JOC*Note*

P(*i*-PrNCH$_2$CH$_2$)$_3$N: Efficient Catalyst for Synthesizing β-Hydroxyesters and α,β-Unsaturated Esters using α-Trimethylsilylethylacetate (TMSEA)

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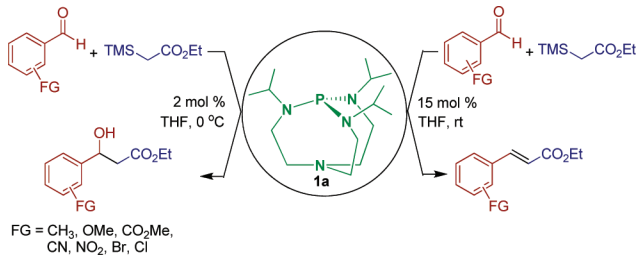

We present an efficient synthesis of β-hydroxyesters and α,β-unsaturated esters via activation of the silicon−carbon bond of α-trimethylsilylethylacetate using catalytic amounts of the commercially available P(*i*-PrNCH$_2$CH$_2$)$_3$N **1a**. Selectivity for either of these two products can be achieved simply by altering the catalyst loading and reaction temperature to afford addition or stereoselective condensation. This method is mild and tolerates a wide array of functional groups.

β-Hydroxyesters are one of the most important classes of intermediates in the synthesis of natural products.[1] The most common method for the synthesis of such intermediates is the carbon−carbon bond-forming Reformatsky reaction first discovered in 1887,[2] which has been extensively studied since then.[3,4] The classical Reformatsky reaction utilizes elevated reaction temperatures and is typically carried out in aromatic solvents such as benzene, which are generally not environmentally friendly.[2−4] An improvement of the Reformatsky reaction involves the use of activated zinc reagents,[5] although the main drawback of this approach is the necessity for preparing fresh metal catalyst in advance, owing to instability of these reagents.[5] As an alternative to the conventional Zn-based Reformatsky methodology, other metals such as iron,[6a] nickel,[6b] magnesium,[6c] manganese[6d] and indium can be employed.[6e,f] However, such metals are required in stoichiometric amounts,[6b,d] and some of them must be reduced by the addition of a reducing metal.[6a,b,d,e] The formation of side products is also an issue in the case of magnesium.[6c]

A later development involved the use of the reaction between an α-silylester and a carbonyl (i.e., the silyl-Reformatsky reaction) to afford the corresponding β-hydroxyester.[7,8a] TBAF (6 mol %) has been employed as a source of fluoride ion for activating the α-silyl group to generate a naked carbanion which then adds to the electrophilic carbonyl. However, product yield was only moderate and the substrate scope was limited.[7a] Use of an α-dimethylsilylester in DMF solvent at 50 °C for 48 h, gave a 39−93% yield of the corresponding β-hydroxyester.[7b] The very strong Schwesinger base P4-*t*Bu (pK_a 40 in CH$_3$CN,[9a] 10 mol %) at −78 °C gave the corresponding β-hydroxyester of the substrate acetophenone in poor yield (29%).[8a]

TBAF (3 mol %) is an effective catalyst for silicon activation in the reaction of TMSEA with aldehydes and ketones at low temperature (−20 °C) affording 24−88% yields of corresponding aldol products.[7c] Activation of the Si−C bond of TMSEA in a reaction with benzaldehyde using 20 mol % of *tris*(2,4,6-trimethoxyphenyl)phosphine at 100 °C in DMF was reported by Imamoto et al.[7d] to give a moderate yield (60%) of corresponding product, but no scope for aldehyde substrates was reported. Hamelin et al. reported silyl-Reformatsky reactions of TMSEA with three aromatic aldehydes using 8 equiv of CsF as catalyst, which gave 62−75% yields of product at ambient temperature, and 62−84% yields using 440 W microwave radiation.[7e] Wieden et al. reported the use of K[Al(OCH$_3$)$_4$] (1 mol %) in refluxing pyridine as solvent in silyl-Reformatsky reactions between TMSEA and three aromatic aldehydes, but only moderate yields (39 and 46%) and a good yield of 81% was observed for the aldol products.[7f]

Because of their significant Lewis basicities, proazaphosphatranes **1** in CH$_3$CN[9b] have been of interest to us as catalysts

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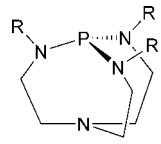


1a : R = *i*-Pr (pK_a = 33.63)
1b : R = Bn
1c : R = *i*-Bu (pK_a = 33.53)
1d : R = Me (pK_a = 32.90)

1

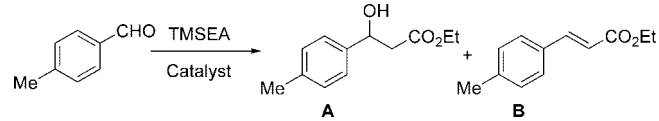
FIGURE 1. Proazaphosphatranes.

and reagents ever since their first synthesis in our laboratories. A key structural feature of **1** is the potential for $N_{basal} \rightarrow P$ transannulation that would enhance the nucleophilicity of the phosphorus. We have reported several instances in which **1** is apparently capable of activating a silicon center, e.g., in the silylation of alcohols using a silyl chloride,[10a,b] the synthesis of cyanohydrins from the addition of trimethylsilyl nitrile to carbonyl compounds,[10c,d] the desilylation of TBDMS ethers,[10e] and in the nucleophilic aromatic substitution of aryl fluorides with aryl silylethers.[10f,g]

In the present work, we report the use of **1a** as a catalyst for the efficient synthesis of β-hydroxyesters via a silyl-Reformatsky reaction, and α,β-unsaturated esters via Peterson olefination, from aldehydes in the presence of TMSEA as shown in the scheme in the Abstract. For optimization of the conditions, the reaction between *p*-tolualdehyde and TMSEA was selected. Excellent catalytic efficiency of **1a** and its commercial availability[11] favored its selection for the aforementioned syntheses. Using 5 mol % **1a**, this reaction at room temperature underwent mainly condensation to give the corresponding α,β-unsaturated ester **B** in 75% yield and the desired aldol product **A** in 19% isolated yield, which is in accord with the **B**/**A** ratio of 8:2 observed by proton NMR spectroscopy in the crude reaction mixture (Table 1, entry 1). Increasing the catalyst loading to 10 mol % under the same reaction conditions increased the yield of the condensation product to 77% while decreasing the yield of aldol product (Table 1, entry 2). Raising the temperature to 80 °C, while keeping the loading of **1a** at 10 mol %, had no significant effect on the yield of condensation product (Table 1, entry 3). A further increase in loading of **1a** to 15 mol % at 25 °C led to a rise in yield of condensation product **B** (83%, Table 1, entry 4). However, reducing the reaction time gave only a 56% yield (Table 1, entry 4).

Gratifyingly, reducing the loading of **1a** to 5 mol % and lowering the temperature to 0 °C resulted in an 82% yield of aldol product **A** (Table 1, entry 5). Further lowering the loading of **1a** to 4 and 2 mol % at 0 °C increased the yield of **A** to 83 and 86% (Table 1, entries 6 and 7, respectively). When the reaction was carried out for 12 h, incomplete conversion and a lower yield was observed (62%, Table 1, entry 7). Lowering the temperature to −20 °C did not increase the yield of aldol product at 2 mol % loading of **1a** (87%, Table 1, entry 8) compared with that attained at 0 °C (86%, Table 1, entry 7). The yields of **A** obtained with **1a**−**d** screened under the optimized conditions given in Table 1, entry 7 for **1a** were good (Table 1, entries 5−7 and 9−12). The yield did not appear to correlate with steric or basicity trends of the proazaphosphatranes, however.

TABLE 1. Survey of Proazaphosphatranes as Catalysts for the Synthesis of β-Hydroxyesters and α,β-Unsaturated Esters[a]



A **B**

entry	catalyst	(mol %)	temp (°C)	yield of A (%)[b]	yield of B (%)[b]
1	**1a**	5	25	19	75
2	**1a**	10	25	14	77
3	**1a**	10	80	7	78
4	**1a**	15	25	−	83 (56)[c]
5	**1a**	5	0	82	5
6	**1a**	4	0	83	−
7	**1a**	2	0	86 (62)[c]	−
8	**1a**	2	−20	87	−
9	**1a**	1	0	81	−
10	**1b**	2	0	79	−
11	**1c**	2	0	81	−
12	**1d**	2	0	85	−

[a] Reaction conditions: (a) aldehyde (2 mmol), TMSEA (2.4 mmol), THF (2 mL), 24 h, 1*N* HCl (3 mL). [b] Yields represent isolated yields after silica gel column chromatography. [c] Reaction was carried out for 12 h.

To explore the scope of our methodology for the synthesis of β-hydroxyesters, a variety of aromatic, aliphatic and heterocyclic aldehydes were tested with **1a** under the optimized conditions given in Table 1, entry 7. Both electron donating and withdrawing groups were well tolerated, affording excellent yields of corresponding aldol product with only traces of dehydrated product detectable by ^{1}H NMR spectroscopy in the crude reaction mixtures (Table 2). Electron donating groups such as methyl (Table 1, entry 7), methoxy at both the *p*- and *o*-position (Table 2, entries 2 and 3, respectively) and halogen groups (Table 2, entries 4, 5 and 6); and electron withdrawing groups such as nitro (Table 2, entry 7), cyano (Table 2, entry 8) and ester (Table 2, entry 9) afforded good yields of corresponding aldol products. The enolizable aliphatic aldehydes in entries 10 and 11 (Table 2) also underwent the silyl Reformatsky transformation, providing good yields of products. Interestingly, α,β-unsaturated *trans*-cinnamaldehyde gave the desired aldol product in excellent isolated yield without significant contamination by 1,4 addition product (Table 2, entry 12). Sterically hindered aldehydes such as 2,6-dimethylbenzaldehyde (Table 2, entry 13) and biphenyl-2-carboxaldehyde (Table 2, entry 14) gave good isolated yields of their corresponding aldol products. Heterocyclic aldehydes also tolerated our reaction conditions. Both 5- and 6-membered ring aldehydes bearing N-, O- and S- heteroatoms gave excellent yields of their corresponding aldols (Table 2, entries 15−17).

We then investigated the synthesis of α,β-unsaturated esters, which are useful synthons in natural product synthesis.[12] Prime methodologies for the synthesis of α,β-unsaturated esters are the Wittig[13] and Horner-Wadsworth-Emmons reactions.[14] The most important disadvantage of both these approaches is the necessity to employ an equivalent amount

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(11) Proazaphosphatranes **1a**, **1c**, and **1d** are commercially available.

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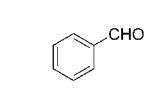
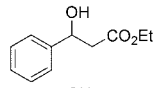
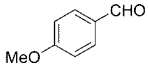
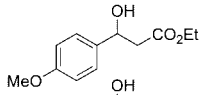
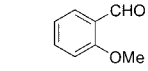
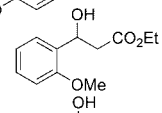
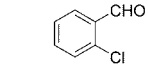
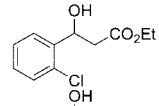
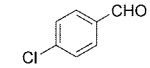
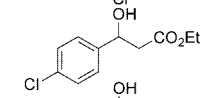
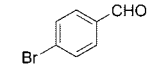
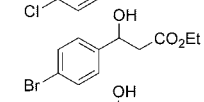
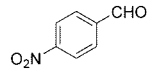
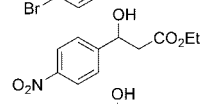
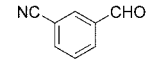
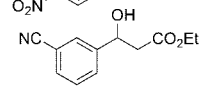
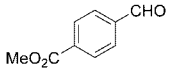
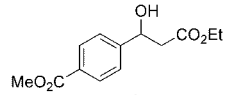
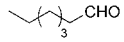
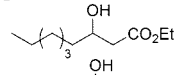
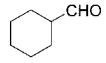
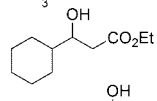
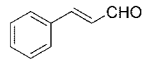
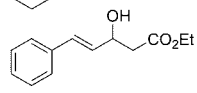
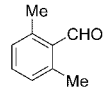
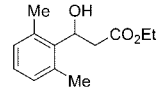
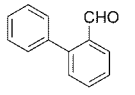
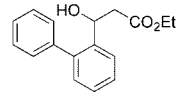
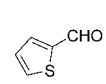
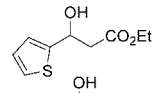
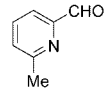
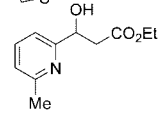
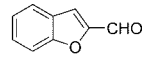
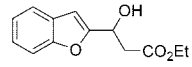
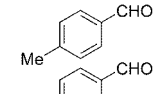
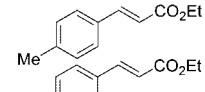
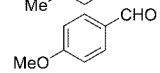
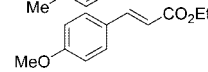
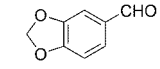
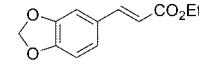
TABLE 2. Scope of the Addition Reaction of Aldehydes with TMSEA Catalyzed by 1a[a]

entry	aldehyde	product	yield (%)[b]	lit. yield (%)
1			71	76,[c] 60,[d] 70,[e] 46,[f] 91[g]
2			76	62[e]
3			77	-
4			87	-
5			78	75[e]
6			87	-
7			92	38[g]
8			84	-
9			71	-
10			73	-
11			77	-
12			76	-
13			87	-
14			78	-
15			76	-
16			81	-
17			79	-

[a] Reaction conditions: (a) aldehyde (2 mmol), TMSEA (2.4 mmol), **1a** (2 mol %), THF (2 mL), 0 °C, 24 h, 1*N* HCl (3 mL). [b] Isolated yield after column chromatography. [c] See ref 7c. [d] See ref 7d. [e] See ref 7e. [f] See ref 8b. [g] See ref 7f.

of strong base.[13,14] The decarboxylation of malonic acid half-esters is also an important route to the synthesis of α,β-unsaturated esters.[15] Advantages of the Knoevenagel reaction are the inexpensive nature of the starting materials, and the easy removal of byproducts (CO_2 and H_2O) to provide pure compounds.[15a−c] However, disadvantages of this method include the use of strongly basic conditions (e.g., the use of pyridine as solvent), excess malonic acid esters, and elevated temperatures. Moreover, the Knoevenagel reaction is not stereoselective, and enolizable aldehydes do not yield the desired products.[15d−f]

TABLE 3. Scope of the Condensation Reaction of Aldehydes with TMSEA Catalyzed by 1a[a]

entry	aldehyde	product	yield (%)[b]	lit yield (%)
1			83	91[c]
2			83	69[c]
3			79	-
4			90	-
5			84(9:1)[d]	65[e]
6			80	-
7			89	-
8			79	-

[a] Reaction conditions: (a) aldehyde (2 mmol), TMSEA (2.4 mmol), **1a** (15 mol %), THF (2 mL), rt, 24 h, 1*N* HCI (3 mL). [b] Isolated yield after column chromatography. [c] See ref 8a. [d] Determined by NMR. [e] See ref 8b.

Another common approach to the synthesis of α,β-unsaturated esters is the Peterson olefination reaction[16] which has advantages over the Wittig and Horner-Wadsworth-Emmons reactions, including easy reaction work up and product purification. Moreover, isolated-product yields are high. Disadvantageously, however, conventional Peterson olefination reactions consume an equivalent amount of a lithium base.[16] Recently Kondo et al. reported the use of a catalytic amount of P4-*t*Bu as an efficient base for the condensation reaction of TMSEA with aldehydes, ketones or formanilides to yield the corresponding α,β-unsaturated esters.[8a] Ozanne et al. have reported the use of catalytic cesium fluoride (12 mol %) in DMSO as solvent for Peterson olefination of α-silylesters with aldehydes or imines.[8b]

As we show in the present work, the conditions in Table 1, entry 4 are suitable for the condensation of TMSEA with aryl and heterocyclic aldehydes to yield the corresponding α,β-unsaturated esters (Table 3). Aliphatic aldehydes, on the other hand, did not give the corresponding α,β-unsaturated ester under our reaction conditions. Along with good tolerance of various functional groups and good to excellent isolated product yields, the reactions in Table 3 were also stereoselective, yielding only

(14) (a) Motoyoshiya, J. *Trends Org. Chem.* **1998**, *7*, 63–73. (b) Nicolaou, K. C.; Harter, M. W.; Gunzner, J. L.; Nadin, A. *Liebigs Ann.* **1997**, *7*, 1283–1301.

(15) (a) Galat, A. *J. Am. Chem. Soc.* **1945**, *68*, 376–377. (b) Klein, J.; Bergmann., E. D. *J. Am. Chem. Soc.* **1957**, *79*, 3452–3454. (c) Shabtai, J.; Ney-Igner, E.; Pines, H. *J. Org. Chem.* **1981**, *46*, 3795–3802. (d) Carmona, A. T.; Fuentes, J.; Robina, I.; García, E. R.; Demange, R.; Vogel, P.; Winters, A. L. *J. Org. Chem.* **2003**, *68*, 3874–3883. (e) Yamanaka, H.; Yokoyama, M.; Sakamoto, T.; Shiraishi, T.; Sagi, M.; Mizugaki, M. *Heterocycles* **1983**, *20*, 1541–1544. (f) Ragoussis, N.; Ragoussis, V. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3529–3533.

(16) (a) Staden, L. F. V.; Gravestock, D.; Ager, D. J. *Chem. Soc. Rev.* **2002**, *31*, 195–200. (b) Peterson, D. J. *J. Org. Chem.* **1968**, *33*, 780–784. (c) Ager, D. J. *Org. React.* **1990**, *38*, 1–223.

trans- products as determined by ^{1}H NMR spectroscopy. Electron donating groups such as methyl (Table 3, entry 1) and methoxy (Table 3, entry 2) provided the corresponding *trans* condensation products in excellent yields. The electron withdrawing cyano group allowed complete conversion to the desired product in excellent yield (Table 3, entry 4). The reaction of *trans*-cinnamaldehyde with TMSEA also showed stereoselectivity, affording the corresponding condensation product as a mixture of two stereoisomers in a 9:1 ratio as determined by ^{1}H NMR spectroscopy (Table 3, entry 5). Sterically hindered 2,6-dimethylbenzaldehyde gave the desired product in excellent yield (Table 3, entry 6). Screening of heterocyclic aldehydes for the condensation reaction gave both good stereoselectivity and very good isolated product yield as was shown for 2-thiophenecarboxaldehyde and 2-benzofurancarboxaldehyde (Table 3, entries 7 and 8, respectively).

In conclusion, we have described a very mild and effective method for the synthesis of aldol products and α,β-unsaturated esters by a simple change in **1a** loading and temperature. This method is general for aromatic, aliphatic and heterocyclic aldehydes, it tolerates a wide spectrum of functional groups (including acid- and base-sensitive examples) and it leads to excellent isolated yields of aldol products. High stereoselectivity is achieved in the condensation reactions, yielding *trans*-products in good to very good isolated yields. The selectivity of the two products upon changing the reaction conditions can be rationalized using the two-stage mechanism proposed by Kondo et al. for the P4-*t*Bu-catalyzed reactions of TMSEA with carbonyl compounds to synthesize α,β-unsaturated esters.[8a] In the first stage, the anion of P4-*t*Bu-TMS$^+$ $^-$$CH_2CO_2Et$ (an intermediate formed from P4-*t*Bu and TMSEA) 1,2-adds to a carbonyl to produce a silylated β-hydroxyester, which in the second stage eliminates HP4-*t*Bu$^+$ $^-$OTMS. This elimination product catalyzes formation of the α,β-unsaturated ester from the silylated β-hydroxyester. Commercial availability of catalyst **1a** and the environmentally desirable lack of metal usage in the syntheses reported here renders our methodology attractive. In comparing yields of β-hydroxyesters attained in our methodology with those found in the literature for five of the methods cited in four entries of Table 2, we found that only one literature yield is higher than is attained with our method, four yields are lower, and three are comparable. In the case of the α,β-unsaturated esters in Table 3, we compared two literature methods cited in three entries of this table, and found that one literature yield was higher than that attained with our methodology and two were lower. Our methodology was ineffective for ketones (e.g., acetophenone, 4-chloro-acetophenone and benzophenone).

Experimental Section

General Reaction Procedure for the Synthesis of β-Hydroxyesters and α,β-Unsaturated esters. In a nitrogen-filled glovebox, a round-bottom flask was charged with **1** (2 mol % for β-hydroxyesters, 15 mol % for α,β-unsaturated esters). Anhydrous THF (2.0 mL) was syringed under argon into the flask, followed by TMSEA (2.40 mmol) at 0 °C (r.t. for α,β-unsaturated esters). The reaction mixture was stirred at 0 °C (r.t. for α,β-unsaturated esters) for 15 min and then aldehyde (2.0 mmol) was added over 5−10 min. The reaction mixture was stirred for 24 h at 0 °C (r.t. for α,β-unsaturated esters) and then it was quenched with 3 mL of aqueous HCl (1*N*). The reaction mixture was stirred at 0 °C (r.t. for α,β-unsaturated esters) for 1 h and then it was neutralized with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 30 mL). The product was purified by column chromatography on silica gel using 10% EtOAc/hexanes, except for heterocyclic substrates (20−25% EtOAc/hexanes).

Product in Table 2, entry 13. The general procedure was used for the synthesis and purification, giving a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.07−6.99 (m, 3H), 5.64 (d, 1H, J = 10.4 Hz), 4.21 (q, 2H, J = 8.0 Hz), 3.09−2.97 (m, 2H), 2.58−2.53 (m, 1H), 2.46 (s, 6H), 1.29 (t, 3H, J = 8.0 Hz) ppm; ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 172.3, 137.3, 135.9, 129.2, 127.2, 67.4, 60.6, 39.7, 20.6, 14.0 ppm; HRMS *m*/*z* Calcd. for $C_{13}H_{18}O_3$: 222.12559. Found: 222.12604.

Product in Table 2, entry 14. The general procedure was used for the synthesis and purification, giving a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.67 (d, 1H, J = 8.0 Hz), 7.43−7.33 (m, 7H), 7.24 (d, 1H, J = 8.0 Hz), 5.27 (d, 1H, J = 9.0 Hz), 4.13−4.07 (m, 2H), 3.45 (s, 1H), 2.73−2.52 (m, 2H), 1.21 (t, 3H, J = 8.0 Hz) ppm; ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 172.6, 141.0, 140.8, 139.9, 130.4, 129.4, 128.6, 128.2, 127.8, 127.5, 126.2, 67.0, 61.0, 42.8, 14.4 ppm; HRMS *m*/*z* Calcd. for $C_{17}H_{18}O_3$: 270.12559. Found: 270.12608.

Product in Table 2, entry 16. The general procedure was used for the synthesis and purification, giving a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.59 (t, 1H, J = 8.0 Hz), 7.15 (d, 1H, J = 8.0 Hz), 7.04 (d, 1H, J = 8.0 Hz), 5.12 (d, 1H, J = 4.0 Hz), 4.53 (d, 1H, J = 4.0 Hz), 4.15 (q, 2H, J = 8.0 Hz), 2.80−2.66 (m, 2H), 2.51 (s, 3H), 1.23 (t, 3H, J = 8.0 Hz) ppm; ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 172.1, 159.9, 157.5, 137.3, 122.3, 117.3, 70.0, 60.9, 43.3, 24.5, 14.4 ppm; HRMS *m*/*z* Calcd. for $C_{11}H_{15}NO_3$: 209.10519. Found: 209.10557.

Product in Table 2, entry 17. The general procedure was used for the synthesis and purification, giving a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.53 (d, 1H, J = 8.0 Hz), 7.45 (d, 1H, J = 8.0 Hz), 7.28−7.19 (m, 2H), 6.66 (s, 1H), 5.28 (d, 1H, J = 8.0 Hz), 4.19 (q, 2H, J = 8.0 Hz), 3.71 (d, 1H, J = 4.0 Hz), 2.95 (d, 1H, J = 4.0 Hz), 1.26 (t, 3H, J = 8.0 Hz) ppm; ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 172.0, 157.7, 155.0, 128.2, 124.5, 123.1, 121.4, 111.5, 103.2, 65.0, 61.3, 40.1, 14.4 ppm; HRMS *m*/*z* Calcd. for $C_{13}H_{14}O_4$: 234.08921. Found: 234.08965.

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Supporting Information Available: Complete experimental details, references to known compounds, copies of ^{1}H and ^{13}C NMR spectra for all products and HRMS reports for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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