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FULL PAPER

Facile Coupling Aldehydes with Alcohols: An Evolved Tishchenko Process in Preparing Unsymmetrical Esters

Heng Liu,[a] and Moris S. Eisen*[a]

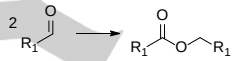
Abstract: A facile coupling process between aldehydes and alcohols to afford unsymmetrical ester compounds is presented herein. This reaction is complementary to the Tishchenko reaction and provides an evolved procedure to access unsymmetrical esters under very mild conditions. Various aldehydes and alcohols are suitable for this transformation. Using the sacrificial trifluoromethyl ketones renders the reaction to proceed in a highly selective way. A plausible mechanism is proposed based on the reaction progress monitoring and deuterium labeling studies.

Introduction

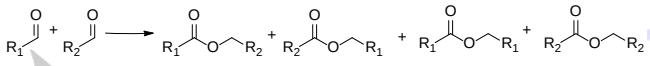
The Tishchenko reaction, *i.e.*, the dimerization of aldehyde to produce the corresponding esters (Scheme 1(1)), has been known for more than a century, and served as a highly efficient and waste-free strategy for the production of ester compounds.[1-11] Nevertheless, it has not been accepted as a common methodology for ester synthesis due to the selectivity-controlling difficulties in preparing unsymmetrical esters.[12] In the cross coupling of two different aldehydes, it is a great challenge to selectively obtain one single unsymmetrical ester from the four possible esters (Scheme 1(2)).[13-18] Previously, endeavors employed steric/electronic discrepancies, or reaction rate differences, or special *ortho*-substituents to promote the crossed Tishchenko reactions between two different aldehydes.[19-23] For instance, by using Ni(0)/NHC complexes, the reaction of CyCHO with PhCHO could give rise to the cross-coupled unsymmetrical ester product $CyCOOCH_2Ph$ in high yields under mild conditions. However, one limitation of this reaction is that it only works between aliphatic and aromatic aldehydes, selectively cross-coupling between two different aliphatic or aromatic aldehydes has not been shown to be feasible.[19] Some recent progresses was made by Connon *et al.*, in which selectively intermolecular crossed Tishchenko reaction in producing asymmetric esters between two different aromatic aldehydes was achieved by incorporating special *ortho* substitutents (usually *bromo*-) to benzaldehyde, and a wide range of aromatic aldehydes are tolerated during this process.[20]

Mechanistically, the Tishchenko reaction involves a hydride transfer step from the hemiacetal intermediate, produced from the coupling of a metal alkoxide and an aldehyde, to a coordinated carbonyl group, of an incoming aldehyde, which subsequently gives back the metal alkoxide intermediate and releases the ester product. During this catalytic cycle, the metal alkoxide species serves as the active species, which is consumed and regenerated consecutively (Scheme 1(3)). We envisage that, if an external alcohol is also present, in addition to the aldehydes, a proton-transfer process between the metal alkoxide $M\text{-}OCH_2R_1$ and the alcohol R_2OH might take place, which thereafter lead to a different metal alkoxide compound $M\text{-}OR_2$ (Scheme 1(4)). This newly formed $M\text{-}OR_2$ species shows high similarity to the previous $M\text{-}OCH_2R_1$, and will subsequently undergo insertion and hydride transfer steps with aldehydes R_1CHO, furnishing the unsymmetrical ester R_1COOR_2 as the final product. If our proposed scenario is operative, the present esterification process can be viewed as an evolved process of the Tishchenko reaction, because in both of the processes it has a similar metal alkoxide as an active species. Comparing with other esterification strategies between aldehyde and alcohols, such as oxidative esterification, dehydrogenative esterification, *etc*., no external strong oxidants are necessary herein, revealing an advanced methodology towards the synthesis of unsymmetrical esters under very mild conditions.[24-37]

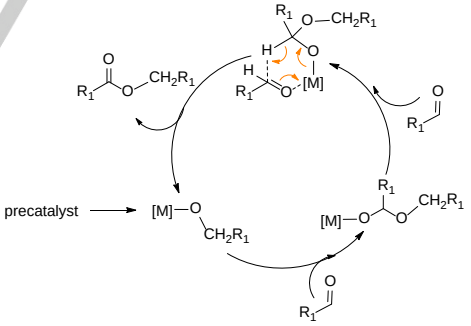
(1) Tishchenko reaction:



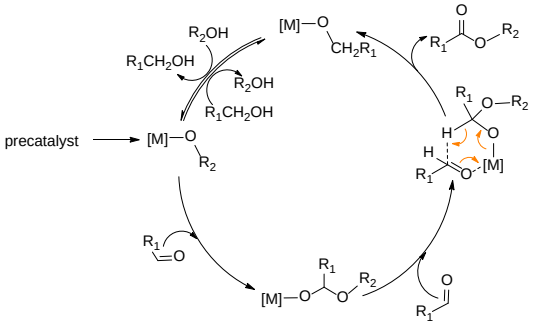
(2) Crossed Tishchenko reaction:



(3) Scheme for Tishchenko reaction:



(4) Schematic combination of proton-transfer into Tishchenko reaction:



Scheme 1. Schemes for traditional Tishchenko reaction between aldehydes (1-3) and evolved Tishchenko reaction between alcohol and aldehyde (4).

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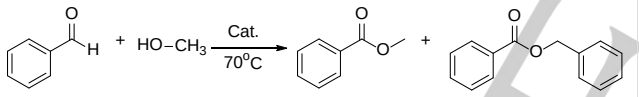
Results and Discussion

Based on the above assumptions, the esterification between benzaldehyde and methanol was established as a model reaction under different conditions. To avoid the homocoupled Tishchenko of benzaldehydes at the beginning of the reaction, the following addition order was employed: MeOH, catalyst, and lastly PhCHO. When $Na[N(SiMe_3)_2]$ was used as the precatalyst, increasing the benzaldehyde equivalents enhanced the yield of asymmetric ester **3aa** significantly, up to 81% was obtained (Table 1, entries 1-3). In this reaction, besides target compound **3aa**, benzyl benzoate (**4**) and benzyl alcohol were also detected as byproducts, for instance, 34% benzyl benzoate was observed when reacting methanol with 3 equivalents of benzaldehyde. Increasing the methanol stoichiometry, however, was detrimental for the yield of **3aa**, leading to decreased yields from 49% to 13% (Table 1, entries 4-5); in spite of this, it is noteworthy that no symmetric ester benzyl benzoate was formed when 3 equivalents of methanol was applied, demonstrating a selective esterification method to produce **3aa**. Several main group, transition metal, and lanthanide complexes were also employed to evaluate the influence of metal centers on reactivities, and except for Ti and Hf compounds, all other homoleptic amido complexes served as highly efficient precursors during the esterification, affording the corresponding methyl benzoate in high yields. Metal alkoxides, NaOMe and $La(O^iPr)_3$, showed quite similar behaviors as their corresponding amido counterparts, inferring the a similar catalytic species is present in both circumstances.

Table 1. Esterification between benzaldehyde and methanol under different conditions. [a]



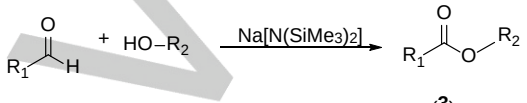
(**1a**) (**2a**) (**3aa**) (**4**)

Entry	Cat.	[PhCHO]/[MeOH]	Time (h)	**3aa** (%)[b]	**4** (%)[c]
1	$NaN(SiMe_3)_2$.	1/1	6h	49	15
2	$NaN(SiMe_3)_2$.	2/1	6h	68	31
3	$NaN(SiMe_3)_2$.	3/1	6h	81	34
4	$NaN(SiMe_3)_2$.	1/2	6h	23	6
5	$NaN(SiMe_3)_2$.	1/3	6h	13	-
6	$LiN(SiMe_3)_2$.	3/1	12h	85	35
7	$KN(SiMe_3)_2$.	3/1	6h	80	28
8	$Mg[N(SiMe_3)_2.]_2$	3/1	6h	73	20
9	$Zn[N(SiMe_3)_2.]_2$	3/1	12h	68	6
10	$Ti(NMe_2)_4$	3/1	24h	3	-
11	$Hf(Bn)_4$	3/1	24h	31	3
12	$Y[N(SiMe_3)_2.]_3$	3/1	4h	87	30
13	$Gd[N(SiMe_3)_2.]_3$	3/1	6h	74	43
14	$La[N(SiMe_3)_2.]_3$	3/1	6h	86	37
15	$NaOCH_3$	3/1	6h	79	30
16	$La(O^iPr)_3$	3/1	12h	81	21

[a] Conditions: 0.007mmol catalysts, [Cat.]/[OH]= 1/50, 700 μL C_6D_6, 70°C; substrates were added in the order of alcohols, catalyst, aldehyde. [b] Yield was determined by ^{1}H NMR spectroscopye based on MeOH. [c] Yield determined by ^{1}H NMR spectroscopy based on PhCHO.

Reactions of benzaldehyde with various alcohols were also conducted. Besides methanol, ethanol and isopropanol were also suitable for this transformation, but with decreased yields, 52% and 12% conversions were obtained for **3ab** and **3ac**, respectively. Reacting ethanol and 2-propanol with an activated aldehyde, 3-nitrobenzaldehyde, showed a significant improvement on the yields, demonstrating again the enhanced activities of aldehydes promoted by electron-withdrawing groups. Interestingly, no detectable conversion was observed during the reaction between benzaldehyde and *tert*-butanol, however, reacting 3-nitrobenzaldehyde with benzyl alcohol afforded product **3de** in moderate yields. It is worth of noting that the chemoselective coupling of benzaldehyde and 3-nitrobenzaldeyde to produce **3de** is very challenging, and the present strategy provides an alternative method, which is complementary to the conventional Tishchenko reactions.

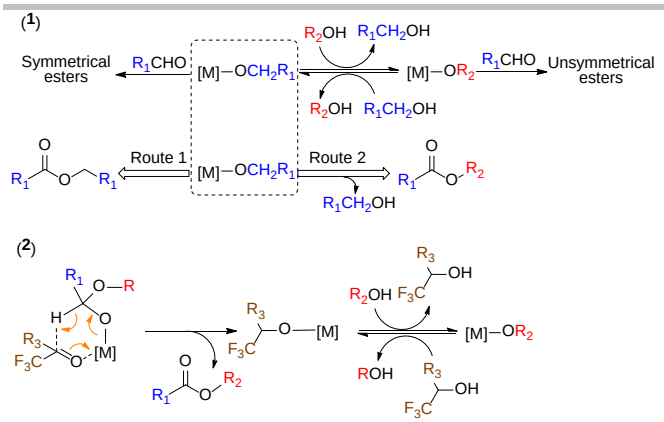
Table 2. Esterification between various aldehydes and alcohols. [a]



(**1**) (**2**) (**3**)

Entry	R_1	R_2	Yield (%)	Product
1	4-ClPh	Me	85%	**3ba**
2	4-NO_2Ph	Me	90%	**3ca**
3	3-NO_2Ph	Me	94%	**3da**
4	4-CNPh	Me	93%	**3ea**
5	4-CF_3Ph	Me	88%	**3fa**
6	4-MePh	Me	71%	**3ga**
7	4-MeOPh	Me	13%	**3ha**
8	2-pyridyl	Me	90%	**3ia**
9	2-thiophen	Me	78%	**3ja**
10	2-furyl	Me	44%	**3ka**
11	1-naphthyl	Me	67%	**3la**
12	2-naphthyl	Me	81%	**3ma**
13	Ph	Et	52%	**3ab**
14	Ph	^{i}Pr	12%	**3ac**
15	3-NO_2Ph	Et	89%	**3db**
16	3-NO_2Ph	^{i}Pr	78%	**3dc**
17	3-NO_2Ph	Bn	60%	**3de**

[a] Conditions: 0.007mmol catalysts, [Cat.]/[CHO]/[OH]= 1/150/50, 700 μL C_6D_6, 70°C, 6h; substrates were added in the order of alcohols, catalyst, aldehyde; yield was determined by ^{1}H NMR spectroscopy of the crude reaction mixture basing on alcohols.



Scheme 2. (1), Competitive routes for metal alkoxide species; (2), plausible procedure for hydride transfer when using trifluoromethyl ketone as an acceptor.

During the above esterification studies, in the later stage of the reaction, two undesired byproducts starts to accumulate, *i.e.*, the symmetrically coupled Tishchenko ester and the substituted benzyl alcohol, which were generated from the Tishchenko cycle and proton transfer step, respectively (Scheme 2 (1)). Therefore, it is demanding to circumvent these byproducts and make the reaction proceed in a selective way. From Scheme 2 (1), we can observe that for the metal alkoxide species, two competitive routes are available, which give rise to the symmetrical ester (route 1) and the unsymmetrical ester (route 2), respectively. We envisage that increasing the alcohol concentration will facilitate the proton transfer step and thus benefit the formation of the unsymmetrical ester. This hypothesis was confirmed by our above optimization studies, in which 3 equivalents of methanol caused the reaction to proceed only via route 2, and furnishing the target unsymmetrical ester as the sole product (table 1, entry 5). Another hypothesis towards the reactions amends the use of ketones that can only serve as "hydrogen acceptor" during the six-membered rate determining step (*vide infra*). The ketones will be reduced into secondary alcohols,[17, 18, 38, 39] and in view of our aforementioned results, in which secondary alcohols performed by far with inferior nucleophilicity than the primary alcohols, most of them will be left unreacted in the reaction mixture. Therefore, using the appropriate ketone will supitpress the Tishchenko cycle and render the reaction to proceed in a "sacrificial fashion" selectively towards the unsymmetrical ester (Scheme 2 (2)). Based on these considerations, *α,α,α*-trifluoroacetophenone ($PhCOCF_3$) was employed as the "hydride acceptor" and the results are summarized in Table 3. As expected, the presence of $PhCOCF_3$ suppresses route 1 efficiently, and only ~3% of the homocoupled symmetrical ester was obtained for the reaction between benzaldehyde and methanol. Using three equivalents of $PhCOCF_3$ is enough to completely shut off the symmetrically coupling cycle, and yield the unsymmetrical ester as the sole ester compounds. Similar results were also observed for other aldehydes and alcohol substrates, indicating that $PhCOCF_3$ acts as an effective "hydride acceptor" during the six-membered transition state, affording the unsymmetrical ester target in a selective way. Two other types of trifluromethyl ketones were also investigated as well, and both of them afforded similar results as $PhCOCF_3$. It is important to mention that no coupling products between the aldehyde and $PhCOCF_3$ were observed in these studies.

Table 3. Esterification of benzaldehyde with methanol in the presence of trifluoromethyl ketones using $Na[N(SiMe_3)_2]$ [a]

Entry	R_1CHO	R_2OH	R_3COCF_3	$[R_3COCF_3]/[OH]$	R_1COOR_2 (%)[c]	$R_1COOCH_2R_1$ (%)[d]
1	Ph	Me	Ph	1/1	76	
2	Ph	Me	Ph	3/1	97	
3[b]	Ph	Me	Ph	1/1	60	
4	3-MePh	Me	Ph	1/1	71	
5	2-naphthyl	Me	Ph	1/1	59	
6	Ph	Et	Ph	1/1	30	
8	Ph	Me	4-BrPh	3/1	93	
9	Ph	Me	4-MePh	3/1	86	

[a] Conditions: 0.007mmol catalysts, [Cat.]/[CHO]/[OH]= 1/150/50, 700 μL C 70°C; substrates were added in the order of alcohols, catalyst, aldehyde, k [b] [Cat.]/[CHO]/[OH]= 1/50/50. [c] Yield was determined by ^1H NMR spectros of the crude reaction mixture based on MeOH. [d] Yield was based on aldeh

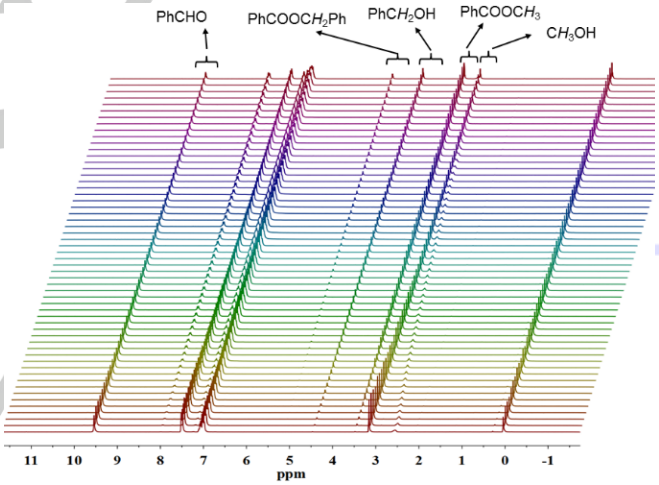
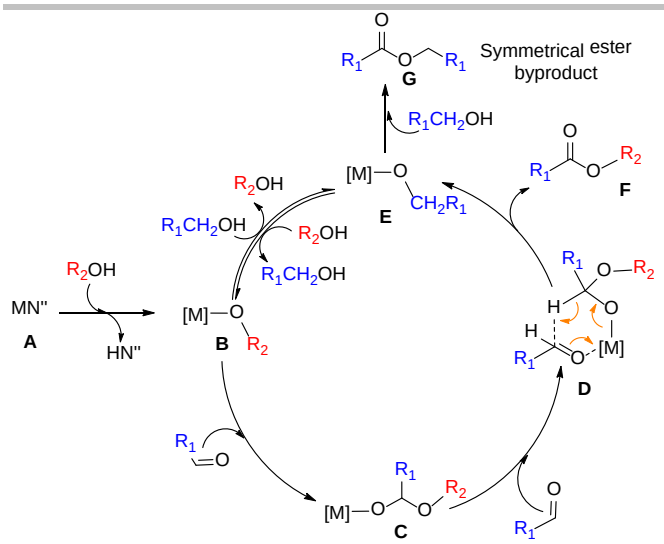


Figure 1. Reaction progress monitoring for $PhCHO/CH_3OH/ Na[N(SiMe_3)_2]$ system.

The progress of the catalytic reaction between PhCHO/MeOH and $Na[N(SiMe_3)_2]$ was followed by ^1H NMR spectroscopy and presented in Figure 1. By tracking the reaction spectroscopically, it is shown that the substituted benzyl alcohol is produced concomitantly with the unsymmetrical ester **3aa** from the beginning of the reaction, with a roughly 1/1 ratio. The benzyl benzoate can be observed only at later stages of the reaction, when most of the MeOH was consumed, and the Tishchenko reaction became predominant. These observations indicates that there is no transesterification between benzyl benzoate and sodium methoxide as an additional pathway in the synthesis of the unsymmetrical ester.



Scheme 3. Proposed schemes for coupling reation betweena aldehydes and alcohols.

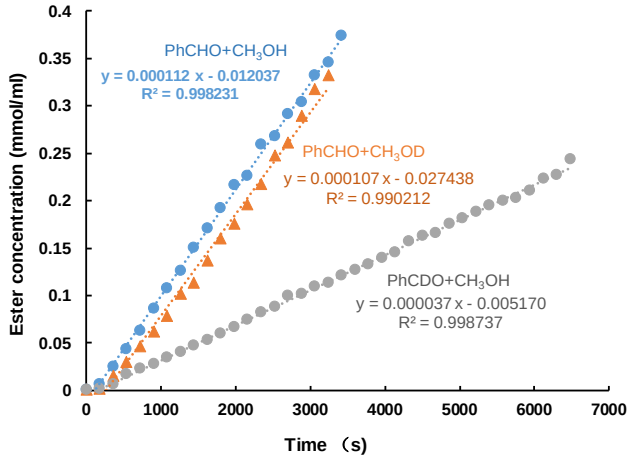


Figure 2. Initial reaction progress of the reaction of precatalyst $NaN(SiMe_3)_2$, PhCHO (or PhCDO), CH_3OH (MeOD).

On the basis of the above experimental results, a plausible reaction mechanism is proposed (Scheme 3). In the first step, the metal amido precatalyst is protonolyzed with the alcohols, affording the metal alkoxide species **B**. Subsequent insertion of an aldehyde into this alkoxide compound will yield the intermediate complex **C**, which undergoes a hydride transfer with an additional aldehyde (**D**) and furnishes the unsymetrical ester **F** and the alkoxo intermediate complex **E.** A proton transfer between complex **E** and the alcohol regenerates the initial metal alkoxide complex **B** and start a new cycle. As the reaction progresses, alcohols will be consumed gradually, which slow down the proton transfer process, and the metal alkoxide species **E** will start coupling two molecules of aldehyde, giving rise to the symmetrical ester byproduct **G**. In the presence of the sacrificial trifluoromethyl ketones, they will outcompete with the aldehyde for the metal hemiacetal complex **C**, and the the hydride transfer will give rise to trifluoromethylbenzylalcoholate metal compounds, which will undergo a rapid proton tranfer with alcohols to regenerate the initial active species **B**. To understand the turnover limiting step, reactions with deuterated substrates were carried out. When reacting benzaldehyde with MeOD using $Na[N(SiMe_3)_2]$, a similar rate constant as with the PhCHO/MeOH system was obtained with a KIE (k_{MeOH}/k_{MeOD}) value of 1.05 (Figure 2), suggesting a rapid proton transfer step between metal alkoxide species and alcohols. On the contrary, reaction of MeOH with benzaldehyde-*d* (PhCDO) were slower as compared to the PhCHO/MeOH systems revealing a primary kinetic isotope effect (k_{PhCHO}/k_{PhCDO} = 3.1). This result indicates that the hydride transfer is the rate-determining step.

Conclusions

In summary, an evolved Tishchenko reaction towards the coupling of aldehydes and alcohols is disclosed herein for the production of asymmetrical ester in high yields and under very mild condistions. The reaction is applicable to wide range of aldehyde and alcohol substrates. The use of sacrificial trifluoromethyl ketones affords the asymmetrical ester in a selective manner. An plausible mechanism for the present reaction was proposed based on reaction progress monitoring and deuterium labeling studies.

Experimental Section

General considerations

All manipulations of air-sensitive materials were performed with the rigorous exclusion of oxygen and moisture in flamed Schlenk-type glassware or *J*-Young Teflon valve-sealed NMR tubes on a dual manifold Schlenk line interfaced to a high vacuum (10^{-5} Torr) line, or in a nitrogen-filled Innovative Technologies glovebox with a medium-capacity recirculator (1 – 2 ppm of O_2). Argon and nitrogen were purified by passage through MnO oxygen-removal column and a Davison 4Å molecular sieve column. Hydrocarbon solvents benzene-d^6 (Cambridge Isotopes), toluene (Bio-Lab), were distilled under vacuum from Na/K alloy. Liquid aldehydes were distilled over sodium bicarbonate and stored in a glovebox prior to use, solid aldehydes were recrystallized twice and then dried for 12 h on a high vacuum line (10^{-5} Torr) and stored in a glovebox prior to use. Methanol, ethanol, isopropanol, *tert*-butanol, benzyl alcohol was dried using sodium (Na) metal (or CaH_2), distilled, and stored over 4 Å molecular sieves. $LiN(SiMe_3)_2$, $NaN(SiMe_3)_2$, $KN(SiMe_3)_2$, $Mg[N(SiMe_3)_2]_2$, $Zn[N(SiMe_3)_2]_2$, $Y[N(SiMe_3)_2]_3$, $Gd[N(SiMe_3)_2]_3$ were prepared according to published procedures.[40-45] All the aforementioned reagents were stored in an inert atmosphere glovebox prior to use. *O*-deuterated methanol was purchased from Sigma Aldrich, and dried according the above procedure, and storing over 4 Å molecular sieves. Deuterated benzaldehyde PhCDO was prepared according to previous reports, storing over 4 Å molecular sieves after being dried.[46] NMR spectra were recorded on Bruker Avance 300, Bruker Avance III 400 spectrometers on crude reaction mixtures. Chemical shifts for ^1H and ^{13}C NMR are referenced to internal protiosolvent and reported relative to tetramethylsilane.

General procedures for coupling aldehydes with alcohols

In a typical experiment, into a J. Young Teflon sealed NMR tube was added desired amount of catalyst in C_6D_6, followed by adding alcohol (50 equiv.) and aldehyde (150 equiv.) respectively (trifluoromethyl ketone was added when necessary). Samples were then sealed and placed in an oil bath preheated to 70 °C, and the reaction progress monitored at regular intervals using ^1H NMR spectroscopy. The yield was calculated from the ratio of esters and alcohols from the crude ^1H NMR spectra (see examples in Figure 1). After completion of the reaction, all the ester pure product was

obtained by flash column chromatography on silica gel (*n*-hexane : EtOAc = 20:1) and compared with previous reports.

Deuterium labeling studies.

Into a J. Young Teflon sealed NMR tube was added desired amount of catalyst in C_6D_6, followed by adding methanol (50 equiv.) (or MeOD) and aldehyde (150 equiv.) (or PhCDO) respectively. Take the tube out of the glove box and freeze it in ice bath until the ^{1}H NMR experiment began. All the experiments were done by changing one substrate or catalyst while keeping the other reagents constant, and the data was collected every two minutes up to 6 hours. The reaction progresses were shown in Figure 2.

Methyl benzoate[47] **(3aa)**: reaction of benzaldehyde (1.044mmol, 106.4 µL) with methanol (0.348mmol, 14.1µL) was carried out following the general procedure described above, affording **3aa** with yield of 81% (based on methanol) from ^{1}H NMR. Purification by flash chromatography on silica gel (*n*-hexane/EtOAc 20/1) gave colorless oil (isolated yield: 34 mg, 72%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13 – 7.86 (m, 2H, H_{Ar}), 7.67 – 7.33 (m, 3H, H_{Ar}), 3.94 (s, 3H, OCH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.13, 132.92, 130.13, 129.57, 128.36, 52.12. MS (APCI): m/z 137.0607(M+H)*.

Methyl 4-chlorobenzoate[48] **(3ba)**: reaction of 4-chlorobenzaldehyde (1.044mmol, 146.8mg) with methanol (0.348mmol, 14.1µL) was carried out following the general procedure described above, affording **3ba** with yield of 85% (based on methanol) from ^{1}H NMR. Purification by flash chromatography on silica gel (*n*-hexane/EtOAc 20/1) gave off-white solid (isolated yield: 49 mg, 83%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 – 7.84 (m, 2H, H_{Ar}), 7.50 – 7.31 (m, 2H, H_{Ar}), 3.89 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.15, 139.26, 130.86, 128.61, 128.45, 51.92. MS (APCI): m/z 171.0204 (M+H)*.

Methyl 4-nitrobenzoate[49] **(3ca):** reaction of 4-nitrobenzaldehyde (1.044mmol, 157.8mg) with methanol (0.348mmol, 14.1µL) was carried out following the general procedure described above, affording **3ca** with yield of 90% (based on methanol) from ^{1}H NMR. Purification by flash chromatography on silica gel (*n*-hexane/EtOAc 20/1) gave off-white solid (isolated yield: 51 mg, 81%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.41 – 8.22 (m, 2H, H_{Ar}), 8.17 (m, 2H, H_{Ar}), 3.98 – 3.86 (m, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.07, 150.35, 135.35, 130.60, 123.44, 52.74. MS (APCI): m/z 182.0476(M+H)*.

Methyl 3-nitrobenzoate[50] **(3da)**: reaction of 3-nitrobenzaldehyde (1.044mmol, 157.8mg) with methanol (0.348mmol, 14.1µL) was carried out following the general procedure described above, affording **3da** with yield of 94% (based on methanol) from ^{1}H NMR. Purification by flash chromatography on silica gel (*n*-hexane/EtOAc 20/1) gave off-white solid (isolated yield: 55 mg, 87%) ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.91 – 8.76 (m, 1H, H_{Ar}), 8.50 – 8.25 (m, 2H, H_{Ar}), 7.74 – 7.50 (m, 1H, H_{Ar}), 3.98 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.86, 148.14, 135.18, 131.73, 129.54, 127.30, 124.51, 52.72. MS (APCI): m/z 182.0411(M+H)*.

Methyl 4-cyanobenzoate[49] **(3ea)** reaction of 4-cyanobenzaldehyde (1.044mmol, 136.9mg) with methanol (0.348mmol, 14.1µL) was carried out following the general procedure described above, affording **3ea** with yield of 93% (based on methanol) from ^{1}H NMR. Purification by flash chromatography on silica gel (*n*-hexane/EtOAc 20/1) gave off-white solid (isolated yield: 49 mg, 87%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 – 8.00 (m, 2H, H_{Ar}), 7.80 – 7.55 (m, 2H, H_{Ar}), 3.93 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.33, 133.79, 132.12, 129.99, 117.87, 116.27, 52.64. MS (APCI): m/z 162.0563 (M+H)*.

Methyl 4-trifluoromethylbenzoate[51] **(3fa)**: reaction of 4-trifluorobenzadehyde (1.044mmol, 140.0µL) with methanol (0.348mmol, 14.1µL) was carried out following the general procedure described above, affording **3fa** with yield of 88% (based on methanol) from ^{1}H NMR. Purification by flash chromatography on silica gel (*n*-hexane/EtOAc 20/1) gave colorless oil (isolated yield: 51 mg, 72%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 (d, *J* = 8.1 Hz, 1H, H_{Ar}), 7.69 (d, *J* = 8.1 Hz, 1H, H_{Ar}), 3.94 (s, 1H, CH_3). MS (APCI): m/z 205.0433(M+H)*.

Methyl 4-methylbenzoate[49] **(3ga)**: reaction of 4-methylbenzaldehyde (1.044mmol, 123.1 µL) with methanol (0.348mmol, 14.1µL) was carried out following the general procedure described above, affording **3ga** with yield of 71% (based on methanol) from ^{1}H NMR. Purification by flash chromatography on silica gel (*n*-hexane/EtOAc 20/1) gave colorless oil (isolated yield: 28 mg, 54%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 – 7.84 (m, 2H, H_{Ar}), 7.19 – 7.14 (m, 2H, H_{Ar}), 3.87 (s, 3H, CH_3), 2.38 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.10, 143.46, 129.48, 128.97, 127.28, 51.39, 21.29. MS (APCI): m/z 151.0758 (M+H)*.

Methyl anisate[49] **(3ha)**: reaction of 4-anisaldehyde (1.044mmol, 126.8µL) with methanol (0.348mmol, 14.1µL) was carried out following the general procedure described above, affording **3ha** with yield of 13% (based on methanol) from ^{1}H NMR. Purification by flash chromatography on silica gel (*n*-hexane/EtOAc 20/1) gave colorless oil (isolated yield: 6 mg, 10%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 – 7.87 (m, 2H, H_{Ar}), 6.95 – 6.73 (m, 2H, H_{Ar}), 3.87 – 3.86 (m, 3H, CH_3), 3.85 – 3.83 (m, 2H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.78, 163.22, 131.48, 122.53, 113.32, 55.21, 51.71. MS (APCI): m/z 166.01 (M+H)*.

Methyl picolinate[52] **(3ia)**: reaction of 2-pyridinecarboxaldehyde (1.044mmol, 99.3 µL) with methanol (0.348mmol, 14.1µL) was carried out following the general procedure described above, affording **3ia** with yield of 90% (based on methanol) from ^{1}H NMR. Purification by flash chromatography on silica gel (*n*-hexane/EtOAc 20/1) gave colorless oil (isolated yield: 40 mg, 83%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.81 – 8.63 (m, 1H, H_{Ar}), 8.28 – 7.96 (m, 1H, H_{Ar}), 7.88 – 7.64 (m, 1H, H_{Ar}), 7.54 – 7.36 (m, 1H, H_{Ar}), 3.99 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.59, 149.69, 147.82, 136.92, 126.83, 125.01, 52.78. MS (APCI): m/z 138.0572 (M+H)*.

Methyl thenoate[53] **(3ja)**: reaction of 2-thenaldehyde (1.044mmol, 97.6 µL) with methanol (0.348mmol, 14.1µL) was carried out following the general procedure described above, affording **3ja** with yield of 78% (based on methanol) from ^{1}H NMR. Purification by flash chromatography on silica gel (*n*-hexane/EtOAc 20/1) gave colorless oil (isolated yield: 29 mg, 60%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 – 7.77 (m, 1H, H_{Ar}), 7.55 – 7.52 (m, 1H, H_{Ar}), 7.11 – 7.06 (m, 1H, H_{Ar}), 3.87 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.83, 133.71, 133.38, 132.22, 127.65, 51.96. MS (APCI): m/z 143.0174 (M+H)*

Methyl 2-furoate[53] **(3ka)**: reaction of 2-furaldehyde (1.044mmol, 87µL) with methanol (0.348mmol, 14.1µL) was carried out following the general procedure described above, affording **3ka** with yield of 44% (based on methanol) from ^{1}H NMR. Purification by flash chromatography on silica gel (*n*-hexane/EtOAc 20/1) gave colorless oil (isolated yield: 15 mg, 34%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 – 7.53 (m, 1H, H_{Ar}), 7.19 – 7.13 (m, 1H, H_{Ar}), 6.54 – 6.46 (m, 1H, H_{Ar}), 3.88 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.95, 146.15, 143.41, 117.80, 111.71, 51.79. MS (APCI): m/z 127.0411 (M+H)*.

Methyl naphthalene-1-carboxylate[49] **(3la)**: reaction of 1-naphthaldehyde (1.044mmol, 141.8µL) with methanol (0.348mmol, 14.1µL) was carried out following the general procedure described above, affording **3la** with yield of 67% (based on methanol) from ^{1}H NMR. Purification by flash chromatography on silica gel (*n*-hexane/EtOAc 20/1) gave off-white solid (isolated yield: 41 mg, 64%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.92 – 8.83 (m, 1H, H_{Ar}), 8.20 – 8.11 (m, 1H, H_{Ar}), 8.01 (d, *J* = 8.2 Hz, 1H, H_{Ar}), 7.91 – 7.80 (m, 1H, H_{Ar}), 7.64 – 7.56 (m, 1H, H_{Ar}), 7.56 – 7.43 (m, 2H, H_{Ar}), 3.99 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.95, 133.71, 133.27, 131.20, 130.11, 128.43, 127.66, 126.95, 126.10, 125.68, 124.39, 51.71. MS (APCI): m/z 187.0838 (M+H)*.

Methyl naphthalene-2-carboxylate[49] **(3ma)**: reaction of 2-naphthaldehyde (1.044mmol, 163.5mg) with methanol (0.348mmol,

14.1µL) was carried out following the general procedure described above, affording **3ma** with yield of 81% (based on methanol) from ^{1}H NMR. Purification by flash chromatography on silica gel (*n*-hexane/EtOAc 20/1) gave off-white solid (isolated yield: 49 mg, 76%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.60 (s, 1H, H_{Ar}), 8.05 (d, *J* = 8.6 Hz, 1H, H_{Ar}), 7.98 – 7.91 (m, 1H, H_{Ar}), 7.90 – 7.82 (m, 2H, H_{Ar}), 7.61 – 7.48 (m, 2H, H_{Ar}), 3.97 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.17, 135.39, 132.36, 130.96, 129.25, 128.13, 128.05, 127.65, 127.26, 126.53, 125.11, 52.03. MS (APCI): m/z 187.0762 (M+H)*.

Methyl benzoate[53] **(3ab)**: reaction of benzaldehyde (1.044mmol, 106.4 µL) with ethanol (0.348mmol, 20.3 µL) was carried out following the general procedure described above, affording **3ab** with yield of 52% (based on methanol) from ^{1}H NMR. Purification by flash chromatography on silica gel (*n*-hexane/EtOAc 20/1) gave colorless oil (isolated yield: 21 mg, 41%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 – 7.95 (m, 2H, H_{Ar}), 7.57 – 7.45 (m, 1H, H_{Ar}), 7.45 – 7.34 (m, 2H, H_{Ar}), 4.51 – 4.19 (q, *J* = 7.2 Hz, 2H, CH_2), 1.36 (t, *J* = 7.2 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.43, 132.68, 130.37, 129.22, 128.07, 60.57, 14.19. MS (APCI): m/z 151.0748 (M+H)*.

Isopropyl benzoate[54] **(3ac)**: reaction of benzaldehyde (1.044mmol, 106.4 µL) with isopropanol (0.348mmol, 26.6µL) was carried out following the general procedure described above, affording **3ac** with yield of 12% (based on methanol) from ^{1}H NMR. Purification by flash chromatography on silica gel (*n*-hexane/EtOAc 20/1) gave colorless oil (isolated yield: 6 mg, 10%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (d, *J* = 7.2 Hz, 2 H, H_{Ar}), 7.55 (t, *J* = 7.6 Hz, 1 H, H_{Ar}), 7.44 (t, *J* = 7.6 Hz, 2 H, H_{Ar}), 4.38 (q, *J* = 5.6 Hz, 2 H, CH(CH_3)$_2$), 1.39 (t, *J* = 5.7 Hz, 6 H, CH(CH_3)$_2$) MS (APCI): m/z 164.0851 (M+H)*.

Ethyl 3-nitrobenzoate[55] **(3db)**: reaction of 3-nitrobenzaldehyde (1.044mmol, 157.8mg) with ethanol (0.348mmol, 20.3µL) was carried out following the general procedure described above, affording **3db** with yield of 89% (based on methanol) from ^{1}H NMR. Purification by flash chromatography on silica gel (*n*-hexane/EtOAc 20/1) gave off-white solid (isolated yield: 50 mg, 74%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.84 – 8.70 (m, 1H, H_{Ar}), 8.39 – 8.17 (m, 2H, H_{Ar}), 7.64 – 7.46 (m, 1H, H_{Ar}), 4.35 (q, *J* = 7.1 Hz, 2H, CH_2), 1.34 (d, *J* = 7.1 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, C_6D_6) δ 161.77, 148.12, 135.17, 131.97, 129.49, 127.12, 124.23, 61.46, 13.78. MS (APCI): m/z 195.0291.

Isopropyl 3-nitrobenzoate[55] **(3dc)**: reaction of 3-nitrobenzaldehyde (1.044mmol, 157.8mg) with isopropanol (0.348mmol, 26.6µL) was carried out following the general procedure described above, affording **3dc** with yield of 78% (based on methanol) from ^{1}H NMR. Purification by flash chromatography on silica gel (*n*-hexane/EtOAc 20/1) gave off-white solid (isolated yield: 44 mg, 61%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.90 – 8.78 (m, 1H, H_{Ar}), 8.45 – 8.30 (m, 2H, H_{Ar}), 7.67 – 7.56 (m, 1H, H_{Ar}), 5.28 (hept, *J* = 6.3 Hz, 1H, CH), 1.39 (d, *J* = 6.3 Hz, 6H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.69, 162.21, 149.45, 135.23, 132.55, 129.38, 126.98, 124.35, 69.38, 21.76. MS (APCI): m/z 209.0431.

Phenylmethyl 3-nitrobenzote[55] **(3de)**: reaction of 3-nitro benzaldehyde (1.044mmol, 157.8mg) with benzyl alcohol (0.348mmol, 36.05µL) was carried out following the general procedure described above, affording **3de** with yield of 60% (based on methanol) from ^{1}H NMR. Purification by flash chromatography on silica gel (*n*-hexane/EtOAc 20/1) gave off-white solid (isolated yield: 38 mg, 42%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.91 – 8.82 (m, 1H), 8.54 – 8.26 (m, 2H), 7.63 (t, *J* = 7.7 Hz, 1H), 7.48 – 7.34 (m, 5H), 5.40 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.21, 148.20, 135.26, 135.14, 131.81, 129.52, 128.63, 128.54, 128.37, 127.37, 124.57, 67.51.MS (APCI): m/z 257.0742.

Supporting Information

^{1}H and ^{13}C NMR of the products (34 pages)

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Keywords: Alcohols • Aldehydes • Esterification • Selective • Tishchenko reaction

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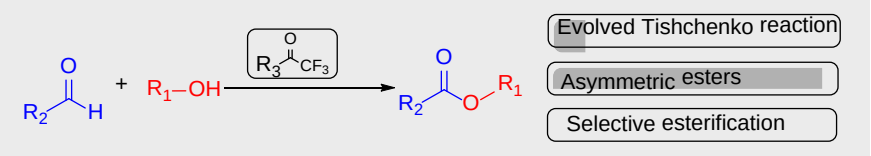

New Esterification **method***

*Heng Liu, Moris S. Eisen**

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Title: Facile Coupling Aldehydes with Alcohols: An Evolved Tishchenko Process in Preparing Unsymmetrical Esters

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An evolved Tishchenko reaction betweeen alcohols and aldehydes to afford unsymmetrical ester compounds is reported herein. The presence of sacrifical trifluoromethyl ketones are able to render the reaction process in the highly selective fashion.