, 1.3 Hz, 1H), 1.22 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ_C 177.4, 162.6 (d, J = 246.5), 136.5, 135.2 (d, J = 3.3), 128.9 (d, J = 8.3), 116.2 (d, J = 112.6), 115,4, 75.2, 39.0, 27.2; **IR** (neat) 2974, 2937, 2874, 1729, 1604, 1509, 1142, 832 cm^{-1}; **HRMS** (DART-TOF+) *m/z*: $[M+NH_4]^+$ calcd for $C_{14}H_{21}FNO_2$ 254.1556; found 254.1554.

1-(4-Chlorophenyl)allyl pivalate (7j') was prepared according to General Procedure D, using 4-chlorobenzaldehyde (0.70 g, 5.0 mmol, 1.0 equiv), vinylmagnesium bromide (1.0 M solution in THF, 5.5 mL, 5.5 mmol, 1.1 equiv), THF (8.0 mL, 0.63 M), and trimethylacetyl chloride (0.92 mL, 7.5 mmol, 1.5 equiv). The crude ester was purified by column chromatography on silica gel (0–4 % EtOAc in hexanes) to afford 0.94 g (74% yield) of the desired product as a pale yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K) δ_H 7.37–7.25 (m, 4H), 6.19 (ddd, *J* = 5.7, 1.5, 1.5 Hz, 1H), 5.95 (ddd, *J* = 17.1, 10.5, 5.7 Hz, 1H), 5.29 (ddd, *J* = 17.1, 1.4, 1.4 Hz, 1H), 5.24 (ddd, *J* = 10.5, 1.3, 1.3 Hz, 1H), 1.22 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ_C 177.3, 138.0, 136.3, 134.0, 128.9, 128.5, 117.1, 75.2, 39.0, 27.2; **IR** (neat) 2974, 2935, 2908, 2873, 1729, 1491, 1497, 1276, 1142, 1098, 820 cm^{-1}; **HRMS** (DART-TOF+) *m/z*: $[M+NH_4]^+$ calcd for $C_{14}H_{21}ClNO_2$ 270.1261; found 270.1369.

General Procedures for the Synthesis of Benzylic and Allylic Nitriles. *General Procedure E: Synthesis of benzylic nitriles from solid benzyl pivalates*. To a flame dried 8-mL thick-walled reaction tube was added α-arylpivalate (0.20 mmol, 1.0 equiv), $NiCl_2$dppf (0.014 g, 0.020 mmol, 0.10 equiv), K_3PO_4 (0.013 g, 0.060 mmol, 0.30 equiv) *or* $Zn(CO_3)_2(OH)_6$ (0.017 g, 0.030 mmol, 0.15 equiv) and $Zn(CN)_2$ (0.013 g, 0.11 mmol, 0.55 equiv) under an atmosphere of Ar (balloon). The tube was capped with a rubber septum and sealed with electrical tape before being evacuated and backfilled with nitrogen 3 times. Then 2.0 mL of freshly degassed DMF[36] was added and the mixture was stirred for 1 minute before diethylzinc (1M in hexanes, 0.03 mL, 0.03 mmol, 0.15 equiv) was added to the solution at room temperature. The test tube was immediately submerged in a pre-heated oil bath at 110 °C. The reaction was left to stir overnight (16 hours) before being quenched with EtOAc and passed through a short plug of silica and celite. A small aliquot was taken for GC-MS analysis before the crude material was purified by silica gel column chromatography.

General Procedure F: Synthesis of benzylic nitriles from liquid benzyl pivalates. To a flame dried 8-mL thick walled reaction tube was added $NiCl_2$dppf (0.014 g, 0.020 mmol, 0.10 equiv), K_3PO_4 (0.013 g, 0.060 mmol, 0.30 equiv) *or* $Zn(CO_3)_2(OH)_6$ (0.017 g, 0.030 mmol, 0.15 equiv) and $Zn(CN)_2$ (0.013 g, 0.11 mmol, 0.55 equiv) under an atmosphere of Ar (balloon). The tube was capped with a rubber septum and sealed with electrical tape before being evacuated and backfilled with nitrogen 3 times. The benzyl pivalate was weighe

d out in a separate flame dried flask. The flask was evacuated and backfilled with nitrogen 3 times, and the benzyl pivalate was then transferred into the flask containing the solids using 2.0 mL of freshly degassed DMF. The mixture was then stirred for 1 minute before diethylzinc (1M in hexanes, 0.03 mL, 0.03 mmol, 0.15 equiv) was added to the solution at room temperature. The test tube was immediately submerged in a pre-heated oil bath at 110 °C. The reaction was left to stir overnight (16 hours) before being quenched with EtOAc and passed through a short plug of silica and celite. A small aliquot was taken for GC-MS analysis before the crude material was purified by silica gel column chromatography.

General Procedure G: Synthesis of allylic nitriles from solid allylic pivalates. To a flame dried 8-mL thick-walled reaction tube was added allylic pivalate (0.20 mmol, 1.0 equiv), $NiCl_2$DME (0.0044 g, 0.020 mmol, 0.10 equiv), dppb (0.017 g, 0.040 mmol, 0.20 equiv), K_3PO_4 (0.013 g, 0.060 mmol, 0.30 equiv), and $Zn(CN)_2$ (0.019 g, 0.16 mmol, 0.80 equiv) under an atmosphere of Ar (balloon). The tube was capped with a rubber septum and sealed with electrical tape before being evacuated and backfilled with nitrogen 3 times. Then 2.0 mL of freshly degassed DMF was added and the mixture was stirred for 1 minute before diethylzinc (1M in hexanes, 0.03 mL, 0.03 mmol, 0.15 equiv) was added to the solution at room temperature and the test tube was submerged in an oil bath at 23 °C. The reaction was left to stir overnight before being quenched with EtOAc and passed through a short plug of silica and celite. A small aliquot was taken for GC-MS analysis before the crude material was purified by silica gel column chromatography.

General Procedure H: Synthesis of allylic nitriles from liquid allylic pivalates. To a flame dried 8-mL thick-walled reaction tube was added $NiCl_2$DME (0.0044 g, 0.020 mmol, 0.10 equiv), dppb (0.017 g, 0.040 mmol, 0.20 equiv), K_3PO_4 (0.013 g, 0.060 mmol, 0.30 equiv), and $Zn(CN)_2$ (0.019 g, 0.16 mmol, 0.80 equiv) under an atmosphere of Ar (balloon). The tube was capped with a rubber septum and sealed with electrical tape before being evacuated and backfilled with nitrogen 3 times. In a separate flame dried flask, the allylic pivalate (0.20 mmol, 1.0 equiv) was weighed out and the flask was evacuated and backfilled with nitrogen 3 times. The allylic pivalate was transferred into the vessel containing the solids using 2.0 mL of freshly degassed DMF. The mixture was then stirred for 1 minute before diethylzinc (1M in hexanes, 0.03 mL, 0.03 mmol, 0.15 equiv) was added to the solution at room temperature and the test tube was submerged in an oil bath at 23 °C. The reaction was left to stir overnight before being quenched with EtOAc and passed through a short plug of silica and celite. A small aliquot was taken for GC-MS analysis before the crude material was purified by silica gel column chromatography.

2-(Naphthalen-2-yl)propanenitrile (2a) was prepared according to General Procedure E, using **1a** (0.051 g, 0.20 mmol, 1.0 equiv), and K_3PO_4 (0.013 g, 0.060 mmol, 0.30 equiv). The crude nitrile was purified by column chromatography on silica gel (slow gradient of 0–10% EtOAc in hexanes) to afford the desired product as a white solid. Trial 1: 34 mg isolated (94% yield); Trial 2: 31 mg isolated (86% yield). **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K) δ_H 7.94–7.79 (m, 4H), 7.58–7.46 (m, 2H), 7.43 (dd, J = 8.5, 1.9 Hz, 1H), 4.07 (q, J = 7.3 Hz, 1H), 1.74 (d, J = 7.3 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ 134.5, 133.5, 132.9, 129.3, 128.0, 127.9, 126.9, 126.6, 125.7, 124.6, 121.7, 31.6, 21.6. The spectral data for this compound matches that reported in the literature.[37]

2-(6-Methoxynaphthalen-2-yl)propanenitrile (2b) was prepared according to General Procedure E, using **1b** (0.057 g, 0.20 mmol, 1.0 equiv) and $Zn(CO_3)_2(OH)_6$ (0.017 g, 0.030 mmol, 0.15 equiv). The crude nitrile was purified by column chromatography on silica gel (slow gradient of 0-12% EtOAc in hexanes) to afford the desired product as a white solid. Trial 1: 33 mg isolated (79% yield); Trial 2: 30 mg isolated (71% yield). **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K) δ_H 7.80–7.71 (m, 3H), 7.39 (dd, J = 8.4, 2.0 Hz, 1H), 7.19 (dd, J = 8.9, 2.5 Hz, 1H), 7.14 (d, J = 2.5 Hz, 1H), 4.03 (q, J = 7.2 Hz, 1H), 3.93 (s, 3H), 1.71 (d, J = 7.3 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ_C 158.2, 134.2, 132.1, 129.5, 128.9, 128.0, 125.5, 125.1, 121.9, 119.7, 105.8, 55.5, 31.4, 21.6. The spectral data for this compound matches that reported in the literature.[38]

2-(Naphthalen-2-yl)acetonitrile (2c) was prepared according to General Procedure E, using **1c** (0.049 g, 0.20 mmol, 1.0 equiv) and K_3PO_4 (0.013 g, 0.060 mmol, 0.30 equiv). The crude nitrile was purified by column chromatography on silica gel (slow gradient of 0–10% EtOAc in hexanes) to afford the desired product as an off-white solid. Trial 1: 28 mg isolated (85% yield); Trial 2: 27 mg isolated (82% yield). **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K) δ_H 7.92–7.80 (m, 4H), 7.58–7.48 (m, 2H), 7.39 (dd, J = 8.5, 1.9 Hz, 1H), 3.92 (s, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ_C 133.5, 132.9, 129.2, 127.9, 127.9, 127.4, 127.0, 126.9, 126.7, 125.6, 118.0 24.0. The spectral data for this compound matches that reported in the literature.[37]

2-(6-Methoxynaphthalen-2-yl)acetonitrile (2d) was prepared according to General Procedure E using **1d** (0.054 g, 0.20 mmol, 1.0 equiv) and K_3PO_4 (0.013 g, 0.060 mmol, 0.30 equiv). The crude nitrile was purified by column chromatography on silica gel (slow gradient of 0–8% EtOAc in hexanes) to afford the desired product as a white solid. Trial 1: 29 mg isolated (74% yield); Trial 2: 30 mg isolated (77% yield). **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K) δ_H 7.80–7.68 (m, 3H), 7.35 (dd, J = 8.4, 2.0 Hz, 1H), 7.19 (dd, J = 8.9, 2.5 Hz, 1H), 7.13 (d, J = 2.5 Hz, 1H), 3.93 (s, 3H), 3.89–3.86 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ_C 158.2, 134.1, 129.3, 128.9, 128.0, 126.8, 126.1, 124.9, 119.8, 118.2, 105.8, 55.5, 23.8. The spectral data for this compound matches that reported in the literature.[38]

6-(Cyanomethyl)naphthalen-2-yl pivalate (2e) was prepared according to General Procedure E using **1e** (0.068 g, 0.20 mmol, 1.0 equiv) and $Zn(CO_3)_2(OH)_6$ (0.017 g, 0.030 mmol, 0.15 equiv). The crude nitrile was purified by column chromatography on silica gel (slow gradient of 2–20% EtOAc in hexanes) to afford the desired product as a white solid. Trial 1: 19 mg isolated (40% yield); Trial 2: 22 mg isolated (42% yield). **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K) δ 7.86–7.80 (m, 3H), 7.54 (d, J = 2.3 Hz, 1H), 7.39 (dd, J = 8.5, 1.9 Hz, 1H), 7.24 (d, J = 2.3 Hz, 1H), 3.92 (s, 2H), 1.41 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ 177.2, 149.3, 133.2, 131.3, 129.1, 128.7, 127.0, 126.8, 126.2, 122.2, 118.4, 117.7, 39.2, 27.2, 23.8 ppm; **IR** (neat) 2975, 2934, 2873, 1749, 1727, 1478, 1142, 1123, 1106, 904 cm^{-1}; **m.p.:** 65–68 °C; **HRMS** (DART-TOF+) *m/z*: $[M+H]^+$ calcd for $C_{17}H_{17}NO_2$ 268.1952; found 268.1956.

2-(Naphthalen-1-yl)acetonitrile (2f) was prepared according to General Procedure F using **1f** (0.048 g, 0.20 mmol, 1.0 equiv) and K_3PO_4 (0.013 g, 0.060 mmol, 0.30 equiv). The crude nitrile was purified by column chromatography on silica gel (10% EtOAc in hexanes) to afford the desired product as a yellow oil. Trial 1: 27 mg isolated (82% yield); Trial 2: 27 mg isolated (82% yield). **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K) δ_H 7.92 (dd, J = 7.9, 1.6 Hz, 1H), 7.89–7.82 (m, 2H), 7.67–7.54 (m, 3H), 7.47 (dd, J = 8.3, 7.1 Hz, 1H), 4.11 (s, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$, 298 K) δ_C 133.8, 130.9, 129.2, 129.1, 127.2, 126.5, 126.5, 125.9, 125.6, 122.5, 117.8, 21.8. The spectral data for this compound matches that reported in the literature.[37]

2-(Benzofuran-2-yl)propanenitrile (2h) was prepared according to General Procedure F using **1h** (0.049 g, 0.20 mmol, 1.0 equiv), $NiCl_2$dppf (0.027 g, 0.040 mmol, 0.20 equiv), $Zn(CO_3)_2(OH)_6$ (0.028 g, 0.050 mmol, 0.25 equiv), $ZnCN_2$ (0.013 g, 0.11 mmol, 0.55 equiv), and $ZnEt_2$ (1M in hexanes, 0.05 mL, 0.05 mmol, 0.25 equiv). The crude nitrile was purified by column chromatography on silica gel (slow gradient of 0–10% EtOAc in hexanes) to afford the desired product as a yellow oil. Trial 1: 20 mg isolated (59% yield); Trial 2: 20 mg isolated (59% yield). **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K) δ_H 7.56 (ddd, J = 7.6, 1.5, 0.7 Hz, 1H), 7.47 (dq, J = 8.3, 0.9 Hz, 1H), 7.35–7.28

(m, 1H), 7.28–7.22 (m, 1H), 6.72 (t, J = 1.0 Hz, 1H), 4.13 (qd, J = 7.2, 1.0 Hz, 1H), 1.78 (d, J = 7.2 Hz, 3H); ^{13}**C NMR** (101 MHz, $CDCl_3$, 298 K) δ_C155.2, 151.8, 127.9, 124.9, 123.4, 121.3, 119.1, 111.4, 104.0, 25.9, 17.7; **IR** (neat) 3029,2985, 2937, 2241, 1496, 1449, 964, 744, 692 cm^{-1}; **HRMS** (DART-TOF+) m/z: $[M+NH_4]^+$ calcd for $C_{11}H_{13}N_2O$ 189.1028; found 189.1023.

2-(Thiophen-2-yl)acetonitrile (2i) was prepared according to General Procedure F using **1i** (0.040 g, 0.20 mmol, 1.0 equiv) and $Zn(CO_3)_2(OH)_6$ (0.017 g, 0.030 mmol, 0.15 equiv). The crude nitrile was purified by column chromatography on silica gel (slow gradient of 0-12% EtOAc in hexanes) to afford the desired product as a yellow oil. Trial 1: 12 mg isolated (48% yield); Trial 2: 11 mg isolated (44% yield). ^{1}**H NMR** (400 MHz, $CDCl_3$, 298 K) δ_H7.27 (dd, J = 5.2, 1.3 Hz, 1H), 7.06 (dq, J = 3.4, 1.1 Hz, 1H), 6.99 (dd, J = 5.2, 3.5 Hz, 1H), 3.92 (d, J = 1.0 Hz, 2H); ^{13}**C NMR** (101 MHz, $CDCl_3$, 298 K) δ_C131.1, 127.5, 127.4, 126.1, 117.0, 18.7. The spectral data for this compound matches that reported in the literature.[39]

(***E***)**-2-Methyl-4-phenylbut-3-enenitrile (8a)** was prepared according to General Procedure G using **7a** or **7a'** (0.047 g, 0.20 mmol, 1.0 equiv). The crude nitrile was purified by column chromatography on silica gel (slow gradient of 0–10% EtOAc in hexanes) to afford the desired product as a yellow oil. Trial 1: 16 mg isolated (52% yield); Trial 2: 18 mg isolated (58% yield) from **7a**. Trial 1: 8.6 mg isolated (27% yield); Trial 2: 14 mg isolated (45% yield) from **7a'**. ^{1}**H NMR** (400 MHz, $CDCl_3$, 298 K) δ_H7.45–7.27 (m, 5H), 6.72 (dd, J = 15.8, 1.5 Hz, 1H), 6.07 (dd, J = 15.8, 6.1 Hz, 1H), 3.51 (qdd, J = 7.2, 6.1, 1.6 Hz, 1H), 1.52 (d, J = 7.2 Hz, 3H); ^{13}**C NMR** (101 MHz, $CDCl_3$, 298 K) δ_C 135.7, 132.5, 128.7, 128.3, 126.5, 124.3, 120.9, 28.4, 19.1; **HRMS** (DART-TOF+) m/z: $[M+NH_4]^+$ calcd for $C_{11}H_{15}N_2$ 175.1235; found 175.1239. The spectral data for this compound matches that reported in the literature.[27c]

(***S***,***E***)**-2-Methyl-4-phenylbut-3-enenitrile ((*S*)-(+)-8a)** was prepared according to General Procedure H using (*R*)-(+)-**7a** (0.047 g, 0.20 mmol, 1.0 equiv), and $KHCO_3$ (0.006 g, 0.060 mmol, 0.30 equiv) as a substitute for K_2PO_4. The reaction was quenched with EtOAc after 12 hours and the crude nitrile was immediately purified by column chromatography on silica gel (slow gradient of 0–10% EtOAc in hexanes) to afford 14 mg (45% yield) the desired product as a yellow oil. The enantiomeric excess was determined to be 87% by HPLC analysis using a chiral column. CHIRALPAK IB, 1.0 mL/min, 5% i-PrOH/hexane, λ = 190 nm; t_R (major): 6.35 min, t_R (minor): 6.65 min. $[\alpha]_D^{25}$ = +20.5° (c 0.38, $CHCl_3$), lit.: $[\alpha]_D^{20}$ = +8.8° (c 0.44, $CHCl_3$).[27c] The spectroscopic data was identical to that of racemic **8a**.

(***E***)**-2-Ethyl-4-phenylbut-3-enenitrile (8b)** was prepared according to General Procedure H using **7b** (0.049 g, 0.20 mmol, 1.0 equiv). The crude nitrile was purified by column chromatography on silica gel (slow gradient of 0–8% EtOAc in hexanes) to afford the desired product as a yellow oil. Trial 1: 14 mg isolated (41% yield); Trial 2: 14 mg isolated (41% yield). ^{1}**H NMR** (400 MHz, $CDCl_3$, 298 K) δ_H7.36–7.16 (m, 5H), 6.66 (dd, J = 15.9, 1.5 Hz, 1H), 5.96 (dd, J = 15.8, 6.4 Hz, 1H), 3.31 (dtd, J = 7.7, 6.3, 1.5 Hz, 1H), 1.82–1.68 (m, 2H), 1.05 (t, J = 7.4 Hz, 3H); ^{13}**C NMR** (101 MHz, $CDCl_3$, 298 K) δ_C135.9, 133.5, 128.8, 128.4, 126.7, 123.1, 120.2, 36.0, 26.8, 11.3; **IR** (neat) 3028, 2970, 2935, 2878, 2241, 1460, 1449, 965, 745, 692 cm^{-1}; **HRMS** (DART-TOF+) m/z: $[M+NH_4]^+$ calcd for $C_{12}H_{17}N_2$ 189.1392; found 189.1390.

(***E***)**-4-Phenylbut-3-enenitrile (8c)** was prepared according to General Procedure H using **7c** or **7c'** (0.044 g, 0.20 mmol, 1.0 equiv). The crude nitrile was purified by column chromatography on silica gel (slow gradient of 0–10% EtOAc in hexanes) to afford the desired product as a white solid. Trial 1: 15 mg isolated (52% yield); Trial 2: 13 mg isolated (45% yield) from **7c**. Trial 1: 14 mg (48% yield); Trial 2: 12 mg (41% yield) from **7c'**. ^{1}**H NMR** (400 MHz, $CDCl_3$, 298 K) δ_H7.33–7.17 (m, 5H), 6.67 (dt, J = 15.7, 1.8 Hz, 1H), 5.98 (dt, J = 15.8, 5.7 Hz, 1H), 3.22 (dd, J = 5.7, 1.8 Hz, 2H); ^{13}**C NMR** (101 MHz, $CDCl_3$, 298 K) δ_C135.8, 134.8, 128.9, 128.4, 126.6, 117.4, 116.9, 20.9. The spectral data for this compound matches that reported in the literature.[40]

(***E***)**-4-(4-(*tert*-Butyl)phenyl)but-3-enenitrile (8d)** was prepared according to General Procedure H using **7d'** (0.055 g, 0.20 mmol, 1.0 equiv). The crude nitrile was purified by column chromatography on silica gel (slow gradient of 0–10% EtOAc in hexanes) to afford the desired product as an off white solid. Trial 1: 28 mg isolated (70% yield); Trial 2: 26 mg isolated (66% yield). ^{1}**H NMR** (400 MHz, $CDCl_3$, 298 K) δ_H7.40–7.34 (m, 2H), 7.33–7.29 (m, 2H), 6.72 (dt, J = 15.8, 1.8 Hz, 1H), 6.01 (dt, J = 15.8, 5.7 Hz, 1H), 3.29 (dd, J = 5.7, 1.8 Hz, 2H), 1.32 (s, 9H); ^{13}**C NMR** (101 MHz, $CDCl_3$, 298 K) δ_C151.7, 134.6, 133.1, 126.4, 125.8, 117.6, 116.0, 34.8, 31.4, 21.0; **IR** (neat) 2960, 2922, 2905, 2872, 2251, 1606, 1491, 1445, 1408, 1248, 956 cm^{-1}; **m.p.**: 43–46 °C; **HRMS** (DART-TOF+) m/z: $[M+NH_4]^+$ calcd for $C_{14}H_{21}N_2$ 217.1705; found 217.1702.

(***E***)**-4-(4-Isopropylphenyl)but-3-enenitrile (8e)** was prepared according to General Procedure H using **7e'** (0.052 g, 0.20 mmol, 1.0 equiv). The crude nitrile was purified by column chromatography on silica gel (slow gradient of 0–8% EtOAc in hexanes) to afford the desired product as an off-white solid. Trial 1: 20 mg isolated (54% yield); Trial 2: 24 mg isolated (65% yield). ^{1}**H NMR** (400 MHz, $CDCl_3$, 298 K) δ_H7.34–7.28 (m, 2H), 7.23–7.15 (m, 2H), 6.71 (dt, J = 15.8, 1.9 Hz, 1H), 6.01 (dt, J = 15.8, 5.7 Hz, 1H), 3.28 (dd, J = 5.7, 1.8 Hz, 2H), 2.90 (hept, J = 7.1 Hz, 1H), 1.25 (d, J = 6.9 Hz, 6H); ^{13}**C NMR** (101 MHz, $CDCl_3$, 298 K) δ_C149.4, 134.7, 133.5, 126.9, 126.6, 117.6, 115.9, 34.0, 24.0, 20.9; **IR** (neat) 2966, 2929, 2871, 2246, 1512, 1464, 1413, 975, 846, 797 cm^{-1}; **m.p.**: 34–35 °C; **HRMS** (DART-TOF+) m/z: $[M+NH_4]^+$ calcd for $C_{13}H_{19}N_2$ 203.1548; found 203.1554.

(***E***)**-4-(4-Methoxyphenyl)but-3-enenitrile (8f)** was prepared according to General Procedure H using **7f'** (0.050 g, 0.20 mmol, 1.0 equiv). The crude nitrile was purified by column chromatography on silica gel (slow gradient of 5–10% EtOAc in hexanes) to afford the desired product as a yellow solid. Trial 1: 26 mg isolated (74% yield); Trial 2: 24 mg isolated (69% yield). ^{1}**H NMR** (400 MHz, $CDCl_3$, 298 K) δ_H7.35–7.28 (m, 2H), 6.90–6.83 (m, 2H), 6.67 (dt, J = 15.7, 1.8 Hz, 1H), 5.91 (dt, J = 15.8, 5.7 Hz, 1H), 3.82 (s, 3H), 3.27 (dd, J = 5.7, 1.8 Hz, 2H); ^{13}**C NMR** (101 MHz, $CDCl_3$, 298 K) δ_C159.9, 134.3, 128.6, 127.9, 117.7, 114.5, 114.3, 55.5, 20.9; **IR** (neat) 3036, 2958, 2938, 2908, 2839, 2244, 1605, 1508, 1247, 1029, 977, 838, 793 cm^{-1}; **m.p.**: 38–39 °C; **HRMS** (DART-TOF+) m/z: $[M+H]^+$ calcd for $C_{11}H_{12}NO$ 174.0919; found 174.0913.

(***E***)**-4-(3-Cyanoprop-1-en-1-yl)phenyl pivalate (8g)** was prepared according to General Procedure H using **7g'** (0.064 g, 0.20 mmol, 1.0 equiv). The crude nitrile was purified by column chromatography on silica gel (slow gradient of 4–20% EtOAc in hexanes) to afford the desired product as a white solid. Trial 1: 28 mg isolated (57% yield); Trial 2: 28 mg isolated (57% yield). ^{1}**H NMR** (400 MHz, $CDCl_3$, 298 K) δ_H7.40–7.34 (m, 2H), 7.06–

7.00 (m, 2H), 6.73 (dt, *J* = 15.7, 1.8 Hz, 1H), 6.01 (dt, *J* = 15.8, 5.6 Hz, 1H), 3.29 (dd, *J* = 5.7, 1.8 Hz, 2H), 1.36 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$, 298 K) δ_C177.1, 151.2, 133.9, 133.4, 127.6, 122.0, 117.3, 116.9, 39.3, 27.3, 20.9; **IR** (neat) 2042, 3025, 2962, 2922, 2905, 2250, 1491,1445, 1408, 956 cm^{-1}; **m.p.**: 47–50 °C; **HRMS** (DART-TOF+) *m/z*: $[M+H]^+$ calcd for $C_{13}H_{18}NO_2$ 244.1338; found 244.1346.

(*E*)-4-(Benzo[*d*][1,3]dioxol-5-yl)but-3-enenitrile (8h) was prepared according to General Procedure H using **7h'** (0.053 g, 0.20 mmol, 1.0 equiv). The crude nitrile was purified by column chromatography on silica gel (slow gradient of 4–20% EtOAc in hexanes) to afford the desired product as a yellow solid. Trial 1: 25 mg isolated (68% yield); Trial 2: 21 mg isolated (57% yield). ^{1}**H NMR** (400 MHz, $CDCl_3$, 298 K) δ_H6.89 (d, *J* = 1.6 Hz, 1H), 6.81 (dd, *J* = 8.0, 1.7 Hz, 1H), 6.77 (d, *J* = 8.0 Hz, 1H), 6.63 (dt, *J* = 15.7, 1.8 Hz, 1H), 5.97 (s, 2H), 5.88 (dt, *J* = 15.7, 5.7 Hz, 1H), 3.26 (dd, *J* = 5.7, 1.8 Hz, 2H); ^{13}**C NMR** (101 MHz, $CDCl_3$, 298 K) δ_C148.3, 147.9, 134.4, 130.2, 121.5, 117.5, 115.0, 108.5, 105.8, 101.4, 20.8; **IR** (neat) 2922, 2910, 2851, 2254, 1491, 1445, 1248, 955, 928 cm^{-1}; **m.p.**: 47–49 °C; **HRMS** (DART-TOF+) *m/z*: $[M+NH_4]^+$ calcd for $C_{11}H_{13}N_2O_2$ 205.0977; found 205.0977.

(*E*)-4-(4-Fluorophenyl)but-3-enenitrile (8i) was prepared according to General Procedure H using **7i'** (0.047 g, 0.20 mmol, 1.0 equiv). The crude nitrile was purified by column chromatography on silica gel (slow gradient of 0–12% EtOAc in hexanes) to afford the desired product as a yellow oil. Trial 1: 14 mg isolated (44% yield); Trial 2: 14 mg isolated (44% yield). ^{1}**H NMR** (400 MHz, $CDCl_3$, 298 K) δ_H7.40–7.28 (m, 2H), 7.09–6.99 (m, 2H), 6.71 (dt, *J* = 15.8, 1.9 Hz, 1H), 5.98 (dt, *J* = 15.8, 5.6 Hz, 1H), 3.29 (dd, *J* = 5.6, 1.8 Hz, 2H); ^{13}**C NMR** (101 MHz, $CDCl_3$, 298 K) δ_C162.7 (d, *J* = 248.0 Hz), 132.5, 131.9 (d, *J* = 3.3 Hz), 128.1 (d, *J* = 8.1 Hz), 117.2, 116.5 (d, *J* = 2.3 Hz), 115.7 (d, *J* = 21.9 Hz), 20.8; **IR** (neat) 3045, 2924, 2252, 1744, 1673, 1601, 1507, 1225, 1158, 965, 841 cm^{-1}; **HRMS** (DART-TOF+) *m/z*: $[M+NH_4]^+$ calcd for $C_{10}H_{12}FN_2$ 179.0985; found 179.0986.

(*E*)-4-(4-chlorophenyl)but-3-enenitrile (8j) was prepared according to General Procedure H using **7j'** (0.050 g, 0.200 mmol, 1.00 equiv). The crude nitrile was purified by column chromatography on silica gel (slow gradient of 0–14% EtOAc in hexanes) to afford the desired product as an off-white solid. Trial 1: 17 mg isolated (47% yield); Trial 2: 19 mg isolated (54% yield). ^{1}**H NMR** (400 MHz, $CDCl_3$, 298 K) δ_H 7.30 (d, *J* = 0.9 Hz, 4H), 6.70 (dt, *J* = 15.8, 1.9 Hz, 1H), 6.04 (dt, *J* = 15.8, 5.6 Hz, 1H), 3.29 (dd, *J* = 5.6, 1.8 Hz, 2H).; ^{13}**C NMR** (101 MHz, $CDCl_3$, 298 K) δ_C 134.2, 134.1, 133.5, 129.0, 127.7, 117.4, 117.1, 20.8.; **IR** (neat) 3046, 2920, 2851, 2249, 1490, 1403, 1090, 976, 842, 787 cm^{-1}; **m.p.**: 43–46 °C; **HRMS** (DART-TOF+) *m/z*: $[M+NH_4]^+$ calcd for $C_{10}H_{12}ClN_2$ 195.0689; found 195.0686

Preparation of Enantioenriched Starting Materials:

(*S*)-1-(Naphthalen-2-yl)ethan-1-ol ((*S*)-(-)-1a): (*R*)-(+)-2-Methyl-CBS-oxazaborolidine (1.0 M in PhMe, 0.3 mL, 0.3 mmol, 0.1 equiv) was dissolved in THF (10 mL, 0.30 M) and the mixture was cooled to -40 °C before BH_3•SMe_2 (2.0 M in THF, 3.0 mL, 6 mmol, 2.0 equiv) was added. This mixture was stirred at the same temperature for 45 minutes before a solution of 2-acetylnaphthone (0.51 g, 3.0 mmol, 1.0 equiv) in THF (5.0 mL) was added slowly over a period of 5 minutes. After 12 hours, MeOH (5.0 mL) was added, followed by water (15 mL), and the mixture was extracted with EtOAc (x3). The combined organic layers were washed with sat. $NaHCO_3$ (x1), brine (x1), dried over $MgSO_4$, and concentrated under reduced pressure. The absolute stereochemistry was assigned by the accepted model for selectivity in CBS reductions,[41] and the crude alcohol was of sufficient purity for use directly in the next step according to General Procedure B using **(*S*)-S1** (0.52 g, 3.0 mmol, 1.0 equiv), triethylamine (0.59 mL, 4.2 mmol, 1.2 equiv), DMAP (0.04 g, 0.30 mmol, 0.10 equiv), trimethylacetyl chloride (0.48 mL, 3.9 mmol, 1.2 equiv), and dichloromethane (5.0 mL, 0.60 M). The crude product was purified by column chromatography on silica gel (5% EtOAc in hexanes) to afford 0.72 g (93% yield over 2 steps) of the desired product as a white solid, which was recrystallized in hexanes to yield a higher enantiopurity. The enantiomeric excess was determined to be 93% by HPLC analysis using a chiral column. CHIRALPAK IG, 1.0 mL/min, 5% i-PrOH/hexane, λ = 254 nm; t_R (major): 4.73 min, t_R (minor): 3.99 min; $[\alpha]_D^{26}$ = -67.7° (c 0.32, $CHCl_3$), lit.: $[\alpha]_D^{24}$ = -82.1° (c 0.80, $CHCl_3$).[19f] The spectroscopic data was identical to that of racemic **1a**.

(*R*,*E*)-4-Phenylbut-3-en-2-yl pivalate ((*R*)-(+)-7a): *L*-(+)-DET (0.10 mL, 0.60 mmol, 0.12 equiv), $Ti(OiPr)_4$ (0.15 mL, 0.50 mmol, 0.10 equiv), **S11** (0.74 g, 5.0 mmol, 1.0 equiv), and freshly crushed 4 Å molecular sieves (0.22 g, 30% w/w) were dissolved in CH_2Cl_2 (15 mL, 0.30 M) and the reaction mixture was cooled to -20 °C. This suspension was stirred for 30 min before anhydrous tBuOOH (4.2 M in PhMe, 0.83 mL, 3.5 mmol, 0.7 equiv)[42] was added dropwise, and stirred at the same temperature for 2.5 hours before being quenched with 4M NaOH (8.0 mL). The mixture was extracted with CH_2Cl_2 (x3) and the combined organic layers were washed with brine (x1), then dried over $MgSO_4$. The residue was purified by column chromatography on silica gel (very slow gradient of 5–16% EtOAc in hexanes) to afford 0.24 g (32% yield) of the desired product as a white solid, which was used directly in the next step according to General Procedure B, using **(*R*)-S11** (0.24 g, 1.6 mmol, 1.0 equiv), triethylamine (0.32 mL, 2.3 mmol, 1.2 equiv), DMAP (0.020 g, 0.16 mmol, 0.10 equiv), trimethylacetyl chloride (0.26 mL, 2.1 mmol, 1.2 equiv), and dichloromethane (4.0 mL, 0.40 M). The crude product was purified by column chromatography on silica gel (slow gradient of 0-6% EtOAc in hexanes) to afford 0.29 g (78% yield) of the desired product as colorless needles. The enantiomeric excess was determined to be 99% by HPLC analysis using a chiral column, CHIRALPAK IG, 1.0 mL/min, 2% i-PrOH/hexane, λ = 190 nm; t_R(major): 3.79 min, t_R (minor): 4.08 min; $[\alpha]_D^{26}$ = +100.1° (c 0.915, $CHCl_3$), lit.: $[\alpha]_D^{25}$ = +106.1° (c 2.78, $CHCl_3$).[28a] The spectroscopic data was identical to that of racemic **7a**.

Synthesis of Naproxen

2-(6-Methoxynaphthalen-2-yl)propanoic acid (6): To a suspension of **2b** (0.070 g, 0.33 mmol, 1.0 equiv) in ethylene glycol (1.0 mL, 0.33 M) was added KOH (10 M solution in H_2O, 0.17 mL, 1.7 mmol, 5.0 equiv). The reaction vessel was sealed with a rubber septum and submerged in an oil bath at 100 °C for 24 h. HCl (1 M, 5.0 mL) was then added dropwise and the mixture was extracted with EtOAc (x3). The combined organic layers were washed with brine (x1), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (5:4:1 hexanes:EtOAc:MeOH) to afford 0.070 g (92% yield) of the desired product as an off-white solid. ^{1}**H NMR** (400 MHz, $CDCl_3$, 298 K) δ_H 7.74–7.64 (m, 3H), 7.41 (dd, *J* = 8.5, 1.9 Hz, 1H), 7.18–7.09 (m, 2H), 3.93–3.84 (m, 4H), 1.59 (d, *J* = 7.1 Hz, 3H); ^{13}**C NMR** (101 MHz, $CDCl_3$, 298 K) δ_C 180.1, 157.9, 135.0, 134.0, 129.5, 129.1, 127.4, 126.3, 126.3, 119.2, 105.8, 55.5, 45.3, 18.3. The spectroscopic data was identical to that of an authentic sample (CAS: 22204-53-1, Oakwood Chemical Cat. No.: 079426).

SUPPORTING INFORMATION

The Supporting Information is available free of charge on the ACS Publications website.

NMR spectra and HPLC traces.

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Notes

The authors declare no competing financial interest.

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