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N-Heterocyclic Carbene Catalyzed Transformylation

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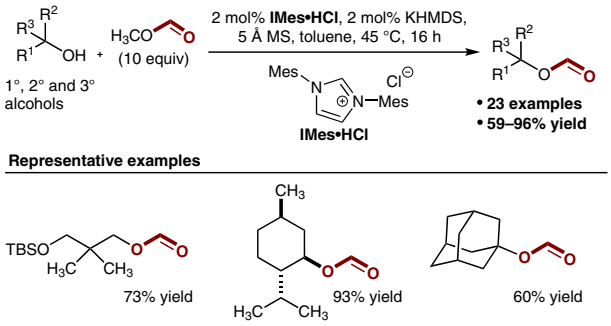
Dedicated to Prof. Herbert Mayr in celebration of his 70th birthday.



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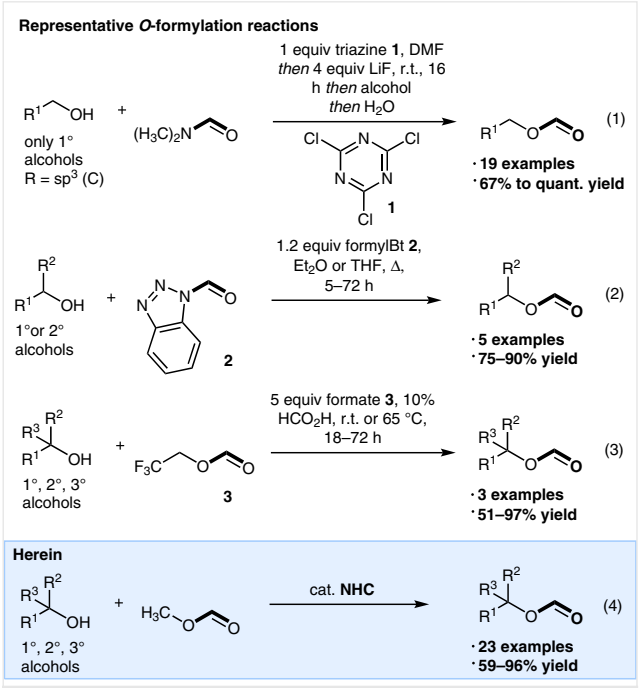
Abstract The N-heterocyclic carbene (NHC) catalyzed transformylation has been developed for the conversion of 1°, 2°, and 3° alcohols to the corresponding formates. The reaction employs low catalyst loadings and methyl formate as the formyl transfer reagent. The scope of the reaction is broad with 23 examples reported with good yields (59–96%). The reaction is insensitive to common nitrogen and oxygen protecting groups and can be achieved in the presence of a number of heterocycles.

Key words N-heterocyclic carbene catalysis, transformylation, formate synthesis

The formylation of alcohols defines a useful protecting group strategy. Formates display acid stability, while being labile under mildly basic conditions to which common esters are often stable.[1] In addition to enabling protection strategies, formates can be exploited in subsequent functional group interconversions. For example, the Oppenauer oxidation directly provides the corresponding carbonyl compounds,[2] reductive cleavage allows deoxygenation,[3] while condensation gives vinylogous carbonates.[4] Physically the formate is sterically undemanding, while often imparting a depressed boiling point in the product. Despite these features the application of formates is limited.[1] In part this may be due to challenges in their synthesis. The most common approaches to their preparation involve in situ generation of formylating species,[5] use of stoichiometric formylating agents,[6] or acid-catalyzed transformylation.[7] Specifically, Vilsmeier–Haack strategies are common[5a] with, for example, recent studies demonstrating that triazine **1** is suited to the chemoselective formylation of primary alcohols [Scheme 1 (1)].[5b] Alternately, Katritzky and Wittenburger independently developed the formylating agents formyl benzotriazole **2** and fluoro ester **3** [Scheme 1 (2) and (3)].[6a,c] While many conditions have been developed for the synthesis of formate esters, limitations remain relating to chemoselectivity, cost of reagents, and in some cases toxicity.

Exploiting our experience in NHC-organocatalysis[8] with esters,[9,10] and building on studies of related transesterifications,[11] we envisioned a transformylation strategy to prepare formate esters [Scheme 1 (4)]. Such a strategy could address a number of limitations in existing methods. Specifically it would be catalytic and exploit simple, cheap, and



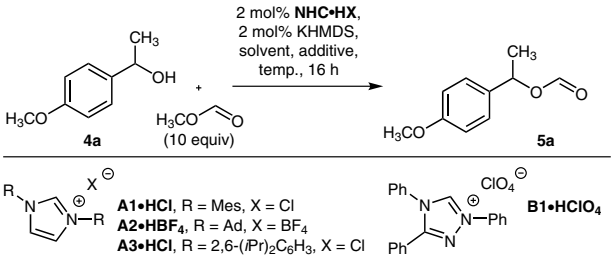
Scheme 1 Background and overview

non-toxic starting materials, and it would also have mild reaction conditions. Herein, we report studies on this chemistry that have delivered simple and mild conditions for the conversion of 1°, 2°, and 3° alcohols into the corresponding formate esters. Key to the success of this approach has been the introduction of 5Å molecular sieves, presumably to suppress reversibility. The reaction displays good generality with 23 examples reported.

Studies commenced by examining the transformylation of secondary alcohol **4a** with 10 equivalents of methyl formate in THF heated to 45 °C in the presence of common bases. While no conversion was observed with triethylamine (Table 1, entry 1), KHMDS provided a 15% yield of benzyl formate **5a** (Table 1, entry 2).[12] While the yield was modest, this result highlights the viability of Brønsted base mediated transformylation reactions. When 2 mol% IMes·HCl precatalyst (**A1**·HCl) was introduced, the yield of benzyl formate **5a** more than doubled (Table 1, entry 3), while changing to toluene, and maintaining the temperature at 45 °C, increased the yield further (Table 1, entry 4). Alternate imidazolium-derived NHCs **A2** and **A3** decreased the yield of **5a** (Table 1, entries 5 and 6), while the less basic Enders triazolium derived NHC **B1**[13] gave none of the expected product (Table 1, entry 7). The outcome of the reaction was slightly poorer when performed at increased temperatures (Table 1, entries 8 and 9), an observation attributed to the volatility of formate **5a**. Similar reaction outcomes were observed in DMF (Table 1, entry 10) while introduction of 5Å molecular sieves to sequester liberated methanol and suppress the reverse reaction increased the yield of **5a** from 65 to 82% (Table 1, entry 4 cf. entry 11). Similar, increases in yield were achieved using 5Å MS in either DMF or THF (Table 1, entries 12 and 13). Having identified conditions that exploit low catalyst loading (2 mol%) and cheap and readily available reagents, the reaction scope was examined.

Having optimized conditions for the formylation of 2° alcohols (i.e., **4a**), we next examined the generality across a range of 1°, 2°, and 3° alcohols. In general, all reactions gave good isolated yields of the expected formates with an order of reactivity in which 1° is faster than 2°, and 2° faster than 3°. In some cases yields were modest, which was often associated with challenges in isolation due to the volatility of lower molecular weight products. Specifically studies started with a range of simple aliphatic 1° alcohols, the corresponding formates **5b–e** were prepared in 80–90% isolated yield (Scheme 2). In addition the reaction tolerated electron-poor aromatic groups, giving **5f** in 65% isolated yield, and electron-rich aromatic groups, providing **5g** and **5h** in 78 and 86% isolated yield respectively. The excellent reactivity of the later substrate was further examined with formate **5h** prepared using 1.1 equivalents of methyl formate (cf. 10 equiv) in 78% yield, furthermore 1.1 equivalents of methyl formate and 1 mol% **A1** gave formate **5h** in 75% yield. Returning to the optimized conditions, the presence

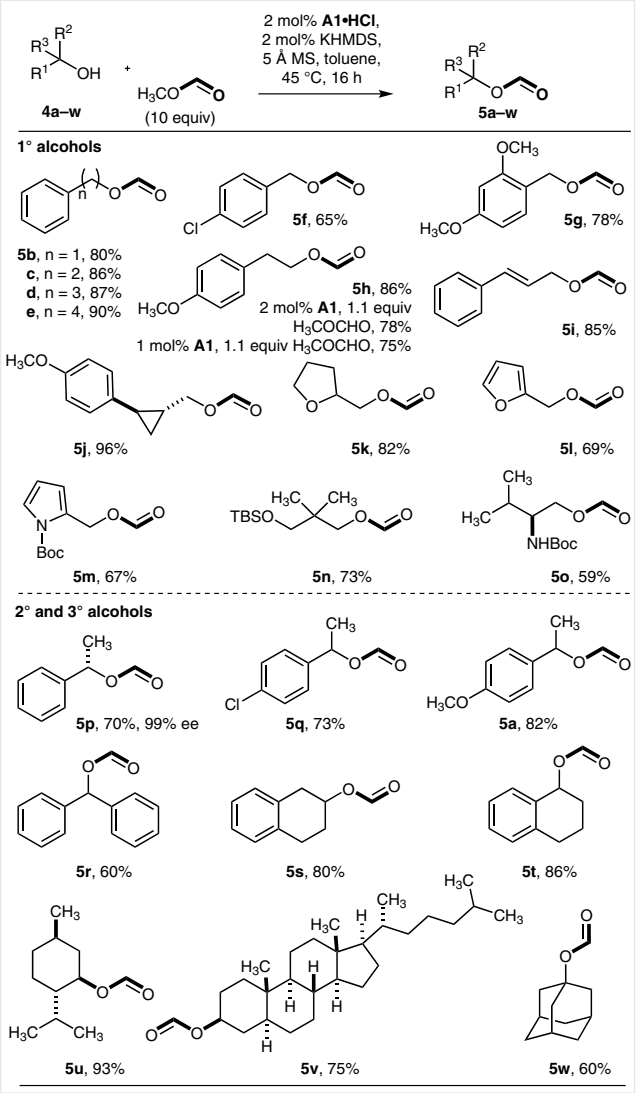
Table 1 Optimization of the NHC-Catalyzed Transformylation



Entry	NHC·HX	Solvent	Additive	Temp (°C)	Yield (%) of **5a**[a]
1	–[b]	THF	–	45	0
2	–	THF	–	45	15
3	**A1**·HCl	THF	–	45	37
4	**A1**·HCl	toluene	–	45	65
5	**A2**·HBF_4	toluene	–	45	54
6	**A3**·HCl	toluene	–	45	42
7	**B1**·$HClO_4$	toluene	–	45	0
8	**A1**·HCl	toluene	–	75	60
9	**A1**·HCl	toluene	–	95	40
10	**A1**·HCl	DMF	–	45	53
11	**A1**·HCl	toluene	5 Å MS	45	82
12	**A1**·HCl	DMF	5 Å MS	45	67
13	**A1**·HCl	THF	5 Å MS	45	68

[a] Isolated yield following chromatography.
[b] Et_3N was used instead of KHMDS.

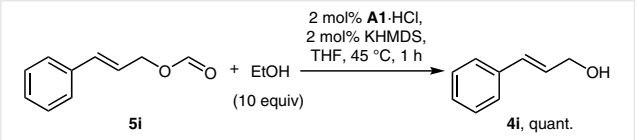
of unsaturation (**4i**), strained rings (**4j**), or aliphatic/aromatic heterocycles (**4k**,**l**) were examined, giving the expected esters **5** with 69–96% isolated yield. The sensitivity of the reaction to common protecting groups such as Boc or TBS was examined with Boc-pyrrole **4m**, TBS ether **4n**, and Boc-valine derivative **4o**, all formylated in acceptable yields. A thorough examination of 2° alcohols commenced with homochiral (*S*)-α-methylbenzyl alcohol (**4p**). This was converted into the corresponding formate **5p** without loss of enantiopurity (**4p**, 99% ee → **5p**, 99% ee). Unsurprisingly, and as observed with 1° alcohols, electron-rich and -poor substrates were equally suited to the reaction conditions giving benzyl formates **5q** and **5a** in good yield. Similarly benzophenone, β-tetralone, and α-tetralone derived alcohols **4r–t** were formylated to give formates **5r–t** in good to excellent isolated yield. Aliphatic alcohols present in more complex bioactive substrates such as menthol (**4u**) and steroid **4v** were converted into formates **5u** and **5v** in 93% and 75% isolated yield, respectively. Finally, adamantanol **4w** was smoothly converted into the corresponding formate **5w** in 60% isolated yield.



Scheme 2 Scope of the NHC-catalyzed transformylation; isolated yields following column chromatography are given

The reversibility of this reaction can be exploited for the deprotection of formate esters. Thus, in the absence of molecular sieves, exposure of cinnamyl formate (**5i**) to 10 equivalents of ethanol and 2 mol% NHC **A1**, provided cinnamyl alcohol **4i** in quantitative yield after 1 hour (Scheme 3).

The NHC-catalyzed formylation of 1°, 2°, and 3° alcohols has been achieved using mild reaction conditions. The presence of common oxygen and nitrogen protecting groups are tolerated, as are various heterocycles. The reaction may occur via either a Lewis or Brønsted base mediated pathway.[14,15] Based on the observation of partial reactivity using simple bases, it is likely that the reaction is occurring via Brønsted base catalysis. Finally, the complementary deprotection has also been demonstrated.



Scheme 3 Deformylation

The formylation presented herein highlights the versatility of NHCs as powerful organocatalysts, which enable various activation modes. Particularly pleasing is the observation that one of the simplest catalysts (IMes) is ideally suited to the reaction, and that good activity can be observed with only 1 mol% catalyst and a slight excess of the formylating reagent.

For details of equipment, sources of chemicals etc., see the Supporting Information. PE = petroleum ether.

Formates 5; General Procedure

To a flame-dried flask containing a stirrer bar and activated 5 Å molecular sieves was added IMes·HCl (**A1**·HCl, 6.8 mg, 0.02 mmol) and toluene (2 mL) under an inert atmosphere. To this stirred suspension 0.5 M KHMDS in toluene (0.04 mL) was added and the mixture stirred for 15 min. An appropriate alcohol (1 mmol) and methyl formate (600 mg, 10 mmol) were then added as a solution in toluene (2 mL) and the flask sealed and heated to 45 °C for 16 h. The crude mixture was loaded directly onto a chromatography column (silica gel) to give the formates.

1-(4-Methoxyphenyl)ethyl Formate (5a)

Yield: 148 mg (82%). ^{1}H and ^{13}C NMR data were identical with the literature.[12]

Benzyl Formate (5b)

Yield: 109 mg (80%). ^{1}H and ^{13}C NMR data were identical with the literature.[5a]

Phenethyl Formate (5c)

Yield: 129 mg (86%). ^{1}H and ^{13}C NMR data were identical with the literature.[16]

3-Phenylpropyl Formate (5d)

Yield: 143 mg (87%). ^{1}H and ^{13}C NMR data were identical with the literature.[17]

4-Phenylbutyl Formate (5e)

Colourless oil; yield: 160 mg (90%); R_f = 0.7 (EtOAc/PE, 1:4).

IR (ATR): 2931w, 1727s, 1496w, 1453m, 1159s, 1030w, 908w, 745m, 698s cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.06 (s, 1 H), 7.31–7.17 (m, 5 H), 4.19 (m, 2 H), 2.66 (m, 2 H), 1.71 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.1, 141.8, 128.3, 125.8, 63.7, 35.3, 28.0, 27.5 (one signal overlapping).

MS (EI): *m*/*z* [M]$^+$ calcd for $C_{11}H_{14}O_2$: 178.1; found: 178.2.

4-Chlorobenzyl Formate (5f)

Yield: 111 mg (65%). ^{1}H and ^{13}C NMR data were identical with the literature.[16]

2,4-Dimethoxybenzyl Formate (5g)

Colourless oil; yield: 153 mg (78%); R_f = 0.3 (EtOAc/PE, 1:4).

IR (ATR): 2938m, 1715s, 1613s, 1588m, 1509s, 1458m, 1438m, 1366m, 1291m, 1269m, 1207s, 1153s, 1130s, 1031s, 922m, 735m cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.12 (s, 1 H), 7.27–7.24 (m, 1 H), 6.49–6.46 (m, 2 H), 5.19 (s, 2 H), 3.83 (s, 3 H), 3.82 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.5, 161.1, 159.0, 131.7, 115.9, 104.0, 98.5, 61.3, 55.5, 55.4.

MS (EI): *m*/*z* [M]$^+$ calcd for $C_{10}H_{12}O_4$: 196.1; found: 196.1.

4-Methoxyphenethyl Formate (5h)

Colourless oil; yield: 153 mg (86%); R_f = 0.5 (EtOAc/PE, 1:4).

IR (ATR): 2937w, 1717s, 1613m, 1584w, 1512s, 1465m, 1442m, 1375w, 1245s, 1155s, 1112s, 1031s, 979m, 921m, 830s, 748w cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.04 (s, 1 H), 7.15 (m, 2 H), 6.86 (m, 2 H), 4.35 (dt, *J* = 7.0, 0.7 Hz, 2 H), 3.79 (s, 3 H), 2.92 (t, *J* = 8.0 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.9, 158.4, 129.8, 129.3, 113.9, 64.6, 55.2, 34.0.

MS (EI): *m*/*z* [M]$^+$ calcd for $C_{10}H_{12}O_3$: 180.1; found: 180.2.

Cinnamyl Formate (5i)

Pale yellow oil; yield: 140 mg (85%); R_f = 0.7 (EtOAc/PE, 1:4).

IR (ATR): 2932w, 1717s, 1494m, 1449m, 1148s, 965s, 899m, 741s, 732m, 691s cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.13 (s, 1 H), 7.41–7.39 (m, 2 H), 7.36–7.32 (m, 2 H), 7.30–7.26 (m, 1 H), 6.70 (d, *J* = 16 Hz, 1 H), 6.29 (dt, *J* = 16, 6.8 Hz, 1 H), 4.85–4.82 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.8, 136.1, 134.9, 128.7, 128.3, 126.7, 122.48, 64.5.

MS (EI): *m*/*z* [M]$^+$ calcd for $C_{10}H_{10}O_2$: 162.1; found: 162.1.

[2-(4-Methoxyphenyl)cyclopropyl]methyl Formate (5j)

Colourless oil; yield: 198 mg (96%); R_f = 0.6 (EtOAc/PE, 1:4).

IR (ATR): 2937w, 1717s, 1612w, 1514s, 1459m, 1244s, 1174s, 1149s, 1114m, 1032s, 948m, 899m, 873m, 826s, 802m, 753w cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.10 (s, 1 H), 7.02 (m, 2 H), 6.82 (m, 2 H), 4.16 (m, 2 H), 3.78 (s, 3 H), 1.89 (m, 1 H), 1.43 (m, 1 H), 0.96 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.2, 158.1, 133.7, 127.3, 114.0, 67.7, 55.4, 21.4, 20.8, 13.4.

MS (EI): *m*/*z* [M]$^+$ calcd for $C_{12}H_{14}O_3$: 206.1; found: 206.1.

(Tetrahydrofuran-2-yl)methyl Formate (5k)

Colourless oil; yield: 107 mg (82%); R_f = 0.5 (EtOAc/PE, 1:4).

IR (ATR): 2951w, 2874w, 1717s, 1450w, 1163s, 1083s, 1018m, 914m, 879w, 843w cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.10 (s, 1 H), 4.27–4.21 (m, 1 H), 4.18–4.06 (m, 2 H), 3.93–3.77 (m, 2 H), 2.07–1.85 (m, 3 H), 1.68–1.56 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.1, 76.4, 68.6, 66.0, 28.1, 25.8.

MS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_6H_{10}O_3$: 153.1; found: 153.0.

Furan-2-ylmethyl Formate (5l)

Colourless oil; yield: 87 mg (69%); R_f = 0.7 (EtOAc/PE, 1:4).

IR (ATR): 2938w, 1717s, 1502w, 1448w, 1361w, 1153s, 1135s, 1016m, 922m, 884m, 818w, 741s, 699w cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.09 (s, 1 H), 7.43 (s, 1 H), 6.44–6.37 (m, 2 H), 5.15 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.6, 148.9, 143.6, 111.2, 110.8, 57.5.

MS (EI): *m*/*z* [M]$^+$ calcd for $C_6H_6O_3$: 126.0; found: 126.0.

***tert*-Butyl 2-[(Formyloxy)methyl]-1*H*-pyrrole-1-carboxylate (5m)**

Pale yellow oil; yield: 151 mg (67%); R_f = 0.7 (EtOAc/PE, 1:4).

IR (ATR): 2980w, 1718s, 1479w, 1458w, 1370m, 1315s, 1254m, 1152s, 1124s, 1064m, 976m, 843m, 771m, 734m, 694m cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.10 (s, 1 H), 7.29 (dd, *J* = 4.0, 4.0 Hz, 1 H), 6.33–6.29 (m, 1 H), 6.14 (t, *J* = 4.0 Hz, 1 H), 5.37 (s, 2 H), 1.59 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.8, 148.9, 128.1, 123.1, 116.2, 110.3, 84.4, 58.9, 28.0.

MS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{15}NO_4$: 226.1; found: 226.0.

3-(*tert*-Butyldimethylsiloxy)-2,2-dimethylpropyl Formate (5n)

Colourless oil; yield: 180 mg (73%); R_f = 0.7 (EtOAc/PE, 1:9).

IR (ATR): 2956m, 1730s, 1473w, 1251m, 1162s, 1094s, 1006w, 940w, 834s, 774s, 668w cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.09 (t, *J* = 0.8 Hz, 1 H), 3.97 (d, *J* = 0.8 Hz, 2 H), 3.34 (s, 2 H), 0.90 (s, 6 H), 0.88 (s, 9 H), 0.02 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.3, 69.2, 68.5, 36.2, 26.0, 21.6, 18.4, 5.5.

MS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{26}O_3Si$: 269.2; found: 269.1.

2-[(*tert*-Butoxycarbonyl)amino]-3-methylbutyl Formate (5o)

Colourless oil; yield: 136 mg (59%); R_f = 0.6 (EtOAc/PE, 1:4).

IR (ATR): 3300br, 2967w, 1691s, 1509m, 1459w, 1391w, 1366m, 1243m, 1154s, 1023m, 865w, 780w cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07 (s, 1 H), 4.61–4.48 (m, 1 H), 4.26–4.14 (m, 2 H), 3.73–3.63 (m, 1 H), 1.81 (oct, *J* = 8.0 Hz, 1 H), 1.44 (s, 9 H), 0.95 (dd, *J* = 8.0, 4 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.8, 155.7, 79.5, 64.2, 54.5, 28.4, 19.4, 18.3.

MS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_{21}NO_4$: 254.1; found: 254.1.

(*S*)-1-Phenylethyl Formate (5p)

Yield: 105 mg (70%). ^{1}H and ^{13}C NMR data were identical with the literature.[16] HPLC (AD-H 5μm, λ = 238 nm, hexane/*i*-PrOH = 98:2, 1.0 mL/min): t_R = 4.797 (minor), 5.140 min (major); er 99.5:0.5.

1-(4-Chlorophenyl)ethyl Formate (5q)

Yield: 135 mg (73%). ^{1}H and ^{13}C NMR data were identical with the literature.[18]

Benzhydryl Formate (5r)

Yield: 105 mg (60%). ^{1}H and ^{13}C NMR data were identical with the literature.[20]

1,2,3,4-Tetrahydronaphthalen-2-yl Formate (5s)

Yield: 141 mg (80%). ^{1}H and ^{13}C NMR data were identical with the literature.[19]

1,2,3,4-Tetrahydronaphthalen-1-yl Formate (5t)

Yield: 152 mg (86%). ^{1}H and ^{13}C NMR data were identical with the literature.[6a]

(–)-Menthyl Formate (5u)

Yield: 171 mg (93%). ^{1}H and ^{13}C NMR data were identical with the literature.[20]

Dihydrocholesterol-Derived Formate 5v

White solid; yield: 313 mg (75%); R_f = 0.7 (EtOAc/PE, 1:9).

IR (ATR): 2932s, 2849s, 1727s, 1466m, 1445m, 1373w, 1177s, 1131m, 995w, 922m, 867w, 803w cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02 (s, 1 H), 4.86–4.77 (m, 1 H), 1.99–1.94 (m, 1 H), 1.87–0.95 (m, 30 H), 0.90–0.85 (m, 9 H), 0.82 (s, 3 H), 0.65 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.9, 73.9, 56.6, 56.42, 56.36, 44.8, 44.7, 40.1, 39.7, 36.9, 36.3, 36.0, 35.61, 35.59, 34.1, 32.1, 28.7, 28.4, 28.2, 27.6, 24.4, 24.0, 23.0, 22.7, 21.4, 18.8, 12.4, 12.2.

MS (EI): m/z $[M]^+$ calcd for $C_{28}H_{48}O_2$: 416.4; found: 416.3.

Adamantan-1-yl Formate (5w)

Yield: 108 mg (60%). ^{1}H and ^{13}C NMR data were identical with the literature.[20]

Acknowledgment

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1588449. Included are experimental procedures, characterization of all new compounds and copies of 1H and 13C NMR spectra.

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