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DABO Boronate Promoted Conjugate Allylation of α,β-Unsaturated Aldehydes using Copper(II) Catalysis

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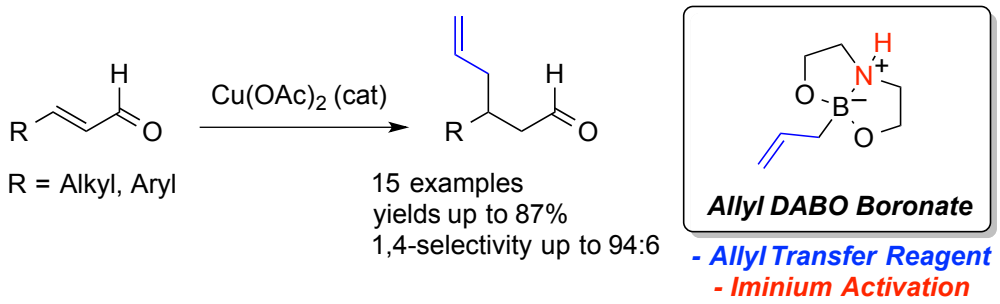


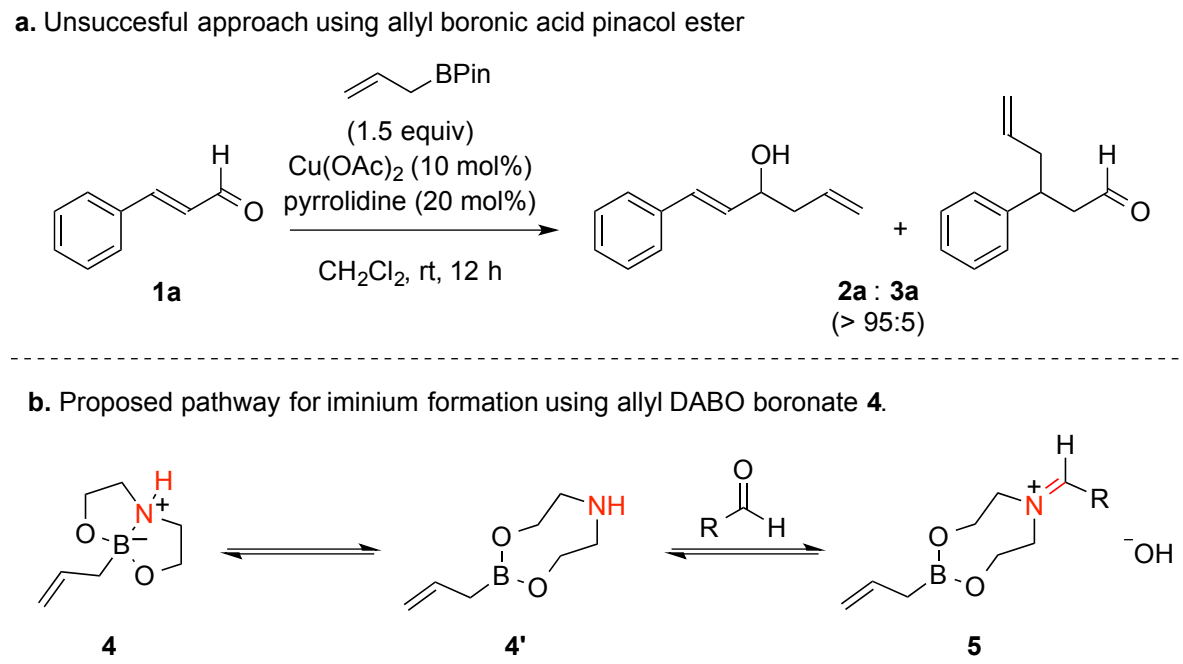
Abstract. The first catalytic method for the selective 1,4-conjugate allylation of α,β-unsaturated aldehydes is reported. The method employs an air stable diethanolamine complexed boronic acid (DABO boronate) as the allyl transfer reagent, and promotes conjugate addition over 1,2-addition. A variety of aryl- and alkyl-substituted enals are tolerated, providing δ,ε-unsaturated aldehyde products in good yields and selectivities under mild conditions.

Metal catalyzed conjugate addition to electron deficient olefins represents a versatile strategy for preparing C–C bonds in a selective manner. Most approaches involve the use of copper or rhodium catalysis, and a wide variety of electrophilic and nucleophilic partners have been studied, contributing to its establishment as a fundamental transformation in organic synthesis.[1,2,3] Despite the ubiquity of such reactions, the conjugate allylation of α,β-unsaturated aldehydes represents a particularly significant challenge with regard to controlling 1,2- over 1,4-selectivity. Common strategies such as the use of organocopper reagents or the Hosomi-Sakurai allylation are ineffective in the case of α,β-unsaturated aldehydes, owing to increased propensity for 1,2-addition.[4] In fact, the only examples of 1,4-selective allylation of enals were reported by Maruoka and involve the use of allylithium or allylcerium reagents in the presence of a fluorinated ATPH Lewis acid at cryogenic temperatures (-78 °C or -100 °C).[5,6] Given the versatility of the allyl group as a synthetic handle as well as the inherent reactivity of aldehydes, we believed a convenient, catalytic protocol for such a transformation would be desirable. Herein we report the development of a copper-catalyzed conjugate allylation of α,β-unsaturated aldehydes using the crystalline and air-stable diethanolamine derived allyl DABO boronate.

Allylboron reagents have found widespread use both in direct and metal catalyzed allylation of carbonyl groups, however these methods are typically selective for 1,2-addition.[7] Yamamoto has previously reported the copper catalyzed 1,4-allylation of electron deficient alkynes with allylboronic acid pinacol ester, although the use of an alkynyl ketone led only to isolation of the corresponding 1,2-addition product.[8] It was envisioned that the use of iminium catalysis to promote 1,4-addition could offer a potential solution.[9] This general strategy has previously been used for example by Cordova in the conjugate arylation of enals with aryl boronic acids using $Pd(OAc)_2$ in conjunction with Jørgensen's catalyst.[10] Disappointingly the combination of

catalytic $Cu(OAc)_2$ and pyrrolidine with allyl boronic acid pinacol ester and cinnamaldehyde **1a** delivered the 1,2-addition adduct **2a** as the major product, with only trace amounts of **3a** (Scheme 1a).[11] Attempts to increase the selectivity with this system were unsuccessful, and in particular it was found that increased amine concentrations led mostly to recovered starting material and **2a** as the sole product, indicating that pyrrolidine may be hampering the catalytic cycle by coordinative saturation of the copper catalyst.

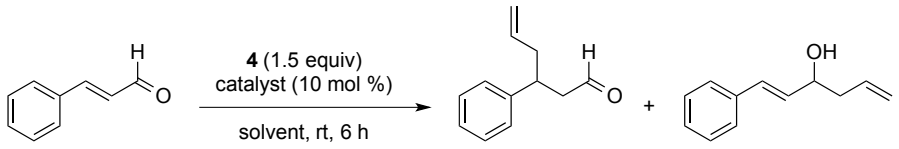
Scheme 1. Initial approach to Cu(II) / amine promoted addition of allylboronic acid pinacol ester to cinnamaldehyde and proposed pathway for iminium ion catalysis



With this in mind, we turned to the diethanolamine complexed allyl boronic acid (DABO boronate) **4**, which was reported by Rychnovsky to be a competent allyl transfer reagent to aldehydes and ketones in the presence of Brønsted acids.[12] Since DABO boronates have been shown to hydrolyze to boronic acids under aqueous conditions, it was hoped that the labile nature of the B–N bond would allow this reagent to serve as a masked boronate and secondary amine

for iminium ion activation of enals (Scheme 1b).[13,14,15,16] This hypothesis was supported by reports that aminoboranes can effectively generate iminium ions in Mannich-type reactions.[17,18] Furthermore, the low inherent reactivity of allyl DABO boronate in the allylation of carbonyls was anticipated to limit direct 1,2-addition. The addition of **4** to aldehyde **1a** using $Cu(OAc)_2$ (10 mol%) in dichloromethane led to an approximately 1:1 ratio of the 1,4- and 1,2 adducts **3a** and **2a**, respectively, albeit in modest yield (Table 1, Entry 1). Optimization of the reaction conditions led to the identification of DMF as the best solvent, in combination with a 10 mol% catalyst loading of $Cu(OAc)_2$, with a 85:15 selectivity in favor of 1,4-addition and an isolated yield of 80% of **3a** (Entry 3). Although other copper sources were explored (e.g., Entries 4 and 5), they were found to be inferior to $Cu(OAc)_2$. Selectivity could further be increased by slow addition of **1a** to a solution of **4** and $Cu(OAc)_2$, delivering **3a** with a 92:8 selectivity and in 87% yield (Entry 6). A control experiment conducted in the absence of catalyst showed that copper is required for 1,4-addition (Entry 8). Attempts at employing amine or phosphine based ligands invariably led to a significant decrease in selectivity.

Table 1. Optimization experiments for the conjugate allylation of cinnamaldehyde (**1a**)



1a **3a** **2a**

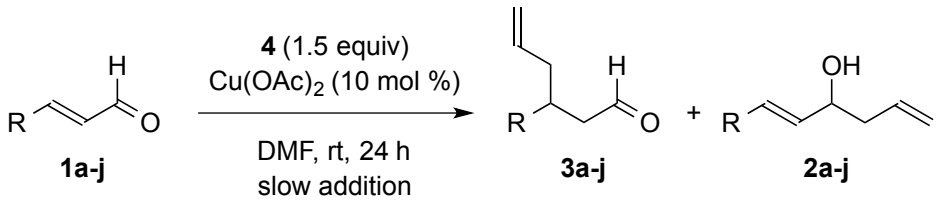
Entry	Solvent	Catalyst	**3a**:**2a**[a]	Yield **3a** (%)[b]
1	CH_2Cl_2	$Cu(OAc)_2$	52:48	29
2	MeCN	$Cu(OAc)_2$	72:28	57
3	DMF	$Cu(OAc)_2$	86:14	78
4	DMF	$CuCl_2$	68:32	59
5	DMF	$Cu(acac)_2$	70:30	63
6[c]	DMF	$Cu(OAc)_2$	92:8	87
7[c, d]	DMF	$Cu(OAc)_2$	89:11	73
8	DMF	-	<5:95	-[e]

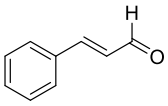
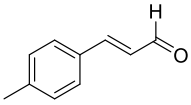
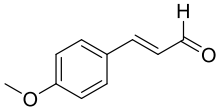
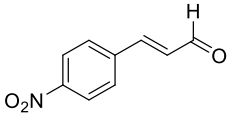
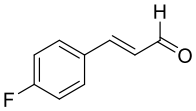
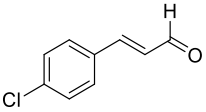
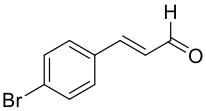
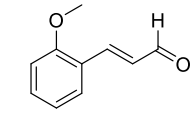
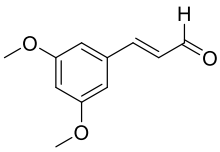
[a] Ratios determined by ^{1}H NMR analysis of the crude reaction mixture using the alkenyl proton signals. [b] Isolated yields after column chromatography. [c] Reaction conducted by slow addition of **1a** over 20 h followed by stirring for an additional 4 h. [d] Reaction conducted using 1.1 equiv of **4**. [e] Incomplete conversion (30%) of starting material was observed. Yield Not Determined.

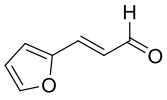
Given the prolonged reaction time and the use of an excess of **4**, the possibility of double allylation was a concern. Over the course of optimizing the reaction conditions, it was found that the workup procedure employed was crucial in avoiding this undesired pathway. While quenching immediately with saturated aq. NH_4Cl led to the formation of a mixture of mono- and bis-allylated products in a 4:1 ratio, quenching the reaction with 10 equivalents of acetic acid to destroy excess **4**, followed by neutralization with saturated aq. $NaHCO_3$ provided the desired product without the formation of the double allylation product. This indicates that aldehyde **3a** is only formed after aqueous workup at which point it can react with remaining **4**. A possible explanation is the initial formation of a stable boron enolate intermediate, as previously reported by Morken in the nickel catalyzed conjugate allylation of activated enones.[19]

Having determined the optimal conditions, the substrate scope was evaluated using a variety of aryl-substituted enals (Table 2). A variety of both electron rich (Entries 2, 3, 8-10) and electron poor aromatics (Entry 4), as well as halogenated substrates (Entries 5-7) are amenable to addition. Substituents at the ortho or meta positions of **1** were also well tolerated (Entries 8 and 9) and furan **1j** was also found to be a suitable substrate (Entry 10). In general, it was found that electron rich substrates reacted with slightly higher selectivity than electron poor aromatics. The use of substituted allyl boronates, such as (*E*)-crotyl DABO boronate was unsuccessful and furnished only the 1,2-addition products.

Table 2. Conjugate allylation of aryl substituted enals **3a-j**



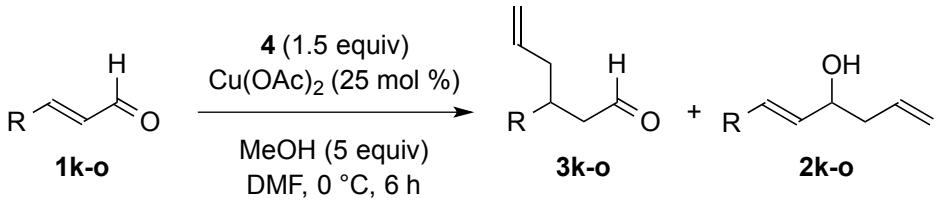
Entry	Substrate		Product		
				Yield (%)[a]	Ratio (**3**:**2**)[b]
1	**1a**		**3a**	87	92:8
2	**1b**		**3b**	83	90:10
3	**1c**		**3c**	87	94:6
4	**1d**		**3d**	76	86:14
5	**1e**		**3e**	80	90:10
6	**1f**		**3f**	81	90:10
7	**1g**		**3g**	84	90:10
8	**1h**		**3h**	88	94:6
9	**1i**		**3i**	80	90:10

10	**1j**		**3j**	75	88:12

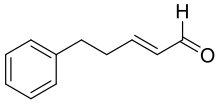
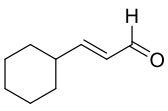
[a] Isolated yields after column chromatography. [b] Ratios determined by ^{1}H NMR analysis of the crude reaction mixture using the alkenyl proton signals.

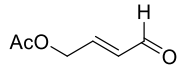
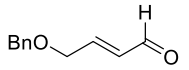
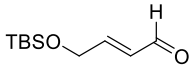
The reaction of alkyl-substituted enals using the previously established protocol furnished numerous by-products other than those arising from 1,2- or 1,4-allylation. This is presumably due to the increased reactivity of unconjugated enals that could favor polymerization pathways and reactions *via* iminium ion and enamine intermediates. Cooling the reaction to 0 °C and adding 5 equivalents of methanol was sufficient to eliminate these issues.[20] Although slow addition of the aldehyde was incompatible with the presence of methanol, good selectivities could still be obtained by increasing the $Cu(OAc)_2$ catalyst loading to 25 mol % (Table 3). Under these conditions, both primary (Entry 1) and secondary alkyl substituents (Entry 2) were tolerated, as well as a variety of protected alcohols (Entries 3-5). Interestingly, submitting acrolein to these reaction conditions afforded only the corresponding 1,2-addition product.

Table 3. Conjugate allylation of alkyl substituted enals **3k-o**



1k-o **3k-o** **2k-o**

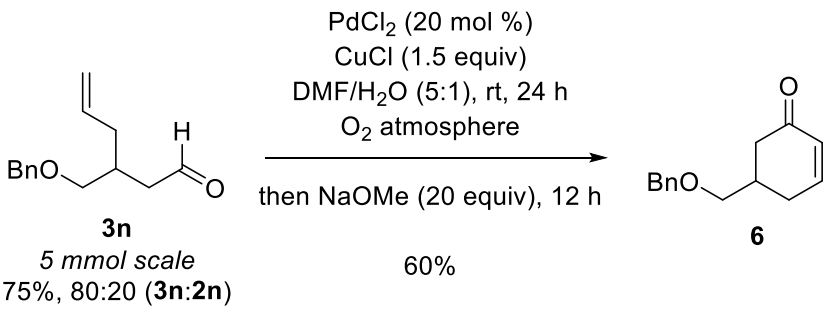
Entry	Enal		Product		
				Yield (%)[a]	Ratio (**3**:**2**)[b]
1	**1k**		**3k**	81	86:14
2	**1l**		**3l**	75	80:20

3	**1m**		**3m**	74	84:16
4	**1n**		**3n**	77	82:18
5	**1o**		**3o**	76	80:20

[a] Isolated yields after column chromatography. [b] Ratios determined by ^{1}H NMR analysis of the crude reaction mixture using the alkenyl proton signals.

To demonstrate the synthetic utility of the resulting products aldehyde **3n** was prepared on a 5 mmol scale and subjected to a one pot Wacker-Tsuji oxidation/condensation sequence to afford 5-substituted cyclohexenone **6** in 60% yield (Scheme 2).[21] Compound **6** was recently used as an intermediate in the total synthesis of huperzine Q.[22]

Scheme 2. Preparation of cyclohexenone **6**



In summary, allyl DABO boronate was shown to be an effective reagent for the conjugate allylation of α,β-unsaturated aldehydes using copper catalysis. In contrast with previous methods, which require the use of air sensitive reagents and cryogenic temperatures, this approach utilizes air stable reagents at or near room temperature and tolerates a wide variety of functional groups. The resulting products contain aldehyde and alkene functional groups that can be elaborated to afford synthetically useful intermediates. Finally, this study represents the first

example of the use of DABO boronates to promote 1,4-addition, expanding upon the known reactivity of these compounds.

Experimental Section

All reactions were performed under argon in flame-dried glassware unless otherwise indicated. Anhydrous dimethylformamide was obtained as ≥ 99.9 % pure and stored under argon. Flash chromatography on silica gel (60 Å, 230-400 mesh) was performed with reagent grade solvents. Analytical thin-layer chromatography (TLC) was performed on pre-coated silica gel plates and visualized with a UV_{254} lamp. Solvent ratios for chromatography and R_f values are reported as v/v ratios. All 1-D (^{1}H, ^{13}C) NMR spectra were obtained on a 400 MHz spectrometer as solutions in deuterated solvents. Chemical shifts are reported in δ ppm values. Proton chemical shifts were internally referenced to the residual proton resonance in $CDCl_3$ (δ 7.26 ppm). Carbon chemical shifts were internally referenced to the solvent resonance in $CDCl_3$ (δ 77.16 ppm). Peak multiplicities are designated by the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad; *J*, coupling constant in Hz (rounded to the nearest 0.5 Hz). Exact mass measurements were performed on quadrupole time-of-flight mass spectrometers utilizing direct analysis in real time ionization (DART-TOF).

Allyl DABO Boronate (4).[12] Prepared according to a known literature procedure and purified by recrystallization from MeCN. Excess diethanolamine in crude **4** is detrimental to the catalyst activity and thus recrystallization is required to obtain good selectivities.

Conjugate Allylation of Aryl Substituted Enals (Method A). To a round bottom flask equipped with a magnetic stirrer charged with allyl DABO boronate **4** (116.3 mg, 0.75 mmol, 1.5 equiv) and $Cu(OAc)_2$ (9.1 mg, 0.050 mmol, 0.10 equiv) was added DMF (3 mL). In a vial, enal **1** (0.50 mmol, 1.0 equiv) was dissolved in DMF (2 mL). This solution was added to the round bottom flask over 20 h using a syringe pump. Stirring was maintained for an additional 4 h after the addition was complete. The reaction was quenched with AcOH (0.29 mL, 5.0 mmol, 10 equiv) and stirred for 30 min before neutralizing with saturated aq. $NaHCO_3$ (15 mL). The resulting solution was extracted with Et_2O (3 x 15 mL) and the combined organics were washed with brine (15 mL) and dried over anhydrous Na_2SO_4. The solvent was removed *in vacuo* and the crude mixture was purified by flash column chromatography over silica gel.

3-Phenylhex-5-enal (3a).[23] Eluted using 5:95 EtOAc:hexanes. Colorless oil (75.8 mg, 87%). R_f 0.43 (10:90 EtOAc:hexanes). Spectral data were identical to those previously reported.

3-(p-Tolyl)hex-5-enal (3b). Eluted using 3:97 EtOAc:hexanes. Colorless oil (78.3 mg, 83%). R_f 0.56 (10:90 EtOAc:hexanes); IR (thin film in CH_2Cl_2) ν_{max} 3053, 2986, 2924, 1721, 1709, 1516, 1441, 1422 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.67 (1H, t, J = 2.0 Hz), 7.15–7.06 (4H, m), 5.67 (1H, dddd, J = 17.0, 10.0, 7.5, 6.5 Hz), 5.07–4.96 (2H, m), 3.32–3.22 (1H, m), 2.81–2.64 (2H, m), 2.49–2.34 (2H, m), 2.32 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.0, 140.4, 136.3, 136.0, 129.4, 127.4, 117.2, 49.6, 41.1, 39.5, 21.1; HRMS (DART) mass calcd for $C_{13}H_{16}O$ $[M + H]^+$: 189.1279, found 189.1286.

3-(4-Methoxyphenyl)hex-5-enal (3c). Eluted using 7:93 EtOAc:hexanes. Colorless oil (88.5 mg, 87%). R_f 0.30 (10:90 EtOAc:hexanes); IR (thin film in CH_2Cl_2) ν_{max} 3053, 2988, 1713, 1514, 1421 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.66 (1H, t, J = 2.0 Hz), 7.15–7.08 (2H, m), 6.88–6.82 (2H, m), 5.66 (1H, dddd, J = 17.0, 10.0, 7.5, 6.5 Hz), 5.05–4.96 (2H, m), 3.78 (4H, s), 3.30–3.20

(1H, m), 2.80–2.61 (2H, m), 2.45–2.30 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.0, 158.4, 136.0, 135.5, 128.5, 117.2, 114.1, 55.3, 49.7, 41.3, 39.1; HRMS (DART) mass calcd for $C_{13}H_{16}O_2$ $[M + H]^+$: 205.1229, found 205.1226.

3-(4-Nitrophenyl)hex-5-enal (3d). Eluted using 20:80 EtOAc:hexanes. Yellow oil (83.1 mg, 76%). R_f 0.15 (10:90 EtOAc:hexanes); IR (thin film in CH_2Cl_2) ν_{max} 3057, 2928, 1724, 1607, 1597, 1522, 1506, 1348, 1265 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.70 (1H, t, J = 1.5 Hz), 8.26–8.05 (2H, m), 7.44–7.31 (2H, m), 5.60 (1H, ddt, J = 16.5, 10.5, 7.0 Hz), 5.09–4.90 (2H, m), 3.45 (1H, p, J = 7.5 Hz), 2.94–2.74 (2H, m), 2.41 (2H, tq, J = 7.0, 1.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.2, 151.4, 146.9, 134.8, 128.6, 124.0, 118.2, 49.1, 40.5, 39.3; HRMS (DART) mass calcd for $C_{12}H_{13}NO_3$ $[M + H]^+$: 220.0974, found 220.0972.

3-(4-Fluorophenyl)hex-5-enal (3e). Eluted using 5:95 EtOAc:hexanes. Colorless oil (77.1 mg, 80%). R_f 0.43 (10:90 EtOAc:hexanes); IR (thin film in CH_2Cl_2) ν_{max} 3055, 2986, 1724, 1640, 1605, 1510, 1422, 1225, 1159 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.67 (1H, t, J = 2.0 Hz, 1H), 7.20–7.10 (2H, m), 7.04–6.95 (2H, m), 5.70–5.57 (1H, m), 5.06–4.96 (2H, m), 3.36–3.24 (1H, m), 2.84–2.63 (2H, m), 2.37 (2H, t, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.4, 161.7 (d, J = 245.0 Hz), 139.2 (d, J = 3.0 Hz), 129.0 (d, J = 7.5 Hz), 117.5, 115.6 (d, J = 21.0 Hz), 49.6, 41.1, 39.1; HRMS (DART) mass calcd for $C_{12}H_{13}FO$ $[M + H]^+$: 193.1029, found 193.1036.

3-(4-Chlorophenyl)hex-5-enal (3f). Eluted using 6:94 EtOAc:hexanes. Colorless oil (84.3 mg, 81%). R_f 0.39 (10:90 EtOAc:hexanes); IR (thin film in CH_2Cl_2) ν_{max} 3053, 2988, 1709, 1493, 1422 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.66 (1H, t, J = 2.0 Hz), 7.30–7.24 (2H, m), 7.16–7.10 (2H, m), 5.69–5.55 (1H, m), 5.05–4.95 (2H, m), 3.34–3.23 (1H, m), 2.83–2.64 (2H, m), 2.37 (2H, tt, J = 7.0, 1.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.2, 142.0, 135.4, 132.5, 129.0, 128.9,

117.6, 49.4, 40.9, 39.1; HRMS (DART) mass calcd for $C_{12}H_{13}ClO$ $[M + H]^+$: 209.0733, found 209.0729.

3-(4-Bromophenyl)hex-5-enal (3g). Eluted using 6:94 EtOAc:hexanes. Colorless oil (106.5 mg, 84%). R_f 0.39 (10:90 EtOAc:hexanes); IR (thin film in CH_2Cl_2) ν_{max} 3053, 2986, 1713, 1491, 1422 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.67 (1H, t, J = 2.0 Hz), 7.47–7.37 (2H, m), 7.11–7.04 (2H, m), 5.69–5.55 (1H, m), 5.06–4.95 (2H, m), 3.33–3.21 (1H, m), 2.83–2.62 (2H, m), 2.37 (2H, tt, J = 7.0, 1.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.1, 142.6, 135.4, 131.8, 129.4, 120.5, 117.7, 49.4, 40.8, 39.2; HRMS (DART) mass calcd for $C_{12}H_{13}BrO$ $[M + H]^+$: 253.0228, found 253.0223.

3-(2-Methoxyphenyl)hex-5-enal (3h). Eluted using 5:95 EtOAc:hexanes. Colorless oil (89.7 mg, 88%). R_f 0.38 (10:90 EtOAc:hexanes); IR (thin film in CH_2Cl_2) ν_{max} 3053, 2986, 2839,1709, 1601, 1586, 1493, 1464, 1439, 1030 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.65 (1H, t, J = 2.5 Hz), 7.20 (1H, ddd, J = 8.0, 7.5, 2.0 Hz), 7.14 (1H, dd, J = 7.5, 2.0 Hz), 6.92 (1H, td, J = 7.5, 1.0 Hz), 6.87 (1H, dd, J = 8.0, 1.0 Hz), 5.70 (1H, dddd, J = 17.0, 10.0, 7.5, 6.5 Hz), 5.07–4.94 (2H, m), 3.83 (3H, s), 3.77–3.66 (1H, m), 2.80–2.63 (2H, m), 2.54–2.44 (1H, m), 2.39 (1H, dtt, J = 14.0, 7.5, 1.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.7, 157.1, 136.4, 131.3, 128.0, 127.7, 120.8, 116.9, 110.8, 55.4, 48.4, 39.2, 33.4; HRMS (DART) mass calcd for $C_{13}H_{16}O_2$ $[M + H]^+$: 205.1229, found 205.1231.

3-(3,5-Dimethoxyphenyl)hex-5-enal (3i). Eluted using 10:90 EtOAc:hexanes. Colorless oil (93.9 mg, 80%). R_f 0.28 (10:90 EtOAc:hexanes); IR (thin film in CH_2Cl_2) ν_{max} 3055, 1724, 1607, 1597, 1464, 1431, 1206, 1153 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.67 (1H, t, J = 2.0 Hz), 6.35 (2H, d, J = 2.0 Hz), 6.32 (1H, t, J = 2.0 Hz), 5.67 (1H, dddd, J = 16.5, 10.0, 8.0, 6.5 Hz), 5.08–4.97 (2H, m), 3.78 (6H, s), 3.22 (1H, p, J = 7.5 Hz), 2.79–2.61 (2H, m), 2.38 (2H, tddd, J = 14.0,

13.0, 8.0, 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.8, 161.1, 146.0, 135.8, 117.3, 105.8, 98.4, 55.4, 49.3, 40.9, 40.2; HRMS (DART) mass calcd for $C_{14}H_{18}O_3$ $[M + H]^+$: 235.1334, found 235.1337.

3-(Furan-2-yl)hex-5-enal (3j).[23] Eluted using 8:92 EtOAc:hexanes. Yellow oil (61.4 mg, 75%). R_f 0.28 (10:90 EtOAc:hexanes). Spectral data were identical to those previously reported.

Conjugate Allylation of Alkyl Substituted Enals (Method B). To a round bottom flask equipped with a magnetic stirrer charged with allyl DABO boronate **4** (116.3 mg, 0.75 mmol, 1.5 equiv) and $Cu(OAc)_2$ (22.7 mg, 0.125 mmol, 0.25 equiv) was added DMF (3 mL). The resulting solution was cooled to 0 °C before adding MeOH (0.10 mL, 2.5 mmol, 5 equiv) followed by enal **1**. The reaction was stirred for 6 h. The workup procedure was identical to method A.

3-Phenethylhex-5-enal (3k). Eluted using 5:95 EtOAc:hexanes. Colorless oil (82.1 mg, 81%). R_f 0.38 (10:90 EtOAc:hexanes); IR (thin film in CH_2Cl_2) ν_{max} 3050, 2988, 1684, 1640, 1422 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.75 (1H, t, J = 2.0 Hz), 7.33–7.24 (2H, m), 7.23–7.13 (3H, m), 5.74 (1H, ddt, J = 16.0, 11.0, 7.0 Hz), 5.13–5.01 (2H, m), 2.63 (2H, ddd, J = 9.0, 7.0, 2.5 Hz), 2.50–2.33 (2H, m), 2.29–2.18 (1H, m), 2.12 (2H, dddd, J = 14.0, 13.0, 9.5, 6.5 Hz), 1.76–1.58 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.7, 142.1, 135.9, 128.6, 128.4, 126.0, 117.5, 48.1, 38.4, 35.9, 33.2, 32.5; HRMS (DART) mass calcd for $C_{14}H_{18}O$ $[M + H]^+$: 203.1436, found 203.1442.

3-Cyclohexylhex-5-enal (3l). Eluted using 2:98 EtOAc:hexanes. Colorless oil (67.4 mg, 75%). R_f 0.60 (10:90 EtOAc:hexanes); IR (thin film in CH_2Cl_2) ν_{max} 2987, 2928, 2855, 1709, 1449, 1421 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.73 (1H, t, J = 2.0 Hz), 5.71 (1H, dddd, J = 16.0, 11.5, 7.5, 6.5 Hz), 5.05–4.97 (2H, m), 2.34 (2H, qdd, J = 17.0, 6.0, 2.0 Hz), 2.24–2.13 (1H, m), 2.01–1.90 (2H, m), 1.78–1.69 (2H, m), 1.69–1.56 (3H, m), 1.39–1.28 (1H, m), 1.27–1.06 (3H,

m), 1.05–0.90 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.4, 137.2, 116.9, 45.7, 40.8, 38.2, 36.3, 30.3, 29.7, 26.8, 26.7; HRMS (DART) mass calcd for $C_{12}H_{20}O$ $[M + H]^+$: 181.1592, found 181.1589.

2-(2-Oxoethyl)pent-4-en-1-yl acetate (3m). Eluted using 16:84 EtOAc:hexanes. Colorless oil (63.2 mg, 74%). R_f 0.14 (10:90 EtOAc:hexanes); IR (thin film in CH_2Cl_2) ν_{max} 3055, 2988, 1724, 1640, 1421 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.77 (1H, t, J = 1.5 Hz), 5.73 (1H, ddt, J = 16.5, 10.5, 7.0 Hz, 1H), 5.12–5.03 (2H, m), 4.15–4.06 (1H, m), 3.99–3.90 (1H, m), 2.54–2.38 (3H, m), 2.24–2.15 (1H, m), 2.14–2.07 (1H, m), 2.04 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.0, 170.7, 134.7, 117.8, 66.3, 45.4, 35.5, 32.2, 20.7; HRMS (DART) mass calcd for $C_9H_{14}O_3$ $[M + H]^+$: 171.1021, found 171.1022.

3-((Benzyloxy)methyl)hex-5-enal (3n).[24] Eluted using 5:95 EtOAc:hexanes. Colorless oil (84.0 mg, 77%). R_f 0.36 (10:90 EtOAc:hexanes). Spectral data were identical to those previously reported.

3-(((*tert*-Butyldimethylsilyl)oxy)methyl)hex-5-enal (3o). Eluted using 3:97 EtOAc:hexanes. Colorless oil (92.3 mg, 76%). R_f 0.57 (10:90 EtOAc:hexanes); IR (thin film in CH_2Cl_2) ν_{max} 2957, 2930, 2857, 1705, 1464, 1421, 1101 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.76 (1H, dd, J = 2.5, 2.0 Hz), 5.81–5.66 (1H, m), 5.08–4.99 (2H, m), 3.60 (1H, dd, J = 10.0, 4.5 Hz, 1H), 3.45 (1H, dd, J = 10.0, 6.5 Hz), 2.49–2.31 (2H, m), 2.29–2.12 (2H, m), 2.02 (1H, dtt, J = 14.0, 7.0, 1.0 Hz), 0.87 (9H, s), 0.02 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.7, 136.1, 117.2, 65.6, 46.0, 36.3, 35.7, 26.0, 18.4, -5.4; HRMS (DART) mass calcd for $C_{13}H_{26}O_2Si$ $[M + H]^+$: 243.1780, found 243.1776.

Synthesis of enone 6. To a round bottom flask equipped with a magnetic stirrer charged with CuCl (148.5 mg, 1.5 mmol, 1.5 equiv) and $PdCl_2$ (35.5 mg, 0.20 mmol, 0.2 equiv) was added

DMF (5 mL) and water (1 mL). To this solution was added aldehyde **3n** (218.3 mg, 1 mmol, 1 equiv) and the reaction vessel was purged with O_2 (balloon). The reaction was stirred for 24 h under O_2 atmosphere before addition of NaOMe (1.08 g, 20 mmol, 20 equiv), after which stirring was maintained for an additional 12 h. The solution was diluted with saturated aq. NH_4Cl (10 mL) and extracted with Et_2O (3 x 15 mL). The combined organics were dried over anhydrous Na_2SO_4. The solvent was removed *in vacuo* and the crude mixture was purified by flash column chromatography over silica gel.

5-((Benzyloxy)methyl)cyclohex-2-en-1-one (6).[25] Eluted using 25:75 EtOAc:hexanes. Colorless oil (129.6 mg, 60%). R_f 0.34 (25:75 EtOAc:hexanes). Spectral data were identical to those previously reported.

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Supporting Information. Spectral data for all compounds including ^1H and ^{13}C NMR.

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