CHAPTER 3[†]

The Aldehyde-Selective Tsuji–Wacker Oxidation:

A Tool for Facile Catalytic Transformations of Hindered Terminal Olefins

3.1 INTRODUCTION

Inspired by the success of the aldehyde-selective Tsuji–Wacker oxidation in our second-generation synthesis of the cyanthiwigin natural product core, we decided to explore the utility of this remarkable transformation in the oxidation of various sterically hindered substrates and to probe the broader applicability of the reaction in chemical synthesis. The results of these investigations are described herein.

3.1.1 BACKGROUND

The use of transition metal catalysts in the preparation of organic compounds has enabled previously unattainable transformations, streamlining otherwise cumbersome synthetic sequences. Although most early applications of transition metal catalysis did

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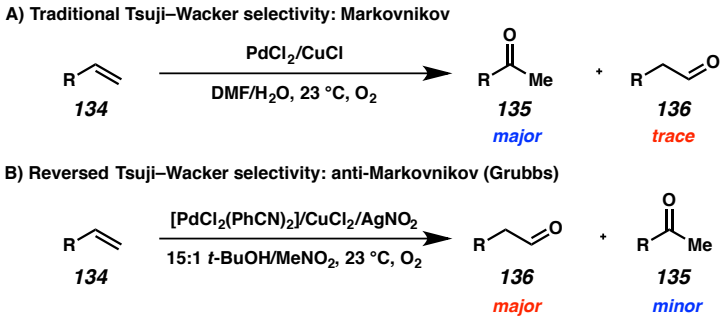
not involve Pd,[1] the discovery of the Wacker process in 1956 stimulated interest in the use of Pd catalysts in synthesis.[2,3] Since then, Pd has emerged as one of the leading transition metals in the catalysis of organic transformations.[4] The popularity of Pd-catalyzed processes is largely due to the wide breadth of organic substrates capable of coordination to Pd, which allows for the promotion of many different types of transformations. Furthermore, Pd-catalyzed reactions often occur with high stereospecificity since they rarely proceed through radical-based pathways.[1]

While Pd catalysis has enhanced many areas of organic synthesis, the selective oxidation of olefins represents an exceptionally important accomplishment due to the ubiquity of alkenes in organic building blocks and their versatility as functional handles. Among the various methods of functionalizing olefins, the Wacker process has proven especially useful for industrial production of acetaldehyde from ethylene and is formally one of the oldest known methods for C–H oxidation. The application of this robust transformation to a broader range of substrates, known as the Tsuji–Wacker reaction, has facilitated the conversion of terminal olefins to methyl ketones with such high regioselectivity that terminal olefins may often be viewed as masked methyl ketones.[5]

The synthetic utility of the Tsuji–Wacker oxidation stems from its efficiency and broad functional group compatibility, and modifications to the original conditions have further expanded its applications.[6,7,8] While traditional Tsuji–Wacker conditions exhibit Markovnikov regioselectivity, forming mainly methyl ketone products (**135**) with only trace amounts of aldehyde (**136**) (Scheme 3.1A), a notable modification reported by the Grubbs group reverses this trend, enabling selective formation of aldehydes as the major products instead (Scheme 3.1B).[9] Early investigations into aldehyde-selective Tsuji–

Wacker processes required biased alkene substrates,[5,10] but Grubbs and co-workers found that use of $AgNO_2$ as a co-catalyst with $PdCl_2(PhCN)_2$ and $CuCl_2 \bullet 2H_2O$ in 15:1 *t*-BuOH/$MeNO_2$ enabled conversion of unbiased terminal alkenes to aldehydes in high yields and selectivities.[11] They further illustrated the catalyst-controlled nature of their system by accomplishing oxidation with high aldehyde selectivity on substrates bearing Lewis-basic directing groups that influence regioselectivity under traditional Tsuji–Wacker conditions.[12]

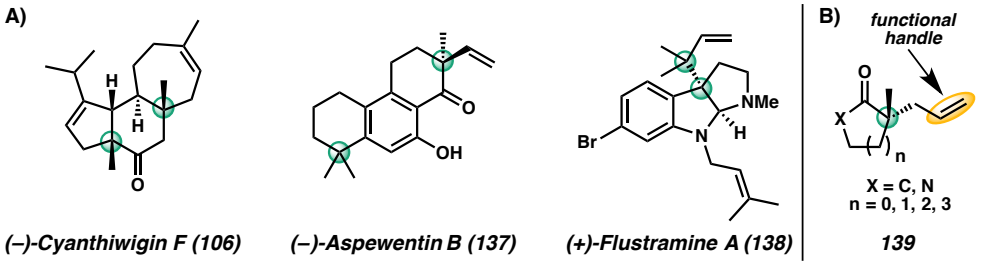
Scheme 3.1 A) Traditional Tsuji–Wacker selectivity. B) Aldehyde-selective Tsuji–Wacker oxidation



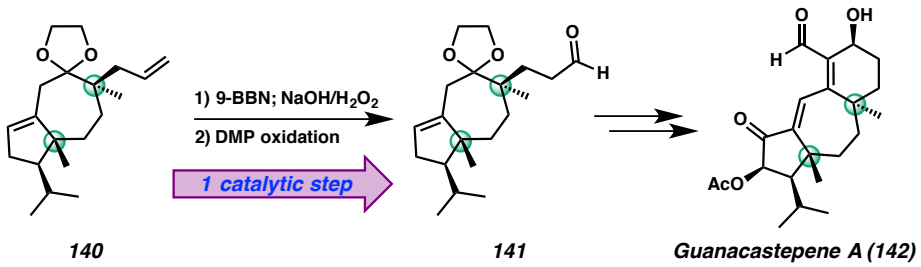
Despite the robustness of the nitrite-modified Tsuji–Wacker reaction, limitations remain. Specifically, oxidation of substrates bearing proximal steric hindrance, such as quaternary carbons, has yet to be demonstrated. Quaternary carbons are prevalent in many structurally complex and biologically interesting organic compounds (Figure 3.1A). The synthetic challenges presented by these sterically demanding motifs have inspired our group to develop a number of strategies for their construction via catalytic enantioselective decarboxylative allylic alkylation, among other methods.[13] While these methods have been employed to great effect in total synthesis,[14,15] the allylic alkylation products (**139**) are also unique substrates for methodological studies given that many

traditionally robust reactions often become problematic under the extreme steric constraints.[16] Structurally, the allyl moiety supplies a versatile functional handle, and the proximal quaternary stereocenter provides a basis from which to examine methodologies that are resilient enough to overcome the high steric demand (Figure 3.1B).

Figure 3.1 A) Examples of natural products containing quaternary carbons. B) Typical products of enantioselective decarboxylative allylic alkylations.



*Scheme 3.2 Example of a common two-step oxidation strategy from Danishefsky's synthesis of guanacastepene A (**142**)*



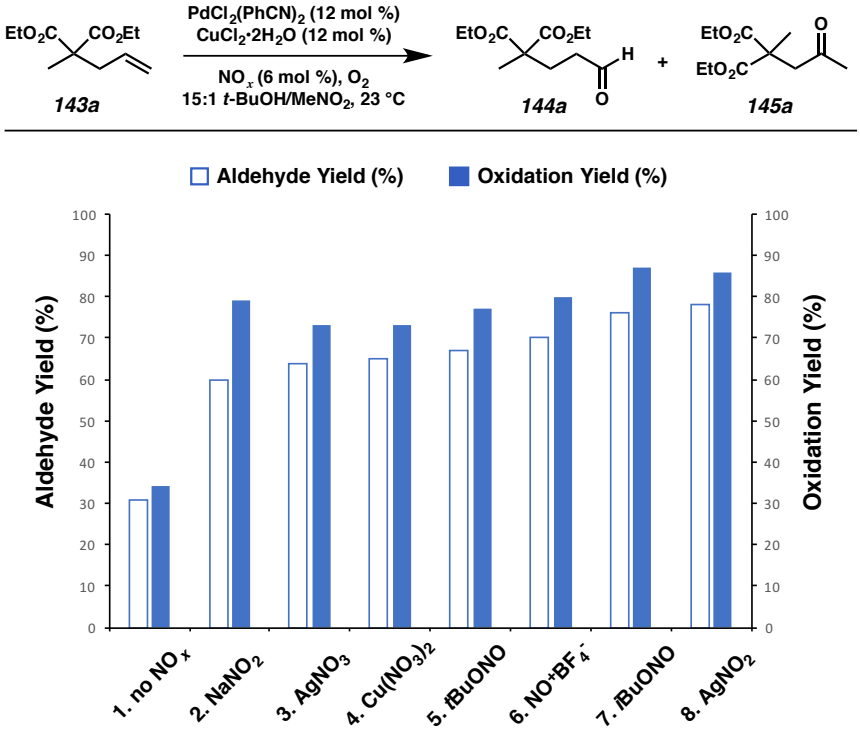
Examples of sterically encumbered substrates are often absent from methodology reports, impeding their utility in complex molecule synthesis. Indeed, the oxidation of hindered terminal alkenes to the corresponding aldehydes is often accomplished in two stoichiometric steps: hydroboration–oxidation, followed by Dess–Martin or Swern oxidation (Scheme 3.2). However, with the modern capabilities of the nitrite-modified Tsuji–Wacker reaction, we hypothesized this sequence could be achieved in a single

catalytic step, thereby streamlining synthetic strategy and generating less waste compared to the stoichiometric processes.

3.2 EXAMINATION OF THE NITRITE CO-CATALYST

We began our investigations by examining the effect of different nitrite sources on the reactivity of malonate derivative **143a** (Figure 3.2). Although various nitrite sources gave comparable yields of desired aldehyde **144a** (Entries 2–7), we found that $AgNO_2$ gave the optimal overall yield and selectivity for this hindered system (Entry 8).[17] Notably, the exclusion of any nitrite source severely impeded oxidation (Entry 1), corroborating theories concerning the critical role nitrite plays in this transformation.[9,11]

*Figure 3.2 Investigation of different nitrite sources in the aldehyde-selective Tsuji–Wacker. Oxidation yield is the sum of the yields of **144a** and **145a**.*



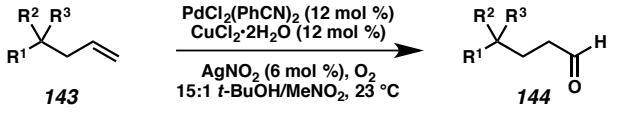
3.3 OXIDATION OF HINDERED TERMINAL ALKENES

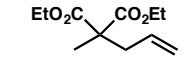
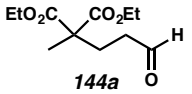
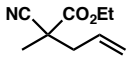
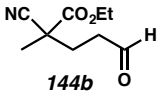
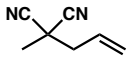
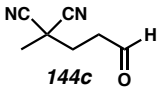
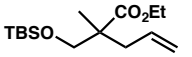
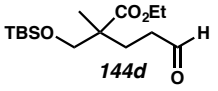
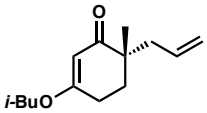
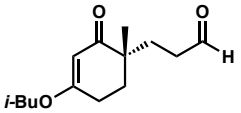
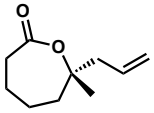
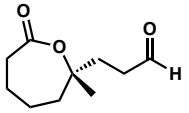
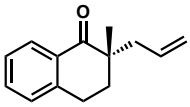
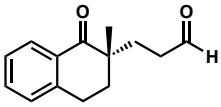
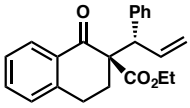
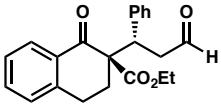
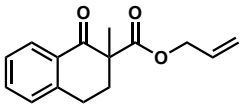
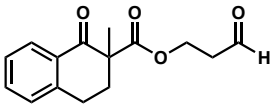
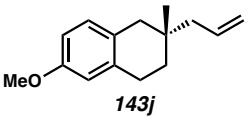
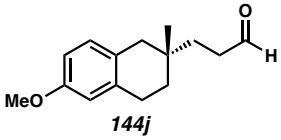
Having elucidated the optimized reaction conditions, we explored the reactivity of various substrates bearing proximal quaternary carbons in the aldehyde-selective Tsuji-Wacker oxidation, beginning with alkenes bearing quaternary carbons at the homoallylic position and later examining substrates with allylic quaternary carbons.

3.3.1 HOMOALLYLIC QUATERNARY ALKENES

Beginning our investigations on allylated malonate derivatives, we were delighted to find that substrates containing ester and nitrile functionalities readily underwent oxidation to the corresponding aldehyde products in excellent yields and high selectivities (Table 3.1, Entries 1–3). Although alcohols were incompatible with the reaction conditions,[18] TBS-ether **143d** was a competent substrate for the transformation, furnishing aldehyde **144d** in high yield (Entry 4). Vinylogous ester **143e** and caprolactone derivative **143f** were also reactive under the conditions, affording aldehydes **144e** and **144f** in good yield (Entries 5–6). Tetralone-derived substrates **143g–143i** also performed well in the reaction (Entries 7–9), although the more sterically congested alkene of **143h** required prolonged reaction time for full conversion (Entry 8). Notably, deoxytetralone derivative **135j** also proved to be a competent substrate, demonstrating that the presence of a carbonyl functionality adjacent to the quaternary carbon is not necessary for oxidation to proceed (Entry 10).[19]

Table 3.1 Substrate scope of the aldehyde-selective Tsuji–Wacker oxidation on hindered alkenes



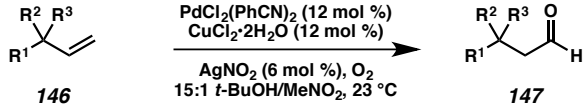
Entry[a]	Alkene Substrate	Aldehyde Product	Yield
1	 143a	 144a	90%[b]
2	 143b	 144b	81%
3	 143c	 144c	89%
4	 143d	 144d	87%
5	 143e	 144e	60%[d,f]
6	 143f	 144f	67%[c]
7	 143g	 144g	80%[c]
8	 143h	 144h	75%[b,e,g]
9	 143i	 144i	74%[c]
10	 143j	 144j	63%[c]

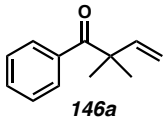
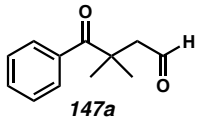
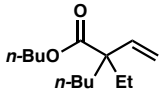
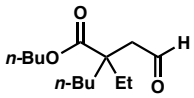
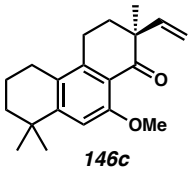
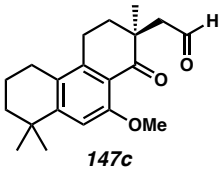
[a]Reactions performed on 0.2 mmol of **143** at 0.05 M over 7–17 h. Isolated yields. [b]Methyl ketone observed, 91–96% aldehyde selectivity. [c]Enal observed, 80–97% aldehyde selectivity. [d]Enal observed, 67% aldehyde selectivity. [e]Reaction time = 40 h. [f]Conducted on 0.08 mmol of **143e**. [g]Conducted on 0.06 mmol of **143h**.

3.3.2 ALLYLIC QUATERNARY ALKENES

Remarkably, alkenes bearing quaternary carbons at the allylic position were also suitable substrates for oxidation (Table 3.2). For instance, α-vinylic ketone **146a** was oxidized to aldehyde **147a** in high yield (Entry 1). Bulkier substitution at the allylic position was also tolerated, with α-vinylic ester **146b** reacting smoothly to generate aldehyde **147b** in good yield (Entry 2). Gratifyingly, oxidation of complex organic molecules was also possible, as conversion of aspewentin B derivative **146c**[20] to aldehyde **147c** proceeded in moderate yield (Entry 3).

Table 3.2 Aldehyde-selective Tsuji–Wacker oxidation of allylic quaternary alkenes



Entry[a]	Alkene Substrate	Aldehyde Product	Yield
1	 **146a**	 **147a**	85%[b]
2	 **146b**	 **147b**	69%[b]
3	 **146c**	 **147c**	64%[c]

[a]Reactions performed on 0.2 mmol of **146** at 0.05 M over 20–48 h. Isolated yields. [b]Methyl ketone observed, 88–91% aldehyde selectivity. [c]Conducted on 0.07 mmol of **146c**.

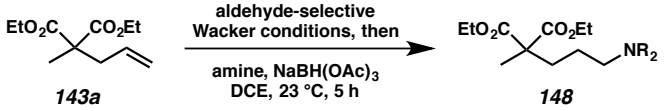
3.4 FORMAL ANTI-MARKOVNIKOV HYDROAMINATION

Inspired by the robustness of this transformation on such sterically encumbered substrates, we recognized an opportunity to expand the synthetic impact of the nitrite-modified Tsuji–Wacker reaction by leveraging the inherent reactivity of the aldehyde products. We envisioned that subsequent reductive amination of the aldehyde could effect formal anti-Markovnikov hydroamination of the olefin starting material. The addition of amines to alkenes has been recognized as an important research topic due to the ubiquity of amines in biologically active small molecules.[21,22] Anti-Markovnikov hydroamination remains a particularly active area of interest since Markovnikov addition is usually favored. While various efforts toward this challenging transformation have been reported, many strategies require air-sensitive transition metal catalysts, harsh conditions, or biased substrates to achieve regioselective hydroamination.[23] Furthermore, in some cases product scope is restricted to tertiary amines,[23h–k] and in other cases the reaction conditions are highly reducing.[23l] Noting these limitations, we anticipated that reductive amination of the aldehyde generated from the aldehyde-selective Tsuji–Wacker oxidation could provide a mild and efficient alternative.

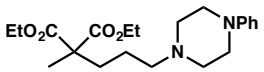
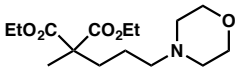
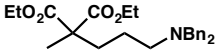
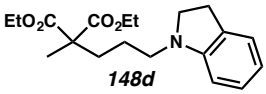
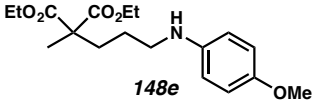
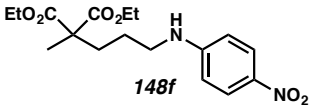
We selected alkene **143a** as the substrate for our formal hydroamination studies due to its excellent performance in the Tsuji–Wacker oxidation. Upon full conversion of the olefin under aldehyde-selective Tsuji–Wacker conditions, filtration through a silica plug and subsequent treatment of the residue with amine and $NaBH(OAc)_3$ at ambient temperature in DCE allowed access to the reductive amination products in good to excellent yields (Table 3.3). Aliphatic (**148a–148c**) and aromatic (**148d**) tertiary amines were prepared in excellent yields through this procedure (Entries 1–4), and electron-rich

(**148e**) and electron-poor (**148f**) anilines were also obtained in high yields (Entries 5–6). Notably, both tertiary and secondary amines are accessible through this operationally simple sequence.

*Table 3.3 Formal anti-Markovnikov hydroamination of **143a** via aldehyde-selective Tsuji–Wacker*



143a ***148***

Entry[a]	Amine	Product	Yield
1	*N*-phenylpiperazine	 ***148a***	98%
2	morpholine	 ***148b***	91%
3	dibenzylamine	 ***148c***	76%
4	indoline	 ***148d***	96%
5	4-methoxyaniline	 ***148e***	86%
6	4-nitroaniline	 ***148f***	95%

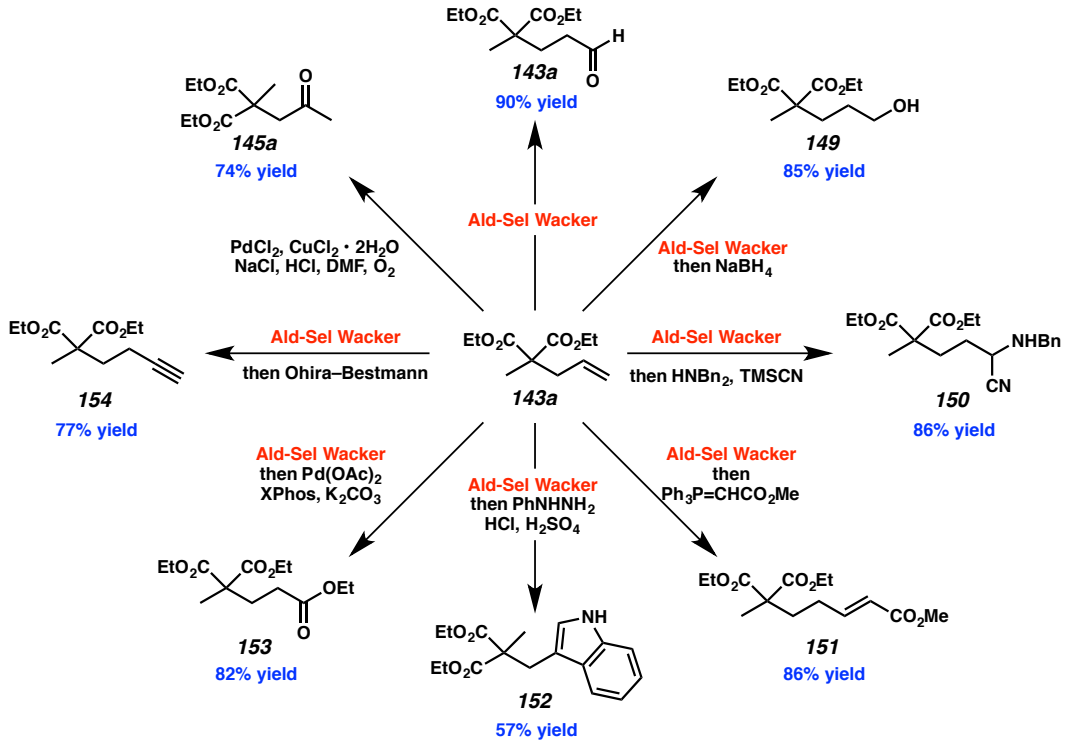
[a]Reactions performed on 0.2 mmol of **143a**. Isolated yields. Conditions for nitrite-Wacker: $PdCl_2(PhCN)_2$ (0.12 equiv), $CuCl_2 \cdot 2H_2O$ (0.12 equiv), $AgNO_2$ (0.06 equiv), 15:1 *t*-BuOH/$MeNO_2$ (0.05 M), 23 °C, 12 h.

3.5 FURTHER SYNTHETIC TRANSFORMATIONS

Encouraged by the success of the formal hydroamination reactions, we sought to extend our two-step procedure to other synthetically useful transformations, enabling

conversion of the alkene starting material to a variety of functional groups. For instance, sodium borohydride reduction of the crude aldehyde afforded formal anti-Markovnikov hydration product **149** in good yield (Scheme 3.3). Likewise, Strecker conditions allowed access to α-aminonitrile **150** while Horner–Wadsworth–Emmons olefination furnished α,β-unsaturated methyl ester **151** in high yield, effecting a two-carbon homologation of alkene **143a**. Fischer indolization also proved successful, affording 3-substituted indole **152** in moderate yield. Further oxidation[24] of the crude aldehyde delivered tris-ethyl ester **153** in high yield whereas treatment with the Ohira–Bestmann reagent enabled conversion of the terminal alkene to a terminal alkyne of one-carbon chain length longer (**154**). Finally, reactivity of alkene **143a** under traditional Tsuji–Wacker conditions was assessed, providing methyl ketone **145a** in good yield.

*Scheme 3.3 Summary of synthetic transformations of alkene **143a***



Ald-Sel Wacker = $PdCl_2(PhCN)_2$ (12 mol %), $CuCl_2 \cdot 2H_2O$ (12 mol %), $AgNO_2$ (6 mol %), O_2, 15:1 *t*-BuOH/$MeNO_2$, 23 °C

3.6 CONCLUDING REMARKS

In summary, we have amplified the synthetic impact of the aldehyde-selective Tsuji–Wacker oxidation by demonstrating its efficacy on diversely functionalized terminal alkenes bearing sterically demanding quaternary carbons at the allylic or homoallylic position, common motifs among intermediates in complex molecule synthesis. Moreover, we have illustrated how the aldehyde products of these reactions can be further transformed, enabling direct conversion of the alkene functional handle to a variety of other functional groups.[25] We anticipate that this operationally simple methodology will find many applications in chemical synthesis since several of these overall transformations are unprecedented or require multiple steps. From these studies it is clear that the aldehyde-selective Tsuji-Wacker oxidation is an extremely versatile tool for the facile catalytic functionalization of terminal olefins.

3.7 EXPERIMENTAL SECTION

3.7.1 MATERIALS AND METHODS

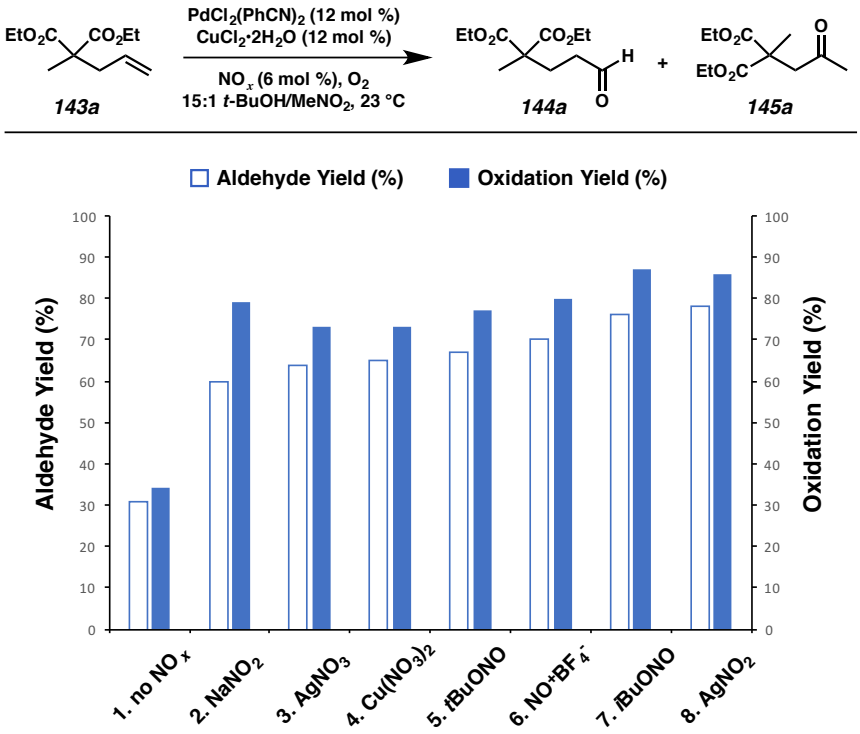
Unless noted in the specific procedure, reactions were performed in flame-dried glassware under argon atmosphere. Dried and deoxygenated solvents (Fisher Scientific) were prepared by passage through columns of activated aluminum before use.[26] Methanol (Fisher Scientific) was distilled from magnesium methoxide immediately prior to use. 1,2-dichloroethane (Fisher Scientific) was distilled from calcium hydride immediately prior to use. Anhydrous ethanol, *tert*-butanol, and *N*,*N*-dimethylformamide were purchased from Sigma Aldrich in sure-sealed bottles and used as received unless otherwise noted. Commercial reagents (Sigma Aldrich or Alfa Aesar) were used as received with the exception of palladium(II) acetate (Sigma Aldrich) and XPhos (Sigma Aldrich), which were stored in a nitrogen-filled govebox. The Ohira–Bestmann reagent[27] and carbomethoxy methylene triphenyl phosphorane ($Ph_3P{=}CHCO_2Me$)[28] were prepared according to known procedures. Triethylamine (Oakwood Chemical) and diisopropylethylamine (Oakwood Chemical) were distilled from calcium hydride immediately prior to use. Brine is defined as a saturated aqueous solution of sodium chloride. Reactions requiring external heat were modulated to the specified temperatures using an IKAmag temperature controller. Reaction progress was monitored by thin-layer chromatography (TLC) or Agilent 1290 UHPLC-LCMS. TLC was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching, potassium permanganate, or *p*-anisaldehyde staining. Silia*Flash* P60 Academic Silica gel (particle size 0.040–0.063 mm) was used for flash chromatography. NMR spectra were recorded on a Varian Mercury 300 spectrometer (at 300 MHz for ^{1}H

NMR and 75 MHz for ^{13}C NMR), a Varian Inova 500 spectrometer (at 500 MHz for ^{1}H NMR and 126 MHz for ^{13}C NMR), or a Bruker AV III HD spectrometer equipped with a Prodigy liquid nitrogen temperature cryoprobe (at 400 MHz for ^{1}H NMR and 101 MHz for ^{13}C NMR), and are reported relative to residual $CHCl_3$ (δ 7.26 for ^{1}H NMR, δ 77.16 for ^{13}C NMR) or C_6H_6 (δ 7.16 for ^{1}H NMR, δ 128.06 for ^{13}C NMR). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Abbreviations are used as follows: s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, m = complex multiplet. Infrared (IR) spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer using thin film samples on KBr plates, and are reported in frequency of absorption (cm^{-1}). High-resolution mass spectra (HRMS) were obtained from the Caltech Mass Spectral Facility using a JEOL JMS-600H High Resolution Mass Spectrometer with fast atom bombardment (FAB+) ionization mode or were acquired using an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI+) mode. Optical rotations were measured with a Jasco P-1010 polarimeter at 589 nm using a 100 mm path-length cell.

3.7.2 PREPARATIVE PROCEDURES

3.7.2.1 CATALYST OPTIMIZATION

Table 3.4 Investigation of different nitrite sources in the aldehyde-selective Tsuji–Wacker

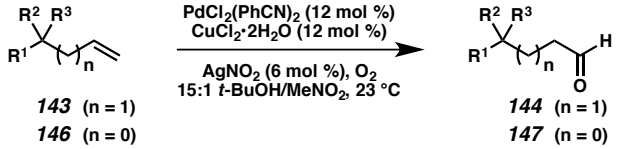


NO_x species	Aldehyde yield (%)[a]	Ketone yield (%)	Oxidation yield (%)[b]	Selectivity (aldehyde:ketone)
$AgNO_2$	78	8	86	10:1
$AgNO_3$	64	9	73	7:1
$NaNO_2$	60	19	79	3:1
$NO^+BF_4^-$	70	10	80	7:1
$Cu(NO_3)_2$	65	8	73	8:1
t-BuONO	67	10	77	7:1
i-BuONO	76	11	87	7:1
no NO_x	31	3	34	10:1

[a] Yields were calculated from the crude ^{1}H NMR spectrum.
[b] Oxidation yield is the sum of the yields of aldehyde **144a** and methyl ketone **145a**.

Procedure for Catalyst Optimization. To a flame-dried 25-mL round-bottom flask with a magnetic stir bar were added bis(benzonitrile)palladium(II) chloride (9.2 mg, 0.024 mmol, 0.12 equiv), copper(II) chloride dihydrate (4.1 mg, 0.024 mmol, 0.12 equiv), and silver nitrite (1.8 mg, 0.012 mmol, 0.06 equiv). The flask was capped with a rubber septum, and *tert*-butyl alcohol (3.75 mL) and nitromethane (0.25 mL) were added sequentially by syringe. The mixture was stirred at 23 °C and sparged with oxygen gas (balloon) for 3 minutes. Alkene **143a** (42.9 mg, 0.20 mmol, 1.00 equiv) was added dropwise by syringe, and the reaction mixture was sparged with oxygen for another minute. The reaction was stirred under oxygen atmosphere at 23 °C for 14 hours, after which the reaction mixture was diluted with water (4 mL) and extracted with dichloromethane (3 x 5 mL). The organic extracts were dried over sodium sulfate, then filtered and concentrated in vacuo. Nitrobenzene (24.6 mg, 0.20 mmol, 1.00 equiv) was added as an internal standard immediately prior to NMR analysis, and the yield and selectivity of the formation of aldehyde **144a** was calculated from the ^{1}H NMR spectrum (d1 = 15s).

3.7.2.2 GENERAL EXPERIMENTAL PROCEDURES

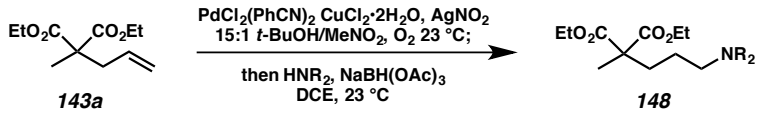


143 **(n = 1)**
146 **(n = 0)**

144 **(n = 1)**
147 **(n = 0)**

General Procedure A. *Aldehyde-selective Wacker-type oxidation of alkenes*.

To a flame-dried 25-mL round-bottom flask with a magnetic stir bar were added bis(benzonitrile)palladium(II) chloride (9.2 mg, 0.024 mmol, 0.12 equiv), copper(II) chloride dihydrate (4.1 mg, 0.024 mmol, 0.12 equiv), and silver nitrite (1.8 mg, 0.012 mmol, 0.06 equiv). The flask was capped with a rubber septum, and *tert*-butyl alcohol (3.75 mL) and nitromethane (0.25 mL) were added sequentially by syringe. The mixture was stirred at 23 °C and sparged with oxygen gas (balloon) for 3 minutes. Alkene **143** or **146** (0.20 mmol, 1.00 equiv) was added dropwise by syringe, and the reaction mixture was sparged with oxygen for another minute. The reaction was stirred under oxygen atmosphere at 23 °C until TLC analysis indicated consumption of starting material. The reaction mixture was diluted with water (4 mL) and extracted with dichloromethane (3 x 5 mL). The organic extracts were dried over sodium sulfate, and then filtered and concentrated in vacuo. The crude residue was purified by silica gel column chromatography, using mixture of hexanes and ethyl acetate as eluent to afford aldehyde **144** or **147**.



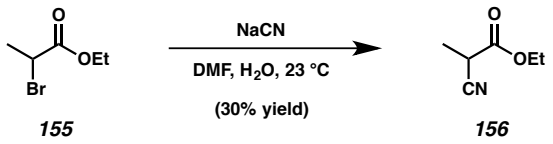
143a *148*

General Procedure B. *Hydroamination of diethyl 2-allyl-2-methylmalonate* ***(143a)***.

To a flame-dried 25-mL round-bottom flask with a magnetic stir bar were added bis(benzonitrile)palladium(II) chloride (9.2 mg, 0.024 mmol, 0.12 equiv), copper(II) chloride dihydrate (4.1 mg, 0.024 mmol, 0.12 equiv), and silver nitrite (1.8 mg, 0.012 mmol, 0.06 equiv). The flask was capped with a rubber septum, and *tert*-butyl alcohol (3.75 mL) and nitromethane (0.25 mL) were added sequentially by syringe. The mixture was stirred at 23 °C and sparged with oxygen gas (balloon) for 3 minutes. Alkene **143a** (42.9 mg, 0.20 mmol, 1.00 equiv) was added dropwise by syringe, and the reaction mixture was sparged with oxygen for another minute. The reaction was stirred under oxygen atmosphere at 23 °C for 12 hours, when TLC analysis indicated consumption of starting material. The solvent was removed under reduced pressure, and the residue was loaded onto a short plug of silica gel, eluting with 30% ethyl acetate in hexanes (100 mL). The oil obtained upon concentration was then redissolved in 1,2-dichloroethane (4 mL) and treated with amine (0.22 mmol, 1.1 equiv) at 23 °C. After one hour, sodium triacetoxyborohydride (63.6 mg, 0.30 mmol, 1.50 equiv) was added in one portion. Stirring was continued at 23 °C for 5 hours, at which time the reaction was diluted with diethyl ether (3 mL), washed with saturated aqueous sodium bicarbonate (5 mL), and extracted with diethyl ether (3 x 5 mL). The organic extracts were dried over sodium sulfate, and then filtered and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography, using mixture of hexanes and ethyl acetate with 0.5% triethylamine as eluent to afford amine **148**.

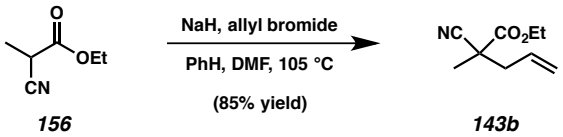
3.7.2.3 SUBSTRATE SYNTHESIS AND CHARACTERIZATION DATA

Compounds **143a** and **159,**[16] **143e,**[29] **143g,**[13b] **143h,**[30] **143i,**[13b] **143f,**[30] and **146a–c,**[20] **160**[30] may be prepared as previously reported by our research group.



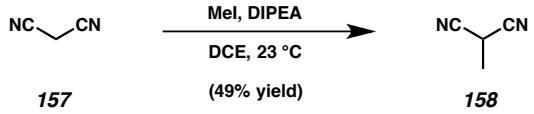
155 *156*

Ethyl-2-cyanopropanoate (156). A round-bottom flask equipped with a magnetic stir bar and thermometer was charged with sodium cyanide (2.44 g, 49.7 mmol, 1.50 equiv), *N*,*N*-dimethylformamide (22 mL), and water (2.2 mL). Alkyl bromide **155** (4.30 mL, 33.1 mmol, 1.00 equiv) was added dropwise over 15 minutes, making sure the internal temperature did not exceed 35 °C throughout addition. After complete addition, the internal thermometer was removed, and the mixture was stirred at 23 °C for 12 hours, at which time the reaction mixture was diluted with diethyl ether and washed sequentially with cold 5% aqueous hydrochloric acid (15 mL) and saturated aqueous sodium bicarbonate (15 mL). The organic layer was dried over sodium sulfate, and then filtered and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (10% → 20% ethyl acetate in hexanes), furnishing cyanoester **156** as a colorless oil (1.27 g, 30% yield). Characterization data match those reported in the literature.[31]



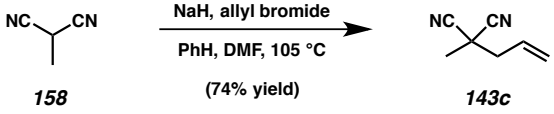
156 ***143b***

Ethyl 2-cyano-2-methylpent-4-enoate (143b). To a suspension of sodium hydride (60% dispersion in mineral oil, 419 mg, 10.5 mmol, 1.05 equiv) in benzene (15 mL) was added a solution of cyanoester **156** (1.27 g, 9.98 mmol, 1.00 equiv) in benzene (12 mL). *N*,*N*-dimethylformamide (8 mL) was added to stabilize the sodium enolate, and the mixture was stirred at 23 °C for 20 minutes before allyl bromide (910 μL mL, 10.5 mmol, 1.05 equiv) was added dropwise. Upon complete addition, the reaction mixture was heated to reflux (105 °C). After 12 hours, the reaction was allowed to cool to room temperature before quenching with water (15 mL) and extracting with diethyl ether (3 x 20 mL). The organic extracts were washed with brine (20 mL) and dried over magnesium sulfate before filtration and concentration under reduced pressure. The crude residue was purified by silica gel column chromatography (11% ethyl acetate in hexanes) to afford alkene **143b** as a colorless oil (1.43 g, 85% yield). R*f* = 0.68 (33% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.81 (ddt, *J* = 16.1, 11.0, 7.3 Hz, 1H), 5.33–5.18 (m, 2H), 4.26 (qd, *J* = 7.1, 1.0 Hz, 2H), 2.67 (ddt, *J* = 13.8, 7.2, 1.2 Hz, 1H), 2.55–2.45 (m, 1H), 1.58 (s, 3H), 1.32 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 169.0, 130.7, 121.2, 119.8, 63.0, 43.8, 42.2, 22.8, 14.2; IR (Neat Film, KBr) 3083, 2985, 1744, 1455, 1233, 1174, 1017, 930; HRMS (FAB+) *m/z* calc'd for $C_9H_{14}NO_2$ $[M+H]^+$: 168.1024, found 168.1012.



157 ***158***

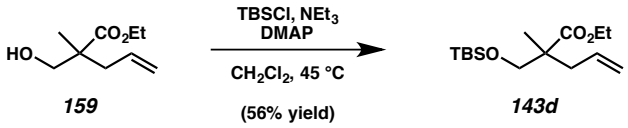
2-Methylmalononitrile (158). To a flame-dried round-bottom flask were added malononitrile **157** (3.00 g, 45.4 mmol, 1.00 equiv) and 1,2-dichloroethane (90 mL). The suspension was cooled to 0 °C using an ice water bath, and diisopropylethylamine (7.91 mL, 45.4 mmol, 1.00 equiv) and methyl iodide (2.83 mL, 45.4 mmol, 1.00 equiv) were added dropwise sequentially. The resulting mixture was stirred at 23 °C for 24 hours, at which time the reaction was quenched with water and transferred to a separatory funnel. The aqueous layer was extracted with ethyl acetate (5 x 50 mL), and the combined organic extracts were washed with brine (50 mL) and dried over sodium sulfate. After filtration and concentration, the crude residue obtained was purified by silica gel column chromatography (5% → 10% → 15% ethyl acetate in hexanes) to furnish 2-methylmalononitrile (**158**) as a white solid (1.77 g, 49% yield). Characterization data match those reported in the literature.[32]



158 ***143c***

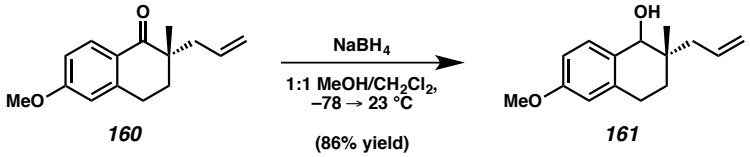
2-Allyl-2-methylmalononitrile (143c). To a suspension of sodium hydride (60% dispersion in mineral oil, 309 mg, 7.72 mmol, 1.05 equiv) in benzene (7.1 mL) was added a solution of 2-methylmalononitrile **158** (589 mg, 7.35 mmol, 1.00 equiv) in benzene (7.1 mL). *N*,*N*-dimethylformamide (3.5 mL) was added to stabilize the sodium enolate, and the mixture was stirred at 23 °C for 20 minutes before allyl bromide (670 μL mL, 7.72 mmol, 1.05 equiv) was added dropwise. Upon complete addition, the reaction mixture

was heated to reflux (105 °C). After 12 hours, the reaction was allowed to cool to room temperature before quenching with water (8 mL) and extracting with diethyl ether (3 x 10 mL). The organic extracts were washed with brine (10 mL) and dried over magnesium sulfate before filtration and concentration under reduced pressure. The crude residue was purified by silica gel column chromatography (10% ethyl acetate in hexanes) to afford alkene **143c** as a colorless oil (653 mg, 74% yield). R*f* = 0.52 (33% ethyl acetate in hexanes);^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.89 (ddt, *J* = 16.7, 10.1, 7.3 Hz, 1H), 5.55–5.31 (m, 2H), 2.68 (ddd, *J* = 7.3, 1.3, 0.8 Hz, 2H), 1.79 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 128.5, 123.6, 115.9, 43.0, 31.7, 24.2; IR (Neat Film, KBr) 3087, 2987, 2927, 1654, 1650, 1454, 1440, 1417, 1276, 1180, 994, 936, 729; HRMS (FAB+) *m/z* calc'd for $C_7H_9N_2$ $[M+H]^+$: 121.0760, found 121.0758.



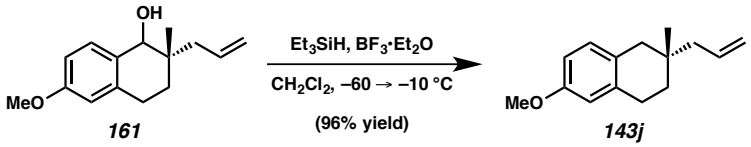
Ethyl 2-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-methylpent-4-enoate (143d). To a flame-dried two-necked round-bottom flask equipped with a reflux condenser and magnetic stir bar were added alcohol **159** (108.2 mg, 0.611 mmol, 1.00 equiv) and dichloromethane (12.2 mL). *tert*-Butyldimethylsilyl chloride (101.2 mg, 0.672 mmol, 1.10 equiv), triethylamine (0.17 mL, 1.22 mmol, 2.00 equiv), and 4-(dimethylamino)pyridine (7.5 mg, 0.0611 mmol, 0.10 equiv) were added at 23 °C, and the mixture was heated to reflux (45 °C). After 42 hours, the reaction was allowed to cool to 23 °C and washed with 2 M aqueous hydrochloric acid (2 x 10 mL) and brine (10 mL), and then dried over sodium sulfate. After filtration and concentration under

reduced pressure, the crude residue was purified by silica gel column chromatography (3% ethyl acetate in hexanes), delivering alkene **143d** as a colorless oil (98.1 mg, 56% yield). R*f* = 0.79 (33% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.72 (ddt, *J* = 16.5, 10.6, 7.4 Hz, 1H), 5.14–4.96 (m, 2H), 4.12 (qd, *J* = 7.2, 0.9 Hz, 2H), 3.70–3.46 (m, 2H), 2.38 (ddt, *J* = 13.6, 7.2, 1.2 Hz, 1H), 2.22 (ddt, *J* = 13.6, 7.7, 1.1 Hz, 1H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.13 (s, 3H), 0.87 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ175.8, 134.1, 118.1, 68.1, 60.4, 48.3, 39.5, 25.9, 19.3, 18.3, 14.4, -5.5; IR (Neat Film, KBr) 2956, 2929, 2857, 1732, 1472, 1386, 1251, 1227, 1101, 837, 776 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{15}H_{31}O_3Si$ $[M+H]^+$: 287.2037, found 287.2040.



(2*S*)-2-Allyl-6-methoxy-2-methyl-1,2,3,4-tetrahydronaphthalen-1-ol (161). To a solution of ketone **160** (64.9 mg, 0.282 mmol, 1.00 equiv) in dichloromethane (2.8 mL) and methanol (2.8 mL) was added a solution of sodium borohydride (21.3 mg, 0.564 mmol, 2.00 equiv) in dichloromethane (1.2 mL) and methanol (1.2 mL) at –78 °C. The reaction mixture was allowed to warm to 23 °C over the course of six hours. When TLC analysis indicated full consumption of starting material, the reaction was quenched with acetone (2.0 mL) and 2N NaOH (2.0 mL). The phases were separated, and the organic layer was immediately washed with brine (10 mL) and dried over sodium sulfate. After filtration and concentration under reduced pressure, the crude residue was purified by silica gel column chromatography (15% ethyl acetate in hexanes), furnishing alcohol **161** as a 1:1 mixture of diastereomers (56.5 mg, 86% yield). R*f* = 0.26 (20% ethyl acetate in

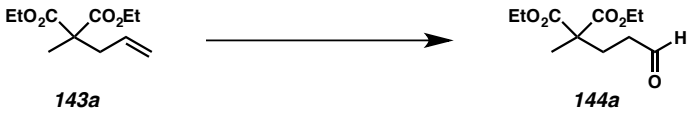
hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.35 (d, *J* = 8.5 Hz, 1H), 7.28 (d, *J* = 8.5 Hz, 1H), 6.79–6.73 (m, 2H), 6.64 (dt, *J* = 5.1, 1.8 Hz, 2H), 6.04–5.83 (m, 2H), 5.16–5.00 (m, 5H), 4.23 (s, 1H), 3.78 (s, 6H), 2.87–2.65 (m, 5H), 2.28 (ddt, *J* = 13.6, 7.3, 1.2 Hz, 1H), 2.13–2.01 (m, 3H), 1.87 (ddd, *J* = 13.5, 9.4, 6.7 Hz, 1H), 1.78 (ddd, *J* = 13.8, 7.5, 6.3 Hz, 1H), 1.55 (dt, *J* = 13.4, 6.6 Hz, 1H), 1.46 (dddd, *J* = 13.6, 5.9, 4.7, 1.0 Hz, 2H), 0.99 (s, 3H), 0.88 (s, 4H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 159.0, 158.9, 137.7, 137.4, 135.3, 135.0, 131.0, 130.9, 130.6, 130.2, 117.7, 117.6, 113.3, 113.2, 112.6, 75.1, 74.9, 55.3, 42.6, 41.6, 37.1, 36.9, 29.4, 29.1, 26.1, 26.0, 21.1, 19.9; IR (Neat Film, KBr) 3430 (br), 2928, 1610, 1501, 1456, 1263, 1159, 1104, 1038, 1015, 912, 802 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{15}H_{20}O_2$ $[M\bullet]^+$: 232.1463, found 232.1439.



(*S*)-2-Allyl-6-methoxy-2-methyl-1,2,3,4-tetrahydronaphthalene (143j). To a solution of alcohol **161** (56.5 mg, 0.243 mmol, 1.00 equiv) in dichloromethane (5.0 mL) was added triethylsilane (0.12 mL, 0.730 mmol, 3.00 equiv) and boron trifluoride diethyl etherate (60 μL, 0.486 mmol, 2.00 equiv) at –60 °C. After 10 minutes, the reaction mixture was warmed to –10 °C and stirred at this temperature for 7 hours. A saturated aqueous solution of potassium carbonate was added, and the mixture was extracted with dichloromethane (2 x 20 mL). The combined organic extracts were dried over sodium sulfate before filtration and concentration under reduced pressure. The crude residue was purified by silica gel column chromatography (5% ethyl acetate in hexanes), affording tetralin **143j** as a colorless oil (50.3 mg, 96% yield). R*f* = 0.67 (20% ethyl acetate in

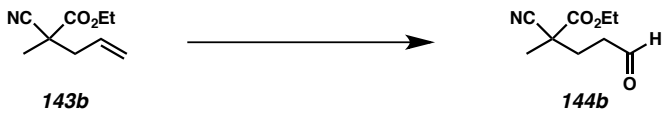
hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.97 (d, *J* = 8.3 Hz, 1H), 6.73–6.63 (m, 2H), 5.91 (ddt, *J* = 16.9, 10.2, 7.5 Hz, 1H), 5.14–4.96 (m, 2H), 3.79 (s, 3H), 2.79 (t, *J* = 6.7 Hz, 2H), 2.60–2.39 (m, 2H), 2.06 (qdt, *J* = 13.7, 7.3, 1.2 Hz, 2H), 1.67–1.47 (m, 2H), 0.96 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 157.5, 137.0, 135.2, 130.5, 128.3, 117.3, 113.4, 112.0, 55.3, 45.4, 41.1, 33.8, 32.6, 26.5, 24.8; IR (Neat Film, KBr) 3073, 2951, 2914, 1611, 1503, 1464, 1267, 1254, 1236, 1153, 1042, 912, 808 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{15}H_{21}O$ $[M+H]^+$: 217.1587, found 217.1584; $[\alpha]^{25}_D$ 6.47 (*c* 1.0, $CHCl_3$).

3.7.2.4 ALDEHYDE CHARACTERIZATION DATA



143a ***144a***

Diethyl 2-methyl-2-(3-oxopropyl)malonate (144a). Aldehyde **144a** was prepared from **143a** using General Procedure A, reaction time: 7 h, column eluent: 7% → 10% ethyl acetate in hexanes. 90% isolated yield. R*f* = 0.45 (33% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.76 (t, *J* = 1.3 Hz, 1H), 4.18 (qd, *J* = 7.2, 0.6 Hz, 4H), 2.56–2.47 (m, 2H), 2.22–2.13 (m, 2H), 1.41 (s, 3H), 1.25 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 201.1, 171.9, 61.6, 52.9, 39.6, 27.9, 20.5, 14.2; IR (Neat Film, KBr) 2984, 1730, 1465, 1381, 1262, 1110, 1023, 861 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{11}H_{19}O_5$ $[M+H]^+$: 231.1227, found 231.1232.

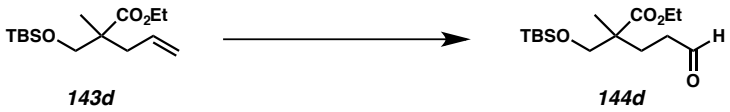


143b ***144b***

Ethyl 2-cyano-2-methyl-5-oxopentanoate (144b). Aldehyde **144b** was prepared from **143b** using General Procedure A, reaction time: 7 h, column eluent: 20% ethyl acetate in hexanes. 81% isolated yield. R*f* = 0.39 (33% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.77 (d, *J* = 0.9 Hz, 1H), 4.25 (qd, *J* = 7.1, 0.7 Hz, 2H), 2.83–2.53 (m, 2H), 2.27 (dddd, *J* = 14.4, 10.0, 5.6, 0.7 Hz, 1H), 2.15–2.02 (m, 1H), 1.61 (d, *J* = 0.7 Hz, 3H), 1.31 (td, *J* = 7.1, 0.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 199.2, 168.8, 119.5, 63.2, 43.1, 39.9, 30.1, 23.6, 14.1; IR (Neat Film, KBr) 2988, 2944, 1744, 1715, 1453, 1255, 1128, 1017, 857 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_9H_{14}NO_3$ $[M+H]^+$: 184.0974, found 184.0976.

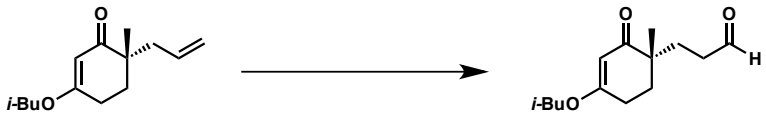
143c ***144c***

2-Methyl-2-(3-oxopropyl)malononitrile (144c). Aldehyde **144c** was prepared from **143c** using General Procedure A, reaction time: 17 h, column eluent: 20% ethyl acetate in hexanes. 89% isolated yield. R*f* = 0.25 (33% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.85 (s, 1H), 3.00–2.84 (m, 2H), 2.38–2.21 (m, 2H), 1.84 (s, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ197.7, 115.67, 39.9, 31.6, 31.2, 25.0; IR (Neat Film, KBr) 2848, 1724, 1454, 1389, 1150, 897, 629 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_7H_9N_2O$ $[M+H]^+$: 137.0715, found 137.0688.



143d ***144d***

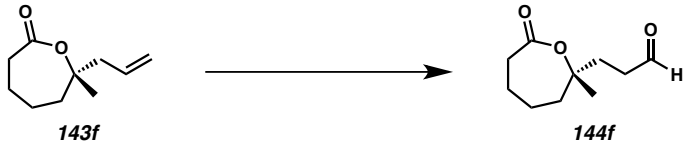
Ethyl 2-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-methyl-5-oxopentanoate (144d). Aldehyde **144d** was prepared from **143d** using General Procedure A, reaction time: 15 h, column eluent: 7% ethyl acetate in hexanes. 87% isolated yield. R*f* = 0.70 (33% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.74 (t, *J* = 1.6 Hz, 1H), 4.10 (q, *J* = 7.1 Hz, 2H), 3.64–3.57 (m, 2H), 2.46–2.40 (m, 2H), 1.97 (ddd, *J* = 14.0, 8.7, 7.1 Hz, 1H), 1.82–1.72 (m, 1H), 1.23 (t, *J* = 7.1 Hz, 3H), 1.13 (s, 3H), 0.85 (s, 9H), 0.01 s, 6 H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 202.1, 175.5, 68.4, 60.7, 47.6, 39.6, 27.2, 25.9, 19.7, 18.3, 14.3, –5.5; IR (Neat Film, KBr) 2955, 2930, 2857, 1728, 1472, 1252, 1184, 1100, 838, 777, 668 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{15}H_{31}O_4Si$ $[M+H]^+$: 303.1986, found 303.1983.



143e ***144e***

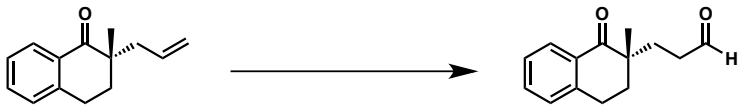
(*S*)-3-(4-Isobutoxy-1-methyl-2-oxocyclohex-3-en-1-yl)propanal (144e). Aldehyde **144e** was prepared from **143e** using General Procedure A, reaction time: 14 h, column eluent: 15% ethyl acetate in hexanes. 60% isolated yield. R*f* = 0.34 (33% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.76 (t, *J* = 1.5 Hz, 1H), 5.24 (s, 1H), 3.57 (d, *J* = 6.5 Hz, 2H), 2.53–2.36 (m, 4H), 2.02 (dq, *J* = 13.3, 6.7 Hz, 1H), 1.93–1.69 (m, 4H), 1.10 (s, 3H), 1.00–0.95 (m, 6H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 203.2, 202.4, 176.3, 101.5, 75.0, 42.7, 39.4, 32.8, 29.1, 27.9, 26.0, 22.6, 19.2; IR (Neat Film, KBr) 2961,

2932, 1724, 1648, 1607, 1384, 1369, 1195, 993, 840 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{14}H_{23}O_3$ $[M+H]^+$: 239.1642, found 239.1638; $[\alpha]^{25}_D$ –5.0 (*c* 0.94, $CHCl_3$).



143f ***144f***

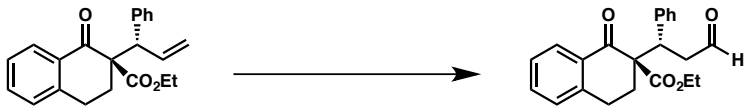
(*S*)-3-(2-Methyl-7-oxooxepan-2-yl)propanal (144f). Aldehyde **144f** was prepared from **143f** using General Procedure A, reaction time: 15 h, column eluent: 20% → 40% ethyl acetate in hexanes. 67% isolated yield. R*f* = 0.30 (67% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.82 (d, *J* = 1.2 Hz, 1H), 2.80–2.57 (m, 4H), 2.11 (ddd, *J* = 14.9, 9.0, 6.3 Hz, 1H), 1.96–1.74 (m, 6H), 1.69–1.57 (m, 1H), 1.44 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 201.8, 174.9, 82.3, 39.4, 38.9, 37.6, 34.9, 24.7, 24.1, 23.7; IR (Neat Film, KBr) 2936, 1720, 1716, 1289, 1185, 1107, 1018, 858 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{10}H_{17}O_3$ $[M+H]^+$: 185.1178, found 185.1177; $[\alpha]^{25}_D$ 1.6 (*c* 2.46, $CHCl_3$).



143g ***144g***

(*S*)-3-(2-Methyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)propanal (144g). Aldehyde **144g** was prepared from **143g** using General Procedure A, reaction time: 12 h, column eluent: 5% ethyl acetate in hexanes. 80% isolated yield. R*f* = 0.15 (20% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.76 (t, *J* = 1.5 Hz, 1H), 8.01 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.49–7.42 (m, 1H), 7.33–7.26 (m, 1H), 7.22 (ddq, *J* = 7.6, 1.5, 0.8 Hz, 1H), 3.01 (t, *J* = 6.3 Hz, 2H), 2.61–2.30 (m, 2H), 2.13–1.82 (m, 4H), 1.21 (s, 3H); ^{13}C

NMR ($CDCl_3$, 126 MHz) δ 202.2, 201.9, 143.1, 133.4, 131.5, 128.9, 128.1, 126.9, 44.1, 39.2, 34.2, 28.8, 25.3, 22.2; IR (Neat Film, KBr) 2929, 1722, 1682, 1600, 1454, 1224, 976, 798, 742 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{14}H_{17}O_2$ $[M+H]^+$: 217.1229, found 217.1258; $[\alpha]^{25}_D$ –1.0 (*c* 1.65, $CHCl_3$).

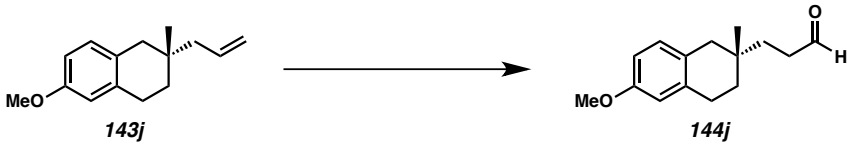


143h ***144h***

Ethyl (*R*)-1-oxo-2-((*S*)-3-oxo-1-phenylpropyl)-1,2,3,4-tetrahydronaphthalene-2-carboxylate (144h). Aldehyde **144h** was prepared from **143h** using General Procedure A, reaction time: 40 h, column eluent: 10% ethyl acetate in hexanes. 75% isolated yield. R*f* = 0.48 (33% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.59 (t, *J* = 1.7 Hz, 1H), 8.00 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.44 (td, *J* = 7.5, 1.5 Hz, 1H), 7.40–7.34 (m, 2H), 7.31–7.24 (m, 2H), 7.24–7.12 (m, 3H), 4.19 (dd, *J* = 8.4, 6.2 Hz, 1H), 4.08 (q, *J* = 7.1 Hz, 2H), 3.13–3.07 (m, 2H), 3.07–2.97 (m, 1H), 2.88 (dt, *J* = 17.8, 4.5 Hz, 1H), 2.34 (ddd, *J* = 13.7, 4.8, 3.7 Hz, 1H), 1.98 (ddd, *J* = 13.8, 11.2, 5.1 Hz, 1H), 1.09 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 200.9, 194.7, 170.2, 142.7, 139.1, 133.6, 132.6, 130.5, 128.7, 128.4, 128.3, 127.5, 126.9, 61.8, 60.5, 46.3, 43.0, 30.5, 26.1, 14.0; IR (Neat Film, KBr) 2978, 2725, 1725, 1689, 1600, 1454, 1298, 1235, 1214, 1018, 909, 742, 703, 648 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{22}H_{23}O_5$ $[M+OH]^+$: 367.1540, found 367.1535; $[\alpha]^{25}_D$ 15.7 (*c* 1.52, $CHCl_3$).

143i ***144i***

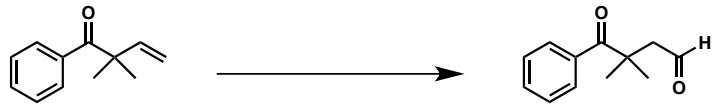
3-Oxopropyl 2-methyl-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (144i). Aldehyde **144i** was prepared from **143i** using General Procedure A, reaction time: 10 h, column eluent: 15% ethyl acetate in hexanes. 74% isolated yield. R*f* = 0.27 (33% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.61 (t, *J* = 1.4 Hz, 1H), 8.02 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.47 (td, *J* = 7.5, 1.5 Hz, 1H), 7.34–7.28 (m, 1H), 7.24–7.19 (m, 1H), 4.54–4.31 (m, 2H), 3.12–2.86 (m, 2H), 2.68 (ddt, *J* = 7.2, 6.0, 1.5 Hz, 2H), 2.58 (ddd, *J* = 13.7, 6.2, 4.9 Hz, 1H), 2.05 (ddt, *J* = 13.8, 9.0, 4.6 Hz, 1H), 1.48 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 199.0, 196.1, 172.9, 143.1, 133.7, 131.6, 128.9, 128.1, 127.0, 58.9, 54.0, 42.5, 33.7, 25.9, 20.4; IR (Neat Film, KBr) 2936, 1732, 1687, 1682, 1601, 1455, 1308, 1265, 1228, 1189, 1114, 743 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{15}H_{17}O_4$ $[M+H]^+$: 261.1127, found 261.1155.



143j ***144j***

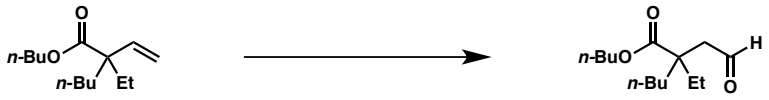
(*S*)-3-(6-Methoxy-2-methyl-1,2,3,4-tetrahydronaphthalen-2-yl)propanal (144j). Aldehyde **144j** was prepared from **143j** using General Procedure A, reaction time: 12 h, column eluent: 5% ethyl acetate in hexanes. 63% isolated yield. R*f* = 0.34 (20% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.79 (t, *J* = 1.9 Hz, 1H), 6.95 (d, *J* = 8.4 Hz, 1H), 6.71–6.66 (m, 1H), 6.64 (d, *J* = 2.7 Hz, 1H), 3.77 (s, 3H), 2.77 (td, *J* = 6.7, 4.2 Hz, 2H), 2.56–2.39 (m, 4H), 1.65–1.60 (m, 2H), 1.58 (t, *J* = 6.8 Hz, 2H), 0.93 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 203.0, 157.7, 136.7, 130.5, 127.7, 113.4, 112.2, 55.4,

41.1, 39.1, 33.9, 32.6, 31.9, 26.4, 24.4; IR (Neat Film, KBr) 2916, 2834, 2719, 1724, 1610, 1503, 1267, 1242, 1040, 808 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{15}H_{20}O_2$ $[M\bullet]^+$: 232.1463, found 232.1473; $[\alpha]^{25}_D$ 85.6 (*c* 1.00, $CHCl_3$).



146a ***147a***

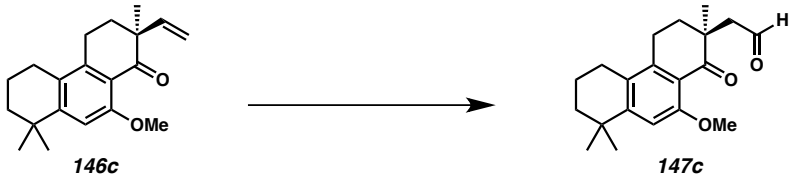
3,3-Dimethyl-4-oxo-4-phenylbutanal (147a). Aldehyde **147a** was prepared from **146a** using General Procedure A, reaction time: 20 h, column eluent: 10% ethyl acetate in hexanes. 85% isolated yield. R*f* = 0.30 (33% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.74 (t, *J* = 1.4 Hz, 1H), 7.70–7.64 (m, 2H), 7.50–7.45 (m, 1H), 7.44–7.38 (m, 2H), 2.83 (d, *J* = 1.5 Hz, 2H), 1.46 (s, 6H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 208.2, 200.6, 138.4, 131.2, 128.3, 127.8, 54.7, 46.1, 26.7; IR (Neat Film, KBr) 2974, 1784, 1712, 1450, 1291, 1114, 967, 714 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{12}H_{15}O_2$ $[M+H]^+$: 191.1067, found 191.1075.



146b ***147b***

Butyl 2-ethyl-2-(2-oxoethyl)hexanoate (147b). Aldehyde **147b** was prepared from **146b** using General Procedure A, reaction time: 45 h, column eluent: 10% ethyl acetate in hexanes. 69% isolated yield. R*f* = 0.36 (10% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.76 (t, *J* = 2.3 Hz, 1H), 4.10 (t, *J* = 6.6 Hz, 2H), 2.62 (d, *J* = 2.3 Hz, 2H), 1.79–1.56 (m, 6H), 1.42–1.32 (m, 2H), 1.31–1.24 (m, 2H), 1.23–1.08 (m, 2H), 0.92 (t, *J* = 7.4 Hz, 3H), 0.87 (t, *J* = 7.2 Hz, 3H), 0.83 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR

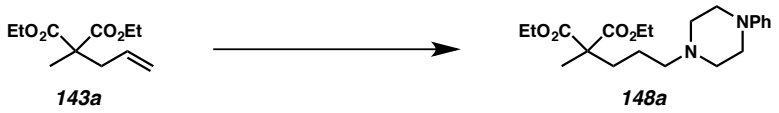
($CDCl_3$, 126 MHz) δ 201.7, 176.0, 64.8, 48.1, 47.3, 35.7, 30.7, 29.0, 26.5, 23.2, 19.3, 14.1, 13.8, 8.7; IR (Neat Film, KBr) 2961, 2936, 2874, 1724, 1459, 1383, 1203, 1139, 1022, 737 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{14}H_{26}O_3$ $[M+H]^+$: 243.1955, found 243.1961.



146c ***147c***

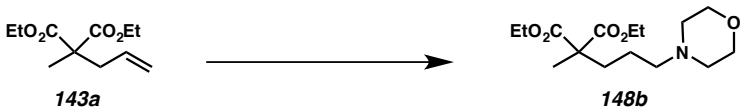
(*S*)-2-(10-methoxy-2,8,8-trimethyl-1-oxo-1,2,3,4,5,6,7,8-octahydrophenanthren-2-yl)acetaldehyde (147c). Aldehyde **147c** was prepared from **146c** using General Procedure A, reaction time: 48 h, column eluent: 5% ethyl acetate in hexanes. 64% isolated yield. R*f* = 0.40 (33% ethyl acetate in hexanes); ^1H NMR ($CDCl_3$, 500 MHz) δ 9.89 (t, *J* = 2.5 Hz, 1H), 6.85 (s, 1H), 3.88 (s, 3H), 2.80 (dd, *J* = 8.0, 4.9 Hz, 2H), 2.67 (dd, *J* = 15.5, 2.3 Hz, 1H), 2.60–2.45 (m, 3H), 2.22–2.11 (m, 1H), 1.96 (dt, *J* = 13.6, 4.9 Hz, 1H), 1.89–1.78 (m, 2H), 1.68–1.61 (m, 2H), 1.30 (s, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 202.3, 200.6, 158.9, 153.1, 143.4, 126.3, 118.9, 108.6, 56.0, 51.3, 45.4, 38.4, 35.0, 33.8, 31.8, 31.7, 27.0, 23.7, 22.0, 19.4; IR (Neat Film, KBr) 2959, 2930, 2866, 1717, 1676, 1591, 1558, 1459, 1401, 1318, 1246, 1227, 1104, 1042, 1013, 972, 850, 734 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{20}H_{26}O_3$ $[M+H]^+$: 315.1955, found 315.1947; $[\alpha]^{25}_D$ 4.03 (*c* 1.00, $CHCl_3$).

3.7.2.5 AMINE CHARACTERIZATION DATA



143a ***148a***

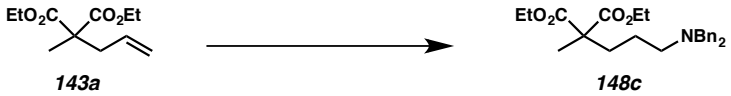
Diethyl 2-methyl-2-(3-(4-phenylpiperazin-1-yl)propyl)malonate (148a). Amine **148a** was prepared from **143a** using General Procedure B, column eluent: 25% ethyl acetate in hexanes with 0.5% triethylamine. 98% isolated yield. R*f* = 0.16 (33% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.29–7.18 (m, 2H), 6.92 (dt, *J* = 7.9, 1.0 Hz, 2H), 6.88–6.79 (m, 1H), 4.18 (q, *J* = 7.1 Hz, 4H), 3.26–3.12 (m, 4H), 2.66–2.53 (m, 4H), 2.45–2.33 (m, 2H), 1.94–1.82 (m, 2H), 1.55–1.44 (m, 2H), 1.41 (d, *J* = 4.4 Hz, 3H), 1.25 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 172.4, 151.4, 129.2, 119.8, 116.1, 61.3, 58.7, 53.6, 53.3, 49.2, 33.5, 21.9, 20.1, 14.2; IR (Neat Film, KBr) 2816, 1731, 1600, 1502, 1257, 1235, 1110, 759, 692 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{21}H_{33}N_2O_5$ $[M+OH]^+$: 393.2384, found 393.2386.



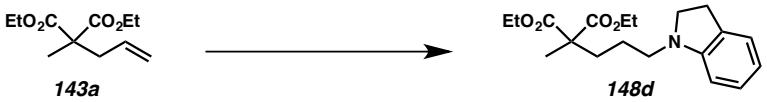
143a ***148b***

Diethyl 2-methyl-2-(3-morpholinopropyl)malonate (148b). Amine **148b** was prepared from **143a** using General Procedure B, column eluent: 8% → 25% ethyl acetate in hexanes with 0.5% triethylamine. 91% isolated yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.17 (q, *J* = 7.1 Hz, 4H), 3.76–3.65 (m, 4H), 2.41 (dd, *J* = 5.8, 3.6 Hz, 4H), 2.37–2.29 (m, 2H), 1.89–1.81 (m, 2H), 1.52–1.36 (m, 5H), 1.23 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 172.4, 66.8, 61.4, 58.9, 53.6, 53.5, 33.4, 21.4, 20.1, 14.2; IR (Neat Film,

KBr) 2958, 1730, 1457, 1256, 1232, 1118, 1023, 862 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{15}H_{28}NO_5$ $[M+H]^+$: 302.1962, found 302.1961.

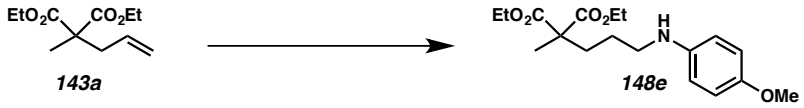


Diethyl 2-(3-(dibenzylamino)propyl)-2-methylmalonate (148c). Amine **148c** was prepared from **143a** using General Procedure B, column eluent: 8% ethyl acetate in hexanes with 0.5% triethylamine. 76% isolated yield. R*f* = 0.72 (33% ethyl acetate in hexanes); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.38–7.27 (m, 8H), 7.25–7.20 (m, 2H), 4.22–4.10 (m, 4H), 3.54 (s, 4H), 2.43 (t, *J* = 7.0 Hz, 2H), 1.88–1.80 (m, 2H), 1.50–1.41 (m, 2H), 1.38 (d, *J* = 0.8 Hz, 3H), 1.22 (td, *J* = 7.1, 0.6 Hz, 6H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 172.5, 139.8, 128.9, 128.3, 126.9, 61.2, 58.3, 53.6, 53.5, 33.3, 21.9, 20.1, 14.2; IR (Neat Film, KBr) 2981, 2796, 1731, 1453, 1245, 1111, 1028, 746, 699 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{25}H_{34}NO_4$ $[M+H]^+$: 412.2482, found 412.2494.

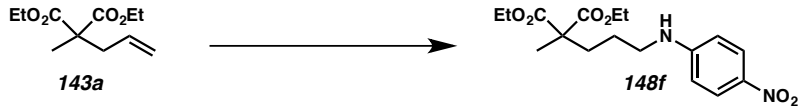


Diethyl 2-(3-(indolin-1-yl)propyl)-2-methylmalonate (148d). Amine **148d** was prepared from **143a** using General Procedure B, column eluent: 6% ethyl acetate in hexanes with 0.5% triethylamine. 96% isolated yield. R*f* = 0.66 (33% ethyl acetate in hexanes); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.12–7.00 (m, 2H), 6.64 (t, *J* = 7.5 Hz, 1H), 6.45 (d, *J* = 7.8 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 4H), 3.32 (t, *J* = 8.3 Hz, 2H), 3.06 (t, *J* = 7.2 Hz, 2H), 2.95 (t, *J* = 8.2 Hz, 2H), 2.01–1.89 (m, 2H), 1.61–1.54 (m, 2H), 1.43 (s, 3H), 1.25 (t, *J* = 7.1 Hz, 7H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 172.5, 152.7, 130.2, 127.4,

124.5, 117.5, 107.0, 61.4, 53.6, 53.1, 49.6, 33.3, 28.7, 22.5, 20.2, 14.2; IR (Neat Film, KBr) 2980, 1730, 1607, 1490, 1254, 1232, 1113, 1022, 746 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{19}H_{28}NO_4$ $[M+H]^+$: 334.2013, found 334.2019.



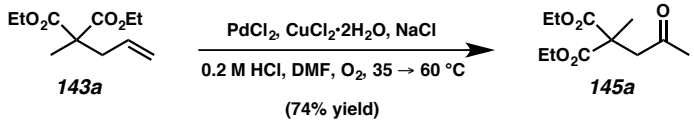
Diethyl 2-(3-((4-methoxyphenyl)amino)propyl)-2-methylmalonate (148e). Amine **148e** was prepared from **143a** using General Procedure B, column eluent: 10% ethyl acetate in hexanes with 0.5% triethylamine. 86% isolated yield. R*f* = 0.45 (33% ethyl acetate in hexanes); ^1H NMR ($CDCl_3$, 400 MHz) δ 6.81–6.71 (m, 2H), 6.60–6.51 (m, 2H), 4.17 (q, *J* = 7.1 Hz, 4H), 3.74 (s, 3H), 3.08 (t, *J* = 6.9 Hz, 2H), 2.00–1.89 (m, 2H), 1.62–1.48 (m, 2H), 1.41 (s, 3H), 1.23 (t, *J* = 7.1 Hz, 7H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 172.4, 152.2, 142.6, 115.1, 114.2, 61.4, 56.0, 53.6, 45.1, 33.3, 24.7, 20.1, 14.2; IR (Neat Film, KBr) 2982, 1730, 1514, 1235, 1187, 1110, 1037, 820 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{18}H_{28}NO_5$ $[M+H]^+$: 338.1962, found 338.1953.



Diethyl 2-methyl-2-(3-((4-nitrophenyl)amino)propyl)malonate (148f). Amine **148f** was prepared from **143a** using General Procedure B, column eluent: 10% → 20% ethyl acetate in hexanes with 0.5% triethylamine. 95% isolated yield. R*f* = 0.31 (33% ethyl acetate in hexanes); ^1H NMR ($CDCl_3$, 500 MHz) δ 8.12–8.04 (m, 2H), 6.54–6.48 (m, 2H), 4.18 (q, *J* = 7.1 Hz, 4H), 3.22 (t, *J* = 6.8 Hz, 2H), 1.98–1.92 (m, 2H), 1.69–1.61

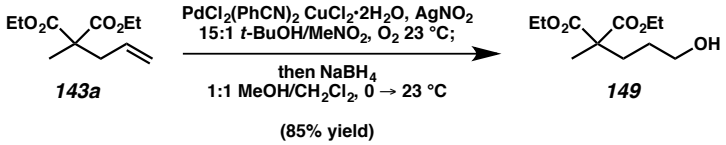
(m, 2H), 1.43 (s, 3H), 1.24 (t, J = 7.1 Hz, 6H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 172.3, 153.3, 138.1, 126.6, 111.1, 61.6, 53.5, 43.5, 33.1, 24.2, 20.2, 14.2; IR (Neat Film, KBr) 3383, 2836, 1748, 1721, 1610, 1475, 1314, 1328, 1190, 1114, 829 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{17}H_{25}N_2O_6$ $[M+H]^+$: 353.1707, found 353.1707.

3.7.2.6 ALKENE TRANSFORMATION PROCEDURES AND CHARACTERIZATION DATA



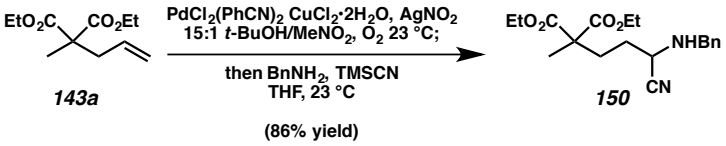
Diethyl 2-methyl-2-(2-oxopropyl)malonate (145a). To a two-necked round-bottom flask were added palladium(II) chloride (10.6 mg, 0.06 mmol, 0.30 equiv), copper(II) chloride dihydrate (20.5 mg, 0.12 mmol, 0.60 equiv), and sodium chloride (15.0 mg, 0.26 mmol, 1.30 equiv). The mixture was diluted with 0.2 M aqueous hydrochloric acid (3.1 mL) and stirred vigorously at 35 °C under oxygen atmosphere (balloon) for 30 minutes. Alkene **143a** (42.9 mg, 0.20 mmol, 1.00 equiv) was added as a solution in *N,N*-dimethylformamide (1.0 mL), and the resulting solution was heated stirred vigorously under oxygen atmosphere at 60 °C for 6 hours. The reaction mixture was allowed to cool to 23 °C and extracted with chloroform (2 x 5 mL). The organic extracts were dried over magnesium sulfate, filtered, and concentrated. The crude residue was purified by silica gel column chromatography (8% ethyl acetate in hexanes) to afford ketone **145a** as a colorless oil (34.3 mg, 74% yield). Rf = 0.24 (33% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.18 (q, J = 7.1 Hz, 4H), 3.08 (s, 2H), 2.15 (s, 3H), 1.51 (s, 3H),

1.24 (t, J = 7.1 Hz, 6H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 205.1, 171.6, 61.7, 51.6, 48.8, 30.5, 20.6, 14.1; IR (Neat Film, KBr) 2984, 1732, 1463, 1376, 1242, 1109, 1024, 863, 798 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{11}H_{19}O_5$ $[M+H]^+$: 231.1227, found 231.1226.



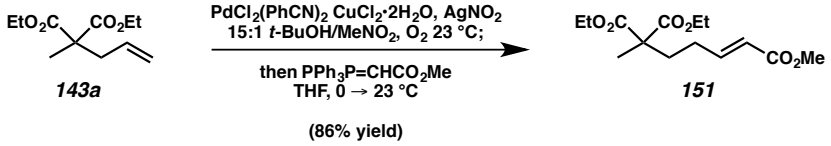
Diethyl 2-(3-hydroxypropyl)-2-methylmalonate (149). To a flame-dried 25-mL round-bottom flask with a magnetic stir bar were added bis(benzonitrile)palladium(II) chloride (9.2 mg, 0.024 mmol, 0.12 equiv), copper(II) chloride dihydrate (4.1 mg, 0.024 mmol, 0.12 equiv), and silver nitrite (1.8 mg, 0.012 mmol, 0.06 equiv). The flask was capped with a rubber septum, and *tert*-butyl alcohol (3.75 mL) and nitromethane (0.25 mL) were added sequentially by syringe. The mixture was stirred at 23 °C and sparged with oxygen gas (balloon) for 3 minutes. Alkene **143a** (42.9 mg, 0.20 mmol, 1.00 equiv) was added dropwise by syringe, and the reaction mixture was sparged with oxygen for another minute. The reaction was stirred under oxygen atmosphere at 23 °C for 12 hours, when TLC analysis indicated consumption of starting material. The solvent was removed under reduced pressure, and the residue was loaded onto a short plug of silica gel, eluting with 30% ethyl acetate in hexanes (100 mL). The oil obtained upon concentration was then redissolved in 1:1 MeOH/CH_2Cl_2 (4 mL total volume) and cooled to 0 °C using an ice water bath. Sodium borohydride (11.3 mg, 0.30 mmol, 1.50 equiv) was added in one portion, and the resulting mixture was stirred at 23 °C for 2 hours, at which time the reaction was quenched with acetone and 2 N aqueous sodium hydroxide (2 mL). The phases were separated, and the organic layer was immediately washed with brine (5 mL)

and dried over sodium sulfate. Filtration and concentration delivered the crude product, which was purified by silica gel column chromatography (35% ethyl acetate in hexanes) to afford alcohol **14** as a colorless oil (39.7 mg, 85% yield). R*f* = 0.18 (33% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.18 (q, *J* = 7.1 Hz, 4H), 3.64 (t, *J* = 6.4 Hz, 2H), 1.98–1.88 (m, 2H), 1.59–1.49 (m, 2H), 1.42 (d, *J* = 2.4 Hz, 3H), 1.24 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.5, 62.9, 61.4, 53.5, 32.0, 27.8, 20.1, 14.2; IR (Neat Film, KBr) 3469 (br), 2982, 2939, 1730, 1460, 1270, 1119, 1020, 859 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{11}H_{21}O_5$ $[M+H]^+$: 233.1389, found 233.1382.



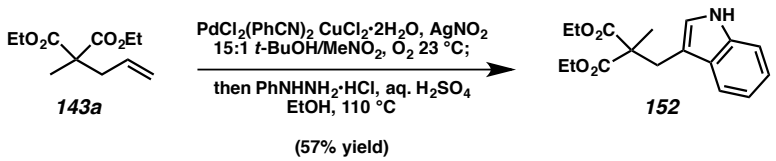
Diethyl 2-(3-(benzylamino)-3-cyanopropyl)-2-methylmalonate (150). To a flame-dried 25-mL round-bottom flask with a magnetic stir bar were added bis(benzonitrile)palladium(II) chloride (9.2 mg, 0.024 mmol, 0.12 equiv), copper(II) chloride dihydrate (4.1 mg, 0.024 mmol, 0.12 equiv), and silver nitrite (1.8 mg, 0.012 mmol, 0.06 equiv). The flask was capped with a rubber septum, and *tert*-butyl alcohol (3.75 mL) and nitromethane (0.25 mL) were added sequentially by syringe. The mixture was stirred at 23 °C and sparged with oxygen gas (balloon) for 3 minutes. Alkene **143a** (42.9 mg, 0.20 mmol, 1.00 equiv) was added dropwise by syringe, and the reaction mixture was sparged with oxygen for another minute. The reaction was stirred under oxygen atmosphere at 23 °C for 12 hours, when TLC analysis indicated consumption of starting material. The solvent was removed under reduced pressure, and the residue was loaded onto a short plug of silica gel, eluting with 30% ethyl acetate in hexanes (100

mL). The oil obtained upon concentration was then redissolved in THF (4 mL total volume) and treated with benzylamine (23 μL, 0.21 mmol, 1.05 equiv) at 23 °C. After one hour, trimethylsilyl cyanide (26 μL, 0.21 mmol, 1.05 equiv) was added, and the resulting mixture was stirred at 23 °C for 7 hours, at which time the volatiles were removed under reduced pressure. The crude residue obtained was purified by silica gel column chromatography (20% ethyl acetate in hexanes) to furnish α-aminonitrile **150** as a colorless oil (59.6 mg, 86% yield). Rf = 0.42 (33% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.37–7.31 (m, 4H), 7.31–7.26 (m, 1H), 4.18 (qd, J = 7.1, 2.2 Hz, 4H), 4.06 (d, J = 12.9 Hz, 1H), 3.82 (d, J = 12.9 Hz, 1H), 3.49 (t, J = 7.0 Hz, 1H), 2.17–2.05 (m, 1H), 2.00 (ddd, J = 13.7, 9.5, 7.4 Hz, 1H), 1.81–1.73 (m, 2H), 1.41 (s, 3H), 1.24 (td, J = 7.1, 2.3 Hz, 6H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 171.9, 138.2, 128.7, 128.5, 127.7, 119.8, 61.6, 53.2, 51.7, 49.8, 31.8, 28.9, 20.2, 14.2; IR (Neat Film, KBr) 3325, 2983, 1728, 1454, 1261, 1189, 1112, 1027, 738, 700 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{19}H_{27}N_2O_4$ $[M+H]^+$: 347.1965, found 347.1970.



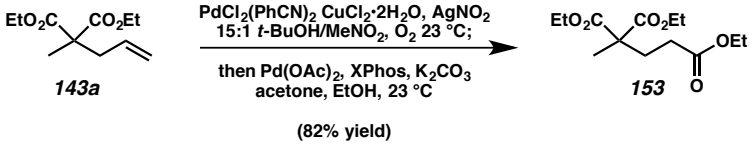
5,5-Diethyl 1-methyl (*E*)-hex-1-ene-1,5,5-tricarboxylate (151). To a flame-dried 25-mL round-bottom flask with a magnetic stir bar were added bis(benzonitrile)palladium(II) chloride (9.2 mg, 0.024 mmol, 0.12 equiv), copper(II) chloride dihydrate (4.1 mg, 0.024 mmol, 0.12 equiv), and silver nitrite (1.8 mg, 0.012 mmol, 0.06 equiv). The flask was capped with a rubber septum, and *tert*-butyl alcohol (3.75 mL) and nitromethane (0.25 mL) were added sequentially by syringe. The mixture

was stirred at 23 °C and sparged with oxygen gas (balloon) for 3 minutes. Alkene **143a** (42.9 mg, 0.20 mmol, 1.00 equiv) was added dropwise by syringe, and the reaction mixture was sparged with oxygen for another minute. The reaction was stirred under oxygen atmosphere at 23 °C for 12 hours, when TLC analysis indicated consumption of starting material. The solvent was removed under reduced pressure, and the residue was loaded onto a short plug of silica gel, eluting with 30% ethyl acetate in hexanes (100 mL). The oil obtained upon concentration was then redissolved in THF (4 mL total volume) and cooled to 0 °C using an ice water bath. Carbomethoxy methylene triphenyl phosphorane (100.3 mg, 0.30 mmol, 1.50 equiv) was added in one portion, and the resulting mixture was stirred at 23 °C for 20 hours, at which time the reaction was transferred to a separatory funnel with diethyl ether and washed sequentially with water (5 mL) and brine (5 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated to a crude yellow oil. Purification by silica gel column chromatography (10% ethyl acetate in hexanes) afforded α,β-unsaturated methyl ester **151** as a colorless oil (49.3 mg, 86% yield). Rf = 0.56 (33% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.93 (dtd, J = 15.3, 6.7, 1.8 Hz, 1H), 5.83 (dt, J = 15.7, 1.7 Hz, 1H), 4.17 (qd, J = 7.2, 1.7 Hz, 4H), 3.71 (d, J = 1.9 Hz, 3H), 2.26–2.10 (m, 2H), 2.04–1.92 (m, 2H), 1.41 (d, J = 1.7 Hz, 3H), 1.24 (td, J = 7.1, 1.7 Hz, 6H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 172.0, 167.0, 148.1, 121.5, 61.5, 53.4, 51.6, 33.9, 27.3, 20.1, 14.2; IR (Neat Film, KBr) 2984, 2951, 1734, 1730, 1659, 1437, 1268, 1234, 1110, 1024, 858 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{14}H_{23}O_6$ $[M+H]^+$: 287.1489, found 287.1485.



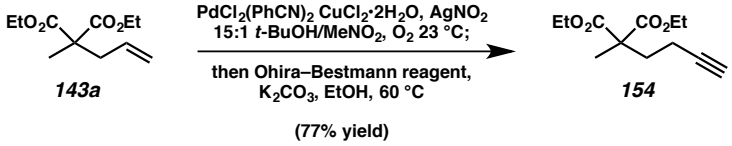
Diethyl 2-((1*H*-indol-3-yl)methyl)-2-methylmalonate (152). To a flame-dried 25-mL round-bottom flask with a magnetic stir bar were added bis(benzonitrile)palladium(II) chloride (23.0 mg, 0.060 mmol, 0.12 equiv), copper(II) chloride dihydrate (10.2 mg, 0.060 mmol, 0.12 equiv), and silver nitrite (4.6 mg, 0.030 mmol, 0.06 equiv). The flask was capped with a rubber septum, and *tert*-butyl alcohol (9.4 mL) and nitromethane (0.60 mL) were added sequentially by syringe. The mixture was stirred at 23 °C and sparged with oxygen gas (balloon) for 3 minutes. Alkene **143a** (107 mg, 0.50 mmol, 1.00 equiv) was added dropwise by syringe, and the reaction mixture was sparged with oxygen for another minute. The reaction was stirred under oxygen atmosphere at 23 °C for 12 hours, when TLC analysis indicated consumption of starting material. The solvent was removed under reduced pressure, and the residue was loaded onto a short plug of silica gel, eluting with 30% ethyl acetate in hexanes (100 mL). The oil obtained upon concentration was then diluted with a pre-heated solution (50 °C) of 4% aqueous sulfuric acid (4.7 mL) and phenyl hydrazine hydrochloride (79.5 mg, 0.550 mmol, 1.10 equiv). After addition of ethanol (3.5 mL), the mixture was heated to reflux at 110 °C for 7 hours. The reaction mixture was cooled to 23 °C and treated with saturated aqueous sodium bicarbonate and ethyl acetate. The phases were separated, and the aqueous layer was extracted with ethyl acetate (2 x 20 mL). The combined organic extracts were dried over sodium sulfate before filtration and concentration under reduced pressure. The crude residue was purified by silica gel column chromatography (20% ethyl acetate in hexanes) to afford indole **152** as yellow oil (86.1 mg, 57% yield).

R*f* = 0.44 (33% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.17 (s, 1H), 7.59 (d, *J* = 7.9 Hz, 1H), 7.32 (dt, *J* = 8.1, 1.0 Hz, 1H), 7.11 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H), 6.98 (d, *J* = 2.4 Hz, 1H), 6.98 (d, *J* = 2.4 Hz, 1H), 4.27–4.10 (m, 4H), 3.41 (d, *J* = 0.9 Hz, 2H), 1.44 (s, 3H), 1.24 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 172.6, 135.9, 128.5, 123.5, 121.9, 119.5, 111.2, 110.5, 61.4, 55.4, 30.7, 20.4, 14.1; IR (Neat Film, KBr) 3403, 2983, 1728, 1458, 1293, 1254, 1106, 1021, 861, 743 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{17}H_{22}NO_4$ $[M+H]^+$: 304.1543, found 304.1548.



Triethyl butane-1,3,3-tricarboxylate (153). To a flame-dried 25-mL round-bottom flask with a magnetic stir bar were added bis(benzonitrile)palladium(II) chloride (9.2 mg, 0.024 mmol, 0.12 equiv), copper(II) chloride dihydrate (4.1 mg, 0.024 mmol, 0.12 equiv), and silver nitrite (1.8 mg, 0.012 mmol, 0.06 equiv). The flask was capped with a rubber septum, and *tert*-butyl alcohol (3.75 mL) and nitromethane (0.25 mL) were added sequentially by syringe. The mixture was stirred at 23 °C and sparged with oxygen gas (balloon) for 3 minutes. Alkene **143a** (42.9 mg, 0.20 mmol, 1.00 equiv) was added dropwise by syringe, and the reaction mixture was sparged with oxygen for another minute. The reaction was stirred under oxygen atmosphere at 23 °C for 12 hours, when TLC analysis indicated consumption of starting material. The solvent was removed under reduced pressure, and the residue was loaded onto a short plug of silica gel, eluting with 30% ethyl acetate in hexanes (100 mL). The oil obtained upon concentration was then redissolved in degassed ethanol (2 mL), and oven-dried potassium carbonate (10.0

mg, 0.072 mmol, 0.36 equiv) was added. After stirring for 20 minutes, a solution of palladium(II) acetate (2.2 mg, 0.01 mmol, 0.05 equiv) and XPhos (9.5 mg, 0.02 mmol, 0.10 equiv) in acetone (2 mL) that had been stirring at 23 °C for 20 minutes was added via syringe under argon atmosphere. The resulting dark green solution was stirred at 23 °C for 6 hours, at which time the volatiles were removed under reduced pressure. The crude residue obtained was purified by silica gel column chromatography (8% ethyl acetate in hexanes) to furnish tri-ester **153** as a colorless oil (45.0 mg, 82% yield). R*f* = 0.53 (33% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.16 (q, *J* = 7.1, 0.8 Hz, 4H), 4.11 (q, *J* = 7.2, 0.9 Hz, 2H), 2.38–2.27 (m, 2H), 2.23–2.13 (m, 2H), 1.39 (s, 3H), 1.23 (td, *J* = 7.1, 0.8 Hz, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 173.0, 171.9, 61.5, 60.6, 53.0, 30.7, 29.9, 20.2, 14.3; IR (Neat Film, KBr) 2982, 2941, 1738, 1732, 1466, 1380, 1243, 1185, 1109, 1025, 860 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{13}H_{23}O_6$ $[M+H]^+$: 275.1489, found 275.1483.



Diethyl 2-(but-3-yn-1-yl)-2-methylmalonate (154). To a flame-dried 25-mL round-bottom flask with a magnetic stir bar were added bis(benzonitrile)palladium(II) chloride (9.2 mg, 0.024 mmol, 0.12 equiv), copper(II) chloride dihydrate (4.1 mg, 0.024 mmol, 0.12 equiv), and silver nitrite (1.8 mg, 0.012 mmol, 0.06 equiv). The flask was capped with a rubber septum, and *tert*-butyl alcohol (3.75 mL) and nitromethane (0.25 mL) were added sequentially by syringe. The mixture was stirred at 23 °C and sparged with oxygen gas (balloon) for 3 minutes. Alkene **143a** (42.9 mg, 0.20 mmol, 1.00 equiv) was

added dropwise by syringe, and the reaction mixture was sparged with oxygen for another minute. The reaction was stirred under oxygen atmosphere at 23 °C for 12 hours, when TLC analysis indicated consumption of starting material. The solvent was removed under reduced pressure, and the residue was loaded onto a short plug of silica gel, eluting with 30% ethyl acetate in hexanes (100 mL). The oil obtained upon concentration was then redissolved in ethanol (4 mL), and potassium carbonate (33.2 mg, 0.24 mmol, 1.20 equiv) and Ohira–Bestmann reagent (46.1 mg, 0.24 mmol, 1.20 equiv) were added. The resulting mixture was stirred at 60 °C for 24 hours, at which time the reaction was quenched with water (4 mL), diluted with diethyl ether (2 mL), and washed with 5% aqueous sodium bicarbonate. The organic layer was dried over magnesium sulfate, filtered, and concentrated. The crude residue obtained was purified by silica gel column chromatography (8% ethyl acetate in hexanes) to furnish alkyne **154** as a colorless oil (35.0 mg, 77% yield). R*f* = 0.72 (33% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.18 (q, *J* = 7.1 Hz, 4H), 2.28–2.06 (m, 4H), 1.95 (t, *J* = 2.5 Hz, 1H), 1.42 (s, 3H), 1.25 (t, *J* = 7.1 Hz, 7H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.9, 83.5, 68.8, 61.5, 53.2, 34.6, 20.0, 14.3, 14.2; IR (Neat Film, KBr) 3291, 2983, 1731, 1465, 1381, 1265, 1189, 1109, 1025, 861, 659 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{12}H_{20}O_4$ $[M+H]^+$: 227.1283, found 227.1287.

3.8 NOTES AND REFERENCES

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(17) Anhydrous CuCl and $CuCl_2$ were also examined as copper sources, but use of $CuCl_2 \bullet 2H_2O$ resulted in the highest yields.

(18) When unprotected **143d** was subjected to the aldehyde-selective Wacker conditions, mixtures containing several inseparable compounds were obtained after purification.

(19) Lactams bearing quaternary carbons at the homoallylic position were also investigated as substrates. These compounds reacted sluggishly, and only low yields (32–37%) of the aldehyde product were obtained, often contaminated by enal side product.

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