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ORIGINAL ARTICLE

Nickel-catalyzed esterification of mandelic acids with alcohols

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Abstract Mandelates and their derivatives are widely used in organic synthesis, drug discovery, biodegradable polymers and other related fields. Therefore, the effective and simple synthesis of these compounds has attracted much attention. In this paper, a nickel(II)-catalyzed esterification of mandelic acids with different alcohols was realized for the synthesis of mandelic acid esters. This transformation was conducted under mild reaction conditions with yields up to 95%, and was successfully utilized in the gram-scale synthesis of medicine cyclandelate.

1. Introduction

Esterification is a common and important transformation in organic synthesis, which reaching almost one-quarter of the bulk reactions in the manufacture of pharmaceuticals and drugs (Otera, 2003; Dugger et al., 2005). Great efforts have been made for the development of efficient protocols for esterification under mild reaction conditions in recent years (Zheng et al., 2021; Padala et al., 2015; Lu et al., 2017; Xiong et al., 2017; Vandamme et al., 2016; Yu et al., 2014; Lozano et al. 2017; Liu et al., 2011; Houston et al., 2004; Maki et al., 2005; Maki et al., 2007). Besides, the direct C—H oxyacylation of functionalized alkanes has also provided feasible approaches towards esters form carboxyl and carbonyl compounds (Li et al., 2016; Huang et al., 2017; Wu et al., 2016; Zhu et al. 2016). For example, Yu and co-workers developed the α-oxyacylation of ketones with benzylic alcohols or acyl peroxides in the presence of Bu_4NI under metal-free conditions (Guo et al., 2014; Zhou et al., 2015); Recently, Zhang group reported the 1,2-dibromoethane- and KI-mediated α-acyloxylation of ketones with carboxylic acids without the use of strong oxidants (Wang et al., 2020). Despite of many achievements witnessed the direct synthesis of functionalized esters still need to be further developed. Scheme 1

Mandelic acid ester containing molecules are valuable biologically active compounds with high therapeutic importance and economic impact. Among them, cyclandelate (I) is a kind of clinical used vasodilator (Bast, et al., 1987; White, et al. 1990). MA-6-APA (II) is a kind of modified penicillin with distinctive bioactivities (Fulenmeier et al., 1976). Homatropine (III) (Glushkov et al., 1977), and oxybutynin (Su et al., 2003) are used as anti-cholinergic medications (Fig. 1). Besides, mandelate derivatives can be readily transformed into other functionalized molecules such as 1,2-diols β-amino alcohols and α-amino acid derivatives, and can be used as key intermediates for the synthesis of various medicine such as Plavix (clopidogrel) (Meijden et al., 2009) and Duloxetine (Majer et al 2009); Traditionally,

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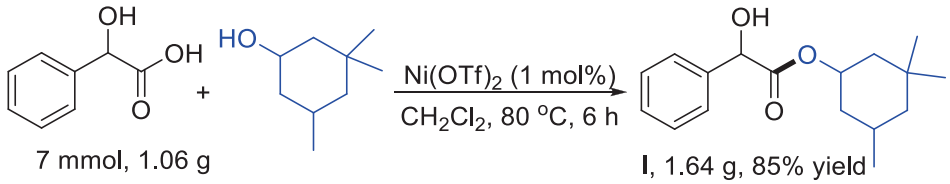


Scheme 1 Gram-scale synthesis of cyclandelate (I).

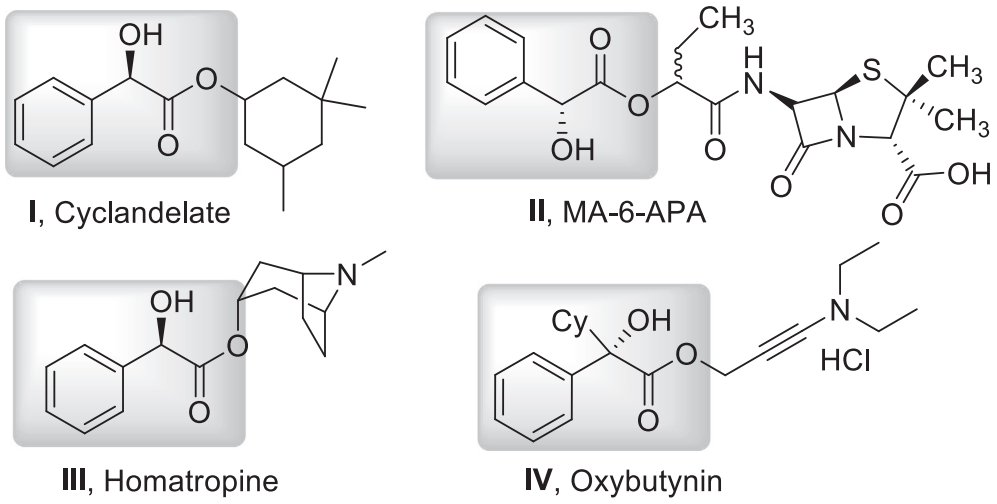


Fig. 1 Some biologically active compounds bearing mandelic acid ester motifs.

mandelate derivatives can be synthesized via two routes, hydrolysis of cyanohydrins (Poechlauer, et al., 2004) and Friedel-Crafts arylation of glyoxalate derivatives (Majer, et al., 2011; Majer, et al., 2008; Dong et al. 2007; Kwiatkowski, et al. 2006; Li, et al., 2006). However, the former route requires the use of toxic cyano reagents such as HCN, and the arenes in the latter route are limited to electron-rich ones. In 2017, Yamamoto reported the synthesis of mandelate derivatives from arylboronic acids and glyoxylate hemiacetals catalyzed by palladium (Sugaya, et al. 2017). Xu and Poterała developed the direct esterification of mandelic acids under the catalysis of zirconocene (Tang, et al., 2017) or in the presence of $SOCl_2$ (Poterała, et al. 2017), respectively. Although significant achievements were realized, more general and convenient approaches towards mandelates are highly demanded.

2. Experimental

Unless otherwise stated, all reagents and solvents were purchased from commercial suppliers and used without further purification. ^{1}H NMR and ^{13}C NMR spectra were recorded at Vaian Inova-400 MHz NMR spectrometer using $CDCl_3$ as solvent and TMS as an internal standard.

*2.1. Typical procedure for synthesis of mandelate **3aa***

A 10 mL Schlenk tube equipped with a stir bar was charged with mandelic acid **1a** (0.5 mmol), methanol **2a** (0.5 mL), and $Ni(OTf)_2$ (1 mol%) at 80 °C for 6 h. After removing of volatile materials from the reaction mixture under vacuum, the resulted residue was purified by flash column chromatography on silica gel to give the methyl 2-hydroxy-2-phenylacetate **3aa**.

2.2. Characterization of products

2.2.1. methyl 2-hydroxy-2-phenylacetate (3aa)

Known compound (Tang, et al. 2017). Yellow liquid, yield 93 %; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, J = 7.4 Hz, 2H), 7.29 (dd, J = 14.9, 7.2 Hz, 3H), 5.14 (s, 1H), 3.88 (s, 1H), 3.67 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.09, 138.37, 128.63, 128.50, 126.67, 72.99, 52.91.

2.2.2. ethyl 2-hydroxy-2-phenylacetate (3ab)

Known compound (Yao, et al. 2008). Yellow liquid, yield 92 %; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, J = 7.3 Hz, 2H), 7.35 (d, J = 6.9 Hz, 3H), 5.15 (d, J = 5.6 Hz, 1H), 4.25~4.12 (m, 2H), 3.63 (s, 1H), 1.23~1.19 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.67, 138.47, 128.56, 128.39, 126.55, 72.92, 62.20, 14.02.

2.2.3. propyl 2-hydroxy-2-phenylacetate (3ac)

Known compound (Tang, et al. 2017). Yellow liquid, yield 94 %; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, J = 7.4 Hz, 2H), 7.37~7.31 (m, 3H), 5.17 (d, J = 4.3 Hz, 1H), 4.14~4.07(m, 2H), 3.59 (d, J = 5.1 Hz, 1H), 1.60 (dt, J = 14.1, 7.1 Hz, 2H), 0.84 (t, J = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.80, 138.50, 128.53, 128.38, 126.51, 72.87, 67.70, 21.82, 10.11.

2.2.4. butyl 2-hydroxy-2-phenylacetate (3ad)

Known compound (Keshavarz, et al. 2019). Yellow liquid, yield 95 %; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d,

J = 7.5 Hz, 2H), 7.37～7.28 (m, 3H), 5.16 (d, *J* = 5.5 Hz, 1H), 4.20～4.09 (m, 2H), 3.74 (d, *J* = 5.7 Hz, 1H), 1.55 (m, J = 14.5, 2H), 1.23 (m, *J* = 14.7 Hz, 2H), 0.84 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) *δ* 173.78, 138.53, 128.51, 128.36, 126.53, 72.92, 65.95, 30.40, 18.85, 13.53.

2.2.5. hexyl 2-hydroxy-2-phenylacetate (3ae)

Known compound (Tang, et al. 2017). Yellow liquid, yield 86 %; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.36 (d, *J* = 7.6 Hz, 2H), 7.32～7.27 (m, 3H), 5.11 (d, *J* = 5.7 Hz, 1H), 4.10 (t, *J* = 6.6 Hz, 2H), 3.57 (d, *J* = 5.7 Hz, 1H), 1.53～1.50 (m, 2H), 1.15 (d, *J* = 15.1 Hz, 6H), 0.80 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) *δ* 173.80, 138.52, 128.52, 128.37, 126.52, 72.89, 66.27, 31.22, 28.35, 25.25, 22.45, 13.93.

2.2.6. octyl 2-hydroxy-2-phenylacetate (3af)

Known compound (Das et al., 2017). Yellow Liquid, yield 81 %; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.43 (d, *J* = 6.9 Hz, 2H), 7.37～7.30 (m, 3H), 5.17 (d, *J* = 5.3 Hz, 1H), 4.16 (t, *J* = 6.6 Hz, 2H), 3.60 (d, *J* = 5.6 Hz, 1H), 1.59～1.55 (m, 2H), 1.33～1.14 (m, 10*H*), 0.89 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) *δ* 173.75, 138.59, 128.50, 128.34, 126.52, 72.91, 66.21, 60.39, 31.70, 28.83, 25.59, 22.61, 21.00, 14.12.

2.2.7. isopropyl 2-hydroxy-2-phenylacetate (3ag)

Known compound (Hong, et al. 2019). White solid, yield 85 %, m.p. 38～39 °C; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.37 (dt, *J* = 17.7, 8.6 Hz, 5H), 5.13 (s, 1H), 5.07 (dt, *J* = 12.4, 6.2 Hz, 1H), 3.96 (s, 1H), 1.28 (d, *J* = 6.2 Hz, 3H), 1.11 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) *δ* 170.97, 138.72, 128.34, 128.11, 126.39, 72.92, 69.74, 60.25, 21.57, 21.27, 20.83, 14.06.

2.2.8. isopentyl 2-hydroxy-2-phenylacetate (3ah)

Known compound (San et al., 2018). Yellow liquid, yield 75 %; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.44 (d, *J* = 4.4 Hz, 2H), 7.37～7.32 (m, 3H), 5.18 (s, 1H), 4.23～4.16 (m, 2H), 3.87 (s, 1H), 1.56～1.51(m, 1H), 1.49～1.47 (m, 2H), 0.87～0.81 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$), Ketone form: *δ* 173.83, 138.56, 128.58, 128.43, 126.58, 72.99, 64.89, 37.11, 24.96, 22.39, 16.20. Enol form: *δ* 173.91, 138.63, 128.55, 126.60, 72.96, 70.63, 34.14, 25.80, 22.33, 11.13.

2.2.9. allyl 2-hydroxy-2-phenylacetate (3ai)

Known compound (Yin, et al. 2009). White solid, yield 78 %, m.p. 41～42 °C; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.44 (dd, *J* = 7.9, 1.4 Hz, 2H), 7.40～7.29 (m, 3H), 5.83～5.78 (m, 1H), 5.23～5.19 (m, 2H), 5.16 (dd, *J* = 4.8, 1.3 Hz, 1H), 4.65～4.60 (m, 2H), 3.60 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) *δ* 173.40, 138.33, 131.22, 128.64, 128.53, 126.64, 118.77, 72.99, 66.48.

2.2.10. prop-2-yn-1-yl 2-hydroxy-2-phenylacetate(3aj)

Known compound (Yin, et al. 2009). Yellow Liquid, yield 83 %; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.42 (d, J = 7.5, 2H), 7.38～7.32 (m, 3H) 5.22 (s, 1H), 4.70 (dd, *J* = 15.5, 2.5 Hz, 2H), 3.81 (s, 1H), 2.49 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) *δ* 172.76, 137.76, 128.65, 128.62, 126.67, 76.75, 75.79, 75.76, 72.93, 53.26.

2.2.11. methyl 2-hydroxy-2-(4-propoxyphenyl)acetate (3ba)

Yellow liquid, yield 78 %; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.32 (d, *J* = 5.2 Hz, 2H), 6.90 (d, *J* = 5.2 Hz, 2H), 5.13 (s, 1H), 3.92 (t, *J* = 4.4 Hz, 2H), 3.75 (s, 3H), 3.62 (s, 1H), 1.83～1.80 (dd, *J* = 4.8 Hz, 9.2 Hz, 2H), 1.05 (t, J = 4.8, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) *δ* 174.36, 159.37, 130.33, 127.93, 114.62, 72.59, 69.55, 52.87, 22.57, 10.53. HRMS (ESI-TOF): *m*/*z* $[M + NH_4]^+$ calcd for $C_{12}H_{20}NO_4$: 242.1387; found: 242.1389.

2.2.12. propyl 2-hydroxy-2-(4-propoxyphenyl)acetate (3bc)

Yellow liquid, yield 76 %; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.30 (d, *J* = 8.8 Hz, 2H), 6.86 (d, *J* = 8.8 Hz, 2H), 5.10 (s, 1H), 4.12～4.04 (m, 2H), 3.88 (t, *J* = 6.6 Hz, 2H), 3.64 (s, 1H), 1.81～1.73 (m, 2H), 1.63～1.54 (m, 2H), 1.02 (t, *J* = 7.4 Hz, 3H), 0.82 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) Ketone form: *δ* 174.10, 159.28, 130.61, 127.82, 114.56, 72.61, 69.58, 64.72, 37.12, 24.95, 22.60, 11.14. Enol form: *δ* 174.03, 159.26, 130.56, 127.80, 114.54, 72.57, 70.47, 34.12, 25.83, 22.35, 16.16, 10.55. HRMS (ESI-TOF): *m*/*z* $[M + NH_4]^+$ calcd for $C_{14}H_{24}NO_4$: 270.1700; found: 270.1693.

2.2.13. butyl 2-hydroxy-2-(4-propoxyphenyl)acetate (3bd)

Yellow liquid, yield 74 %; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32～7.28 (m, 2H), 6.86 (q, *J* = 4.9 Hz, 2H), 5.09 (s, 1H), 4.13 (qt, *J* = 10.8, 6.7 Hz, 2H), 3.89 (t, *J* = 6.6 Hz, 2H), 3.52 (s, 1H), 1.83～1.74 (m, 2H), 1.61～1.49 (m, 2H), 1.31～1.18 (m, 2H), 1.02 (t, *J* = 7.4 Hz, 3H), 0.85 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) *δ* 173.94, 159.17, 130.50, 127.72, 114.46, 72.48, 69.47, 65.76, 30.39, 22.51, 18.83, 13.51, 10.45. HRMS (ESI-TOF): *m*/*z* $[M + NH_4]^+$ calcd for $C_{15}H_{26}NO_4$: 284.1856; found: 284.1848.

2.2.14. isopropyl 2-hydroxy-2-(4-propoxyphenyl)acetate (3bg)

White solid, yield 70 %, m.p. 63～64 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32～7.28 (m, 2H), 6.88～6.84 (m, 1H), 5.08～5.02 (m, 2H), 3.90 (t, *J* = 6.6 Hz, 1H), 3.50 (s, 1H), 1.84～1.75 (m, 1H), 1.26 (d, *J* = 6.3 Hz, 2H), 1.10 (d, *J* = 6.3 Hz, 1H), 1.02 (t, *J* = 7.4 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) *δ* 173.39, 159.10, 130.57, 127.66, 114.41, 72.51, 69.84, 69.45, 22.52, 21.52, 10.47. HRMS (ESI-TOF): *m*/*z* $[M + Na]^+$ calcd for $C_{14}H_{20}NaO_4$: 275.1254; found: 275.1266.

2.2.15. isopentyl 2-hydroxy-2-(4-propoxyphenyl)acetate (3bh)

Yellow liquid, yield 72 %; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.29 (d, *J* = 8.8 Hz, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 5.08 (s, 1H), 4.13 (pd, *J* = 10.9, 6.2 Hz, 2H), 3.87 (t, *J* = 6.6 Hz, 2H), 3.64 (s, 1H), 1.83～1.74 (m, 2H), 1.56～1.42 (m, 2H), 1.01 (t, *J* = 7.4 Hz, 3H), 0.89 (dd, *J* = 6.6, 1.0 Hz, 1H), 0.83 (dd, *J* = 7.8, 6.5 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) Ketone form: *δ* 174.10, 159.28, 130.61, 127.83, 114.56, 72.61, 69.58, 64.72, 37.12, 34.12, 24.95, 22.39, 16.21, 11.37. Enol form: 174.03, 159.26, 130.56, 127.80, 114.54, 72.57, 70.47, 34.07, 25.83, 22.60, 22.35, 16.16, 11.12, 10.55. HRMS (ESI-TOF): *m*/*z* $[M + Na]^+$ calcd for $C_{16}H_{24}NaO_4$: 303.1567; found: 303.1567.

2.2.16. methyl 2-hydroxy-2-(4-(trifluoromethyl)phenyl)acetate (3ca)

Known compound (Sugaya, et al. 2017). White solid, yield 90 %, m.p. 40~41 °C; ^{1}H NMR (400 MHz, $CDCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, J = 13.5, 4H), 5.25 (s, 1H), 4.22 (s, 1H), 3.74 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.38, 141.93, 131.59 (q, J_{C-F} = 33.33 Hz), 126.89, 125.42 (q, J_{C-F} = 4.04 Hz), 123.94 (q, J_{C-F} = 270.1 Hz), 72.29, 53.19.

2.2.17. ethyl 2-hydroxy-2-(4-(trifluoromethyl)phenyl)acetate (3cb)

White solid, yield 89 %, m.p. 87~88 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, J = 8.3 Hz, 4H), 5.22 (s, 1H), 4.21 (dd, J = 25.0, 6.9 Hz, 2H), 3.89 (s, 1H), 1.21 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.90, 142.20, 130.13 (q, J_{C-F} = 32.32 Hz), 126.81, 125.34 (q, J_{C-F} = 2.02 Hz), 121.27 (q, J_{C-F} = 273.71 Hz),72.29, 62.53, 13.84. HRMS (+ESI-TOF): m/z $[M + NH_4]^+$ calcd for $C_{11}H_{15}F_3NO_3$: 266.0999; found: 266.1005.

2.2.18. propyl 2-hydroxy-2-(4-(trifluoromethyl)phenyl)acetate (3cc)

White solid, yield 90 %, m.p. 73~74 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (dd, J = 14.5, 7.8 Hz, 4H), 5.24 (s, 1H), 4.11 (d, J = 7.0 Hz, 2H), 3.90 (s, 1H), 1.59 (dd, J = 13.9, 6.9 Hz, 2H), 0.81 (t, J = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.00, 142.27, 130.78 (q, J_{C-F} = 32.32 Hz), 126.80, 125.34 (q, J_{C-F} = 4.04 Hz), 121.26 (q, J_{C-F} = 272.7 Hz), 72.26, 67.98, 21.70, 9.94. HRMS (ESI-TOF): m/z $[M + NH_4]^+$ calcd for $C_{12}H_{17}F_3NO_3$: 280.1155; found: 280.1163.

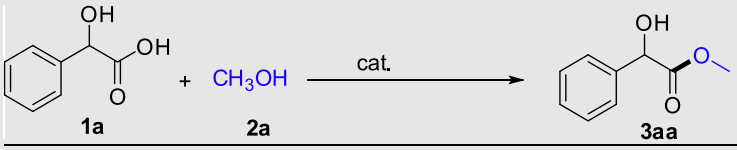
2.2.19. benzyl 2-hydroxy-2-phenylacetate (3ak)

Known compound (Tang, et al. 2017). Yellow liquid, yield 84 %; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, J = 7.1 Hz, 2H), 7.38~7.30 (m, 6H), 7.20 (d, J = 2.8 Hz, 2H), 5.23 (t, J = 8.2 Hz, 2H), 5.14 (d, J = 12.3 Hz, 1H), 3.44 (d, J = 5.8 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.49, 138.17, 134.98, 128.62, 128.50, 128.53, 128.47, 127.96, 126.60, 72.98, 67.70.

2.2.20. phenethyl 2-hydroxy-2-phenylacetate (3al)

Known compound (Tang, et al. 2017). White solid, yield 85 %, m.p. 60~62 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35~7.31 (m, 5H), 7.21 (d, J = 5.4 Hz, 3H), 7.02 (d, J = 3.2 Hz, 2H), 5.11 (d, J = 5.6 Hz, 1H), 4.40~4.28 (m, 2H), 3.57 (d, J = 5.6 Hz, 1H), 2.90~2.78 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.63, 138.30, 137.25, 128.88, 128.63, 128.56, 128.46, 126.67, 126.64, 72.93, 66.56, 34.90.

Table 1 Screening the optimized reaction conditions[a].



Entry	Catalyst (mol%)	Solvent	Temp. (°C)	t (h)	Yield (%)
1	$Yb(OTf)_3$ (1)	–	80	12	37
2	$Ni(OTf)_2$ (1)		80	12	68
3	$Yb(OTf)_2{\cdot}H_2O$ (1)		80	12	50
4	$Zn(OTf)_2$ (1)		80	12	20
5	$Sc(OTf)_3$ (1)		80	12	62
6	$La(OTf)_3$ (1)		80	12	55
7	$Bi(OTf)_3$ (1)		80	12	24
8	$Sn(OTf)_2$ (1)		80	12	31
9	TfOH (1)		80	12	–
10	$Ni(OTf)_2$ (0.5)		80	12	55
11	$Ni(OTf)_2$ (1.5)		80	12	64
12	$Ni(OTf)_2$ (1)		80	4	83
13	$Ni(OTf)_2$ (1)		80	6	86
14	$Ni(OTf)_2$ (1)		80	8	81
15	$Ni(OTf)_2$ (1)		50	6	57
16	$Ni(OTf)_2$ (1)		100	6	71
17[b]	$Ni(OTf)_2$ (1)	CH_3CN	80	6	–
18[b]	$Ni(OTf)_2$ (1)	DMSO	80	6	–
19[b]	$Ni(OTf)_2$ (1)	DCM	80	6	84
20[b]	$Ni(OTf)_2$ (1)	THF	80	6	–
21[b]	$Ni(OTf)_2$ (1)	DMF	80	6	–

[a] Reaction conditions: mandelic acid **1a** (0.5 mmol), methanol **2a** (0.5 mL), and catalyst in a 10 mL thick walled pressure tube at indicated temperature for 4–12 h. Isolated yield. [b] Reaction conditions: mandelic acid **1a** (0.5 mmol), methanol **2a** (5 equiv), $Ni(OTf)_2$ (1 mol%), and solvent (1 mL) in a 10 mL tube at 80 °C for 6 h. Isolated yield.

2.2.21. 3-phenylpropyl 2-hydroxy-2-phenylacetate (3am)

Known compound (Tang, et al. 2017). Yellow Liquid, yield 83 %; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, J = 4.8 Hz, 2H), 7.48 ~ 7.40 (m, 3H), 7.34 (t, J = 4.0 Hz, 2H), 7.27 (t, J = 4.8 Hz, 1H), 7.10 (d, J = 4.8 Hz, 2H), 5.28 (s, 1H), 4.22 (t, J = 6.3 Hz, 2H), 3.91 (s, 1H), 2.58 (t, J = 4.8 Hz, 2H), 2.01 ~ 1.94 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.75, 140.77, 138.57, 128.65, 128.52, 128.48, 128.42, 126.62, 126.11, 72.94, 65.24, 31.77, 30.02.

2.2.22. 4-nitrobenzyl 2-hydroxy-2-phenylacetate (3an)

Known compound (Sugaya, et al. 2017). White solid, yield 81 %, m.p. 141~142 °C; ^{1}H NMR (400 MHz, DMSO d_6) δ 8.16 (d, J = 8.7 Hz, 2H), 7.46~7.37 (m, 4H), 7.33 (dt, J = 20.1, 7.0 Hz, 3H), 6.23 (d, J = 5.2 Hz, 1H), 5.30 (d, J = 5.1 Hz, 1H), 5.28 (s, 2H); ^{13}C NMR (101 MHz, DMSO d_6) δ 172.92, 142.50, 138.23, 128.60, 127.86, 126.63, 123.64, 73.09, 73.06, 65.47.

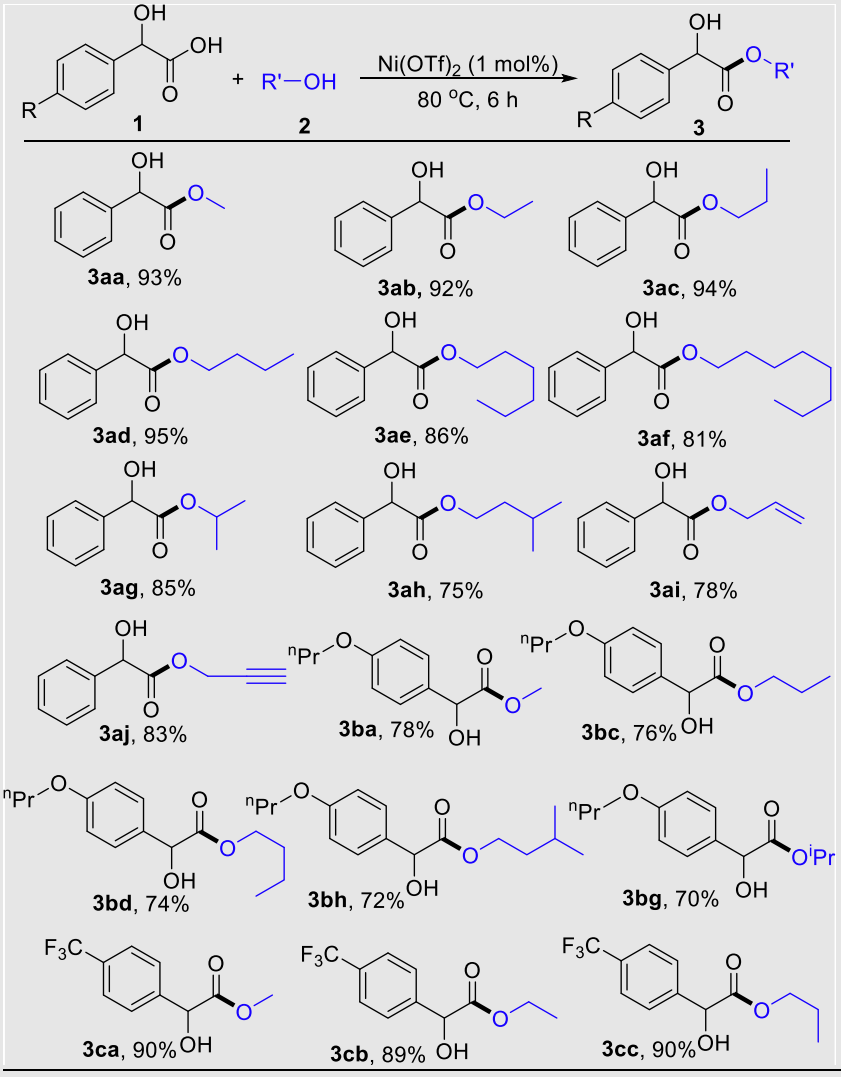
2.2.23. 2-hydroxy-2-(4-(trifluoromethyl)phenyl)acetate (3ao)

White solid, yield 77 %, m.p. 63~64 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, J = 7.8 Hz, 1H), 7.40 (dt, J = 12.2, 5.5 Hz, 7H), 7.11 (d, J = 7.5 Hz, 1H), 5.65 (d, J = 15.1 Hz, 1H), 5.52 (d, J = 15.1 Hz, 1H), 5.30 (s, 1H), 3.70 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.54, 147.48, 141.76, 133.91, 130.96, 129.37, 128.80, 127.17, 125.79 (q, J = 3.7 Hz), 125.36, 72.57, 64.73.

2.2.24. 4-chlorobenzyl 2-hydroxy-2-phenylacetate (3ap)

Known compound (Gao, et al. 2019). White solid, yield 80 %, m.p. 136~137 °C; ^{1}H NMR (400 MHz, DMSO d_6) δ 7.43 (d, J = 6.8 Hz, 2H), 7.35 (d, J = 7.6 Hz, 5H), 7.29 (d, J = 8.4 Hz,

Table 2 Substrate scope of alcohols and mandelic acids[a].



[a] Reaction conditions: mandelic acid **1** (0.5 mmol), alcohol **2** (0.5 mL), and $Ni(OTf)_2$ (1 mol%) in a 10 mL thick walled pressure tube at 80 °C for 6 h. Isolated yield.

2H), 6.14 (d, J = 5.3 Hz, 1H), 5.23 (d, J = 5.3 Hz, 1H), 5.11 (d, J = 2.9 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.73, 138.69, 133.94, 133.68, 129.05, 128.39, 128.29, 128.11, 126.57, 72.97, 65.73.

2.2.25. 2-chlorobenzyl 2-hydroxy-2-phenylacetate (3aq)

White solid, yield 82 %, m.p. 87~88 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (dd, J = 7.8, 1.8 Hz, 2H), 7.38~7.34 (m, 4H), 7.24 (td, J = 7.5, 1.9 Hz, 1H), 7.23~7.13 (m, 2H), 5.30 (d, J = 3.8 Hz, 2H), 5.27 (s, 1H), 3.63 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.37, 138.12, 133.55, 132.77, 129.74, 129.61, 129.50, 128.67, 128.60, 126.91, 126.67, 73.03, 64.99. HRMS (ESI-TOF): m/z $[M + Na]^+$ calcd for $C_{15}H_{13}ClNaO_3$: 299.0445; found: 299.0448.

2.2.26. 2-nitrobenzyl 2-hydroxy-2-(4-(trifluoromethyl)phenyl) acetate (3co)

White solid, yield 78 %, m.p. 123~124 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (dd, J = 7.7, 1.7 Hz, 1H), 7.66 (d, J = 8.3 Hz, 4H), 7.49~7.54 (m, 2H), 7.16~7.13 (m, 1H), 5.61~5.49 (m, 2H), 5.36 (s, 1H), 3.60 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.54, 147.48, 141.76, 133.92, 131.20, 130.96, 129.37, 128.80, 127.17, 125.79 (q, J = 3.7 Hz), 125.36, 122.71, 72.57, 64.73. HRMS (ESI-TOF): m/z $[M-H]^-$ calcd for $C_{16}H_{11}F_3NO_5$: 373.0589; found: 373.0585.

2.2.27. 2-chlorobenzyl 2-hydroxy-2-(4-(trifluoromethyl)phenyl) acetate (3cq)

White solid, yield 75 %, m.p. 73~74 °C; ^{1}H NMR (400 MHz, DMSO d_6) δ 7.69 (q, J = 8.5 Hz, 4H), 7.44 (d, J = 8.0 Hz, 1H), 7.37~7.30 (m, 2H), 7.30~7.24 (m, 1H), 6.45 (s, 1H), 5.40 (s, 1H), 5.19 (d, J = 2.9 Hz, 2H); ^{13}C NMR (101 MHz, DMSO d_6) δ172.04, 144.32, 133.45, 133.06, 130.48, 130.44, 129.74, 127.90, 127.59, 125.59, 125.55, 125.52, 125.48, 72.29, 64.02, 63.99, 63.95, 40.56, 40.35, 40.14, 39.93, 39.72, 39.51, 39.30. HRMS (ESI-TOF): m/z $[M-H]^-$ calcd for $C_{16}H_{11}ClF_3O_3$: 343.0349; found: 343.0341.

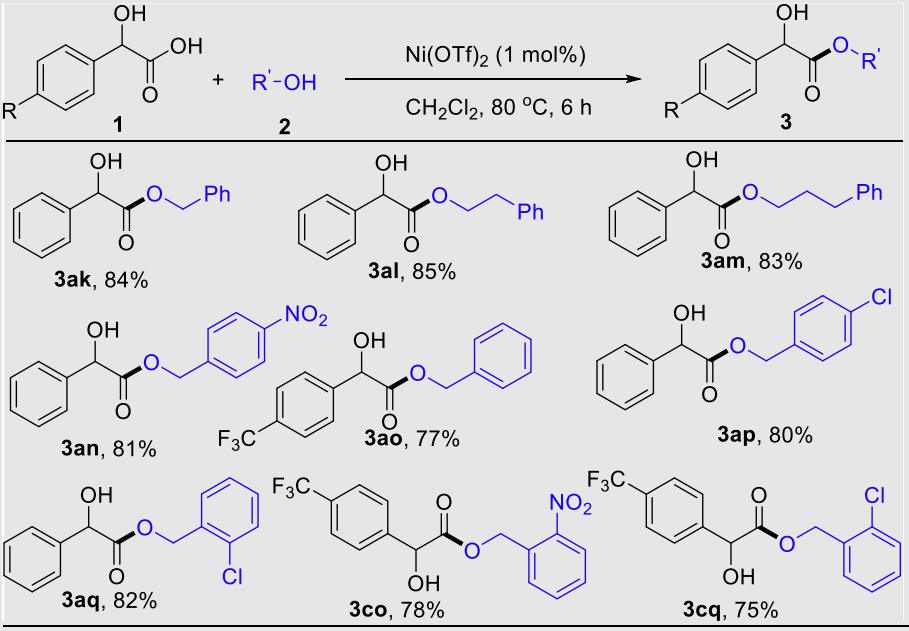
2.2.28. 3,3,5-trimethylcyclohexyl 2-hydroxy-2-phenylacetate

Known compound (Tang, et al. 2017). White solid, yield 85 %, m.p. 52~53 °C (Reference value:50~53 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (dt, J = 7.9, 1.6 Hz, 2H), 7.38~7.28 (m, 3H), 5.12 (d, J = 1.6, 1H), 5.00~4.90 (m, 1H), 3.76 (s, 1H), 2.05~1.12 (m, 4H), 1.02~0.84 (m, 10*H*), 0.79~0.67(m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.38, 138.58, 28.49, 128.27 126.42, 47.36, 47.33, 43.77, 43.32, 40.19, 39.72, 32.94, 32.87, 32.31, 32.24, 27.06, 26.98, 25.48, 25.41, 22.21, 22.13.

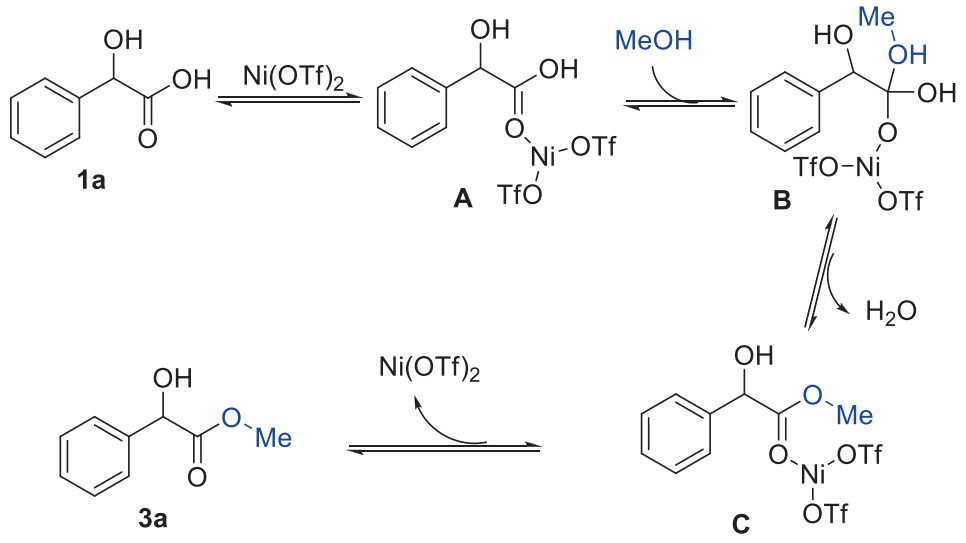
3. Results and discussion

Bearing this idea in mind, we started our investigation by reaction conditions optimization employing the reaction of mandelic acid (**1a**) in methanol (**2a**) as the model reaction, as shown in Table 1. Firstly, common Lewis acid catalysts such as $Yb(OTf)_3$, $Ni(OTf)_2$, $Zn(OTf)_2$, $Sc(OTf)_3$, $La(OTf)_3$, $Bi(OTf)_3$, $Sn(OTf)_2$, and TfOH were analyzed, and $Ni(OTf)_2$ was found a suitable catalyst to give methyl mandelate **3aa** in 68 % yield (Entries 1–9, Table 1). Next, the loading of catalyst was optimized via using 0.5 mol% and 1.5 mol% of Ni $(OTf)_2$. Lower catalyst loading led to decreased yield, while increase the loading of catalyst to 1.5 mol% did not gave a

Table 3 Substrate scope of aromatic alcohols with mandelic acid[a].



[a] Reaction conditions: mandelic acid **1** (0.5 mmol), alcohol **2** (5 equiv), $Ni(OTf)_2$ (1 mol%) in CH_2Cl_2 (1 mL) in a 10 mL thick walled pressure tube at 80 °C for 6 h. Isolated yields.



Scheme 2 Proposed mechanism.

higher yield (Entries 10–11, Table 1). Interestingly, an isolated yield of 86 % was obtained if the reaction was conducted for 6 h (Entries 12–14, Table 1). Further investigation indicated that 80 °C was an optimal reaction temperature (Entries 15–16, Table 1). We finally tested the reaction in different solvents, such as CH_3CN, DMSO, CH_2Cl_2, THF, and DMF (Entries 17–21, Table 1). The reaction in CH_2Cl_2 gave a yield of 84 %. Thus, CH_2Cl_2 was chosen as the best solvent for this transformation.

With the optimized reaction conditions established, we investigated the substrate scope of simple alcohol reacted with mandelic acid as in Table 2. As expected, alcohols such as ethanol, propanol, butanol, hexanol and octanol were all suitable reaction partners to give corresponding mandelic acid esters in 81–95 % yields (**3ab-3af**). Isopropanol and isoamyl alcohol reacted with mandelic acid to deliver products **3ag** and **3ah** in 85 % and 75 % yields, respectively. Reactive allyl alcohol and propargyl alcohol led to products **3ai** and **3aj** in yields of 78 % and 83 %. Substituted mandelic acids were also used as substrates. For example, electron-donating alkoxy and electron-withdrawing trifluoromethyl substituted mandelic acids reacted with variously substituted alcohols to give products **3ba-3 cc** in 70–90 % yields. Aliphatic α-hydroxycarboxylic acid compounds have also been tried, unfortunately, no corresponding ester compounds have been obtained.

To expand the substrate to aromatic alcohols with high boiling points, we utilized CH_2Cl_2 as the solvent. As in Table 3, phenylmethanol, 2-phenylethanol, and 3-phenylpropan-1-ol reacted smoothly with mandelic acid to generate esters **3ak-3am** in 83–85 % yields. Nitro- and chloro-substituted phenylmethanol underwent the esterification to produce **3an-3aq** in 77–82 % yields.

To investigate the practicality of this esterification procedure, a gram-scale reaction between mandelic acid and 3,3,5-trimethylcyclohexanol was conducted to produce medicine cyclandelate (**I**) in 85 % yield (1.64 g). The result indicated that current catalyst system may be suitable to industrial productions (Scheme 1).

A mechanism for this transformation was proposed and listed in Scheme 2. The coordination of $Ni(OTf)_2$ to mandelic acid **1a** gives intermediate **A**, which was attacked by methanol **2a** to form intermediate **B**. The subsequent dehydration of **B** leads to intermediate **C**. Finally, product **3a** is generated after de-coordination.

4. Conclusions

In summary, we have developed a nickel (II)-catalyzed esterification of mandelic acid with various alcohols for the synthesis of mandelic acid ester derivatives. Nickel trifluoromethanesulfonate was used as efficient catalyst to deliver the α-hydroxy esters in yields up to 95 %. The features of the reaction lie in the mild reaction conditions, low catalyst loading and broad substrates scope. Moreover, gram-scale synthesis of medicine cyclandelate was realized in 85 % yield.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.arabjc.2022.104407.

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