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Neodymium(III)-Mediated Reformatsky-Type Reactions of α-Halo Ketones with Carbonyl Compounds

Stefan F. Kirsch*[a] and Clémence Liébert[a]

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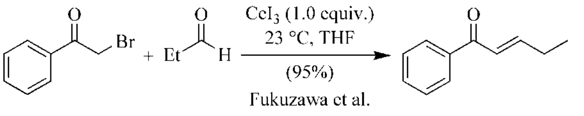
In a neodymium(III) iodide induced process, α-bromo ketones **1** and aldehydes **2** are effectively converted into aldol products **3**. This Reformatsky-type reaction proceeds through the formation of a neodymium enolate at room temperature in CH_2Cl_2. The analogous reaction in the presence of $NdBr_3$/NaI at 50 °C in THF favors the formation of corresponding aldol–Tishchenko products **5** in good yields. Studies to define the scope and limitations of these reactions mediated by neodymium(III) salts are also described.

Introduction

Although historically the use of lanthanide reagents in organic synthesis has involved only a handful of rather simple lanthanide salts, these reagents have provided an extensive series of remarkable reactions.[1] For example, the most spectacular development has occurred with the one-electron reductant $[SmI_2(thf)_x]$, which is now a standard reagent for a variety of attractive processes.[2] Only recently, the divalent lanthanide chemistry was expanded to other metals in the series such as $[TmI_2(dme)_2]$[3] and $[NdI_2(thf)_5]$.[4] Whereas lanthanide(III) salts are commonly used as Lewis acidic reagents for carbonyl activation,[5,6] organolanthanide reagents are mainly based on cerium trichloride (e.g. $CeCl_3$/RLi).[1,7] Since the pioneering work by Imamoto and coworkers in the early 1980s,[8] organocerium compounds are widely applied to facilitate a variety of nucleophilic addition reactions.[9] Owing to the fact that cerium is unlikely the best of the available lanthanides for every transformation using organolanthanide compounds,[10] we initiated studies to improve the efficiency of trivalent lanthanide reagents by variation of the metal. Herein, we report a new approach to aldol products through neodymium organyls by utilizing the reaction of α-halo ketones and carbonyl compounds in the presence of stoichiometric amounts of neodymium(III) salts.

The classical Reformatsky reaction is a convenient protocol for carbon–carbon bond formation by using the zinc-induced reaction of α-halocarbonyl compounds with aldehydes and ketones.[11] During this redox process, insertion of zinc into the halogen–carbon bond takes place forming a nucleophilic equivalent to a zinc enolate. Additionally, other metals in low oxidation states have been utilized for the oxidative addition step to generate various metal enolates.[12] In 1985, Fukuzawa and coworkers developed an alternative and facile route for the formation of cerium(III) enolates that does not involve oxidation of the metal species.[13] Therein, treatment of α-bromo ketones with CeI_3 in THF at 23 °C resulted in the formation of the corresponding enolates, which in the presence of an aldehyde electrophile gave α,β-unsaturated ketones through a formal aldol condensation [Equation (1)].[14] Because there is only a limited number of reports on the use of other trivalent lanthanide salts for this type of carbon–carbon bond formation,[15] we envisioned that an improvement of this reaction might be accomplished by employing neodymium(III) salts instead of cerium triiodide.[16]



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Results and Discussion

To this end, we initiated our preliminary studies of the neodymium(III)-mediated carbon–carbon bond formation with substrates **1a** and **2a** as previously employed by Fukuzawa and coworkers.[13] We were pleased to find that formation of ketol product **3aa** was best accomplished by treatment of a preformed mixture of α-bromo ketone **1a** and aldehyde **2a** with 1.2 equiv. of NdI_3 in CH_2Cl_2 at 0 °C for 18 h (Scheme 1). Under these rather mild conditions, 3-hydroxy-1-phenylpentan-1-one (**3aa**) was obtained in 80% yield as the sole product.

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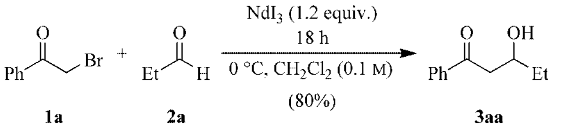
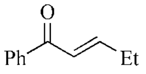
[a] Department Chemie, Technische Universität München,
Lichtenbergstr. 4, 85747 Garching, Germany
Fax: +49-89-2891-3315
E-mail: stefan.kirsch@ch.tum.de

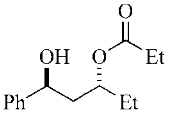


Scheme 1. Formation of **3aa** from **1a** and **2a** in the presence of NdI$_3$.

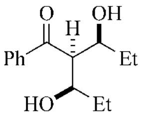
Depending on the reaction temperature, the use of stoichiometric amounts of NdI$_3$ in CH$_2$Cl$_2$ also produced α,β-unsaturated ketone **4aa** (through subsequent elimination of **3aa**), *anti* 1,3-diol monoester **5aa** (through the aldol–Tishchenko reaction), and diol **6aa** (through a second aldol reaction of **3aa**). For example, decreasing the reaction temperature to –20 °C also led to the exclusive formation of ketol product **3aa** (73%), although a longer period of time was required to reach complete consumption of the starting material. Nevertheless, when the reaction was performed at 23 °C, expected ketol product **3aa** was formed in rather low yield (19%). These conditions resulted in the formation of **4aa** as the major product (36%) accompanied by trace amounts of **5aa** (<5%) and **6aa** (<5%). Although trace amounts of **5aa** and **6aa** were quite frequently detected during our optimization studies, we could not identify reaction conditions leading to the exclusive formation of either product.



4aa



5aa



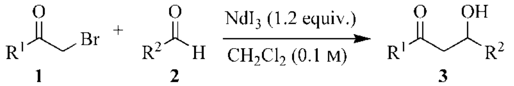
6aa

Solvent had a marked influence on product formation. Whereas the formation of ketol **3aa** was not observed in cyclohexane, DMF, or Et$_2$O at 23 °C,[17] the use of THF at 23 °C resulted in the formation of α,β-unsaturated ketone **4aa** in 72% yield. Interestingly, toluene was an excellent solvent for the neodymium(III)-mediated carbon–carbon bond formation reaction providing ketol product **3aa** even at 40 °C in good yield (74%). Increasing the reaction temperature in toluene to 90 °C led to lower yields of **3aa** (42%), whereas acetophenone was isolated as the major byproduct in 40% yield.

Mixtures of 2-bromoacetophenone (**1a**) and propionaldehyde (**2a**) in CH$_2$Cl$_2$ were exposed to further commercially available neodymium(III) salts to initiate the Reformatsky-type conversion. Although the desired transformation was found to be clean in the presence of NdI$_3$, treatment with NdBr$_3$ or NdCl$_3$, in contrary, did not afford ketol **3aa** in CH$_2$Cl$_2$ at 23 °C.

Table 1 illustrates the scope of the NdI$_3$-mediated reaction. A broad variety of α-bromo carbonyls with R^1 being aryl and heteroaryl substituents readily add to simple aldehyde **1a** in the presence of NdI$_3$ in CH$_2$Cl$_2$ at 0 °C to give the corresponding products in moderate to very good yields (Table 1, Entries 1–9). Although the neodymium enolate derived from electron-deficient substrate **1f** reacted to give ketol **3fa**, this reaction was conducted at 23 °C to obtain reasonable yields (Table 1, Entry 6). The reactions of α-halo carbonyls bearing alkyl substituents for R^1 proved less useful as they did not afford product formation under the standard conditions. In these cases, 3.0 equiv. of SnCl$_2$ was utilized as an efficient additive to obtain desired ketol products **3**.[13a] For instance, α-bromo carbonyl compound **1j**

Table 1. Formation of ketols **3** from α-bromo ketones **1** and aldehydes **2**.

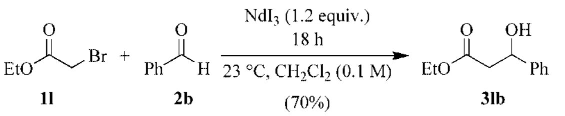


Entry	R^1 (**1**)	No.	R^2 (**2**)	no.	Conditions[a]	Product	Yield **3** [%][b]
1	Ph	**1a**	Et	**2a**	0 °C, 18 h	**3aa**	80
2	3-BrC$_6$H$_4$	**1b**	Et	**2a**	0 °C, 48 h	**3ba**	78
3	4-ClC$_6$H$_4$	**1c**	Et	**2a**	0 °C, 18 h	**3ca**	68
4	4-MeC$_6$H$_4$	**1d**	Et	**2a**	0 °C, 18 h	**3da**	74
5	4-PhC$_6$H$_4$	**1e**	Et	**2a**	0 °C, 72 h	**3ea**	71
6	4-O$_2$NC$_6$H$_4$	**1f**	Et	**2a**	23 °C, 18 h	**3fa**	44
7	2,5-(MeO)$_2$C$_6$H$_3$	**1g**	Et	**2a**	0 °C, 18 h	**3ga**	62
8	1-(benzofuran-2-yl)	**1h**	Et	**2a**	0 °C, 18 h	**3ha**	67
9	2-thienyl	**1i**	Et	**2a**	0 °C, 18 h	**3ia**	82
10[c]	*t*Bu	**1j**	CH$_2$Ph	**2f**	23 °C, 48 h	**3jf**	36
11[d,e]	Me	**1k**	Ph	**2b**	23 °C, 4 h	**3kb**	65
12	Ph	**1a**	Ph	**2b**	23 °C, 18 h	**3ab**	77
13	Ph	**1a**	4-NO$_2$–C$_6$H$_4$	**2c**	23 °C, 18 h	**3ac**	27
14	Ph	**1a**	C≡CPh	**2d**	0 °C, 18 h	**3ad**	44
15	Ph	**1a**	CH$_2$Ph	**2e**	0 °C, 18 h	**3ae**	78
16	Ph	**1a**	CH(CH$_3$)$_2$	**2f**	0 °C, 18 h	**3af**	61
17	Ph	**1a**	C$_6$H$_{11}$	**2g**	0 °C, 18 h	**3ag**	62
18	Ph	**1a**	CH(CH$_3$)Ph	**2h**	0 °C, 18 h	**3ah**	70[f]

[a] Conditions: 1.0 equiv. of **1** (0.1 M), 1.0 equiv. of **2**, 1.2 equiv. of NdI$_3$, CH$_2$Cl$_2$. [b] Yield of pure product after column chromatography. [c] Addition of 3 equiv. of SnCl$_2$. [d] Conditions: 1.0 equiv. of **1** (0.1 M), 1.0 equiv. of **2**, 1.2 equiv. of NdI$_3$, 3.0 equiv. of SnCl$_2$, THF. [e] 1-Chloropropan-2-one was used. [f] *erythro*:*threo*, 70:30.

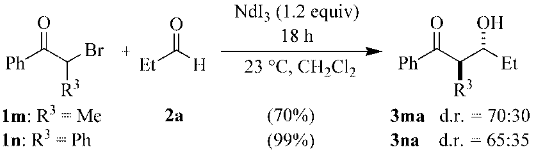
with R^1 = *t*Bu reacted with aldehyde **2f** to give ketol product **3jf** in 36% yield by using a combination of NdI_3 and $SnCl_2$ in CH_2Cl_2 at 23 °C (Table 1, Entry 10).[15] Both aliphatic and aromatic aldehydes were successfully employed in these transformations (Table 1, Entries 12–18). Only the sterically hindered pival aldehyde failed to undergo the Reformatsky-type transformation.

Of primary importance, the neodymium(III)-mediated reaction was also found to proceed smoothly by using α-bromo ester **1l** as a classical Reformatsky substrate. In this case, exposure of **1l** and benzaldehyde to 1.2 equiv. of NdI_3 in CH_2Cl_2 at 23 °C for 18 h afforded corresponding product **3lb** in 70% yield [Equation (2)]. Under similar conditions, cerium(III) salts were reported to be ineffective.[12a]



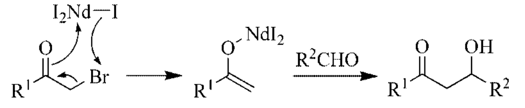
(2)

As exemplified for secondary bromides **1m** and **1n**, substrates capable of generating diastereoisomers were effectively converted into the desired products, albeit with poor diastereoselectivity (Scheme 2). Typical *anti:syn* ratios in these NdI_3-mediated reactions are in the range of 70:30, only marginally depending on the reaction temperature and solvent.



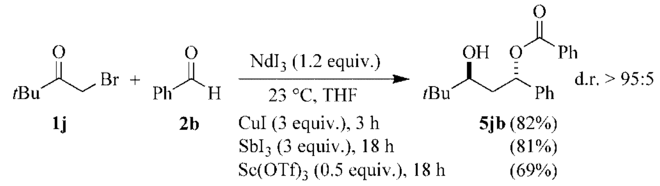
Scheme 2. Diastereoselectivity in NdI_3-mediated Reformatsky-type reactions.

Although we have not yet conducted detailed mechanistic studies, we believe that neodymium enolates might be initially formed from α-bromo ketones or α-bromo esters upon treatment with NdI_3, as it was postulated by Fukuzawa and coworkers for the reactivity of CeI_3 (Scheme 3).[13] This step apparently proceeds through halide oxidation instead of the metal center being formally oxidized. Subsequent reaction with the electrophilic aldehydes results in the formation of the observed products.



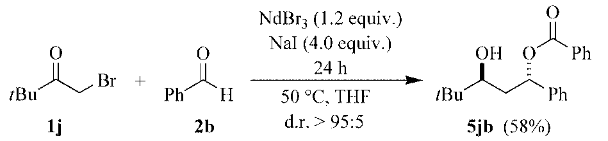
Scheme 3. Plausible mechanism through neodymium(III) enolates.

To further expand the scope of neodymium(III)-mediated carbon–carbon bond formations, we briefly examined the effect of additives on product distribution. In general, the addition of $SnCl_2$ proved to facilitate the formation of ketols **3**. For example, substrates **1j** and **1k** did not undergo the Reformatsky-type reaction in the absence of $SnCl_2$ (Table 1, Entries 11 and 12). To our surprise, the use of CuI, SbI_3, and $Sc(OTf)_3$ in THF favored the aldol–Tishchenko reaction to give diol monoesters **5** as predominant products.[18,19] Accordingly, reaction of substrate **1j** with benzaldehyde in the presence of 1.2 equiv. of NdI_3 and 3 equiv. of CuI in THF at 23 °C generated *anti* diol monoester **5jb** in 82% isolated yield (Scheme 4). The formation of the *syn* product was not observed under these conditions. With 3 equiv. of SbI_3 as the additive, the starting carbonyl reacted smoothly to give **5jb** in 81% yield. In the case of $Sc(OTf)_3$, substoichiometric amounts were sufficient to cause the aldol–Tishchenko reaction.

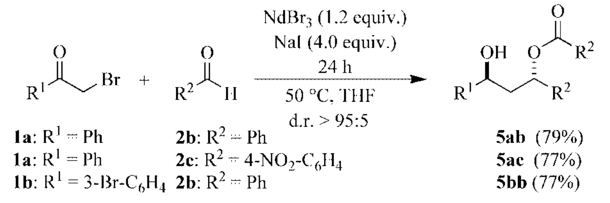


Scheme 4. NdI_3-mediated aldol–Tishchenko reactions in the presence of additives.

Alternatively, diol monoester **5jb** was obtained through the neodymium(III)-mediated aldol–Tishchenko reaction by utilizing a combination of $NdBr_3$ and NaI in THF at 50 °C [Equation (3)]. Notably, the *anti* product was found as a single diastereoisomer. To obtain reproducible results for this conversion, it was mandatory to stir the mixture of $NdBr_3$ and NaI in THF at 50 °C for at least 24 h before adding substrates **1j** and **2b** to this mixture. In the absence of $NdBr_3$, the aldol–Tishchenko reaction did not take place. $NdBr_3$ without the addition of NaI was unreactive. Although a couple of aryl-substituted α-bromo carbonyls **1** also reacted to give aldol–Tishchenko products **5** as major products by using these reaction conditions [Equation (4)], the conversion proved to be not as general as the synthesis of ketols **3** discussed previously. For example, reaction of 2-bromo-1-(thiophen-2-yl)ethanone (**1i**) with benzaldehyde (**2b**) failed to give expected diol monoester **5ib**, providing



(3)



(4)

instead ketol **3ib** in 32% yield after 24 h through a Reformatsky-type reaction. The subsequent Tishchenko reaction was found to be slow in the case of this substrate.

Conclusions

The feasibility of employing neodymium(III) salts to induce a Reformatsky-type reaction of α-halo carbonyls with aldehydes was demonstrated. We show for the first time that depending upon the reaction conditions the use of NdI_3 can lead to the exclusive formation of aldol products under mild conditions. It is anticipated that the lessons learned in this series of experiments should result in new applications for trivalent neodymium salts in organic synthesis.

Experimental Section

General: All reactions were carried out with magnetic stirring under an Ar atmosphere; NdI_3 was handled in a glove box. Common solvents [pentane (P), ethyl acetate (EtOAc), tetrahydrofuran (THF), and CH_2Cl_2] were distilled prior to use. All other reagents and solvents were used as received. ^{1}H NMR spectra were obtained with a 500 MHz, 360 MHz, or 250 MHz FT-NMR spectrometers. ^{13}C NMR spectra were recorded at 90.6 MHz and 62.9 MHz. Chemical shifts are reported in ppm relative to solvent signal. Multiplicity is indicated as follows: s (singlet), d (doublet), t (triplet), q (quadruplet), m (multiplet), dd (doublet of doublets). Flash chromatography was performed with E. Merck silica gel (43–60 µm). The eluent used is reported in parentheses. Thin-layer chromatography (TLC) was performed on precoated glass-backed plates (Merck Kieselgel 60 F_{254}), and components were visualized by observation under UV light or by treating the plates with $KMnO_4/H_2SO_4$ followed by heating.

Representative Procedure for the Formation of 3 by Using NdI_3: 3-Hydroxy-1-phenylpentan-1-one (3aa):[20] A solution of 2-bromo-1-phenylethanone (**1a**; 39.8 mg, 0.20 mmol) in dry CH_2Cl_2 (2 mL)was added to neodymium triiodide (124.0 mg, 0.24 mmol). Propionaldehyde **2a** (0.20 mmol) was then added at once, and the resulting solution was cooled to 0 °C. After stirring for 18 h, the reaction was quenched by the addition of a saturated aqueous solution of sodium thiosulfate (0.5 mL), and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2×2 mL). The combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel (20% EtOAc/P) to afford **3aa** (28.3 mg, 0.16 mmol, 80%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.01 (t, J = 7.4 Hz, 3 H), 1.48–1.73 (m, 2 H), 3.03 (dd, J = 17.7, 8.8 Hz, 1 H), 3.18 (dd, J = 17.7, 2.8 Hz, 1 H), 3.28 (br. s, 1 H), 4.10–4.19 (m, 1 H), 7.46 (t, J = 7.4 Hz, 2 H), 7.58 (t, J = 7.3 Hz, 1 H), 7.95 (d, J = 7.2 Hz, 2 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 10.1, 29.5, 44.7, 69.2, 128.2, 128.8, 133.6, 137.0, 201.1 ppm. LRMS (EI): m/z (%) = 178 (4) $[M]^+$, 160 (18), 149 (22), 120 (24), 106 (22), 105 (100), 77 (63). HRMS: calcd. for $C_{11}H_{14}O_2$ $[M]^+$178.0994; found 178.0995.

1-(3-Bromophenyl)-3-hydroxypentan-1-one (3ba): Following the general procedure, **3ba** was obtained as a pale yellow oil (78%) after flash chromatography on silica (20% EtOAc/P). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.01 (t, J = 7.4 Hz, 3 H), 1.50–1.66 (m, 2 H), 3.01 (dd, J = 17.7, 8.6 Hz, 1 H), 3.11 (dd, J = 17.7, 3.1 Hz, 1 H, OH), 4.10–4.17 (m, 1 H), 7.34 (t, J = 7.8 Hz, 1 H), 7.69 (d, J = 8.1 Hz, 1 H), 7.86 (d, J = 7.8 Hz, 1 H), 8.06 (s, 1 H) ppm. ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 10.0, 29.6, 45.0, 69.1, 123.2, 126.7, 130.4, 131.3, 136.4, 138.7, 199.5 ppm. LRMS (EI): m/z (%) = 258 (21) $[M]^+$, 183 (100), 157 (26), 155 (28), 76 (21). HRMS: calcd. for $C_{11}H_{13}O_2Br$ $[M]^+$ 258.0078; found 258.0079.

1-(4-Chlorophenyl)-3-hydroxypentan-1-one (3ca): Following the general procedure, **3ca** was obtained as a pale yellow oil (68%) after flash chromatography on silica (20% EtOAc/P). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.00 (t, J = 7.5 Hz, 3 H), 1.46–1.72 (m, 2 H), 3.00 (dd, J = 17.6, 8.6 Hz, 1 H), 3.12 (dd, J = 17.6, 3.1 Hz, 1 H, OH), 4.09–4.18 (m, 1 H), 7.43 (d, J = 8.6 Hz, 2 H), 7.89 (d, J = 8.6 Hz, 2 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 10.1, 29.5, 44.8, 69.2, 129.1, 129.6, 135.3, 140.1, 199.8 ppm. LRMS (EI): m/z (%) = 212 (2) $[M]^+$, 141 (35), 139 (100), 111 (23). HRMS: calcd. for $C_{11}H_{13}O_2Cl$ $[M]^+$ 212.0604; found 212.0601.

3-Hydroxy-1-(*p*-tolyl)pentan-1-one (3da):[21] Following the general procedure, **3da** was obtained as a pale yellow oil (74%) after flash chromatography on silica (20% EtOAc/P). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.01 (t, J = 7.4 Hz, 3 H), 1.47–1.70 (m, 2 H), 2.41 (s, 3 H), 2.99 (dd, J = 17.5, 8.9 Hz, 1 H), 3.16 (dd, J = 17.5, 2.7 Hz, 1 H), 3.33 (br. s, 1 H), 4.12–4.14 (m, 1 H), 7.26 (d, J = 8.1 Hz, 2 H), 7.85 (d, J = 8.1 Hz, 2 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 10.1, 21.8, 29.5, 44.5, 69.3, 128.3, 129.5, 134.5, 144.5, 200.8 ppm. LRMS (EI): m/z (%) = 192 (4) $[M]^+$, 134 (20), 119 (100), 105 (18), 91 (36). HRMS: calcd. for $C_{12}H_{16}O_2$ $[M]^+$ 192.1150; found 192.1150.

3-Hydroxy-1-(4-phenyl)phenylpentan-1-one (3ea): Following the general procedure, **3ea** was obtained as a pale yellow oil (71%) after flash chromatography on silica (20% EtOAc/P). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.04 (t, J = 7.4 Hz, 3 H), 1.53–1.73 (m, 2 H), 3.06 (dd, J = 17.5, 8.9 Hz, 1 H), 3.22 (dd, J = 17.5, 2.8 Hz, 1 H), 3.32 (br. s, 1 H), 4.14–4.19 (m, 1 H), 7.38–7.51 (m, 3 H), 7.62 (dd, J = 8.1, 1.3 Hz, 2 H), 7.69 (d, J = 8.4 Hz, 2 H), 8.03 (d, J = 8.4 Hz, 2 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 10.1, 29.6, 44.7, 69.3, 127.3, 127.4, 128.5, 128.8, 129.1, 135.7, 139.9, 146.3, 200.7 ppm. LRMS (EI): m/z (%) = 254 (10) $[M]^+$, 228 (22), 196 (34), 188 (34), 182 (100), 152 (33). HRMS: calcd. for $C_{17}H_{18}O_2$ $[M]^+$ 254.1307; found 254.1304.

3-Hydroxy-1-(4-nitrophenyl)pentan-1-one (3fa): Following the general procedure, **3ga** was obtained as a pale yellow oil (44%) after flash chromatography on silica (20% EtOAc/P). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.03 (t, J = 7.4 Hz, 3 H), 1.50–1.75 (m, 2 H), 2.89 (br. s, 1 H), 3.10 (dd, J = 17.8, 7.4 Hz, 1 H), 3.18 (dd, J = 17.8, 4.2 Hz, 1 H), 4.19 (app t, J = 5.8 Hz, 1 H), 8.11 (d, J = 8.9 Hz, 2 H), 8.32 (d, J = 8.9 Hz, 2 H) ppm. ^{13}C NMR (90.9 MHz, $CDCl_3$): δ = 10.3, 29.7, 45.6, 69.1, 124.0, 129.3, 141.4, 150.7, 199.2 ppm. LRMS (EI): m/z (%) = 223 (1) $[M]^+$, 205 (18), 194 (31), 150 (100). HRMS: calcd. for $C_{11}H_{13}NO_4$ $[M]^+$ 223.0845; found 223.0845.

1-(2,5-Dimethoxyphenyl)-3-hydroxypentan-1-one (3ga): Following the general procedure, **3ga** was obtained as a pale yellow oil (62%) after flash chromatography on silica (20% EtOAc/P). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.98 (t, J = 7.4 Hz, 3 H), 1.43–1.66 (m, 2 H), 2.99 (dd, J = 18.0, 9.2 Hz, 1 H), 3.24 (br. s, 1 H), 3.26 (dd, J = 18.0, 2.5 Hz, 1 H), 3.78 (s, 3 H), 3.86 (s, 3 H), 4.02–4.12 (m, 1 H), 6.90 (d, J = 9.0 Hz, 1 H), 7.03 (dd, J = 9.0, 3.2 Hz, 1 H), 7.26 (d, J = 3.2 Hz, 1 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 10.1, 29.6, 50.1, 55.9, 56.2, 69.6, 113.4, 113.9, 120.8, 128.1, 153.5, 153.6, 202.8 ppm. LRMS (EI): m/z (%) = 238 (33) $[M]^+$, 202 (16), 165 (100), 119 (31). HRMS: calcd. for $C_{13}H_{18}O_4$ $[M]^+$ 238.1205, found 238.1205.

1-(Benzofuran-2-yl)-3-hydroxypentan-1-one (3ha): Following the general procedure, **3ha** was obtained as a pale yellow oil (67%) after flash chromatography on silica (20% EtOAc/P). ^{1}H NMR (360 MHz, $CDCl_3$): δ = 1.02 (t, J = 7.5 Hz, 3 H), 1.55–1.69 (m, 2 H), 3.06 (dd, J = 17.0, 8.9 Hz, 1 H, OH), 3.16 (dd, J = 17.0, 3.0 Hz, 1 H), 4.15–4.21 (m, 1 H), 7.31 (t, J = 7.9 Hz, 1 H), 7.48 (t, J = 7.1 Hz, 1 H), 7.54–7.59 (m, 2 H), 7.70 (d, J = 7.7 Hz, 1 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 10.0, 29.7, 45.2, 69.3, 112.6, 113.6, 123.6, 124.2, 127.1, 128.7, 152.6, 155.9, 191.7 ppm. LRMS (EI): m/z (%) = 218 (24) $[M]^+$, 200 (45), 160 (60), 145 (100), 118 (19). HRMS: calcd. for $C_{13}H_{14}O_3$ $[M]^+$ 218.0943; found 218.0946.

3-Hydroxy-1-(thiophen-2-yl)pentan-1-one (3ia): Following the general procedure, **3ia** was obtained as a pale yellow oil (82%) after flash chromatography on silica (20% EtOAc/P). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.00 (t, J = 7.4 Hz, 3 H), 1.47–1.72 (m, 2 H), 2.98 (dd, J = 17.0, 8.8 Hz, 1 H), 3.12 (dd, J = 17.0, 3.0 Hz, 1 H), 3.19 (br. s, 1 H), 4.08–4.17 (m, 1 H), 7.14 (dd, J = 4.8, 3.8 Hz, 1 H), 7.66 (dd, J = 4.8, 1.0 Hz, 1 H), 7.73 (dd, J = 3.8, 1.0 Hz, 1 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 10.1, 29.6, 45.4, 69.5, 128.4, 132.6, 134.4, 144.2, 193.7 ppm. LRMS (EI): m/z (%) = 184 (5) $[M]^+$, 167 (24), 155 (14), 126 (34), 111 (100). HRMS: calcd. for $C_9H_{12}O_2S$ $[M]^+$ 184.0558; found 184.0559.

1-Hydroxy-4,4-dimethyl-1-phenylpentan-3-one (3jf):[22] Following the general procedure, **3jf** was obtained as a pale yellow oil (36%) after flash chromatography on silica (20% EtOAc/P). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.12 (s, 9 H), 2.60 (dd, J = 17.8, 8.2 Hz, 1 H), 2.71 (dd, J = 17.8, 3.7 Hz, 1 H), 2.74 (dd, J = 13.6, 6.1 Hz, 1 H), 2.87 (dd, J = 13.6, 7.3 Hz, 1 H), 3.16 (br. s, 1 H), 4.27–4.29 (m, 1 H), 7.22–7.35 (m, 5 H) ppm. ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 26.4, 42.5, 43.0, 44.5, 69.1, 126.7, 128.6, 129.5, 138.3, 217.3 ppm. LRMS (EI): m/z (%) = 202 (22) $[M - H_2O]^+$, 121 (34), 92 (29), 85 (53), 57 (100). HRMS: calcd. for $C_{14}H_{18}O$ $[M - H_2O]^+$ 202.1358; found 202.1362.

4-Hydroxy-4-phenylbutan-2-one (3kb):[23] Following the general procedure, **3kb** was obtained as a pale yellow oil (65%) after flash chromatography on silica (20% EtOAc/P). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.20 (s, 3 H), 2.77–2.96 (m, 2 H), 3.28 (br. s, 1 H), 5.16 (dd, J = 8.6, 3.9 Hz, 1 H), 7.28–7.37 (m, 5 H) ppm. ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 30.9, 52.1, 70.0, 125.8, 127.9, 128.7, 142.9, 209.1 ppm. LRMS (EI): m/z (%) = 164 (78) $[M]^+$, 146 (56), 131 (20), 107 (100), 105 (57). HRMS: calcd. for $C_{10}H_{12}O_2$ $[M]^+$ 164.0837; found 164.0836.

3-Hydroxy-1,3-diphenylpropan-1-one (3ab): Following the general procedure, **3ab** was obtained as a pale yellow oil (77%) after flash chromatography on silica (20% EtOAc/P). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.38 (d, J = 6.1 Hz, 2 H), 3.61 (br. s, 1 H), 5.36 (t, J = 6.1 Hz, 1 H), 7.31–7.60 (m, 8 H), 7.96 (d, J = 7.3 Hz, 2 H) ppm. ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 47.5, 70.2, 125.9, 127.8, 128.3, 128.7, 128.8, 133.8, 136.8, 143.1, 200.3 ppm. LRMS (EI): m/z (%) = 226 (36) $[M]^+$, 208 (43), 120 (53), 105 (100). HRMS: calcd. for $C_{15}H_{14}O_2$ $[M]^+$ 226.0994; found 226.0995.

3-Hydroxy-3-(4-nitrophenyl)-1-phenylpropan-1-one (3ac): Following the general procedure, **3ac** was obtained as a pale yellow oil (27%) after flash chromatography on silica (20% EtOAc/P). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.33 (dd, J = 17.9, 8.3 Hz, 1 H), 3.43 (dd, J = 17.9, 3.8 Hz, 1 H), 3.85 (d, J = 3.0 Hz, 1 H), 5.44–5.48 (m, 1 H), 7.48 (t, J = 7.6 Hz, 2 H), 7.59–7.64 (m, 3 H), 7.95 (dd, J = 8.6, 1.3 Hz, 2 H), 8.24 (d, J = 8.6 Hz, 2 H) ppm. ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 47.1, 69.4, 124.0, 126.7, 128.3, 129.0, 134.2, 136.4, 147.6, 150.4, 200.0 ppm. LRMS (EI): m/z (%) = 271 (33) $[M]^+$, 253 (24), 120 (23), 105 (100). HRMS: calcd. for $C_{15}H_{13}NO_4$ $[M]^+$ 271.0845; found 271.0846.

3-Hydroxy-1,5-diphenylpent-4-yn-1-one (3ad): Following the general procedure, **3ad** was obtained as a pale yellow oil (44%) after flash chromatography on silica (20% EtOAc/P). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.45 (dd, J = 17.6, 3.7 Hz, 1 H), 3.46 (br. s, 1 H), 3.59 (dd, J = 17.6, 7.8 Hz, 1 H), 5.21–5.28 (m, 1 H), 7.29–7.31 (m, 3 H), 7.41–7.64 (m, 5 H), 8.00 (dd, J = 8.5, 1.2 Hz, 2 H) ppm. ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 45.7, 59.3, 85.2, 88.7, 122.6, 128.3, 128.4, 128.6, 128.9, 131.9, 133.9, 136.6, 199.0 ppm. LRMS (EI): m/z (%) = 250 (27) $[M]^+$, 249 (52), 131 (58), 105 (100). HRMS: calcd. for $C_{17}H_{14}O_2$ $[M]^+$ 250.0994; found 250.0995.

3-Hydroxy-1,4-diphenylbutan-1-one (3ae): Following the general procedure, **3ae** was obtained as a pale yellow oil (78%) after flash chromatography on silica (20% EtOAc/P). ^{1}H NMR (360 MHz, $CDCl_3$): δ = 2.85 (dd, J = 13.6, 6.3 Hz, 1 H), 2.98 (dd, J = 13.6, 7.2 Hz, 1 H), 3.10–3.15 (m, 2 H), 3.22 (br. s, 1 H), 4.48–4.55 (m, 1 H), 7.22–7.36 (m, 5 H), 7.45 (t, J = 7.2 Hz, 2 H), 7.59 (t, J = 7.3 Hz, 1 H), 7.913 (d, J = 7.1 Hz, 2 H) ppm. ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 43.1, 44.3, 69.1, 126.7, 128.2, 128.7, 128.8, 129.6, 133.6, 136.9, 138.2, 200.6 ppm. LRMS (EI): m/z (%) = 222 (11) $[M - H_2O]^+$, 150 (50), 120 (16), 105 (100). HRMS: calcd. for $C_{16}H_{14}O$ $[M - H_2O]^+$ 222.1045; found 222.1046.

3-Hydroxy-4-methyl-1-phenylpentan-1-one (3af): Following the general procedure, **3af** was obtained as a pale yellow oil (61%) after flash chromatography on silica (20% EtOAc/P). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.99 (d, J = 5.5 Hz, 3 H), 1.02 (d, J = 5.5 Hz, 3 H), 1.74–1.87 (m, 1 H), 3.03 (dd, J = 17.5, 9.2 Hz, 1 H), 3.18 (dd, J = 17.5, 2.6 Hz, 1 H), 3.19 (br. s, 1 H), 4.00–4.01 (m, 1 H), 7.47 (t, J = 7.5 Hz, 2 H), 7.58 (td, J = 7.5, 2.3 Hz, 1 H), 7.96 (dd, J = 7.5, 1.3 Hz, 2 H) ppm. ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 18.0, 18.7, 33.3, 42.1, 72.6, 128.2, 128.8, 133.6, 137.2, 201.4 ppm. LRMS (EI): m/z (%) = 192 (1) $[M]^+$, 149 (40), 120 (12), 105 (100). HRMS: calcd. for $C_{17}H_{14}O_2$ $[M]^+$ 250.0994; found 250.0995.

3-Cyclohexyl-3-hydroxy-1-phenylpropan-1-one (3ag):[12o] Following the general procedure, **3ag** was obtained as a pale yellow oil (62%) after flash chromatography on silica (20% EtOAc/P). ^{1}H NMR (360 MHz, $CDCl_3$): δ = 1.01–1.36 (m, 5 H), 1.41–1.55 (m, 1 H), 1.61–1.82 (m, 4 H), 1.93–1.94 (m, 1 H), 3.05 (dd, J = 17.4, 9.1 Hz, 1 H), 3.16 (s, 1 H), 3.19 (dd, J = 17.4, 2.6 Hz, 1 H), 3.96–4.03 (m, 1 H), 7.44–7.50 (m, 2 H), 7.55–7.62 (m, 1 H), 7.95–7.99 (m, 2 H) ppm. ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 26.3, 26.4, 26.7, 28.5, 29.2, 42.3, 43.3, 72.0, 128.2, 128.8, 133.6, 137.2, 201.5 ppm. LRMS (EI): m/z (%) = 232 (1) $[M]^+$, 150 (70), 120 (13), 105 (100). HRMS: calcd. for $C_{15}H_{20}O_2$ $[M]^+$ 232.1463; found 232.1464.

3-Hydroxy-2-methyl-1-phenylpentan-1-one (3ma):[24] Following the general procedure, **3ma** was obtained as a pale yellow oil (70%) after flash chromatography on silica (20% EtOAc/P). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.99 (t, J = 7.4 Hz, 1 H, *syn*), 1.00 (t, J = 7.4 Hz, 2 H, *anti*), 1.28 (d, J = 7.3, Hz, 1 H, *syn*), 1.29 (t, J = 7.3 Hz, 2 H, *anti*), 1.44–1.55 (m, 2 H, *syn* and *anti*), 1.57–1.65 (m, 2 H, *syn* and *anti*), 2.89 (br. s, 0.70 H, *anti*), 3.08 (br. s, 0.30 H, *syn*), 3.52 (dq, J = 3.1, 7.2 Hz, 0.30 H, *syn*), 3.57–3.63 (m, 0.70 H, *anti*), 3.79–3.84 (m, 0.70 H, *anti*), 3.96–3.99 (m, 0.30 H, *syn*), 7.49–7.53 (m, 2 H, *syn* and *anti*), 7.59–7.63 (m, 1 H, *syn* and *anti*), 7.97–7.99 (m, 2 H, *syn* and *anti*) ppm. ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 10.3 (*anti*), 10.6 (*syn*), 11.2 (*syn*), 15.6 (*anti*), 27.4 (*syn*), 27.9 (*anti*), 44.3 (*syn*), 45.5 (*anti*), 73.1 (*syn*), 75.5 (*anti*), 128.5 (*anti*), 128.6 (*syn*), 128.8 (*anti*), 128.9 (*syn*), 133.4 (*anti*), 133.5 (*syn*), 136.2 (*anti*), 136.9 (*syn*), 205.9 (*syn* and *anti*) ppm. LRMS (EI): m/z (%) = 192 (2) $[M]^+$, 174 (13), 134 (55), 123 (28), 105 (100), 77 (57). HRMS: calcd. for $C_{12}H_{16}O_2$ $[M]^+$ 192.1150; found 192.1159.

Ethyl 3-Hydroxy-3-phenylpropanoate (3lb): Following the general procedure, **3lb** was obtained as a pale yellow oil (70%) after flash chromatography on silica (20% EtOAc/P). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.27 (t, J = 7.1 Hz, 3 H), 2.65–2.82 (m, 2 H), 2.91 (br. s, 1 H), 4.19 (q, J = 7.1 Hz, 2 H), 5.14 (dd, J = 8.1, 4.7 Hz, 1 H), 7.28–7.40 (m, 5 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 14.3, 43.5, 61.0, 70.5, 125.8, 128.0, 128.7, 142.7, 172.6 ppm. LRMS (EI): m/z (%) = 194 (42) [M]$^+$, 107 (100), 105 (74), 79 (38). HRMS: calcd. for $C_{11}H_{14}O_3$ [M]$^+$ 194.0943; found 194.0942.

Representative Procedure for the Formation of 5 by Using $NdBr_3$: 3-Hydroxy-1,3-diphenylpropyl Benzoate (5ab):[19h] A mixture of neodymium tribromide (46.1 mg, 0.12 mmol) and NaI (59.6 mg, 0.40 mmol) in THF (1 mL) was stirred at 50 °C for 18h. Then, a solution of 2-bromo-1-phenylethanone (19.9 mg, 0.10 mmol) and benzaldehyde (21.2 mg, 0.20 mmol) in THF (0.5 mL) was added. Stirring was continued for 18 h. The reaction was quenched by the addition of a saturated aqueous solution of sodium thiosulfate (0.5 mL), and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 2 mL). The combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel (20% EtOAc/P) to afford **5ab** (26.2 mg, 0.08 mmol, 79%). ^{1}H NMR (360 MHz, $CDCl_3$): δ = 2.15–2.46 (m, 2 H), 2.92 (br. s, 1 H), 4.80 (dd, J = 6.1, 3.2 Hz, 1 H), 6.33 (dd, J = 10.2, 3.0 Hz, 1 H), 7.21–7.64 (m, 13 H), 7.94–8.10 (m, 2 H) ppm. ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 46.6, 70.3, 73.7, 125.7, 126.2, 127.4, 127.9, 128.3, 128.4, 128.5, 129.6, 129.9, 133.1, 140.4, 143.7, 166.3 ppm. LRMS (EI): m/z (%) = 314 (12) [M – H_2O]$^+$, 210 (60), 105 (100). HRMS: calcd. for $C_{22}H_{18}O_2$ [M – H_2O]$^+$ 314.1306; found 314.1307.

3-Hydroxy-4,4-dimethyl-1-phenylpentyl Benzoate (5jb):[19h] Following the general procedure, **5jb** was obtained as a yellow oil (58%). ^{1}H NMR (360 MHz, $CDCl_3$): δ = 0.93 (s, 9 H), 1.88–1.89 (m, 1 H), 2.20–2.21 (m, 1 H), 2.66 (br. s, 1 H), 3.41 (br. d, J = 10.6 Hz, 1 H), 6.34 (dd, J = 10.8, 2.5 Hz, 1 H), 7.24–7.59 (m, 8 H), 8.09–8.10 (m, 2 H) ppm. ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 25.7, 34.5, 39.8, 74.2, 75.1, 126.1, 127.8, 128.4, 128.5, 129.7, 130.1, 133.1, 141.2, 166.5 ppm. LRMS (EI): m/z (%) = 312 (5) [M]$^+$, 294 (7), 507 (35), 133 (85), 105 (100). HRMS: calcd. for $C_{20}H_{24}O_3$ [M]$^+$ 312.1725; found 312.1723.

3-Hydroxy-3-phenyl-1-(thiophen-2-yl)propan-1-one (3ib):[19h] Following the general procedure for the formation of **5**, **3ib** was obtained as a yellow oil (32%). ^{1}H NMR (360 MHz, $CDCl_3$): δ = 3.31 (s, 1 H), 3.33 (d, J = 3.0 Hz, 1 H), 3.51 (d, J = 3.0 Hz, 1 H), 5.32–5.36 (m, 1 H), 7.13 (dd, J = 5.0, 3.9 Hz, 1 H), 7.28–7.33 (m, 1 H), 7.36–7.40 (m, 2 H), 7.43–7.46 (m, 2 H), 7.68 (dd, J = 5.0, 1.1 Hz, 1 H), 7.71 (dd, J = 3.9, 1.1 Hz, 1 H) ppm. ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 48.1, 70.4, 125.9, 127.9, 128.4, 128.7, 132.8, 134.6, 142.9, 144.0, 192.9 ppm. LRMS (EI): m/z (%) = 214 (75) [M – H_2O]$^+$, 213 (100), 185 (29), 111 (42).

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