Synthesis of Bicyclo[2.2.2]octenols via Ni(0)-Catalyzed Alkylative Cyclization of Multi-functional Aldehydes

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Abstract

Nickel-catalyzed three-component coupling reactions of \(\alpha,\beta,\gamma,\delta\)-unsaturated dienals, alkynes, and alkynyltin reagents to produce more functionalized aldehydes have been achieved. The aldehydes produced were subjected to a Ni(0)-catalyzed alkylative cyclization reaction to provide direct access to highly functionalized bicyclo[2.2.2]octenols. In addition to their existence as substructures of complex natural molecules, these compounds possess interesting stereochemical properties, and can be interesting three-dimensional scaffolds for library design.

Keywords: Nickel Cyclization; Aldehydes; Bicyclo[2.2.2]octenols

Introduction

Bicyclo-[2.2.2]-octenols constitute important precursors that are potentially useful for synthesis of more complex molecules.\cite{1} These substructures exist in many natural products, and methods to synthesize them have attracted considerable interest.\cite{2} The compounds also represent three-dimensional scaffolds that could be interesting in library designs. In the course of mechanistic studies of allyl silane and allyl stannane additions to aldehydes, Denmark reported an alternate synthesis of compounds of this type.\cite{3} However, the development of a multicomponent coupling entry to aldehydes of this type would provide rapid access to structures of this class not easily accessed by the allylstanne methodology.\cite{4} An important feature of our strategy is the development of a procedure for site-selective sequential 1,6-, 1,4-, and 1,2-additions to \(\alpha,\beta,\gamma,\delta\)-unsaturated aldehydes to generate a complex bridged bicyclic framework (Figure 1).

\textbf{Figure 1.} Synthesis of bridged bicyclic framework
Experimental

Reagents were commercially available and were used without purification. Tetrahydrofuran (THF) was treated under nitrogen using a solvent purification system (Innovative Technology, Inc., Model 3 SPS-400-3). All reactions were conducted in a flame-dried glassware under an atmosphere of nitrogen or argon. Ni(COD)$_2$ and Ni(acac)$_2$ were stored in a glove box under argon. 2,4-Hexadienal existed commercially as trans: cis in 9:1 ratio. 4-Methyl-2,4-pentadienial was prepared from methacrolein according to known literature procedures. $^1$H and $^{13}$C spectra were obtained at rt on a Varian Mercury 400 or Varian Unity 500 MHz instruments. High resolution mass spectra (HRMS) were obtained on a Kratos MS 80 mass spectrometer by the Central Instrument Facility, Department of Chemistry, Wayne State University, Detroit, Michigan.

A. General procedure for three component couplings of $\alpha$, $\beta$, $\gamma$, $\delta$-unsaturated aldehydes, alkynes and alkynyltins.

A 0.02 M solution of Ni(acac)$_2$ (0.1-0.2 equiv) in THF was stirred at 0 °C, and a solution of DIBAL (0.1-0.2 equiv, 1.0 M in hexane) was added dropwise, followed by the addition of the alkynyltin reagent (1.6 eq, unless otherwise noted) and alkyne (2.0 eq, unless otherwise noted). The $\alpha$, $\beta$, $\gamma$, $\delta$-unsaturated aldehyde (1.0 equiv) and TMSCl (3.0 equiv) were then added neat, and the reaction mixture was allowed to warm to rt and was stirred for 7-10 h. The mixture was quenched by the addition of conc. HCl (12 equiv, 2.0 M in acetone), stirred for 15 min, and was poured into conc. NH$_4$F solution (4 times the volume of the reaction mixture before quench). The two-phase mixture was vigorously stirred for 30 min and then filtered through Celite and washed with diethyl ether. The aqueous layer was extracted with diethyl ether; the combined organic layers were washed with sat. NaHCO$_3$, brine, and dried over MgSO$_4$. The product was purified by flash chromatography on SiO$_2$ using hexane and CH$_2$Cl$_2$ as a solvent system to afford aldehyde 1.

7-Hexyl-5-methyl-9-phenyl-non-2,6-dien-8-ynal (1a).

Following the general procedure, 2,4-hexadienal (0.22 mL, 2.0 mmol), 1-octyne (0.35 mL, 2.4 mmol), tributyl(phenylethynyl)tin (0.77 mL, 2.2 mmol), Ni(acac)$_2$ (51.4 mg, 0.2 mmol), DIBAL (0.2 mL, 0.2 mmol in 1 M solution), and TMSCl (0.3 mL, 2.4 mmol) were stirred for 7 h to produce, after flash chromatography (3:1 Hexane:CH$_2$Cl$_2$), 197 mg (32%) of product as a thick brown oil. $^1$H-NMR (500 MHz, CDCl$_3$) δ 9.48 (d, $J = 8.0$ Hz, 1H), 7.40-7.43 (m, 2H), 7.29-7.34 (m, 3H), 6.84 (dt, $J = 15.5, 7.3$ Hz, 1H), 6.13 (dd, $J = 15.5, 8.3$ Hz 1H), 5.50 (d, $J = 9.0$ Hz, 1H), 3.04 (sept, $J = 7.3$ Hz, 1H), 2.33-2.46 (m, 2H), 2.18 (t, $J = 7.5$ Hz, 2H), 1.53-1.57 (m, 2H), 1.27-1.37 (m, 6H), 1.10 (d, $J = 6.5$ Hz, 3H), 0.87-0.91 (m, 3H) $^{13}$C-NMR (125 MHz, CDCl$_3$) δ 194.3, 157.2, 141.4, 134.2, 131.6, 128.6, 128.6, 123.9, 123.7, 94.3, 88.1, 40.5, 37.2,
Following the general procedure, 2,4-hexadienal (0.22 mL, 2.0 mmol), 1-pentyne (0.39 mL, 4.0 mmol), tributyl(phenylethynyl)tin (1.4 mL, 4.0 mmol), Ni(acac)$_2$ (51.4 mg, 0.2 mmol), DIBAL (0.2 mL, 0.2 mmol in 1 M solution), and TMSCl (0.51 mL, 4.0 mmol) were stirred for 7 h to produce, after flash chromatography (3:1 hexane:CH$_2$Cl$_2$), 222 mg (42%) of product as a thick brown oil. $^1$H-NMR (500 MHz, CDCl$_3$) $\delta$ 9.48 (d, $J = 8.0$ Hz, 1H), 7.41-7.43 (m, 2H), 7.29-7.34 (m, 3H), 6.84 (dt, $J = 15.5$, 7.3 Hz, 1H), 6.13 (dd, $J = 15.0$, 7.5 Hz, 1H), 5.5 (d, $J = 10.0$ Hz, 1H), 3.04 (sept, $J = 7.4$ Hz, 1H), 2.33-2.46 (m, 2H), 2.12-2.21 (m, 2H), 1.59 (sextet, $J = 7.5$ Hz, 2H), 1.11 (d, $J = 7.0$ Hz, 3H), 13C-NMR (125 MHz, CDCl$_3$) $\delta$ 194.3, 157.3, 141.6, 134.2, 131.6, 128.6, 128.4, 123.7, 123.6, 94.2, 88.0, 40.5, 39.3, 34.9, 21.9, 20.8, 13.6 IR (film, cm$^{-1}$) 2958, 2868, 1692, 1490, 1442, 974, 756, 691 HRMS (EI) m/e calcd. for C$_{19}$H$_{22}$O 266.16707, found 266.16725 (M$^+$).

5-Methyl-7,9-diphenyl-nona-2,6-dien-8-ynal (1c).

Following the general procedure, 2,4-hexadienal (0.44 mL, 4.0 mmol), phenyl acetylene (0.88 mL, 8.0 mmol), tributyl(phenylethynyl)tin (2.1 mL, 6.0 mmol), Ni(acac)$_2$ (206 mg, 0.8 mmol), DIBAL (0.8 mL, 0.8 mmol in 1 M solution), and TMSCl (1.52 mL, 12.0 mmol) were stirred for 4 h to produce, after flash chromatography (3:1, then 2:1 hexane:CH$_2$Cl$_2$), 590 mg (49%) of product as a thick brown oil. $^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 9.52 (d, $J = 8.0$ Hz, 1H), 7.65-7.68 (m, 2H), 7.52-7.55 (m, 2H), 7.30-7.41 (m, 5H), 6.90 (dt, $J = 15.6$ Hz, 7.8 Hz, 1H), 6.26 (d, $J = 15.6$ Hz, 1H), 6.17-6.23 (m, 2H), 3.25-3.35 (m, 1H), 2.49-2.60 (m, 2H), 1.25 (d, $J = 6.4$ Hz, 3H), 13C-NMR (100 MHz, CDCl$_3$) $\delta$ 194.2, 156.7, 141.9, 137.9, 134.4, 131.8, 128.8, 128.7, 128.2, 126.3, 124.0, 123.4, 96.1, 86.7, 40.4, 35.6, 20.6 IR (film, cm$^{-1}$) 2958, 2925, 1689, 1597, 1490, 1447, 1362, 1222, 147, 1026, 974, 756, 692 HRMS (EI) m/e calcd. for C$_{22}$H$_{20}$O 300.15142, found 300.15164 (M$^+$).

7-Methoxymethyl-5-methyl-9-phenyl-nona-2,6-dien-8-ynal (1d).

Following the general procedure, 2,4-hexadienal (0.22 mL, 2.0 mmol), methyl propargyl ether (0.35 mL, 4.0 mmol), tributyl(phenylethynyl)tin (1.12 mL, 3.2 mmol), Ni(acac)$_2$ (77 mg, 0.3 mmol), DIBAL (0.3 mL, 0.3 mmol in 1 M solution), and TMSCl (0.76 mL, 6.0 mmol) were stirred for 4 h to produce, after flash chromatography (1:1 hexane:CH$_2$Cl$_2$, then 6:1 hexane:ethyl acetate), 182 mg (34%) of product as a thick brown oil. $^1$H-NMR (500 MHz, CDCl$_3$) $\delta$ 9.47 (d, $J = 8.0$ Hz, 1H), 7.41-7.44 (m, 2H), 7.28-7.33 (m, 3H), 6.82 (dt, $J = 15.0$ Hz, 7.4 Hz, 1H), 6.12 (dd, $J = 15.5$, 8.3 Hz, 1H), 5.79 (d, $J = 9.5$ Hz, 1H), 3.98 (s, 2H), 3.36 (s, 3H), 3.07 (septet, $J = 7.3$ Hz 1H), 2.36-2.47 (m, 2H), 1.12 (d, $J = 6.5$ Hz, 3H), 13C-NMR (125 MHz, CDCl$_3$) $\delta$ 194.2, 156.7, 143.1, 134.3, 131.7, 128.6, 128.6, 123.3, 120.7, 94.9, 86.0, 75.0, 58.3, 40.2, 34.6, 20.5
IR (film, cm\(^{-1}\)) 2962, 2928, 2817, 1688, 1596, 1442, 1358, 1190, 1097, 1025, 974, 917, 756, 691 HRMS (EI) m/e calcd. for C\(_{18}\)H\(_{20}\)O\(_2\) 268.14633, found 268.14618 (M\(^+\)).

4-Methyl-9-phenyl-7-propyl-nona-2,6-dien-8-ynal (1e).

Following the general procedure, 4-methyl 2,4-pentadienal (0.22 mL, 2.0 mmol), 1-pentyne (0.39 mL, 4.0 mmol), tributyl(phenylethynyl)tin (1.12 mL, 3.2 mmol), Ni(acac)\(_2\) (103 mg, 0.4 mmol), DIBAL (0.4 mL, 0.4 mmol in 1 M solution), and TMSCl (0.76 mL, 6.0 mmol) were stirred for 10 h to produce, after flash chromatography (3:1 then 2:1 hexane: CH\(_2\)Cl\(_2\)), 149 mg (28%) of product as a thick brown oil. \(^1\)H-NMR (500 MHz, CDCl\(_3\)) \(\delta\) 9.51 (d, \(J = 7.5\) Hz, 1H), 7.42-7.44 (m, 2H), 7.30-7.34 (m, 3H), 6.82 (dd, \(J = 15.5, 7.0\) Hz, 1H), 6.11 (ddd, \(J = 15.5, 8.0, 1.0\) Hz, 1H), 5.58 (t, \(J = 7.5\) Hz, 1H), 2.59-2.66 (m, 1H), 2.49 (ddd, \(J = 14.5, 7.0, 2.5\) Hz, 2H), 2.18 (t, \(J = 7.3\) Hz, 2H), 1.56-1.63 (m, 2H), 1.17 (d, \(J = 7.0\) Hz, 3H), 0.92 (t, \(J = 7.5\) Hz, 3H), \(\delta\) 194.5, 163.5, 134.0, 131.6, 131.6, 128.6, 128.4, 125.9, 94.4, 88.1, 39.4, 37.4, 36.8, 21.9, 19.0, 13.7, IR (film, cm\(^{-1}\)) 2960, 2931, 2869, 1692, 1490, 1456, 1363, 1222, 1122, 975, 756 HRMS (EI) m/e calcd. for C\(_{19}\)H\(_{22}\)O\(_2\) 266.16707, found 266.16749 (M\(^+\)).

5-Methyl-7-phenyl-deca-2,6-dien-8-ynal (1f).

Following general procedure 3.9, 2,4-hexadienal (0.22 mL, 2.0 mmol), methyl propargyl ether (0.35 mL, 4.0 mmol), tributyl(phenylethynyl)tin (1.12 mL, 3.2 mmol), Ni(acac)\(_2\) (103 mg, 0.4 mmol), DIBAL (0.4 mL, 0.4 mmol in 1 M solution), and TMSCl (0.76 mL, 6.0 mmol) were stirred for 4 h to produce, after flash chromatography (2:1 hexane: CH\(_2\)Cl\(_2\)), 143 mg (30%) of product as a thick brown oil. \(^1\)H-NMR (500 MHz, CDCl\(_3\)) \(\delta\) 9.50 (d, \(J = 8.0\) Hz, 1H), 7.56-7.58 (m, 2H), 7.31-7.34 (m, 2H), 7.21-7.28 (m, 1H), 6.86 (dt, \(J = 15.5\) Hz, 7.3 Hz, 1H), 6.16 (ddt, \(J = 15.5, 8.0, 1.5\) Hz, 1H), 6.09 (d, \(J = 9.5\) Hz, 1H), 3.12-3.21 (m, 1H), 2.42-2.52 (m, 2H), 2.09 (s, 3H), 1.16 (d, \(J = 6.5\) Hz, 3H), \(\delta\) 194.5, 163.5, 134.0, 131.6, 131.6, 128.6, 128.4, 125.9, 123.7, 94.4, 88.1, 39.4, 37.4, 36.8, 21.9, 19.0, 13.7, IR (film, cm\(^{-1}\)) 2960, 2931, 2869, 1692, 1490, 1456, 1363, 1222, 1122, 975, 756 HRMS (EI) m/e calcd. for C\(_{17}\)H\(_{18}\)O 238.1358, found 238.1361 (M\(^+\)).

7-tert-Butyl-5-methyl-9-phenyl-nona-2,6-dien-8-ynal (1g).

Following the general procedure, 2,4-hexadienal (0.33 mL, 3.0 mmol), tert-butyl acetylene (0.44 mL, 3.6 mmol), tributyl(phenylethynyl)tin (1.16 mL, 3.3 mmol), Ni(acac)\(_2\) (77 mg, 0.3 mmol), DIBAL (0.3 mL, 0.3 mmol in 1 M solution), and TMSCl (0.51 mL, 4.0 mmol) were stirred for 10 h to produce, after flash chromatography (3:1 hexane: CH\(_2\)Cl\(_2\)), 252 mg (30%) of product as a thick brown oil. \(^1\)H-NMR (500 MHz, CDCl\(_3\)) \(\delta\) 9.47 (d, \(J = 8.0\) Hz, 1H), 7.56-7.58 (m, 2H), 7.31-7.34 (m, 2H), 7.21-7.28 (m, 1H), 6.86 (dt, \(J = 15.5\) Hz, 7.3 Hz, 1H), 6.16 (ddt, \(J = 15.5, 8.0, 1.5\) Hz, 1H), 6.09 (d, \(J = 9.5\) Hz, 1H), 3.12-3.21 (m, 1H), 2.42-2.52 (m, 2H), 2.09 (s, 3H), 1.16 (d, \(J = 6.5\) Hz, 3H), \(\delta\) 194.3, 157.1, 140.6, 138.5, 134.3, 128.5, 127.9, 126.3, 124.2, 92.5, 77.0, 40.4, 35.2, 20.6, 14.7 IR (film, cm\(^{-1}\)) 2962, 2871, 1693, 1490, 1442, 1263, 1198, 974, 850 HRMS (EI) m/e calcd. for C\(_{17}\)H\(_{16}\)O 238.1358, found 238.1361 (M\(^+\)).
3H) $^{13}$C-NMR (125 MHz, CDCl$_3$) δ 194.2, 157.3, 137.3, 134.2, 133.8, 131.5, 128.6, 128.3, 123.9, 95.7, 87.5, 40.7, 35.9, 34.8, 29.6, 20.8 IR (film, cm$^{-1}$) 2963, 2870, 1692, 1597, 1532, 1489, 1360, 1320, 1263, 1198, 1154, 1012, 974, 908, 850, 816,756, 691 HRMS (EI) m/e calcd. for C$_{20}$H$_{24}$O 280.18272, found 280.18295 (M$^+$).

B. General procedure for the cyclization of enynals followed by Prins cyclization.

A 0.05 M THF solution of Ph$_3$P (0.4 eq) was transferred to Ni(COD)$_2$ (0.2 eq in THF) by cannula at 0 °C followed by addition of Me$_2$Zn (3.0 eq). The resulting solution was stirred for 3 min, after which a 0.1 M THF solution of aldehyde 1 (1.0 eq) was added dropwise at 0 °C via syringe pump. The ice bath was removed and the reaction (0.01 M solution with respect to the aldehyde) was stirred for 15 min at rt, quenched with a saturated solution of NH$_4$Cl, extracted with ether and dried over MgSO$_4$. The crude reaction mixture was dissolved in a THF solution (0.05 M) and solid TsOH (3.0 eq) was added. The reaction was stirred at rt for 30 min or until starting material was consumed as judged by TLC analysis, quenched with a saturated solution of NaHCO$_3$, extracted with ether, and dried over MgSO$_4$. The solvent was evaporated under vacuum and the crude product was purified by chromatography on silica gel using hexane/ethyl acetate as eluent to afford bicyclooctenol 5.


Following the general procedure, compound 1a (65 mg, 0.21 mmol), triphenylphosphine (22 mg, 0.0844 mmol), Ni(COD)$_2$ (11.6 mg, 0.042 mmol), dimethylzinc (0.32 mL, 0.633 mmol in 2.0 M solution in toluene), and p-toluene sulfonic acid (TsOH) (0.63 mmol, 109 mg) were employed to produce, after column chromatography (12:1 hexane: ethyl acetate) 39 mg of a light yellow oil (57% yield of two inseparable diastereomers 3:1 d.r). Major isomer $^1$H-NMR (500 MHz, CDCl$_3$) δ 7.36-7.38 (m, 5H), 5.37 (d, $J$ = 2.0 Hz, 1H), 5.00 (d, $J$ = 2.0 Hz, 1H), 4.25 (dt, $J$ = 8.5, 3.0 Hz, 1H), 2.54-2.56 (m, 1H), 2.32 (m, 1H), 2.24-2.28 (m, 1H), 2.10 (ddd, $J$ = 13.5, 8.5, 2.5 Hz, 1H), 1.72-1.79 (m, 1H), 1.37-1.44 (m, 9H), 1.22-1.27 (m, 6H), 1.08 (d, $J$ = 8.0 Hz, 3H), 0.85 (t, $J$ = 7.0 Hz, 3H), 0.75 (ddd, $J$ = 12.5, 5.5, 2.0 Hz, 1H), diagnostic shifts for minor isomer δ 5.02 (d, $J$ = 2.0 Hz, 1H), 4.01 (dt, $J$ = 8.5, 3.0 Hz, 1H), 1.89 (ddd, $J$ = 13.5, 8.5, 2.0 Hz, 1H) $^{13}$C-NMR (125 MHz, CDCl$_3$) δ 147.80, 141.2, 140.9, 139.1, 128.5, 127.7, 127.3, 113.6, 66.9, 48.9, 40.4, 36.4, 34.4, 33.2, 31.9, 30.6, 29.9, 29.1, 22.8, 20.5, 14.3 IR (film, cm$^{-1}$) 3406, 3056, 2952, 2926, 2856, 1600, 1527, 1492, 1447, 1376, 1275, 1066, 988, 934, 896, 780, 762, 700, 650 HRMS (EI) m/e calcd. for C$_{23}$H$_{32}$O 324.24532, found 324.24588 (M$^+$).


Following the general procedure, compound 1b (42 mg, 0.158 mmol), triphenylphosphine (17 mg, 0.0632 mmol), Ni(COD)$_2$ (9 mg, 0.0316 mmol), dimethylzinc (0.24 ml, 0.474 mmol 2.0 M solution in toluene), and p-toluene sulfonic acid (TsOH) (0.47 mmol, 82 mg) were employed to produce, after column
chromatography (10:1 hexane: ethyl acetate) 24 mg of light yellow oil (59% combined yield of two inseparable diastereomers 3:1 d.r) 1H-NMR (500 MHz, CDCl3) δ 7.26-7.33 (m, 5H), 5.38 (d, J = 2.0 Hz, 1H), 5.00 (d, J = 2.0 Hz, 1H), 4.25 (dt, J = 8.5 Hz, 3.0 Hz, 1H), 2.54-2.56 (m, 1H), 2.29-2.32 (m, 1H), 2.23-2.28 (m, 1H), 2.04-2.10 (m, 1H), 1.99 (ddd, J = 14.5, 9.5, 2.0 Hz, 1H), 1.72-1.78 (m, 1H), 1.55-1.60 (m, 1H), 1.41-1.49 (m, 2H), 1.22-1.32 (m, 2H), 1.08 (d, J = 8.5 Hz, 3H), 0.84-0.89 (m, 4H), diagnostic shifts for minor isomer δ 5.02 (d, J = 2.0 Hz, 1H), 4.01 (dt, J = 8.0, 2.5 Hz, 1H), 1.88 (ddd, J = 13.5, 8.5, 2.0 Hz, 1H), 0.93 (d, J = 6.5 Hz, 3H) 13C-NMR (125 MHz, CDCl3) δ 148.0, 141.2, 140.8, 139.2, 128.5, 127.7, 127.3, 113.6, 66.9, 48.8, 40.4, 36.3, 35.4, 34.4, 30.6, 22.5, 20.5, 14.7 IR (film, cm⁻¹) 3403, 3058, 2953, 2928, 1599, 1492, 1454, 1375, 1064, 987, 780, 727 HRMS (EI) m/e calcd. for C20H26O 282.19837 found 282.19842 (M⁺).

Following the general procedure, compound 1c (40 mg, 0.13 mmol), triphenylphosphine (14 mg, 0.053 mmol), Ni(COD)2 (7.5 mg, 0.027 mmol), dimethylzinc (0.2 mL, 0.40 mmol 2.0 M solution in toluene), and p-toluene sulfonic acid (TsOH) (0.39 mmol, 67 mg) were employed to produce, after column chromatography hexane: (7:1 hexane: ethyl acetate) 29 mg (70% yield of two partially separable isomers 2.5:1 d.r) of a light yellow thick gum. Recrystallization from pentane produced light yellow crystals of which an x-ray structure was obtained. Major isomer 1H-NMR (500 MHz, CDCl3) δ 7.26-7.33 (m, 5H), 7.35-7.37 (m, 2H), 7.29-7.32 (m, 2H), 7.24-7.27 (m, 1H), 7.16-7.19 (m, 2H), 7.09-7.12 (m, 1H), 5.31 (d, J = 1.5 Hz, 1H), 4.93 (d, J = 1.0 Hz, 1H), 4.40 (m, 1H), 2.98 (t, J = 2.8 Hz, 1H), 2.47-2.50 (m, 1H), 2.12 (ddd, J = 14.0, 11.0, 2.5 Hz, 1H), 1.95-2.03 (m, 1H), 1.76-1.82 (m, 1H), 1.34-1.44 (m, 2H), 1.13 (d, J = 7.5 Hz, 3H), 0.87 (ddd, J = 12.5, 5.5, 2.0 Hz, 1H) diagnostic chemical shifts for minor isomer δ 13C-NMR (125 MHz, CDCl3) δ 148.0, 141.5, 140.7, 140.4, 128.5, 128.1, 128.0, 127.9, 127.5, 126.5, 115.3, 66.7, 51.3, 40.3, 37.3, 33.7, 30.7, 20.4 IR (film, cm⁻¹) 3388, 3054, 3025, 2859, 1598, 1491, 1443, 1056, 899, 772, 698 727 HRMS (EI) m/e calcd. for C20H26O 316.18272 found 316.18246 (M⁺).

6-Methoxymethyl-7-methyl-5-(1-phenyl-vinyl)-bicyclo[2.2.2]oct-5-en-2-ol (5d).
Following the general procedure, compound 1d (49 mg, 0.183 mmol), triphenylphosphine (19 mg, 0.053 mmol), Ni(COD)2 (10 mg, 0.0366 mmol), dimethylzinc (0.275 mL, 0.55 mmol 2.0 M solution in toluene), and p-toluene sulfonic acid (TsOH) (0.55 mmol, 94 mg) were employed to produce, after column chromatography (5:1 hexane: ethyl acetate) 33 mg of a light yellow oil (64% yield of two partially separable diastereomers 4:1 d.r). Major isomer : 1H-NMR (500 MHz, CDCl3) δ 7.26-7.33 (m, 5H), 5.41 (d, J = 1.0 Hz, 1H), 5.03 (d, J = 1.0 Hz, 1H), 4.22 (m, 1H), 4.18 (d, J = 9.5 Hz, 1H), 3.73 (d, J = 9.5 Hz, 1H), 3.34 (s, 3H), 2.71-2.72 (m, 1H), 2.35 (m, 1H), 1.92 (ddd, J = 13.0, 8.0, Hz, 2.0 Hz, 1H), 1.78-1.83 (m, 1H), 1.59-1.65
(m, 1H), 1.38 (dd, J = 13.5, 2.5 Hz, 2H), 1.09 (d, J = 7.0 Hz, 3H), 0.8 (ddd, 12.0, 5.0, 1.5 Hz, 1H), $^{13}$C-NMR (125 MHz, CDCl$_3$) δ 146.7, 145.0, 140.4, 136.6, 128.6, 128.0, 127.5, 114.7, 70.20, 65.5, 58.9, 47.9, 40.6, 36.2, 33.6, 30.2, 20.5 IR (film, cm$^{-1}$) 3424, 2927, 2862, 2819, 1574, 149, 1446, 1377, 1306, 1184, 1132, 1076, 1026, 986, 954, 906, 781, 702 HRMS (EL) m/e calcd. for C$_{19}$H$_{24}$O 284.17763, found 284.17754 (M$^+$.)


Following the general procedure, compound 1e (32 mg, 0.12 mmol), triphenylphosphine (12.6 mg, 0.048 mmol), Ni(COD)$_2$ (6.6 mg, 0.024 mmol), dimethylzinc (0.18 mL, 0.36 mmol 2.0 M solution in toluene), and p-toluene sulfonic acid (TsOH) (0.35 mmol, 62 mg) were employed to produce, after column chromatography (10:1 hexane: ethyl acetate) 24 mg of a light yellow oil (56% combined yield of partially separable diastereomers 6:1 d.r). Major isomer $^1$H-NMR (500 MHz, CDCl$_3$) δ 7.27-7.38 (m, 5H), 5.37 (d, J = 2.0 Hz, 1H), 5.02 (d, J = 2.0 Hz, 1H), 3.96 (dt, J = 8.5 Hz, 3.0 Hz, 1H), 2.64-2.66 (m, 1H), 2.21-2.28 (m, 1H), 2.00-2.06 (m, 1H), 1.71 (ddd, J = 15.0, 13.0, 10.8 Hz, 1H), 1.59-1.63 (m, 1H), 1.37-1.49 (m, 4H), 1.23-1.33 (m, 1H), 0.87 (t, J = 7.3 Hz, 3H), 0.85 (d, J = 7.0 Hz, 3H), 0.82 (dd, J = 5.5, 1.8 Hz, 1H) diagnostic chemical shifts for minor isomer δ 4.86 (t, J = 1.8 Hz, 1H), 4.79 (dd, J = 2.0, 1.0 Hz, 1H), 4.06b (m, 1H), 2.03 (ddd, J = 14.0, 9.0, 2.5 Hz, 1H) 1.75 (m, 3H), 0.92 (d, J = 7.5 Hz, 3H) $^{13}$C-NMR (125 MHz, CDCl$_3$) δ 148.1, 142.1, 141.7, 134.8, 137.2, 127.7, 127.4, 113.7, 71.6, 43.5, 41.7, 35.4, 33.1, 32.4, 30.1, 22.3, 20.2, 14.6 IR (film, cm$^{-1}$) 3388, 3080, 3054, 2951, 2924, 2867, 1605, 1573, 1492, 1444, 1373, 1321, 1153, 1118, 1069, 1054, 1027, 963, 942, 895, 776 HRMS (EL) m/e calcd. for C$_{20}$H$_{26}$O 282.19837 found 282.19824 (M$^+$.).

5-Isopropenyl-7-methyl-6-phenyl-bicyclo[2.2.2]oct-5-en-2-ol (5f).

Following the general procedure, compound 1f (47 mg, 0.20 mmol), triphenylphosphine (20.7 mg, 0.08 mmol), Ni(COD)$_2$ (10.8 mg, 0.039 mmol), dimethylzinc (0.3 mL, 0.59 mmol 2.0 M solution in toluene), and p-toluene sulfonic acid (TsOH) (0.6 mmol, 103 mg) were employed to produce, after column chromatography (7:1 hexane: ethyl acetate) 28 mg of a light yellow oil (56% combined yield of partially separable diastereomers 2.5:1 d.r). Major isomer $^1$H-NMR (500 MHz, CDCl$_3$) δ 7.27-7.38 (m, 5H), 5.37 (d, J = 2.0 Hz, 1H), 5.02 (d, J = 2.0 Hz, 1H), 3.96 (dt, J = 8.5 Hz, 3.0 Hz, 1H), 2.64-2.66 (m, 1H), 2.21-2.28 (m, 1H), 2.00-2.06 (m, 1H), 1.71 (ddd, J = 15.0, 13.0, 10.8 Hz, 1H), 1.59-1.63 (m, 1H), 1.37-1.49 (m, 4H), 1.23-1.33 (m, 1H), 1.03-1.10 (m, 1H), 0.87 (t, J = 7.3 Hz, 3H), 0.85 (d, J = 7.0 Hz, 3H), 0.82 (dd, J = 5.5, 1.8 Hz, 1H) diagnostic chemical shifts for minor isomer δ 4.86 (t, J = 1.8 Hz, 1H), 4.79 (dd, J = 2.0, 1.0 Hz, 1H), 4.06b (m, 1H), 2.03 (ddd, J = 14.0, 9.0, 2.5 Hz, 1H) 1.75 (m, 3H), 0.92 (d, J = 7.5 Hz, 3H) $^{13}$C-NMR (125 MHz, CDCl$_3$) δ 144.29, 142.1, 141.7, 137.2, 127.7, 127.4, 113.7, 71.6, 43.5, 41.7, 35.4, 33.1, 32.4, 30.1, 22.3, 20.2, 14.6 IR (film, cm$^{-1}$) 3388, 3080, 3054, 2953, 2928, 2867, 1605, 1573, 1492, 1444, 1373, 1321, 1153, 1118, 1069, 1054, 1027, 963, 942, 895, 776 HRMS (EL) m/e calcd. for C$_{20}$H$_{26}$O 282.19837 found 282.19824 (M$^+$.).
1373, 1062, 990, 940, 772, 699 HRMS (EI) m/e calcd. for C₁₉H₂₂O 254.16707, found 254.16694(M⁺).

6-tert-Butyl-7-methyl-5-(1-phenyl-vinyl)-bicyclo[2.2.2]oct-5-en-2-ol (5g).

To a THF solution of Ni(COD)₂ (6.1 mg, 0.022 mmol in 8.0 mL THF) at 0 °C, 1 mL THF solution of triphenylphosphine (11.5 mg, 0.044 mmol) was transferred via cannula followed by of dimethyl zinc solution (0.17 mL, 0.33 mmol 2.0 M solution in toluene). The resulting solution was stirred at 0 °C after which compound 1g (31 mg, 0.11 mmol in 2 mL THF) was added dropwise over 20 min via syringe pump and the reaction was heated to 50 °C for 1 h. After work up described in general procedure 3.10; the crude aldehyde was dissolved in 11 mL of THF and 10.0 eq (209 mg, 1.10 mmol) of p-toluene sulfonic acid (TsOH) was added. The reaction was stirred at 50 °C for 3 h, then work up according to general procedure 3.10 yielded, after column chromatography (8:1 hexane: ethyl acetate) 16 mg (50% yield of two inseparable isomers 2.5:1 d.r) of a light yellow oil. Major isomer ¹H-NMR (500 MHz, CDCl₃) δ 7.47-7.49 (m, 2H), 7.25-7.35 (m, 3H), 5.54 (d, J = 1.5 Hz, 1H), 4.97 (d, J = 1.5 Hz, 1H), 4.00 (dt, J = 9.0 Hz, 3.0 Hz, 1H), 2.85 (t, J = 2.3 Hz, 1H), 2.11-2.13 (m, 1H), 1.87 (dd, J = 11.5, 8.5 Hz, 1H), 1.70-1.74 (m, 1H), 1.53-1.58 (m, 1H), 1.43 (s, 1H), 1.19 (s, 9H), 0.98 (d, J = 7.0 Hz, 3H), 0.73-0.78 (m, 2H) diagnostic peaks for minor isomer δ 5.51 (d, J = 1.5 Hz, 1H), 4.93 (d, J = 1.5 Hz, 1H), 4.22-4.24 (m, 1H), 2.77 (t, J = 2.8 Hz, 1H), 1.09 (d, J = 7.0 Hz, 3H) ¹³C-NMR (125 MHz, CDCl₃) δ 150.3, 141.7, 139.6, 139.5, 128.5, 128.5, 127.8, 127.4, 127.1, 112.2, 72.4, 66.7, 46.8, 46.7, 40.2, 39.2, 38.1, 38.00, 35.3, 34.4, 31.6, 30.8 30.0, 29.9, 23.2, 20.5 IR (film, cm⁻¹) 3450, 3082, 2951, 2927, 1600, 1573, 1492, 1458, 1393, 1360, 1248, 143, 1067, 990, 894, 781, 711, 650 HRMS (EI) m/e calcd. for C₂₁H₂₈O 296.21402, found 296.21391 (M⁺).

Results and discussion

Our strategy is based on nickel-catalyzed three component coupling and cyclization reactions following initial developments from Ikeda⁵ and from our lab.⁴ Our initial report described sequential 1,4- and 1,2 additions of enones to generate cyclic allylic alcohols en route to highly functionalized benzene derivatives. This work extends the strategy by examining the nickel-catalyzed multicomponent addition of alkynes, α,β,γ,δ-unsaturated dienals, and alkynyl tin reagents (Table 1). While the average yield of the above reactions ranged from low to moderate; however, it was nonetheless interesting to be able to make such multi-functional aldehydes in a single step, since multi-step synthesis of these aldehydes may result in a lower overall yield. The aldehyde can be γ- or δ- substituted (aldehyde precursors of 1a and 1e), the alkyne can be aliphatic, aromatic, or ether tethered. The alkynyltin can be aromatic or aliphatic, and the reaction may tolerate other functionalities not explicitly present in this study.
Scheme 1: Nickel-catalyzed three-component couplings of dienals, alkynes, and alkynyl tin reagents

A plausible mechanism for the formation of aldehyde 1 is proposed in Figure 2. Coordination of the enal and the alkyne with the nickel species followed by oxidative cyclization generates the Ni(II) complex 2. Transmetallation with the alkynyl tin reagent followed by reductive elimination and then protonation of the silyl enolate with acid produces aldehyde 1.

Figure 2: A plausible mechanism of nickel-catalyzed coupling reaction

It is interesting to note that the product resulting from coupling at the δ-position of the dienal was the only regioisomer observed, and no product that would result from
coupling on the β-position could be detected.\textsuperscript{[4,5]} This may be due to the formation of η\textsuperscript{3}-allyl nickel complex 2, which is more stable than η\textsuperscript{1}-complex 3 that would result from coupling at the β-position of the aldehyde (Figure 3).\textsuperscript{[4c]}

![Figure 3: Possible nickel complex intermediate for couplings with dienals](image)

**Figure 3:** Possible nickel complex intermediate for couplings with dienals

Compound 1 features the introduction of the alkyne and the aldehyde functional groups in a cis orientation, which is essential for a second nickel-catalyzed cyclization to take place. Accordingly, treatment of aldehyde 1 with a catalytic amount of Ni(0), triphenylphosphine, and dimethylzinc produced the cyclic intermediate 4, which, upon treatment with 2.0 equiv of TsOH, produced bicyclo-[2.2.2]-octenol 5 in good yield (Scheme 2). The structures of products 5a-d and 5f were confirmed by NOE experiments. The stereochemical assignments of 5e and 5g should be considered tentative due to weak NOE's or overlapping signals that prevented an unambiguous assignment of stereochemistry.

![Scheme 2: Synthesis of bicyclo[2.2.2]octenols from nickel-catalyzed cyclizations of dien-yn-als](image)

**Scheme 2:** Synthesis of bicyclo[2.2.2]octenols from nickel-catalyzed cyclizations of dien-yn-als.

In the absence of the phosphine ligand, a 1:1 ratio of diastereomers is obtained, resulting from lower diastereoselectivity in the 1 to 4 conversion. We examined the effect of different Lewis acids on the outcome of the generation of 5, and the results are summarized in Table 1. Titanium tetrachloride and tin tetrachloride were apparently too reactive and resulted in formation of unidentified products (entries 2 and 3).
Trifluoroacetic acid, methylaluminum dichloride, and dimethylaluminum chloride were all ineffective resulting in recovery of starting material, and BF\(_3\)-OEt\(_2\) resulted in low yield (entries 4-7).

![Mechanism of nickel-catalyzed alkylative cyclizations of dien-yn-als](image)

Table 1: Effect of Lewis Acids on Bicyclo [2.2.2]octenols from Aldehyde 1e

<table>
<thead>
<tr>
<th>Aldehyde</th>
<th>LA</th>
<th>% Alcohol</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TsOH</td>
<td>70</td>
</tr>
<tr>
<td>2</td>
<td>TiCl(_4)</td>
<td>mixture of many isomers (reaction not clean)</td>
</tr>
<tr>
<td>3</td>
<td>SnCl(_4)</td>
<td>mixture of different isomers (reaction is not clean)</td>
</tr>
<tr>
<td>4</td>
<td>TFA</td>
<td>no reaction</td>
</tr>
<tr>
<td>5</td>
<td>BF(_3)-OEt(_2)</td>
<td>27%</td>
</tr>
<tr>
<td>6</td>
<td>Me(_2)AlCl</td>
<td>no reaction</td>
</tr>
<tr>
<td>7</td>
<td>MeAlCl(_2)</td>
<td>no reaction</td>
</tr>
</tbody>
</table>

A plausible mechanistic interpretation of the above reaction is summarized in Figures 4 and 5. Coordination of the nickel complex to aldehyde 1, followed by oxidative cyclization produces the Ni(II) metallacycle \(6a,7\). Transmetalation of \(6\) with dimethylzinc produces complex \(7\), which upon reductive elimination yields compound \(4\).
Formation of compound 5 can be interpreted as proceeding by a Prins-type cyclization mechanism (Figure 5). Protonation of aldehyde 4 followed by electrophilic cyclization produces the cationic bicyclic intermediate 8. Proton loss results in the formation of 5. The stereochemistry of 5a-d and 5f were confirmed by nOe analysis, and X-ray crystallographic analysis confirmed the structure of 5c (Scheme 3).

![Figure 5: Mechanism of the Prins-type cyclization reaction leading to bicyclo[2.2.2]octenols](image)

**Scheme 3: NOE values of some bicyclo[2.2.2]octenols**

It is important to mention that the hydroxyl group in compound 5 is always syn to the dienyl moiety. The two diastereomers observed in compound 5 are due to the mixture of *exo* and *endo* orientation of R1 and R2. Such observation is confirmed by the oxidation of a 1:1 mixture of diastereomers of 5a to a 1:1 mixture of ketones 9a and 9b (Scheme 4).
Scheme 4: Oxidation of compound 5a to the corresponding ketone

The likely origin of stereoselectivity in the generation compound 5 is depicted in Figure 5. Syn-clinal orientation of the carbonyl group relative to the dienyl moiety allows secondary orbital interactions that favor this orientation.

Figure 6: Interpretations of observed stereochemistry of bicyclo[2.2.2]octenols

Conclusion

Ni(0)-catalyzed three-component coupling reactions of α,β,γ,δ-unsaturated dienals with alkynes and alkynyltin reagents affords highly functionalized aldehydes. These aldehydes can be further transformed to highly functionalized bicyclo[2.2.2]-octenols by nickel-catalyzed alkylationate cyclizations followed by acid-promoted Prins-type cyclization reactions. The rapid and unusual entry to these bicyclo[2.2.2]-octenols may be useful in library design studies that take advantage of their interesting structure and shape.

References

Graphical Abstract

H\(_2\)C=\(\text{R}_1\)\(\text{R}_2\) + \(\text{R}_1\) + Bu\(_3\)Sn \(\text{R}_4\) \(\text{Ni(acac)}_2\)(0.2 eq)/ DIBAL(0.2 eq) \(\text{TMSCl} \) (3.0 eq)

H\(_2\)C=\(\text{R}_1\)\(\text{R}_2\) \(\text{R}_3\)\(\text{R}_4\)

O\(\text{R}_1\)\(\text{R}_2\)\(\text{R}_3\)\(\text{R}_4\) \(\text{Ni(COD)}_2\) \(\text{Me}_2\text{Zn, PPh}_3\) 0\(^\circ\)C, 15 min, rt

O\(\text{R}_1\)\(\text{R}_2\)\(\text{R}_3\)\(\text{R}_4\) \(\text{TsOH,} \) (3 eq) 0.5-1 h, rt

Major