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General and Highly α-Regioselective Zinc-Mediated Prenylation of Aldehydes and Ketones

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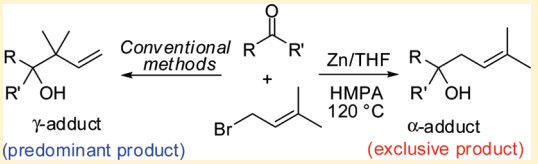
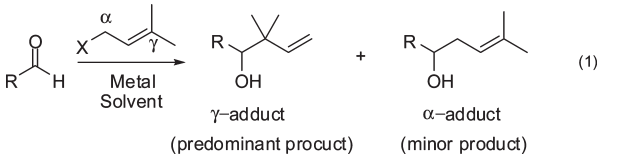
Supporting Information

ABSTRACT: A simple, efficient, and general α-prenylation approach for the synthesis of a variety of α-prenylated alcohols has been successfully developed. A wide range of α-prenylated alcohol derivatives could be obtained in good yields by highly α-regioselective zinc-mediated prenylation of various aldehydes and ketones with prenyl bromide at 120 °C in HMPA. By simply altering the reaciton solvent and temperature, the method allows the achievement of a highly notable opposite regiocontrol, providing the expected regiochemical product. The method provides a convenient route for the direct α-prenylation of carbonyl compounds in a highly α-regioselective manner using a cheap and convenient mediator. Two possible pathways are proposed to account for the formation of these synthetically difficult-to-obtain molecules.



The α-prenylated alcohol structural unit is found in a large number of interesting natural products such as shikonin, inotodiol, and terpenpoids.[1] The structure is also important organic building block and versatile synthon.[2] Moreover, many natural compounds containing this fragment have been isolated continually from natural sources in recent years.[3] The synthesis of this important structure, therefore, has been the focus of synthetic organic chemists.[4] In principle, the metal-mediated nucleophilic prenyl addition to aldehydes is the most reliable method to construct α-prenylated alcohols, but there is considerable difficulty in controlling the α-regioselectivity of the addition. The reason is that the metal-mediated prenylation of carbonyl compounds with prenyl halides occurs regioselectively at the γ-position (eq 1).[5] Although considerable efforts have been made to explore the simple and direct α-regioselectivity addition of carbonyl compounds, less progress with this approach has been achieved because of severe difficulty in regioselectivity control. Only a limited number of examples of α-selective carbonyl prenylation have been reported, and they usually require relatively expensive samarium or reactive barium and generally give mixtures containing an amount of undesired γ-addition product.[6] In practice, α-prenylated alcohols are often reached by alternative methods that are flawed by low synthetic efficiency such as harsh reaction conditions, multiple-step synthesis, or use of not readily available substances.[4]



Although the addition of a prenylmetal reagent to a carbonyl compound represents a very straightforward route to α-prenylated alcohol derivatives, only one highly α-regioselective prenylation example has been reported by Cuerva and Oltra using titanocene(III) complexes as the catalyst so far in the literature.[7] The substrate generality of this reaction, however, remained limited. In particular, the reaction with nonconjugated aldehydes and ketones resulted only in the formation of γ-adducts because of the weak coordination between the carbonyl and Ti^{III}. Furthermore, this method suffered from the preparation of the titanocene(III) complexes, bis(cyclopentadienyl)titanium(III) chloride. These disadvantages prevented a general application of this approach. Thus, our continued interest in the synthesis of drug-like molecules, derived from a prenyl fragment containing the natural products, spurred us to investigate an alternative and practical method to directly access the α-prenylated alcohols by addition of prenyl metal to aldehyde. We recently reported a highly α-regioselective zinc-mediated addition of prenyl bromide to 1,4,5,8-tetramethoxynaphthalene-2-carbaldedehyde.[8] The reaction offered a concise, high-yielding, and highly α-regioselective route from aldehyde to shikonin compared with the reported syntheses of shikonin.[4a,b9] We therefore considered whether we might be able to exploit similar reaction to directly access α-prenylated alcohols by addition of the prenylzinc to different aldehydes and ketones. We report herein the successful attainment of this goal. This methodology enables the efficient synthesis of α-prenylated alcohol via a highly α-regioselective prenylmetal-aldehyde addition using convenient and inexpensive zinc as the mediator with broad substrate scope. Although zinc has been often used for the addition of allyl metal reagents to carbonyl compounds,[5a,10] zinc as a mediator employed in prenylmetal-aldehyde α-regioselectivity addition has not been well demonstrated so far. As a related reaction, Loh's group reported

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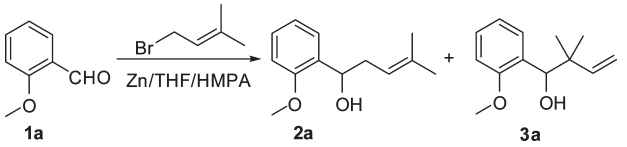
Table 1. Optimization of Reaction Conditions



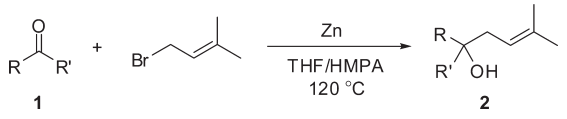
entry	solvent	T (°C)	t	**2a** (%)	**3a** (%)
1	Et_2O	reflux	3 d	ND	92
2	THF	reflux	3 d	trace	94
3	THF/HMPA	reflux	3 d	13	72
4	HMPA	100	8 h	60	10
5	HMPA	120	8 h	87	trace
6	HMPA	130	12 h	91	ND
7	DMF	130	12 h	31	ND
8	DMSO	130	12 h	20	ND

the first example of the indium-, tin-, and zinc-mediated addition reaction of crotyl bromide with aldehydes to give α-adduct. However, they found that when the same conditions were extended to the α-prenylation of aldehydes, it did not work.[4f]

RESULTS AND DISCUSSION

Our work started with the determination of optimal reaction conditions using the addition of prenylzinc bromide with 2-methoxybenzaldehyde **1a** as model reaction. In an initial study, when prenylzinc bromide reacted with aldehyde **1a** in diethyl ether (Et_2O), only γ-addition took place leading to γ-adduct **3a** in an isolated yield of 92% (Table 1, entry 1). Interesting, a trace amount of α-adduct was detected by GC−MS and ^{1}H NMR when the reaction was performed in more basic tetrahydrofuran (THF) (entry 2). Moreover, we observed the same reaction for which addition of HMPA to the THF solution increased the amount of α-adduct. In THF−HMPA both γ- and α-adducts were obtained in 72% and 13% isolated yields, respectively (entry 3). The experiments described in entries 1−3 in Table 1 showed that the solvent played an important role in product distribution. Based on this observation, could the regioselectivity be controlled by the use of different solvent? There are many precedents in which the regioselectivity depends on the reaction solvent used (Et_2O or THF vs HMPA), particularly the work of Reich and co-workers about the impact of HMPA on the organolithium chemistry (CIP vs SSIP interactions).[11] To examine this hypothesis, we turned our attention on the use of HMPA as a solvent. As expected, a dramatic increase in the yield of α-adduct was observed by evaporation of the initial reaction solvent (THF), addition of HMPA, and heating the reaction to 100 °C. As shown in entry 4, the α-regioselecivity was significantly shifted toward the formation of α-adduct **2a** in HMPA, producing **3a** in only a 10% yield. These results indicated that the use of polar aprotic solvent HMPA in the addition promoted isomerization of the γ-adduct to the corresponding α-adduct. When the reaction was carried out in Et_2O or THF, the process of isomerization was more difficult than in HMPA. This difference can probably be attributed to the greater basicity of HMPA.[12] Because HMPA is a stronger Lewis base than Et_2O and THF, it could be expected to complex more strongly with the zinc atom of initially formed γ-prenylated zinc alcoholate, thereby causing the zinc−oxygen bond to be more ionic in HMPA.

Table 2. α-Prenylation of Various Aldehydes and Ketones



entry	substrate	product	yield (%)
1	2-FC_6H_4CHO **1b**	**2b**	92
2	3-FC_6H_4CHO **1c**	**2c**	85
3	4-FC_6H_4CHO **1d**	**2d**	80
4	4-BrC_6H_4CHO **1e**	**2e**	79
5	2,6-$Cl_2C_6H_3CHO$ **1f**	**2f**	88
6	3,4-$(OCH_2O)C_6H_3CHO$ **1g**	**2g**	84
7	2-furaldehyde **1h**	**2h**	79
8	2-thenaldehyde **1i**	**2i**	83
9	isonicotinaldehyde **1j**	**2j**	80
10	cinnamaldehyde **1k**	**2k**	81
11	*c*-$C_6H_{11}CHO$ **1l**	**2l**	84
12	cyclohexanone **1m**	**2m**	75
13	$C_6H_5COCH_3$ **1n**	**2n**	87
14	4-$ClC_6H_4COCH_3$ **1o**	**2o**	91
15	4-$OCH_3C_6H_4COCH_3$ **1p**	**2p**	86
16	2-$ClC_6H_4COCH_3$ **1q**	**2q**	88
17	4-$OHC_6H_4COCH_3$ **1r**	**2r**	80

In addition, the addition reaction in refluxing Et_2O for 3 d did not lead to the desired α-adduct, only γ-addition adduct. However, the α-adduct could be found in the reaction when the same reaction was performed in refluxing THF. High reaction temperature in HMPA (100 °C) led to the increased α-addition product. α-Regioselectivity increased significantly when a higher temperature was applied. Thus, we further reasoned that the temperature also has an important influence on the regioselective outcome of the addition. High reaction temperature facilitated the generation of the α-adduct, whereas low reaction temperature favored γ-regioselective addition. We then proceeded to perform the reaction at a higher temperature. To our delight, when reacting aldehyde **1a** with prenylzinc bromide in HMPA at 120 °C, the α-adduct **2a** was obtained in 87% yield together with a trace amount of the γ-adduct (entry 5). Further increase in the temperature and the reaction time improved the yield of α-adduct to 91% (entry 6). These results showed that the higher temperature used in the reaction condition was also effective in isomerizing the initially formed γ-isomer to the α-isomer. The results of the reaction of **1a** under these conditions with prenylzinc bromide are listed in Table 1. It was evident that this reaction was solvent- and temperature-dependent and led predominantly to the α-addition product. In order to probe the function of HMPA and to eventually replace this carcinogen by a less toxic solvent, we examined several other solvents that exhibit the properties similar to those of HMPA. To our disappointment, changing the solvent from HMPA to *N*,*N*-dimethylformamide (DMF) or dimethyl sulfoxide (DMSO) caused the yield of α-adduct to decrease sharply and afforded some unidentified byproduct (entries 7 and 8). This may be ascribed to the different solvation structure of the zinc ion in these solvents[13] and different metal complexation.[14]

Having established the optimized conditions for α-regioselective addition, we proceeded to investigate the scope of substrates using a wide range of aldehydes. Gratifyingly, as shown in

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Scheme 1. Proposed Mechanism for the Reaction Regiocontrol

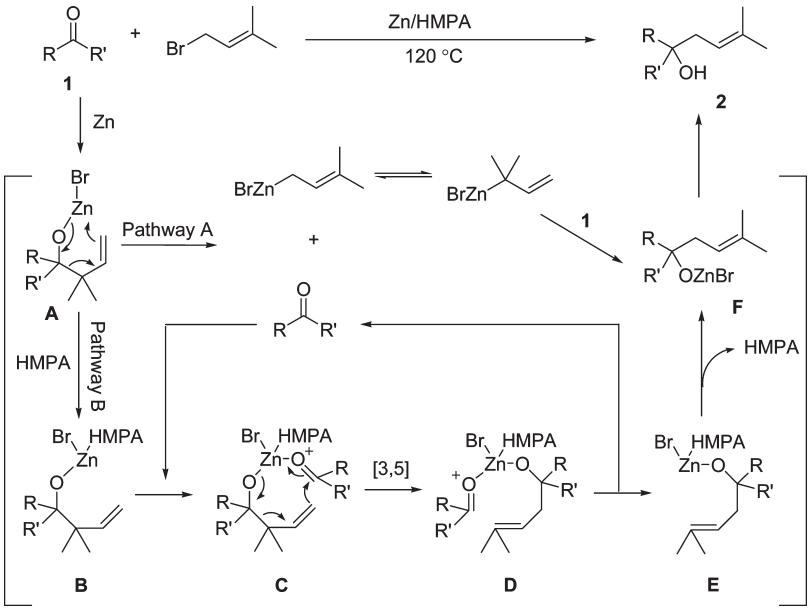

Table 2, all of these substrates underwent highly α-regioselective prenylation and afforded the prenylation product in good to high yields after purification by column chromatography on silica gel. Prenyl bromide was readily reacted with aryl aldehydes bearing *ortho*, *meta*, and *para* substitutions on the aryl ring to give the corresponding products **2b**−**2d** in good to high yields. For example, 2-fluorobenzaldehyde **1b** gave the α-prenylation product with the highest yield (92% yield) (entry 1), the α-prenylated alcohol from 3-fluorobenzaldehyde **1c** was obtained with 85% yield (entry 2), and 4-fluorobenzaldehyde **1d** gave 80% yield (entry 3). The reactions performed smoothly with aryl aldehydes containing electron-donating **1g** (entry 6) and electron-withdrawing groups **1b**−**1f** (entries 1−5). Heterocyclic aldehydes containing oxygen **1h** (entry 7), sulfur **1i** (entry 8), and nitrogen **1j** (entry 9) were also found to give the corresponding α-prenylation products **2h**−**2j** in satisfactory yields using the present conditions. A noteworthy observation was that this prenylation was highly chemoselective, reacting selectively with the carbonyl group without affecting the α,β-unsaturated bond moiety of cinnamaldehyde **1k** (entry 10). Another outstanding advantage of the zinc-promoted α-prenylation method was that this reaction tolerated nonconjugated aldehydes such as cyclohexanecarboxaldehyde **1l** very well (entry 11) and afforded functionalized α-prenylation product **2l** that was difficult to prepare by other methods.[7]

Inspired by the results from aldehyde, we were subsequently interested in the regioselectivity of zinc-mediated prenylation of ketones, which were inherently subject to less electrophilic and higher steric hindrance than aldehydes. Aliphatic and aromatic ketones were surveyed. We treated cyclohexanone **1m**, acetophenone **1n**, and substituted acetophenones **1o**−**1r** with prenyl bromide using the same conditions with aldehydes. In this way we also obtain desired α-adducts **2m**, **2n**, **2o**, **2p**, **2q**, and **2r**, respectively (entries 12−17). The regiochemical outcomes were similar to those using aldehydes, thus confirming the validity of this procedure.

Such satisfactory results displayed by zinc-mediated prenylation reaction prompted us to investigate the mechanism. A plausible scenario of the α-regioselective prenylation of carbonyl compounds is illustrated in Scheme 1. Two possible pathways are proposed to account for the formation of these compounds. One pathway involves the formation of the γ-prenylation product, which originate from the nucleophilic attack of the γ-carbon of the prenylzinc bromide, via a cyclic transition state analogous to that reported previously.[15] The initially formed zinc alcoholate **A** undergoes a bond cleavage to generate the parent aldehyde or ketone and primary prenylzinc in situ. This behavior is similar to that observed in earlier work by Benkeser et al.[16] Subsequently a metallotropic equilibrium between primary and tertiary prenylzinc occurs in the presence of HMPA.[12a] The resulting tertiary prenylzinc adds again to the aldehyde with a different regioselectivity compared to that of the reaction in THF to afford zinc alcoholate **F** via a six-membered cyclic transition state (path A). Another possible pathway also involves the formation of γ-prenylation product at the beginning. Then HMPA would be able to coordinate the zinc atom of initially formed zinc alcoholate **A** as observed for various metal ions[13a] and more particularly for lithium,[11] thus activating the organozinc reagent as a Lewis base (path B). The origin of activation by HMPA is believed to be the enhanced Lewis acidity of zinc.[17] The metal zinc center in the resulting complex **B** maintains sufficient Lewis acidity and further coordinates the aldehyde, which results in the formation of the transition state **C**.[18] The latter reaction involves a [3,5]-sigmatropic shift at an elevated temperature, proceeding via a eight-membered transition state. Though [3,5]-sigmatropic shifts are not theoretically allowed by the Woodward−Hoffmann rules, it seems to be possible as Birney and co-workers reported.[19] We would like to classify this rearrangement as a metallo-[3,5]-sigmatropic shift. The σ-bond migrates across the conjugated π-system containing the zinc counterion to form more stable transition state **D**, which is sterically less hindered and thermodynamically more stable. Subsequently, the parent aldehyde or ketone is regenerated from metal zinc−oxygen bond cleavage of transition state **D** to reenter the reaction. Finally, the dissociation of HMPA from the intermediate **E** liberates the ligand to afford zinc alcoholate **F**.

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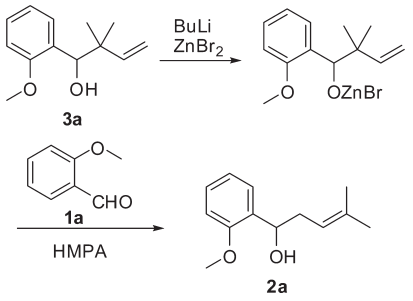
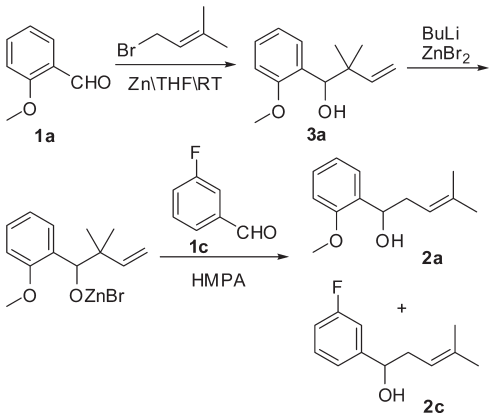
Scheme 2. Reaction of Zinc Alcoholate and 2-Methoxybenzaldehyde



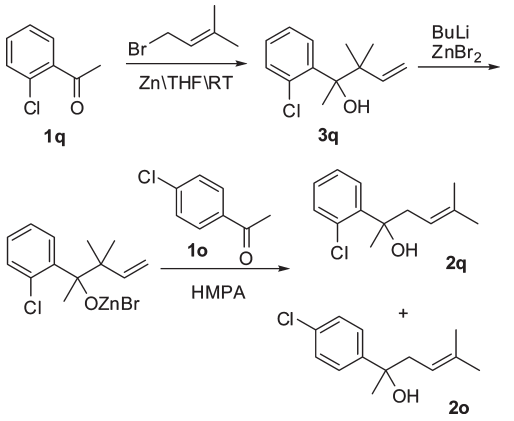
Scheme 3. Crossover Reaction between 2-Methoxybenzaldehyde and 3-Fluorobenzaldehyde



To test the proposed mechanism, we treated γ-adduct **3a** first with BuLi and then with zinc bromide to afford the zinc alcoholate,[20] which allowed to react with 2-methoxybenzaldehyde **1a** at 120 °C in HMPA (Scheme 2). Analysis of the reaction mixture by GC−MS and ^{1}H NMR indicated complete consumption of **3a** and the formation of **2a**, which favors the proposed mechanism.

We next studied the crossover reaction between 2-methoxybenzaldehyde **1a** and 3-fluorobenzaldehyde **1c**. 2-Methoxybenzaldehyde **1a** reacted with prenylzinc bromid in THF at room temperature to afford the γ-adduct **3a** after workup procedure. Treatment of pure γ-adduct **3a** first with BuLi and then with zinc bromide, followed by reaction with 3-fluorobenzaldehyde **1c** at 120 °C in HMPA, afforded the crossover products **2a** and **2c** in 21% and 34% yields, respectively, after column chromatography (Scheme 3). Furthermore, a crossover reaction between 2-chloroacetophenone **1q** and 4-chloroacetophenone **1o** was also conducted under the aforementioned conditions (Scheme 4). Similarly to the case of the reaction with aldehydes, reaction with ketones gave products **2q** and **2o** in 32% and 44% yields, respectively, after chromatographic purification. By performing the crossover reaction, we thought it was possible to distinguish between pathway A and B. However, transition state C or D cannot be observed in the reaction. Thus, it should be noted that the possibility of pathway A could not be completely ruled out.

Scheme 4. Crossover Reaction between 2-Chloroacetophenone and 4-Chloroacetophenone



CONCLUSION

In conclusion, we have developed a general and practical zinc-mediated α-prenylation method using aldehydes and ketones for the straightforward synthesis of α-prenylated alcohol derivatives. This approach provides the easiest pathway for accessing this class of valuable compounds. Although somewhat higher temperatures are needed, the reaction is easy to perform and is more convenient than the previously described carbonyl prenylation methods,[6a,7] which require metal complexes as catalysts that are not always easy to prepare. By simply altering the reaction solvent and temperature, a remarkable reversal of regioselectivity can be achieved to give the desired regiochemical outcome. Moreover, our investigations have shown that this α-regioselective zinc-meditated prenylation is highly feasible for a wide range of substrates including aliphatic, aromatic, conjugated, and nonconjugated aldehydes and ketones. Two possible pathways are proposed to account for the formation of these synthetically difficult-to-obtain molecules. Further study to show the synthetic utility of the highly α-regioselective zinc-mediated prenylation is now in progress. Several attempts have been made to replace the carcinogenic HMPA, but it is still the solvent of choice in terms of high yields of the desired product in this highly α-regioselective prenylation so far. Efforts are still in progress to replace HMPA by a safer, but still efficient solvent for the zinc-mediated addition.

EXPERIMENTAL SECTION

General Procedure for the Synthesis of α-Adducts 2. Example for the Synthesis of **2a**. Prenyl bromide (0.5 mL, 4.37 mmol) was added into a suspension of activated zinc powder[21] (500 mg, 7.7 mmol) in dry THF (15 mL); the reaction mixture was stirred for 1 h at room temperature. The solution was filtered through a Schlenk filter and kept under N_2 for the following reaction. A solution of 2-methoxybenzaldehyde **1a** (272 mg, 2.0 mmol) in dry THF (3 mL) was added to the solution of prenylzinc bromide prepared above. The solution was stirred for 1 h at room temperature. Then HMPA (1.1 mL) was added into the reaction mixture, followed by removal of initial reaction solvent (THF). The mixture was heated to 120 °C for 8 h. After cooling to room temperature, the reaction was quenched with saturated NH_4Cl solution. The mixture was extracted with dichloromethane and washed with brine, dried, and concentrated. The residue was purified by flash column chromatography (petroleum ether/ethyl acetate, 15/1, v/v) to afford the α-adduct **2a** (358 mg, 87% yield) as pale yellow oil. ^{1}H NMR

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(400 MHz, $CDCl_3$): δ 7.34 (d, J = 7.2 Hz, 1H), 7.24 (t, J = 7.2 Hz, 1H), 6.96 (t, J = 7.6 Hz, 1H), 6.87 (d, J = 8.4 Hz, 1H), 5.22 (t, J = 7.6 Hz, 1H), 4.90 (t, J = 6.0 Hz, 1H), 3.84 (s, 3H), 2.57 (br. s, 1H), 2.53−2.43 (m, 2H), 1.72 (s, 3H), 1.60 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.5, 134.7, 132.2, 128.2, 126.8, 120.7, 120.5, 110.4, 70.5, 55.3, 36.2, 25.9, 17.9. HRMS (ESI): m/z calcd for $C_{13}H_{18}O_2Na$ $[M + Na]^+$ 229.1199, found 229.1200.

Characterization of 2b. Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (dt, J = 7.6 Hz, J = 1.6 Hz, 1H), 7.27−7.21 (m, 1H), 7.15 (t, J = 7.6 Hz, 1H), 7.01 (t, J = 8.8 Hz, 1H), 5.19 (t, J = 7.6 Hz, 1H), 5.03−4.99 (m, 1H), 2.53−2.42 (m, 2H), 2.07 (d, J = 4.0 Hz, 1H), 1.73 (s, 3H), 1.61 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.8 (d, J = 243.7 Hz), 136.0, 131.2 (d, J = 13.0 Hz), 128.6 (d, J = 8.5 Hz), 127.2 (d, J = 4.0 Hz), 124.1 (d, J = 3.3 Hz), 119.4, 115.1 (d, J = 21.0 Hz), 68.0 (d, J = 2.2 Hz), 37.0, 25.9, 17.9. HRMS (ESI): m/z calcd for $C_{12}H_{15}FONa$ $[M + Na]^+$ 217.0999, found 217.1003.

Characterization of 2c. Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32−7.26 (m, 1H), 7.12−7.07 (m, 2H), 6.95 (dt, J = 8.0 Hz, J = 2.0 Hz, 1H), 5.14 (dt, J = 6.8 Hz, J = 1.2 Hz, 1H), 4.66 (t, J = 6.8 Hz, 1H), 2.49−2.36 (m, 2H), 2.15 (s, 1H), 1.73 (s, 3H), 1.61 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.9 (d, J = 243.4 Hz), 147.0 (d, J = 7.4 Hz), 136.2, 129.8 (d, J = 8.7 Hz), 121.4 (d, J = 2.9 Hz), 119.3, 114.1 (d, J = 21.1 Hz), 112.7 (d, J = 22.0 Hz), 73.3 (d, J = 1.7 Hz), 38.2, 25.9, 17.9. HRMS (ESI): m/z calcd for $C_{12}H_{15}FONa$ $[M + Na]^+$ 217.0999, found 217.0997.

Characterization of 2d. Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 (t, J = 8.2 Hz, 2H), 7.02 (t, J = 8.4 Hz, 2H), 5.14 (t, J = 6.8 Hz, 1H), 4.65 (t, J = 6.0 Hz, 1H), 2.50−2.34 (m, 2H, CH_2), 2.07 (s, 1H), 1.72 (s, 3H), 1.60 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.1 (d, J = 243.7 Hz), 140.0 (d, J = 2.6 Hz), 135.9, 127.5, 127.4, 119.5, 115.2, 114.9, 73.4, 38.4, 25.9, 17.9. HRMS (ESI): m/z calcd for $C_{12}H_{15}FONa$ $[M + Na]^+$ 217.0999, found 217.0992.

Characterization of 2e. Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (d, J = 8.4 Hz, 2H), 7.23 (d, J = 8.4 Hz, 2H), 5.13 (t, J = 6.8 Hz, 1H), 4.64 (t, J = 6.4 Hz, 1H), 2.48−2.35 (m, 2H), 1.73 (s, 3H), 1.60 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.2, 136.2, 131.4, 131.4, 127.6, 127.6, 121.1, 119.2, 73.3, 38.3, 25.9, 18.0. HRMS (ESI): m/z calcd for $C_{12}H_{15}BrONa$ $[M + Na]^+$ 277.0198, found 277.0199.

Characterization of 2f. Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28 (d, J = 8.0 Hz, 2H), 7.12 (t, J = 8.0 Hz, 2H), 5.41 (t, 1H), 5.20 (t, J = 7.2 Hz, 1H), 2.87 (br. s, 1H), 2.83−2.58 (m, 2H), 1.70 (s, 3H), 1.58 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.6, 135.4, 134.4, 129.3, 129.3 128.8, 128.8, 119.2, 72.0, 34.3, 25.8, 17.8. HRMS (ESI): m/z calcd for $C_{12}H_{14}Cl_2ONa$ $[M + Na]^+$ 267.0314, found 267.0315.

Characterization of 2g. Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.88 (s, 1H), 6.82−6.74 (m, 2H), 5.94 (s, 2H), 5.14 (dt, J = 6.6 Hz, J = 1.2 Hz, 1H), 4.58 (dd, J = 8.0 Hz, J = 5.2 Hz, 1H), 2.49−2.32 (m, 2H), 2.04 (br. s, 1H), 1.72 (s, 3H), 1.62 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.4, 141.5, 133.2, 130.4, 114.5, 114.0, 102.8, 101.2, 95.7, 68.7, 33.1, 20.7, 12.8. HRMS (ESI): m/z calcd for $C_{13}H_{16}O_3Na$ $[M + Na]^+$ 243.0992, found 243.0994

Characterization of 2h. Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (t, J = 0.8 Hz, 1H), 6.33 (dd, J = 1.6 Hz, J = 2.8 Hz, 1H), 6.23 (d, J = 3.2 Hz, 1H), 5.14 (t, J = 7.2 Hz, 1H), 4.69 (t, J = 6.8 Hz, 1H), 2.63−2.52 (m, 2H), 2.05 (s, 1H), 1.73 (s, 3H), 1.65 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.4, 141.9, 135.7, 119.0, 110.1, 105.9, 67.6, 34.5, 25.9, 17.9. HRMS (ESI): m/z calcd for $C_{10}H_{14}O_2Na$ $[M + Na]^+$ 189.0886, found 189.0888.

Characterization of 2i. Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24 (dd, J = 1.6 Hz, J = 4.2 Hz, 1H), 6.98−6.96 (m, 2H), 5.18 (t, J = 6.8 Hz, 1H), 4.93 (t, J = 7.2 Hz, 1H), 2.63−2.50 (m, 2H), 2.17 (d, J = 4.0 Hz, 1H), 1.73 (s, 3H), 1.64 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.3, 136.0, 126.6, 124.4, 123.6, 119.3, 70.1, 38.3, 25.9, 18.1. HRMS (ESI): m/z calcd for $C_{10}H_{14}OS$ $[M + Na]^+$ 205.0658, found 205.0657.

Characterization of 2j. Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.51 (d, J = 5.6 Hz, 2H), 7.29 (d, J = 5.6 Hz, 2H), 5.14 (t, J = 7.6 Hz, 1H), 4.69 (t, J = 6.4 Hz, 1H), 2.72 (br. s, 1H), 2.44 (t, J = 7.2 Hz, 2H), 1.73 (s, 3H), 1.59 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.1, 149.2, 149.2, 136.0, 121.1, 121.1, 119.0, 72.3, 37.9, 25.8, 17.9. HRMS (ESI): m/z calcd for $C_{11}H_{16}NO$ $[M + H]^+$ 178.1226, found 178.1228.

Characterization of 2k. Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (d, J = 7.6 Hz, 2H), 7.31 (t, J = 7.6 Hz, 2H), 7.23 (t, J = 7.2 Hz, 1H), 6.60 (d, J = 16.0 Hz, 1H), 6.25 (dd, J = 6.4 Hz, J = 16.0 Hz, 1H), 5.20 (t, J = 7.2 Hz, 1H), 4.30 (q, J = 6.4 Hz, 1H), 2.39−2.31 (m, 2H), 1.83 (s, 1H), 1.74 (s, 3H), 1.66 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.9, 135.6, 132.0, 130.1, 128.6, 127.6, 126.5, 126.5, 119.3, 72.5, 36.4, 26.0, 18.1. HRMS (ESI): m/z calcd for $C_{14}H_{18}ONa$ $[M + Na]^+$ 225.1250, found 225.1247.

Characterization of 2l. Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.17 (t, J = 6.8 Hz, 1H), 3.35−3.34 (m, 1H), 2.22−2.09 (m, 2H), 1.87 (d, 1H), 1.74 (s, 3H), 1.64 (s, 3H), 1.78−0.97 (m, 11H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.1, 120.7, 75.8, 43.1, 32.9, 29.2, 28.2, 26.6, 26.3, 26.1, 25.9, 17.9. HRMS (ESI): m/z calcd for $C_{12}H_{22}ONa$ $[M + Na]^+$ 205.1563, found 205.1565.

Characterization of 2m. Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.24 (t, J = 7.6 Hz, 1H), 2.15 (d, J = 7.6 Hz, 2H), 1.75 (s, 3H), 1.64 (s, 3H), 1.61−1.39 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 134.4, 117.9, 70.9, 39.5, 36.3, 36.3, 25.1, 24.8, 21.2, 21.2, 17.0. HRMS (ESI): m/z calcd for $C_{11}H_{20}ONa$ $[M + Na]^+$ 191.1406, found:.191.1410.

Characterization of 2n. Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (d, J = 7.6 Hz, 2H), 7.34 (t, J = 7.6 Hz, 2H), 7.23 (t, J = 7.6 Hz, 1H), 5.00 (t, J = 8.0 Hz, 1H), 2.54 (d, J = 8.4 Hz, 2H), 2.04 (s, 1H), 1.68 (s, 3H), 1.61 (s, 3H), 1.53 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.1, 136.5, 128.1, 128.1, 126.5, 124.9, 124.9, 118.9, 74.5, 42.5, 29.8, 26.1, 18.1. HRMS (ESI): m/z calcd for $C_{13}H_{18}ONa$ $[M + Na]^+$ 213.1250, found:.213.1254

Characterization of 2o. Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 (d, J = 8.4 Hz, 2H), 7.29 (d, J = 8.4 Hz, 2H), 4.97 (t, J = 7.6 Hz, 1H), 2.51 (d, J = 7.2 Hz, 2H), 2.01 (s, 1H), 1.69 (s, 3H), 1.61 (s, 3H), 1.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.7, 136.9, 132.3, 128.1, 128.1, 126.4, 126.4, 118.4, 74.2, 42.4, 29.8, 26.0, 18.0. HRMS (ESI): m/z calcd for $C_{13}H_{17}ClONa$ $[M + Na]^+$ 247.0860, found:. 247.0863.

Characterization of 2p. Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 (d, J = 8.8 Hz, 2H), 6.88 (d, J = 8.8 Hz, 2H), 5.02 (t, J = 8.8 Hz, 1H), 3.82 (s, 3H), 2.52 (d, J = 8.8 Hz, 2H), 1.98 (s, 1H), 1.69 (s, 3H), 1.62 (s, 3H), 1.52 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.2, 140.4, 136.2, 126.0, 126.0, 119.0, 113.4, 113.4, 74.2, 55.2, 42.6, 29.8, 26.0, 18.0. HRMS (ESI): m/z calcd for $C_{14}H_{20}O_2Na$ $[M + Na]^+$ 243.1356, found:.243.1355.

Characterization of 2q. Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (dd, J = 7.8 Hz, J = 1.6 Hz, 1H), 7.34 (dd, J = 7.8 Hz, J = 1.6 Hz, 1H), 7.25 (td, J = 8.0 Hz, J = 1.6 Hz, 1H), 7.18 (td, J = 7.6 Hz, J = 2.0 Hz, 1H), 4.92 (t, J = 7.6 Hz, 1H), 3.02−2.69 (m, 2H), 2.55 (s, 1H), 1.69 (s, 3H), 1.67 (s, 3H), 1.63 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.2, 136.4, 131.3, 130.9, 128.1, 128.0, 126.8, 118.8, 75.1, 39.3, 27.2, 25.9, 18.0. HRMS (ESI): m/z calcd for $C_{13}H_{17}ClONa$ $[M + Na]^+$ 247.0860, found:.247.0861.

Characterization of 2r. Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20 (t, J = 8.0 Hz, 1H), 7.01 (t, J = 2.0 Hz, 1H), 6.94 (dddd, J = 8.0 Hz, J = 1.6 Hz, J = 1.2 Hz, J = 0.8 Hz, 1H), 6.71 (dddd, J = 8.0 Hz, J = 2.6 Hz, J = 1.2 Hz, J = 0.8 Hz, 1H), 5.42 (br.s, 1H), 5.00 (t, J = 8.0 Hz, 1H), 2.53 (d, J = 8.0 Hz, 2H), 2.17 (s, 1H), 1.68 (s, 3H), 1.62 (s, 3H), 1.52 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.9, 150.0, 136.9, 129.4, 118.6, 117.2, 113.5, 112.2, 74.7, 42.3, 29.7, 26.0, 18.0. HRMS (ESI): m/z calcd for $C_{13}H_{18}O_2Na$ $[M + Na]^+$ 229.1199, found:.229.1200.

General Procedure for the Synthesis of γ-Adducts 3. Example for the synthesis of **3a**. Prenyl bromide (0.5 mL, 4.37 mmol) was

added into a suspension of activated zinc powder[21] (500 mg, 7.7 mmol) in dry THF (15 mL); the reaction mixture was stirred for 1 h at room temperature. The solution was filtered through a Schlenk filter and kept under N_2 for the following reaction. A solution of 2-methoxybenzaldehyde **1a** (272 mg, 2.0 mmol) in dry THF (3 mL) was added to the solution of prenylzinc bromide prepared above. The solution was stirred for 1 h at room temperature and then quenched with saturated NH_4Cl solution. The mixture was extracted with dichloromethane and washed with brine, dried, and concentrated. The residue was purified by flash column chromatography (petroleum ether/ethyl acetate, 15/1, v/v) to afford the γ-adduct **3a** (386 mg, 94% yield) as pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28 (d, J = 8.0 Hz, 1H), 7.23 (t, J = 7.2 Hz, 1H), 6.94 (t, J = 7.6 Hz, 1H), 6.86 (d, J = 8.4 Hz, 1H), 5.96 (dd, J = 10.8 Hz, J = 17.6 Hz, 1H), 5.07 (d, J = 10.8 Hz, 1H), 5.02 (d, J = 17.6 Hz, 1H), 4.84(s, 1H), 3.80 (s, 3H), 2.55 (br. s, 1H), 1.03(s, 3H), 0.98 (s, 3H).

■ ASSOCIATED CONTENT

Supporting Information. Detailed crossover experimental procedure and copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) Zinc powder was activated using acetic acid in MeOH. After 20 min of stirring, the metal was filtered, washed, and dried under full vacuum for 3 h.