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Nickel-catalyzed carbonylative Negishi cross-coupling reactions

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Abstract

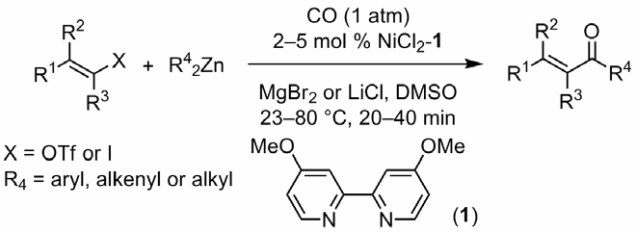
Catalytic carbonylative Negishi cross-coupling reactions are described. This method readily provides various enones from enol triflates and diorganozinc reagents with catalytic amounts of nickel(II) chloride–4,4′-dimethoxyl-2,2′-bipyridyl under carbon monoxide atmosphere. The rate of carbon monoxide insertion is increased by the addition of lithium or magnesium halides and the use of polar solvents. Alkenyl iodides can also be used in place of enol triflates.

Keywords: Carbonylative cross-coupling; Negishi reaction; Nickel catalysis; Enone

Enones are important structural motifs and versatile functional groups for conjugate addition and cycloaddition reactions. They are normally accessed by the oxidation of ketones or olefins, aldol condensation reactions, cross-metathesis reactions, Wittig-type reactions, and the acylation of organometallic reagents.[1] They can also be synthesized through catalytic carbonylative cross-coupling reactions.[2] This three-component coupling reaction can be used for complementary strategic bond disconnection in convergent total synthesis.

Compared to the recent advancement of cross-coupling reactions,[3,4] the catalytic carbonylative cross-coupling reactions are relatively underexplored. The first example of this type of transformation was reported by Heck in 1968, using arylmercuric chloride as the nucleophilic coupling component.[5] Tanaka[6] and Stille[7] subsequently developed the carbonylative coupling reactions using organotin reagents. Since then, several methods have been developed for the carbonylative Stille[8] and Suzuki[9] reactions.[10] However, the carbonylative Negishi reactions are less studied. Early development focuses on carbonylative aryl–alkyl, aryl–alkenyl, and allyl–alkyl couplings using palladium–triphenylphosphine catalyst systems.[11] While the dialkylnickel complexes are known to catalyze the carbonylative aryl–aryl couplings, this protocol gives considerable amounts of direct coupling and over-reaction side products.[12] We report herein a facile nickel-catalyzed carbonylative Negishi coupling reaction for general enone synthesis. This protocol avoids the use of toxic organotin reagents and allows the direct preparation of the nucleophilic coupling components from the main-group organometallic reagents or halides. We focus on the coupling of enol triflates and organozinc reagents generated from the Grignard reagents in this work (Scheme 1).

The development of carbonylative cross-coupling reactions has been hindered by the intervention of direct



Scheme 1. Nickel-catalyzed carbonylative Negishi coupling reaction.

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coupling reactions. This problem is not seen in the alkoxy- and amino-carbonylation reactions because the reductive elimination of alkoxo and amino metal complexes is rather slow.[13] The nickel-catalyzed carbonylative Negishi reaction described here is further challenged by the CO-deactivation of nickel catalysts and organozinc reagents. Nevertheless, we have found that the rate of reductive elimination, CO insertion, and catalyst stability can be tuned with metal ligands, additives,[14] and solvents[15] to achieve good results for this transformation.

We used the carbonylative coupling between cyclohexenyl triflate (**2**) and phenylzinc reagents (**3**) as the system for catalyst optimization. Some of the results are presented in Table 1. We first found that the palladium catalysts were less reactive than the nickel catalysts. For example, $Pd(PPh_3)_4$ gave the desired products only in the presence of CuI (entry 1). Employing a more polar solvent improved the yield; however, the conversion was still low (entry 2). In contrast, good conversions were achieved with various nickel catalysts (entries 3–5). We therefore focused our efforts on the nickel catalyst systems.

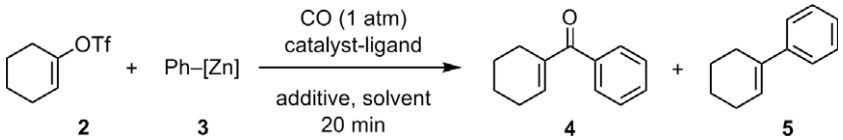
We found several important factors that influence the efficiency of this reaction. First, replacing the air-sensitive $Ni(COD)_2$ with air-stable $NiCl_2$·glyme greatly improved the reproducibility. Second, the yield of this reaction was further increased by using diorganozinc reagents. Third, the reaction rate was substantially enhanced when conducted in polar solvents. The highest reaction rate was observed in DMSO. Fourth, the addition of lithium or magnesium halides improved the ratio of **4**:**5** and reaction rate. For example, the reaction between **2** and Ph_2Zn generated in situ from PhMgBr and $ZnBr_2$ (1.8:1) in the presence of 2 mol % of $NiCl_2$·glyme gave **4** and **5** in a 3:1 ratio with 100% conversion (entry 5).

We next examined the effects of ligand on this reaction. We have found that dialkylamine ligands and N-heterocyclic carbene ligands completely deactivated the nickel catalysts. While tri-*tert*-butylphosphine provided good results in the initial testing (entry 6), it gave irreproducible results when reactions were performed on a larger scale. Attempts to increase the catalyst stability by employing diphosphine ligands or P,N-ligands also resulted in catalyst deactivation (entries 7 and 8).

Eventually, we found that 2,2′-bipyridyl (**7**) increased the catalyst lifetime considerably while it still maintained good catalyst activity and carbonylation rate (entry 9). Further stabilization of the catalyst with tripyridyl (**8**) ligand led to the catalyst deactivation (entry 10). We have also found that the introduction of electron-withdrawing or electron-donating groups to the bipyridyl ligands decreased the rate of the reaction (entries 11 and 12). However, the ratio of **4**:**5** was significantly improved. The best results were obtained when the reaction was conducted with 2 mol % of $NiCl_2$–**1** at 50 °C in DMSO. The desired product **4** was isolated in 89% yield (entry 12).

To confirm that diphenylzinc was the active nucleophilic coupling component, we independently prepared the salt-free diphenylzinc[16] and allowed it to react with **2** in the

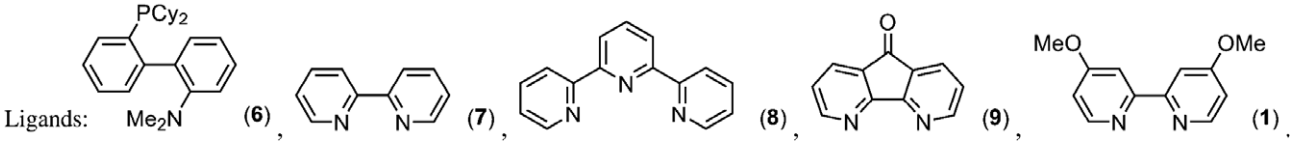
Table 1
Optimization of the reaction conditions



2 **3** **4** **5**

Entry	Catalyst–ligand (loading)	Ph–[Zn][a]	Additive	Solvent	Temp (°C)	Ratio[b] (**4**:**5**)	Conversion (isolated yield) (%)
1	$Pd(PPh_3)_4$ (5 mol %)	PhZnI	CuI (16 mol %)	THF	23	6:1	15
2	$Pd(PPh_3)_4$ (5 mol %)	PhZnI	CuI (16 mol %)	THF–DMSO (1:1)	23	1:2	27
3	$Ni(COD)_2$ (5 mol %)	PhZnI	—	THF–DMSO (1:1)	23	3:1	75
4	$NiCl_2$ (5 mol %)	PhZnBr	$MgBr_2$ (1.0 equiv)	THF–DMSO (1:1)	23	7:1	70
5	$NiCl_2$ (2 mol %)	Ph_2Zn	$MgBr_2$ (1.8 equiv)	DMSO	23	3:1	100
6	$NiCl_2$–P^tBu_3 (2 mol %)	Ph_2Zn	$MgBr_2$ (1.8 equiv)	DMSO	23	4:1	72
7	$NiCl_2$–DPPE (2 mol %)	Ph_2Zn	$MgBr_2$ (1.8 equiv)	DMSO	23	—	0
8	$NiCl_2$–**6** (2 mol %)	Ph_2Zn	$MgBr_2$ (1.8 equiv)	DMSO	23	—	0
9	$NiCl_2$–**7** (2 mol %)	Ph_2Zn	$MgBr_2$ (1.8 equiv)	DMSO	23	5:1	81
10	$NiCl_2$–**8** (2 mol %)	Ph_2Zn	$MgBr_2$ (1.8 equiv)	DMSO	23	—	0
11	$NiCl_2$–**9** (2 mol %)	Ph_2Zn	$MgBr_2$ (1.8 equiv)	DMSO	50	11:1	66
12	$NiCl_2$–**1** (2 mol %)	Ph_2Zn	$MgBr_2$ (1.8 equiv)	DMSO	50	11:1	100 (89)

[a] 1.3 equiv Ph–[Zn] was used. $PhZnBr/MgBr_2$ was generated in situ from mixing PhMgBr and $ZnBr_2$ (1:1). $Ph_2Zn/MgBr_2$ was generated in situ from mixing PhMgBr and $ZnBr_2$ (1:0.55).
[b] Determined by GC (uncalibrated).



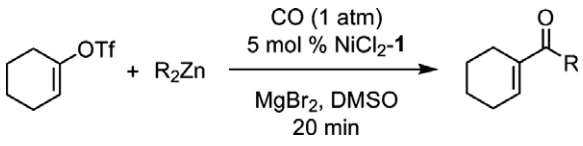
presence of 2 mol % of $NiCl_2$–**1** and 1.8 equiv of $MgBr_2$. Identical results were obtained as the in situ method. The desired product **4** was isolated in 87% yield and the ratio of **4**:**5** was found to be 12:1.

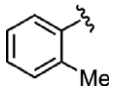
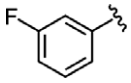
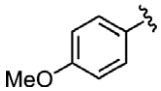
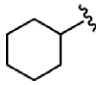
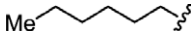
After obtaining the optimal reaction conditions,[17] we explored the scope of this nickel-catalyzed carbonylative Negishi coupling reaction of **2** with various diorganozinc reagents (Table 2). Substitution at the 2-position of the diarylzinc reagent resulted in lower reaction rate. A slight elevation of the reaction temperature was required to ensure good conversion (entry 1). Electron-deficient diarylzinc reagents reacted equally well as diphenylzinc (entry 2), and electron-rich diarylzinc reagents provided an excellent ratio of carbonylative to direct coupling product (entry 3).

We have also demonstrated that dialkenylzinc and dialkylzinc can be used as the nucleophilic coupling component. The carbonylative coupling of **2** with di(*iso*-propenyl)zinc provided the corresponding dienone in good yield (entry 4). Dienones are valuable substrates for the Nazarov reaction.[18] The carbonylative alkenyl–alkyl coupling also required slightly higher reaction temperature. Both primary and secondary dialkylzinc reagents reacted well with **2** (entries 5 and 6). Notably, no direct coupling product was observed when reacting **2** with dicyclohexylzinc (entry 5). It should also be noted that the nature of the additive ($MgBr_2$, $MgCl_2$, or LiCl) does not significantly affect the reaction. The diorganozinc can be generated in situ from $RMgBr/ZnBr_2$ (entries 1–4), $RMgCl/ZnCl_2$ (entry 5), or $RLi/ZnCl_2$ (entry 6).

We have also explored the scope of the enol triflate (Table 3). Cyclopentenyl triflate coupled with diarylzincs equally well (entries 1 and 2). Increasing the steric hindrance of the enol triflate did not significantly affect the reaction. The carbonylative coupling of 5-methylcyclopentenyl triflate with diarylzinc or dialkylzinc reagents gave comparable results (entries 3 and 4). As expected, the reaction of 2,6-dimethylcyclohexenyl triflate with di(2-tolyl)zinc was slower. It required the addition of more diarylzinc reagent to complete the reaction (entry 5).

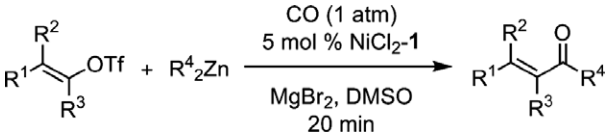
Table 2
Exploration of the scope of the nucleophilic coupling component[a]

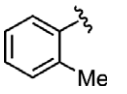
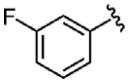
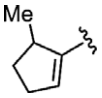
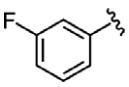
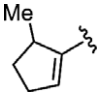
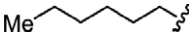
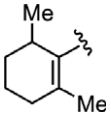
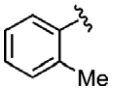
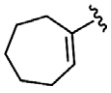
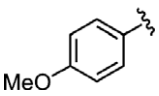
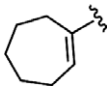


Entry	R	Temp (°C)	Ratio[b]	Yield (%)
1		80	15:1	92
2		50	12:1	89
3		50	>100:1	85
4[c]		50	5:1	79
5[d]		80	—[e]	91
6[f]		80	18:1	78

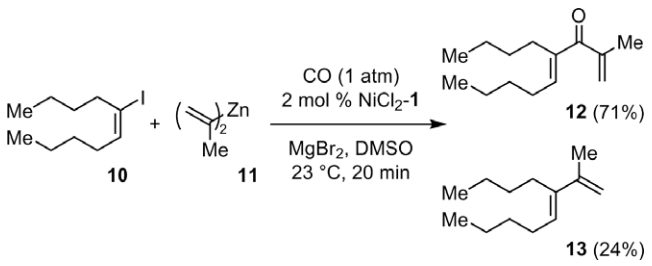
[a] Reaction conditions: 1 mmol enol triflate, 1.3 mmol diorganozinc reagent generated from RMgBr and $ZnBr_2$.
[b] Ratios of the carbonylative to direct coupling products determined by GC (uncalibrated).
[c] Reaction time: 32 min.
[d] CyMgCl and $ZnCl_2$ were used.
[e] Direct coupling product not detected by GC.
[f] *n*-Hex–Li and $ZnCl_2$ were used.

Table 3
Exploration of the scope of the vinyl triflate[a]



Entry	Triflate	R^4	Temp (°C)	Ratio[b]	Yield (°C)
1			80	21:1	95
2			50	12:1	86
3			50	16:1	87
4[c]			80	15:1	72
5[d]			80	22:1	88
6[e]			50	>100:1	92%
7			50	8:1	85%

[a] Reaction conditions: 1 mmol enol triflate, 1.3 mmol diorganozinc reagent generated from RMgBr and $ZnBr_2$.
[b] Ratios of the carbonylative to direct coupling products determined by GC (uncalibrated).
[c] Reaction time: 12 min.
[d] With 2.6 mmol diorganozinc; reaction time: 40 min.
[e] With 2 mol % catalyst; reaction time: 32 min.



Scheme 2. Nickel-catalyzed carbonylative Negishi coupling reaction of alkenyl iodide.

Finally, cycloheptenyl triflate was also shown to be a good substrate for this reaction (entries 6 and 7).

As acyclic enol triflates cannot be obtained easily from the corresponding ketones with a well-defined olefin geometry, we turned our attention to acyclic alkenyl iodides. Alkenyl iodides are readily available from hydrozirconation–halogenation of the alkynes with excellent regioselectivity and stereoselectivity.[19] We have found that alkenyl iodides showed higher reactivity than enol triflates. For example, the carbonylative coupling of **10** with dialkenylzinc in the presence of 2 mol % $NiCl_2$–**1** at room temperature gave the desired dienone **12** in 71% yield (Scheme 2). However, the ratio of carbonylative to direct coupling product was diminished (3:1).

In summary, we have developed an efficient nickel catalyst system for the carbonylative Negishi coupling reactions. The reaction of enol triflates or alkenyl iodides with diorganozinc reagents under 1 atm CO atmosphere in the presence of $NiCl_2$–**1** catalyst and lithium or magnesium halides gave enones in good yield. Carbonylative alkenyl–aryl, alkenyl–alkenyl, and alkenyl–alkyl coupling can all be achieved.

Acknowledgments

We thank the UT Southwestern and Welch foundation for financial supports. C.C. is Southwestern Medical Foundation Scholar in Biomedical Research.

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17. *General procedure:* A round-bottom flask equipped with magnetic stirbar was charged with $ZnBr_2$ (1.48 g, 6.6 mmol) or $ZnCl_2$ (0.90 g, 6.6 mmol) and flame-dried under vacuum. Anhydrous THF (12 mL) was then introduced followed by a THF or Et_2O solution of the Grignard or organolithium reagent (12 mmol) at room temperature. After stirring overnight, the solvents were removed under vacuum (0.1 mmHg) or by distillation under ambient pressure at 100 °C. The diorganozinc reagents and $MgBr_2$ generated in situ were then dissolved in DMSO (40 mL), leaving 25% of $MgBr_2$ undissolved.
In a separate flask, carbon monoxide was bubbled through a solution of enol triflate (1.0 mmol) in degassed DMSO (1 mL) for 2 min before a solution of diorganozinc reagent (0.165 M in DMSO, 1.3 mmol, 8 mL) was added via syringe pump (25 mL/h) at 50 °C with continuous carbon monoxide bubbling (54 mL/min). The amount of dissolved $MgBr_2$ was calculated to be 1.8 equiv ($1.3 \times 12/6.6 \times 0.75 = 1.8$). After 30 sec, a solution of $NiCl_2$–**1** (0.2 M in THF, 0.02 mmol, 0.1 mL) was introduced. The reaction mixture turned deep red, which faded to pale yellow upon the completion of the reaction. *CAUTION: The catalyst deactivation leads to the generation of Ni(CO)$_4$, which is toxic and volatile. It may be released from the reaction vessel through carbon monoxide bubbling. This reaction should be performed in a well-ventilated fume hood.* After cooling to room temperature, the solution was passed through a short pad of silica gel to remove DMSO and inorganic salts. The silica gel was washed with 10% Et_2O–pentane solution. The filtrate was concentrated and purified by flash column chromatography.
5-Methylcyclopent-1-enyltrifluoromethanesulfonate: $R_f = 0.35$ (pentane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.61 (m, 1H), 2.90 (m, 1H), 2.36 (m, 2H), 2.24 (m, 1H), 1.56 (m, 1H), 1.14 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.2, 118.9 (q, $J = 318.6$ Hz), 116.1, 37.7, 29.9, 26.4, 18.0; MS(EI) 230 $[M]^+$.
(5E)-5-Iodo-dec-5-ene $R_f = 0.67$ (pentane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.17 (t, $J = 7.6$ Hz, 1H), 2.35 (t, $J = 7.3$ Hz, 2H), 2.04 (m, 2H), 1.43 (m, 2H), 1.35 (m, 6H), 0.91 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.4, 103.5, 38.2, 31.4, 31.3, 30.6, 22.2, 21.5, 14.0, 13.9; MS(EI) 266 $[M]^+$.
Table 1, entry 11: $R_f = 0.39$ (10% Et_2O–pentane); FTIR (neat, cm^{-1}) 2933, 1644, 1276, 1255, 702; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (m, 2H), 7.51 (m, 1H), 7.42 (m, 2H), 6.58 (m, 1H), 2.44 (m, 2H), 2.29 (m, 2H), 1.77 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.3, 144.1, 138.7, 131.2, 129.1, 128.0, 26.1, 23.9, 22.0, 21.6; MS(EI) 186 $[M]^+$.
Table 2, entry 1: $R_f = 0.39$ (10% Et_2O–pentane); FTIR (neat, cm^{-1}) 2928, 1649, 1252, 730; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (m, 2H), 7.20 (m, 1H), 6.49 (m, 1H), 2.40 (m, 1H), 2.44 (m, 2H), 2.26 (s, 3H), 2.24 (m, 2H), 1.75 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.3, 146.4, 140.0, 139.7, 135.5, 130.5, 129.1, 127.4, 124.9, 26.3, 22.9, 21.9, 21.6, 19.5; MS(EI) 200 $[M]^+$.
Table 2, entry 2: $R_f = 0.39$ (10% Et_2O–pentane); FTIR (neat, cm^{-1}) 2935, 1649, 1584, 1436, 1260, 792, 745; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (m, 2H), 7.32 (m, 1H), 7.18 (m, 1H), 6.61 (m, 1H), 2.40 (m, 2H), 2.29 (m, 2H), 1.76–1.64 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.6, 162.3 (d, $J = 247.5$ Hz), 144.8, 140.8 (d, $J = 6.3$ Hz), 138.5, 129.7 (d, $J = 7.8$ Hz), 124.8 (d, $J = 3.0$ Hz), 118.1 (d, $J = 21.3$ Hz), 116.0 (d, $J = 22.4$ Hz), 26.2, 23.8, 21.9, 21.5; MS(EI) 204 $[M]^+$.
Table 2, entry 3: $R_f = 0.07$ (10% Et_2O–pentane); FTIR (neat, cm^{-1}) 2933, 1638, 1600, 1251, 1170, 839, 756; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, $J = 8.5$ Hz, 2H), 6.92 (d, $J = 8.5$ Hz, 2H), 6.49 (m, 1H), 3.86 (s, 3H), 2.40 (m, 2H), 2.26 (m, 2H), 1.76–1.66 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.2, 162.4, 141.6, 138.6, 131.6, 131.0, 113.3, 55.4, 25.9, 24.3, 22.1, 21.7; MS(EI) 216 $[M]^+$.
Table 2, entry 4: $R_f = 0.27$ (10% Et_2O–pentane); FTIR (neat, cm^{-1}) 2931, 1641, 1168, 926, 779; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.68 (m, 1H), 5.56 (m, 1H), 5.41 (m, 1H), 2.27–2.43 (m, 4H), 1.93 (s, 3H), 1.70–1.58 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.0, 143.7, 141.8, 138.1, 122.3, 25.9, 23.7, 22.0, 21.6, 19.2; MS(EI) 150 $[M]^+$.
Table 2, entry 5: $R_f = 0.43$ (10% Et_2O–pentane); FTIR (neat, cm^{-1}) 2930, 2855, 1663, 1449, 1196; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.89 (m, 1H), 2.97 (dddd, $J = 11.4$, 11.4, 3.2, 3.2 Hz, 1H), 2.25–2.21 (m, 4H), 1.80–1.58 (m, 9H), 1.43–1.17 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.1, 138.9, 138.1, 44.1, 29.8 (2C), 26.1, 25.9 (2C), 25.7, 23.3, 22.0, 21.6; MS(EI) 192 $[M]^+$.
Table 2, entry 6: $R_f = 0.30$ (10% Et_2O–pentane); FTIR (neat, cm^{-1}) 2930, 1667, 1229; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.89 (m, 1H), 2.61 (t, $J = 7.4$ Hz, 2H), 2.24 (m, 4H), 1.62–1.55 (m, 6H), 1.29 (m, 6H), 0.89 (t, $J = 6.0$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.2, 139.5, 139.2, 37.0, 31.7, 29.1, 26.0, 24.9, 23.1, 22.5, 22.0, 21.6, 14.1; MS(EI) 194 $[M]^+$.
Table 3, entry 1: $R_f = 0.39$ (10% Et_2O–pentane); FTIR (neat, cm^{-1}) 2955, 1643, 1608, 1355, 734; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.17 (m, 4H), 6.37 (m, 1H), 2.72 (m, 2H), 2.57 (m, 2H), 2.32 (s, 3H), 2.02 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.7, 149.1, 146.3, 139.8, 135.7, 130.8, 129.6, 127.6, 124.9, 34.2, 30.6, 23.0, 19.6; MS(EI) 186 $[M]^+$.
Table 3, entry 2: $R_f = 0.26$ (10% Et_2O–pentane); FTIR (neat, cm^{-1}) 2956, 1644, 1585, 1439, 1355, 1270, 779, 736; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (m, 1H), 7.43–7.38 (m, 2H), 7.21 (dt, $J = 8.3$, 7.9, 2.2 Hz, 1H), 6.57 (m, 1H), 2.74 (m, 2H), 2.63 (m, 2H), 2.01 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.6, 162.4 (d, $J = 246$ Hz), 147.6, 144.3, 141.0 (d, $J = 6.5$ Hz), 129.8 (d, $J = 7.8$ Hz), 124.5 (d, $J = 3.0$ Hz), 118.7 (d, $J = 21.3$ Hz), 115.6 (d, $J = 22.5$ Hz), 34.4, 31.7, 22.7; MS(EI) 190 $[M]^+$.
Table 3, entry 3: $R_f = 0.34$ (10% Et_2O–pentane); FTIR (neat, cm^{-1}) 2956, 1646, 1585, 1439, 1349, 1269, 748; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (m, 1H), 7.44–7.37 (m, 2H), 7.22 (dt, $J = 8.2$, 8.2, 2.5 Hz, 1H), 6.46 (m, 1H), 3.26 (m, 1H), 2.65 (m, 1H), 2.47 (m, 1H), 2.24 (m, 1H), 1.59 (m, 1H), 1.17 (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.8, 162.4 (d, $J = 247.5$ Hz), 148.5, 146.5, 141.2 (d, $J = 6.2$ Hz), 129.8 (d, $J = 7.8$ Hz), 124.6 (d, $J = 3.0$ Hz), 118.7 (d, $J = 21.4$ Hz), 115.7 (d, $J = 22.4$ Hz), 39.5, 32.5, 31.9, 19.4. MS(EI) 204 $[M]^+$.
Table 3, entry 4: $R_f = 0.35$ (10% Et_2O–pentane); FTIR (neat, cm^{-1}) 2954, 2930, 2865, 1666, 1376; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.66 (m, 1H), 3.04 (m, 1H), 2.62 (t, $J = 7.5$ Hz, 2H), 2.42 (m, 1H), 2.47 (m, 1H), 2.17 (m, 1H), 1.61–1.49 (m, 3H), 1.29 (m, 5H), 1.07 (d, $J = 6.9$ Hz, 3H), 0.88 (t, $J = 6.3$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.5, 150.0, 142.5, 39.3, 38.2, 32.0, 31.8, 31.6, 29.0, 24.8, 22.5, 19.7, 14.0; MS(EI) 194 $[M]^+$.
Table 3, entry 5: $R_f = 0.29$ (10% Et_2O–pentane); FTIR (neat, cm^{-1}) 2928, 2867, 1649, 1453, 1243, 911, 740; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (dd, $J = 7.7$, 1.1 Hz, 1H), 7.35 (dt, $J = 7.5$, 7.5, 1.4 Hz, 1H), 7.23 (m, 2H), 2.66 (m, 2H), 2.55 (s, 3H), 2.07 (m, 2H), 1.74 (m, 2H), 1.65 (m, 1H), 1.55 (s, 3H), 1.46 (m, 1H), 0.94 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.2, 138.9, 138.5, 138.4, 137.6, 131.8, 131.1, 130.4, 125.6, 32.3, 30.8, 30.4, 21.3, 20.9, 19.9, 19.4; MS(EI) 228 $[M]^+$.
Table 3, entry 6: $R_f = 0.11$ (10% Et_2O–pentane); FTIR (neat, cm^{-1}) 2920, 2849, 1638, 1600, 1251, 1170, 754; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (m, 2H), 6.91 (m, 2H), 6.59 (t, $J = 6.8$ Hz, 1H), 3.85 (s, 3H), 2.59 (m, 2H), 2.33 (m, 2H), 1.83 (m, 2H), 1.59 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.8, 162.4, 145.7, 145.2, 131.8, 130.9, 113.2, 55.4, 32.3, 29.2, 28.5, 26.6, 26.1; MS(EI) 230 $[M]^+$.
Table 3, entry 7: $R_f = 0.43$ (10% Et_2O–pentane); FTIR (neat, cm^{-1}) 2922, 2851, 1642, 1448, 1129; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.77 (t, $J = 6.8$ Hz, 1H), 5.56 (m, 1H), 5.42 (m, 1H), 2.46 (m, 2H), 2.32 (m, 2H), 1.93 (s, 3H), 1.78 (m, 2H), 1.57–1.49 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.4, 146.0, 144.7, 143.9, 122.8, 32.3, 29.1, 27.5, 26.4, 26.0, 19.2; MS(EI) 164 $[M]^+$.
(Z)-4-Butyl-2-methylnona-1,4-dien-3-one (**12**): $R_f = 0.47$ (10% Et_2O–pentane); FTIR (neat, cm^{-1}) 2957, 2927, 1643, 1100; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.27 (t, $J = 7.4$ Hz, 1H), 5.59 (m, 1H), 5.44 (m, 1H), 2.35 (m, 2H), 2.24 (m, 2H), 1.96 (s, 3H), 1.55–1.29 (m, 8H), 0.94–0.88 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.8, 144.5, 143.7, 140.6,

123.2, 31.2, 31.1, 28.3, 26.3, 22.8, 22.5, 19.1, 14.0, 13.9; MS(EI) 208 $[M]^+$.

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19. For reviews, see: Reviews: (a) Schwartz, J.; Labinger, J. A. *Angew. Chem., Int. Ed. Engl.* **1976**, *88*, 402–409; (b) Negishi, E.; Takahashi, T. *Synthesis* **1988**, 1–19; (c) Wipf, P.; Jahn, H. *Tetrahedron* **1996**, *52*, 12853–12910; (d) Wipf, P.; Kendall, C. *Top. Organomet. Chem.* **2005**, *8*, 1–25. For directed-hydrozirconation, see: (e) Zhang, D.; Ready, J. M. *J. Am. Chem. Soc.* **2007**, *129*, 12088–12089.