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High Regiocontrol in the Zinc-Mediated Crotylation of Aldehydes and Ketones: A Straightforward and Facile Approach to Linear Homoallylic Alcohols in DMPU

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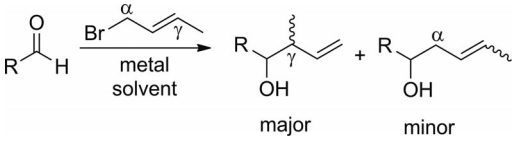
The α-regioselectivity of carbonyl crotylation is a long-standing problem in the realm of C–C bond formation reactions. We demonstrate that zinc-mediated crotylation of aldehydes and ketones can afford α-linear homoallylic alcohols exclusively to provide a simple solution for this problem. In this context, we describe a method for the α-regioselective crotylation of aldehydes and ketones by using an easily available starting material, such as crotyl bromide, zinc dust, and the less-toxic solvent DMPU. The reaction has broad substrate scope and is highly efficient. Moreover, a metallo-[3,5]-sigmatropic rearrangement is proposed to account for the high α-regioselectivity in the zinc-mediated crotylation.

Introduction

α-Linear homoallylic alcohols are a class of useful compounds in organic synthesis, being easily converted into many important building blocks for natural product and biologically important molecule synthesis.[1] In principle, the crotylation of aldehydes and ketones with crotylmetals is the most straightforward approach to access this class of valuable compounds. However, most current metal-mediated or -catalyzed crotylation reactions of carbonyl compounds are γ-regioselective to provide the γ-adducts predominantly (Scheme 1).[2] α-Selectivity is difficult to achieve because γ-allylations are dominant with direct organometallic additions.[3]



Scheme 1. Current crotylation of aldehydes with crotyl bromide.

Only a few methods of α-crotylation of aldehyde have been described, and they usually give mixtures containing variable amounts of undesired γ-addition products.[4] At present, linear homoallylic alcohols are usually obtained by the reaction of other crotyl sources (such as the γ-adduct of homoallylic alcohol as the crotyl donor) with aldehydes.[1,5] From a synthetic point of view, the methodology involving direct crotylation of carbonyls with crotyl halides is more significant to prepare linear homoallylic alcohols. As far as we know, only two highly α-regioselective crotylations of limited aldehydes have been reported in the presence of In or $In(OTf)_3$ by Loh's group and Ramachandram's group.[6] Furthermore, there are no examples of ketones provided in these methods. Indeed, in some studies on indium, compounds such as $In(OTf)_3$ proved to be ineffective in ketone allylborations.[7] However, the α-regioselective crotylation of ketones is also desirable due to the ability to prepare tertiary linear homoallylic alcohols, which have proven to be important building blocks and versatile synthons.[8] Thus, the search continues for a more general and effective solution with broad substrate scope for the direct synthesis of linear homoallylic alcohols.

Recently, our group reported a highly α-regioselective zinc-mediated prenylation of carbonyls.[9] In contrast with other methods,[10] ketones are tolerated in this reaction. We therefore considered whether we could expand this method to the corresponding crotylation reaction. Herein, we report a facile and general zinc-mediated method for the crotylation of aldehydes and ketones with high α-regioselectivity in 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)pyrimidinone (DMPU) to afford linear homoallylic alcohols in good to high yields.

The significant advantages offered by this method we have developed are: (1) The high α-regioselectivity. (2) The high generality with broad substrate scope that covers aldehydes and ketones compared to the previous reports that were only limited to a rather limited range of aldehydes. (3) The use of a simple and operationally convenient procedure. (4) The low toxicity of the DMPU solvent compared to previous toxic hexamethylphosphoramide (HMPA). (5) The low price and convenience of zinc.

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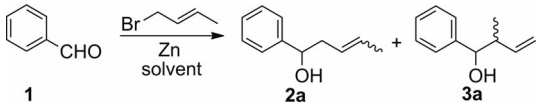
Results and Discussion

Initial experiments were carried out by using the reaction between benzaldehyde and crotyl bromide as the model (Table 1). To our delight, high α-regioselectivity was observed in the crotylation with 71% of α-product **2a** (Table 1, Entry 1), which is similar to the previous prenylation reaction.[9] Due to the carcinogenicity of HMPA, we explored alternative solvents for the crotylation reaction based on previous work on organozinc reagents,[11] such as dimethyl sulfoxide (DMSO), *N*,*N*-dimethylformamide (DMF), tetramethylurea (TMU), DMPU, and 1,3-dimethyl-2-imidazolidinone (DMI). The results showed that DMPU was the most suitable solvent for the crotylation reaction to afford α-adduct **2a** exclusively in 68% yield (Table 1, Entry 5). When using DMSO and DMF as the solvents, the reactions gave low yields of the α-adduct together with variable amounts of the γ-addition byproducts (Table 1, Entries 2 and 3). High α-regioselectivities were also acquired when the crotylation was performed in TMU and DMI as solvents, but the yields of the α-product were low (Table 1, Entries 4 and 8). DMPU has a low toxicity and is almost harmless to human beings.[12] We thus chose to use DMPU as the solvent for further investigation. To enable the addition to be carried out under much milder conditions, we examined the reaction at a lower temperature. Unfortunately, our attempts were not satisfactory. Decreasing the reaction temperature from 130 to 110 °C caused the yield of the α-adduct to decrease and afforded an amount of γ-adduct **3a**, even though the reaction time was prolonged to 20 h (Table 1, Entry 6). These results highlighted the key role of temperature in the regiocontrol of the reaction. A high temperature was necessary to accelerate the α-crotylation reaction. Further optimization indicated that the reaction temperature could be decreased to 120 °C with almost no change in regioselectivity (Table 1, Entry 7).

Table 1. Optimization of reaction conditions.[a]

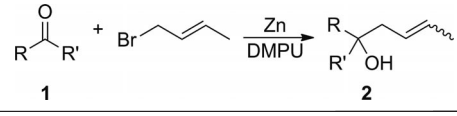


Entry	Solvent	*T* [°C]	*t* [h]	**2a** [%][b]	**3a** [%][b]
1	HMPA	130	12	71	ND
2	DMSO	130	14	22	3
3	DMF	130	14	43	5
4	TMU	130	14	58	ND
5	DMPU	130	14	68	ND
6	DMPU	110	20	49	12
7	DMPU	120	14	65	trace
8	DMI	120	14	59	3

[a] Reactions were carried out with aldehyde (1.0 equiv.), crotyl bromide (2.5 equiv.), and zinc (3.0 equiv.). [b] Isolated yield.

On the basis of these results, we conducted the crotylation of benzaldehyde bearing various kinds of substituents to investigate the generality of this method. As shown in Table 2, a variety of aromatic aldehydes underwent highly α-regioselective crotylation and afforded the corresponding α-addition products in good to high yield. The α-regioselective crotylation was effective for any substitution pattern at the benzaldehyde. For example, 2-methoxybenzaldehyde (**1b**) gave the α-crotylation product in 79% yield (Table 2, Entry 1), the α-crotylated alcohol from 3-methoxybenzaldehyde (**1c**) was obtained in 86% yield (Table 2, Entry 2), and 4-methoxybenzaldehyde (**1d**) and piperonaldehyde (**1e**) gave 85 and 75% yield, respectively (Table 2, Entries 3 and 4). Also, the α-crotylation reaction proceeded effectively for various benzaldehydes substituted with either electron-donating or electron-withdrawing groups (Table 2, Entries 1–5 and 6–9). Generally, benzaldehydes bearing electron-donating substituents provided better yields (Table 2, Entries 2, 3, and 5). For those fluoro-substituted substrates, the yields turned out to be slightly lower (Table 2, Entries 6 and 7). In addition to aromatic aldehydes, we also demonstrated the crotylation of aliphatic aldehydes producing α-adducts **2k** and **2l** in complete α-regioselectivity (Table 2, Entries 10 and 11). It should be noted that α-adducts **2k** and **2l** are volatile due to their relatively low molecular weight, which did not allow efficient recovery of the expected compounds upon removal of the solvent. Consequently, the actual yields of **2k** and **2l** are likely higher than those of the isolated products.

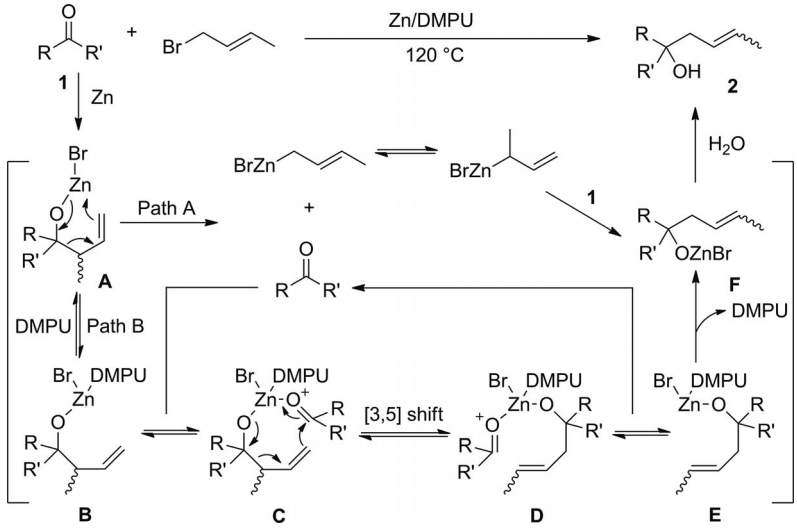
Table 2. α-Crotylation of various aldehydes and ketones.



Entry	Substrate	Product	Yield[%][a] (*E*/*Z*)[b]
1	2-$CH_3OC_6H_4CHO$ (**1b**)	**2b**	79 (70:30)
2	3-$CH_3OC_6H_4CHO$ (**1c**)	**2c**	86 (70:30)
3	4-$CH_3OC_6H_4CHO$ (**1d**)	**2d**	85 (58:42)
4	3,4-$(OCH_2O)C_6H_3CHO$ (**1e**)	**2e**	75 (58:42)
5	4-$CH_3C_6H_4CHO$ (**1f**)	**2f**	96 (67:33)
6	4-FC_6H_4CHO (**1g**)	**2g**	62 (66:34)
7	3-FC_6H_4CHO (**1h**)	**2h**	76 (67:33)
8	4-ClC_6H_4CHO (**1i**)	**2i**	85 (63:37)
9	4-BrC_6H_4CHO (**1j**)	**2j**	84 (75:25)
10	cyclopropanecarbaldehyde (**1k**)	**2k**	42 (61:39)
11	2-methylpropanal (**1l**)	**2l**	37 (71:29)
12	$C_6H_5COCH_3$ (**1m**)	**2m**	78 (53:47)
13	4-$CH_3OC_6H_4COCH_3$ (**1n**)	**2n**	71 (67:33)
14	4-$CH_3C_6H_4COCH_3$ (**1o**)	**2o**	74 (55:45)
15	2-$ClC_6H_4COCH_3$ (**1p**)	**2p**	78 (73:27)
16	4-$ClC_6H_4COCH_3$ (**1q**)	**2q**	83 (74:26)

[a] Isolated yield. [b] Determined by ^{1}H NMR spectroscopy and GC–MS.

We next turned our attention to see whether this highly α-regioselective zinc-mediated crotylation could be expanded to ketones, which are generally less reactive than aldehyde due to their poor electrophilicity and high steric hindrance. We were gratified to find that the α-crotylation was not limited to aldehydes. When reacting acetophenone



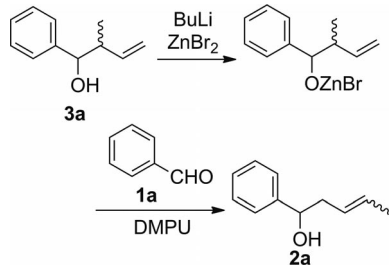
Scheme 2. Proposed mechanism for the α-regioselective crotylation.

(**1m**) and substituted acetophenones **1n**–**q** with crotylzinc bromide in DMPU, desired α-adducts **2m**–**q** were obtained in good yields (Table 2, Entries 12–16). These results highlighted the generality and usefulness of our developed method.

On the basis of the mechanistic proposal of prenylation in our previous study,[9] two possible pathways are proposed to account for the high α-regioselectivity in the zinc-mediated crotylation of aldehydes and ketones, as illustrated in Scheme 2, which are different from the conventional crotyl transfer mechanism.[5d,13] Both pathways involve the formation of γ-crotylation product **A** at the beginning. On the one hand, zinc alcoholate **A** undergoes retro-allylation via a six-membered transition state first. The parent aldehyde or ketone and primary crotylzinc are thus generated in situ. Then, a metallotropic equilibrium between primary and tertiary crotylzinc occurs in basic DMPU.[14] Finally, the resulting tertiary crotylzinc reacts again with the aldehyde or ketone to afford zinc alcoholate **F** via a six-membered transition state (path A). On the other hand, the reaction appears to involve the coordination of DMPU by the zinc atom of initially formed zinc alcoholate **A** to form complex **B** followed by a [3,5] sigmatropic shift[15] via an eight-membered transition state and elimination of carbonyl to afford intermediate **E**. Finally, elimination of DMPU from **E** results in the formation of zinc alcoholate **F** (path B).

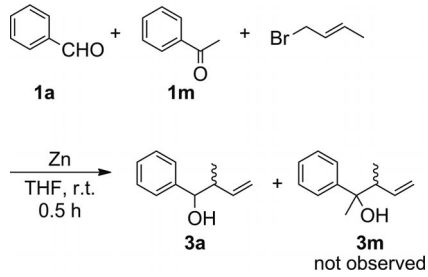
With the aim to demonstrate the proposed mechanism, we carried out the following experiment. First, α-adduct **3a** was synthesized and then treated with BuLi and zinc bromide. The resulting zinc alcoholate reacted with benzaldehyde (**1a**) at 120 °C in DMPU to give desired α-adduct **2a** in 72% isolated yield (Scheme 3). This result indicated that the proposed mechanism appeared to be a reasonable assumption.

To further clarify the mechanism, we carried out a competitive study by using an equimolar mixture of benzaldehyde (**1a**) and acetophenone (**1m**). The mixture was treated with crotylzinc at room temperature for 0.5 h. During the

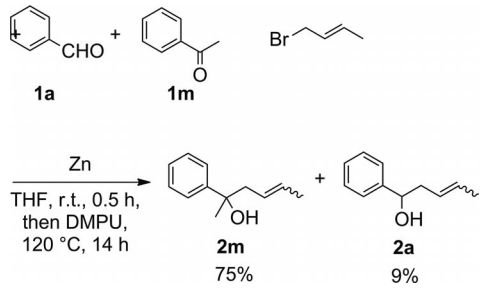


Scheme 3. Reaction of zinc alcoholate and benzaldehyde.

reaction course, only aldehyde-derived γ-adduct **3a** was observed. The formation of keto-derived γ-adduct **3m** was not observed by TLC or GC–MS (Scheme 4). This result indicated that the relative order of reactivity of carbonyls to crotylzinc is aldehyde > ketone. Then, DMPU was introduced, and the mixture was heated at 120 °C for 14 h. The reaction provided keto-derived α-adduct **2m** in 75% yield together with a small amount of aldehyde-derived α-adduct **2a** (9% yield, Scheme 5). We speculate that major product **2m** probably results from the coordination of initially formed zinc alcoholate to DMPU and acetophenone (**1m**) followed by rearrangement to liberate benzaldehyde (**1a**). Support for this conjecture derives from the fact that the aldehyde is more reactive toward the organozinc reagent than the ketone under our reaction conditions. If pathway A is the preferred one, the major product should be aldehyde-derived α-adduct **2a**, which results from the addition of the tertiary crotylzinc generated in situ to benzaldehyde (**1a**). Thus, these data render an explanation of pathway A for the regioselectivity less plausible. In pathway B, it is quite probable that the Lewis acidity of zinc of initially formed γ-adduct **A** is enhanced by coordination with DMPU. The metal zinc center in resulting complex **B** maintains sufficient Lewis acidity and further coordinates the carbonyl, which results in the formation of transition state **C**.



Scheme 4. A competitive study of benzaldehyde and acetophenone at room temperature.



Scheme 5. A competitive study of benzaldehyde and acetophenone at 120 °C.

Conclusions

In conclusion, we have developed a simple and direct procedure for the α-crotylation of a wide range of aldehydes and ketones mediated by inexpensive and convenient zinc in an environmentally benign solvent. This method, simple to conduct and not requiring complex catalysts, is not only mechanistically interesting but also represents a valuable extension to the realm of ketones because the direct α-crotylation with crotylmetals is currently limited to aldehydes. On the basis of the results of our reaction, we may conclude that our method has higher α-regioselectivity and broader substrate scope than existing carbonyl α-crotylation methods. Further studies to show the synthetic utility of the highly α-regioselective crotylation is now in progress.

Experimental Section

General: All aldehydes and ketones were commercially available. Liquid aldehydes and ketones were freshly distilled before used and solid aldehydes were used as purchased without further purification. Solvents were treated prior to use according to the standard methods. Other reagents were used as purchased without further purification. ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, in $CDCl_3$ with chemical shift (δ) given in ppm relative to TMS as an internal standard. Multiplicities are indicated, s (singlet), d (doublet), t (triplet), q (quartet), br. s (broad singlet), m (multiplet). High-resolution mass spectra (HRMS) were recorded by using electrospray ionization (ESI) with a micrOTOF-Q II instrument (Bruker).

General Procedure for the Synthesis of α-Adducts 2: Crotyl bromide (0.4 mL, 3.8 mmol) was added to a suspension of activated zinc powder[16] (300 mg, 4.6 mmol) in dry THF (10 mL); the reaction mixture was stirred for 1 h at room temperature. The solution was filtered through a Schlenk filter and kept under an atmosphere of N_2 for the following reaction. A solution of carbonyl compound **1** (1.5 mmol) in dry THF (3 mL) was added to a solution of crotylzinc bromide prepared above. The solution was stirred for 1 h at room temperature. Then, DMPU (2.0 mL) was added into the reaction mixture, followed by removal of the initial reaction solvent (THF). The mixture was heated to 120 °C for 14 h. The residue was purified by flash column chromatography to afford α-adduct **2**.

2a: Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, *E* isomer): δ = 7.34–7.27 (m, 5 H), 5.68–5.54 (m, 1 H), 5.46–5.39 (m, 1 H), 4.71 (dd, *J* = 8.0, 5.2 Hz, 1 H), 2.59–2.41 (m, 2 H), 2.08 (s, 1 H), 1.68 (d, *J* = 6.8 Hz, 3 H) ppm. ^{1}H NMR (400 MHz, $CDCl_3$, *Z* isomer): δ = 4.66 (dd, *J* = 8.0, 4.8 Hz, 1 H), 1.60 (d, *J* = 6.8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, *E* isomer): δ = 144.13, 128.39, 128.39, 127.61, 127.50, 125.86, 125.86, 125.71, 73.89, 36.90, 12.96 ppm. ^{13}C NMR (100 MHz, $CDCl_3$, *Z* isomer): δ = 144.08, 129.42, 128.36, 128.36, 127.42, 126.81, 125.82, 125.82, 73.52, 42.79, 18.04 ppm. HRMS (ESI): calcd. for $C_{11}H_{14}ONa$ [M + Na]$^+$ 185.0943; found 185.0944.

2b: Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, *E* isomer): δ = 7.33 (dd, *J* = 7.6, 1.6 Hz, 1 H), 7.26–7.21 (m, 1 H), 6.96 (td, *J* = 7.6, 0.8 Hz, 1 H), 6.87 (dd, *J* = 8.0, 0.8 Hz, 1 H), 5.63–5.54 (m, 1 H), 5.51–5.44 (m, 1 H), 4.95–4.91 (m, 1 H), 3.86 (s, 3 H), 2.58–2.40 (m, 3 H), 1.60 (d, *J* = 6.8 Hz, 3 H) ppm. ^{1}H NMR (400 MHz, $CDCl_3$, *Z* isomer): δ = 3.84 (s, 3 H), 1.68 (d, *J* = 6.0 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, *E* isomer): δ = 156.49, 132.01, 128.26, 126.91, 126.75, 126.49, 120.69, 110.44, 70.41, 55.29, 34.89, 12.91 ppm. ^{13}C NMR (100 MHz, $CDCl_3$, *Z* isomer): δ = 156.41, 132.05, 128.49, 128.18, 127.56, 126.75, 120.69, 110.42, 69.79, 55.27, 40.73, 18.05 ppm. HRMS (ESI): calcd. for $C_{12}H_{16}O_2Na$ [M + Na]$^+$ 215.1048; found 215.1050.

2c: Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, *E* isomer): δ = 7.28–7.24 (m, 1 H), 6.96–6.91 (m,2 H), 6.82 (dd, *J* = 8.0, 1.6 Hz, 1 H), 5.68–5.58 (m, 1 H), 5.46–5.38 (m, 1 H), 4.70 (dd, *J* = 8.0, 5.2 Hz, 1 H), 3.82 (s, 3 H), 2.61–2.43 (m, 2 H), 2.06 (s, 1 H), 1.62 (d, *J* = 6.8 Hz, 3 H) ppm. ^{1}H NMR (400 MHz, $CDCl_3$, *Z* isomer): δ = 4.65 (dd, *J* = 8.0, 5.2 Hz, 1 H), 1.70 (d, *J* = 6.4 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, *E* isomer): δ = 159.74, 145.92, 129.40, 127.58, 125.71, 118.20, 112.95, 111.41, 73.79, 55.23, 36.86, 12.97 ppm. ^{13}C NMR (100 MHz, $CDCl_3$, *Z* isomer): δ = 159.74, 145.87, 129.37, 126.80, 125.71, 118.15, 112.95, 111.33, 73.41, 42.74, 29.70, 18.02 ppm. HRMS (ESI): calcd. for $C_{12}H_{16}O_2Na$ [M + Na]$^+$ 215.1048; found 215.1053.

2d: Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, *E* isomer): δ = 7.29 (d, *J* = 8.4 Hz, 2 H), 6.88 (d, *J* = 8.8 Hz, 2 H), 5.66–5.54 (m,1 H), 5.45–5.37 (m,1 H), 4.68–4.61 (m,1 H), 3.80 (s, 3 H), 2.61–2.38 (m,2 H), 2.01 (s, 1 H), 1.61 (d, *J* = 6.8 Hz, 3 H) ppm. ^{1}H NMR (400 MHz, $CDCl_3$, *Z* isomer): δ = 2.05 (s, 1 H), 1.68 (d, *J* = 6.4 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, *E* isomer): δ = 159.03, 136.35, 127.38, 127.11, 127.11, 125.87, 113.77, 113.77, 73.52, 55.28, 36.82, 12.99 ppm. ^{13}C NMR (100 MHz, $CDCl_3$, *Z* isomer): δ = 158.97, 136.30, 129.21, 127.07, 127.07, 126.98, 113.77, 113.77, 73.18, 55.28, 42.73, 18.06 ppm. HRMS (ESI): calcd. for $C_{12}H_{16}O_2Na$ [M + Na]$^+$ 215.1048; found 215.1049.

2e: Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, *E* isomer): δ = 6.89 (s, 1 H), 6.83–6.76 (m, 2 H), 5.95 (s, 2 H), 5.68–5.55 (m, 1 H), 5.44–5.37 (m, 1 H), 4.64–4.57 (m, 1 H), 2.59–2.32 (m, 2 H), 1.98 (d, *J* = 2.4 Hz, 1 H), 1.62 (d, *J* = 6.8 Hz, 3 H) ppm. ^{1}H NMR (400 MHz, $CDCl_3$, *Z* isomer): δ = 6.87 (s, 1 H), 2.04 (d, *J* = 2.0 Hz, 1 H), 1.69 (d, *J* = 6.0 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, *E* isomer): δ = 147.73, 146.89, 138.27, 127.57, 126.76, 119.24, 108.03, 106.43,

100.97, 73.74, 36.92, 12.98 ppm. ^{13}C NMR (100 MHz, $CDCl_3$, *Z* isomer): δ = 147.72, 146.82, 138.22, 129.40, 125.66, 119.18, 108.03, 106.43, 100.95, 73.38, 42.81, 18.03 ppm. HRMS (ESI): calcd. for $C_{12}H_{14}O_3Na$ [M + Na]$^+$ 229.0841; found 229.0842.

2f: Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, *E* isomer): δ = 7.24 (d, *J* = 8.8 Hz, 2 H), 7.16 (d, *J* = 8.0 Hz, 2 H), 5.67–5.57 (m, 1 H), 5.46–5.38 (m, 1 H), 4.69–4.62 (m, 1 H), 2.60–2.34 (m, 2 H), 2.34 (s, 3 H), 1.98 (s, 1 H), 1.61 (d, *J* = 6.8 Hz, 3 H) ppm. ^{1}H NMR (400 MHz, $CDCl_3$, *Z* isomer): δ = 2.03 (s, 1 H), 1.68 (dd, *J* = 6.0 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, *E* isomer): δ = 141.20, 137.17, 129.09, 129.09, 127.47, 125.88, 125.82, 125.82, 73.75, 36.86, 21.14, 18.09 ppm. ^{13}C NMR (100 MHz, $CDCl_3$, *Z* isomer): δ = 141.15, 137.06, 129.30, 129.06, 129.06, 126.97, 125.78, 125.78, 73.38, 42.77, 21.14, 13.02 ppm. HRMS (ESI): calcd. for $C_{12}H_{16}ONa$ [M + Na]$^+$ 199.1099; found 199.1098.

2g: Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, *E* isomer): δ = 7.35–7.24 (m, 2 H), 7.02 (t, *J* = 8.6 Hz, 2 H), 5.68–5.56 (m, 1 H), 5.42–5.36 (m, 1 H), 4.69 (dd, *J* = 7.2, 6.0 Hz, 1 H), 2.58–2.32 (m, 2 H), 2.09 (s, 1 H), 1.59 (d, *J* = 6.8 Hz, 3 H) ppm. ^{1}H NMR (400 MHz, $CDCl_3$, *Z* isomer): δ = 4.65 (dd, *J* = 8.0, 5.2 Hz, 1 H), 1.69 (d, *J* = 6.4 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, *E* isomer): δ = 162.16 (d, *J* = 244.0 Hz), 139.82 (d, *J* = 3.6 Hz), 127.87, 127.53, 127.44, 125.38, 115.26, 115.04, 73.22, 37.00, 12.94 ppm. ^{13}C NMR (100 MHz, $CDCl_3$, *Z* isomer): δ = 162.12 (d, *J* = 243.4 Hz), 139.77 (d, *J* = 3.5 Hz), 129.72, 127.48, 127.39, 126.51, 115.23, 115.03, 72.84, 42.89, 18.03 ppm. HRMS (ESI): calcd. for $C_{11}H_{13}FONa$ [M + Na]$^+$ 203.0848; found 203.0841.

2h: Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, *E* isomer): δ = 7.33–7.27 (m, 1 H), 7.14–7.06 (m, 2 H), 6.95 (t, *J* = 8.4 Hz, 1 H), 5.71–5.56 (m, 1 H), 5.44–5.37 (m, 1 H), 4.72 (dd, *J* = 7.2, 5.8 Hz, 1 H), 2.58–2.29 (m, 2 H), 2.14 (s, 1 H), 1.60 (d, *J* = 6.8 Hz, 3 H) ppm. ^{1}H NMR (400 MHz, $CDCl_3$, *Z* isomer): δ = 4.67 (dd, *J* = 8.0, 4.8 Hz, 1 H), 1.69 (d, *J* = 6.4 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, *E* isomer): δ = 162.96 (d, *J* = 243.8 Hz), 146.83 (d, *J* = 6.3 Hz), 129.84 (d, *J* = 8.6 Hz), 128.12, 125.17, 121.40 (d, *J* = 2.7 Hz), 114.24 (d, *J* = 21.1 Hz), 112.77 (d, *J* = 22.0 Hz), 73.17 (d, *J* = 1.8 Hz), 36.89, 12.95 ppm. ^{13}C NMR (100 MHz, $CDCl_3$, *Z* isomer): δ = 162.96 (d, *J* = 243.8 Hz), 146.78 (d, *J* = 6.1 Hz), 129.98, 129.81 (d, *J* = 8.5 Hz), 126.28, 121.36 (d, *J* = 3.0 Hz), 114.2 (d, *J* = 21.3 Hz), 112.74 (d, *J* = 21.9 Hz), 72.75 (d, *J* = 1.6 Hz), 42.77, 18.03 ppm. HRMS (ESI): calcd. for $C_{11}H_{13}FONa$ [M + Na]$^+$ 203.0848; found 203.0836.

2i: Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, *E* isomer): δ = 7.33–7.27 (m, 4 H), 5.70–5.56 (m, 1 H), 5.43–5.36 (m, 1 H), 4.72–4.68 (m, 1 H), 2.58–2.31 (m, 2 H), 2.05 (s, 1 H), 1.60 (d, *J* = 6.0 Hz, 3 H) ppm. ^{1}H NMR (400 MHz, $CDCl_3$, *Z* isomer). δ = 4.67–4.64 (m, 1 H), 2.10 (s, 1 H), 1.69 (d, *J* = 6.0 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, *E* isomer): δ = 142.57, 133.11, 128.49, 128.49, 128.05, 127.24, 127.24, 125.21, 73.14, 36.95, 12.96 ppm. ^{13}C NMR (100 MHz, $CDCl_3$, *Z* isomer): δ = 142.53, 133.02, 129.91, 128.47, 128.47, 127.20, 127.20, 126.31, 72.74, 42.81, 18.02 ppm. HRMS (ESI): calcd. for $C_{11}H_{13}ClONa$ [M + Na]$^+$ 219.0553; found 219.0563.

2j: Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, *E* isomer): δ = 7.46 (d, *J* = 8.0 Hz, 2 H), 7.24 (d, *J* = 8.0 Hz, 2 H), 5.69–5.56 (m, 1 H), 5.42–5.35 (m, 1 H), 4.68 (dd, *J* = 7.2, 5.8 Hz, 1 H), 2.57–2.31 (m, 2 H), 2.11 (s, 1 H), 1.59 (d, *J* = 6.8 Hz, 3 H) ppm. ^{1}H NMR (400 MHz, $CDCl_3$, *Z* isomer): δ = 4.63 (dd, *J* = 8.0, 6.4 Hz, 1 H), 1.69 (d, *J* = 6.4 Hz, 3 H) ppm.^{13}C NMR (100 MHz, $CDCl_3$, *E* isomer): δ = 143.09, 131.44, 131.44, 128.09, 127.60, 127.60, 125.17, 121.21, 73.18, 36.90, 12.97 ppm. ^{13}C NMR (100 MHz, $CDCl_3$, *Z* isomer): δ = 143.05, 131.42, 131.42, 129.96, 127.57, 127.57, 126.27, 121.12, 72.77, 42.78, 18.03 ppm. HRMS (ESI): calcd. for $C_{11}H_{13}BrONa$ [M + Na]$^+$ 263.0048; found 263.0047.

2k: Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, *E* isomer): δ = 5.97–5.81 (m, 1 H), 5.15–5.09 (m, 2 H), 2.68 (t, *J* = 5.6 Hz, 1 H), 2.39–2.36 (m, 1 H), 1.76 (s, 1 H), 1.11 (d, *J* = 6.4 Hz, 3 H), 0.94–0.91 (m, 1 H), 0.51–0.49 (m, 2 H), 0.28 (s, 2 H) ppm. ^{1}H NMR (400 MHz, $CDCl_3$, *Z* isomer): δ = 2.79 (t, *J* = 5.6 Hz, 1 H), 2.45–2.42 (m,1 H), 1.85 (s, 1 H), 0.56–0.53 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, *E* isomer): δ = 138.87, 113.62, 77.73, 43.03, 14.42, 13.49, 1.44, 0.01 ppm. ^{13}C NMR (100 MHz, $CDCl_3$, *Z* isomer): δ = 138.84, 112.83, 77.59, 41.83, 12.98, 12.58, 1.38, 0.16 ppm. HRMS (ESI): calcd. for $C_8H_{14}ONa$ [M + Na]$^+$ 149.0942; found 149.0942.

2l: Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, *E* isomer): δ = 5.83–5.74 (m, 1 H), 5.12 (d, *J* = 12.8 Hz, 2 H), 3.10 (s, 1 H), 2.38–2.31 (m, 1 H), 1.78–1.73 (m, 1 H), 1.46 (s, 1 H), 1.03 (d, *J* = 6.4 Hz, 3 H), 0.97 (d, *J* = 6.4 Hz, 3 H), 0.92 (d, *J* = 6.4 Hz, 3 H) ppm. ^{1}H NMR (400 MHz, $CDCl_3$, *Z* isomer): δ = 5.07 (d, *J* = 6.4 Hz, 2 H), 3.18 (s, 1 H), 1.38 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, *E* isomer): δ = 140.53, 116.09, 79.42, 41.41, 30.36, 19.87, 17.10, 16.41 ppm. ^{13}C NMR (100 MHz, $CDCl_3$, *Z* isomer): δ = 141.91, 114.60, 79.52, 40.62, 30.50, 19.64, 16.96, 13.54 ppm. HRMS (ESI): calcd. for $C_8H_{16}ONa$ [M + Na]$^+$ 151.1099; found 151.1098.

2m: Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, *E* isomer): δ = 7.47–7.42 (m, 2 H), 7.36–7.31 (m, 2 H), 7.25–7.22 (m, 1 H), 5.68–5.54 (m, 1 H), 5.30–5.19 (m, 1 H), 2.65–2.59 (m, 2 H), 2.12 (s, 1 H), 1.64 (d, *J* = 8.0 Hz, 3 H), 1.51 (s, 3 H) ppm. ^{1}H NMR (400 MHz, $CDCl_3$, *Z* isomer): δ = 2.45–2.39 (m, 2 H), 2.02 (s, 1 H), 1.61 (d, *J* = 6.8 Hz, 3 H), 1.56 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, *E* isomer): δ = 147.99, 130.57, 128.12, 128.12, 126.49, 125.86, 124.82, 124.82, 73.66, 47.23, 29.90, 18.05 ppm. ^{13}C NMR (100 MHz, $CDCl_3$, *Z* isomer): δ = 147.88, 128.33, 128.33, 126.57, 125.86, 124.96, 124.96, 124.84, 74.41, 41.22, 29.74, 13.01 ppm. HRMS (ESI): calcd. for $C_{12}H_{16}ONa$ [M + Na]$^+$ 199.1099; found 199.1101.

2n: Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, *E* isomer): δ = 7.35 (d, *J* = 8.8 Hz, 2 H), 6.87 (d, *J* = 8.8 Hz, 2 H), 5.66–5.54 (m,1 H), 5.31–5.20 (m,1 H), 3.81 (s, 3 H), 2.62–2.37 (m,2 H), 2.01 (s, 1 H), 1.64 (d, *J* = 6.0 Hz, 3 H), 1.50 (s, 3 H) ppm. ^{1}H NMR (400 MHz, $CDCl_3$, *Z* isomer): δ = 2.01 (s, 1 H), 1.61 (d, *J* = 6.8 Hz, 3 H), 1.54 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, *E* isomer): δ = 157.25, 139.19, 129.37, 124.97, 124.97, 124.11, 112.39, 112.39, 72.34, 54.20, 46.26, 28.93, 17.05 ppm. ^{13}C NMR (100 MHz, $CDCl_3$, *Z* isomer): δ = 157.18, 139.05, 129.58, 127.11, 125.00, 125.00, 112.68, 112.68, 73.10, 54.44, 40.24, 28.77, 12.01 ppm. HRMS (ESI): calcd. for $C_{13}H_{18}O_2Na$ [M + Na]$^+$ 229.1205; found 229.1208.

2o: Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, *E* isomer): δ = 7.33 (t, *J* = 8.0 Hz, 2 H), 7.15 (d, *J* = 8.0 Hz, 2 H), 5.67–5.53 (m, 1 H), 5.30–5.20 (m, 1 H), 2.59 (d, *J* = 7.2 Hz, 1 H), 2.38 (d, *J* = 8.4 Hz, 1 H), 2.34 (s, 3 H), 2.10 (s, 1 H), 1.64 (d, *J* = 6.4 Hz, 3 H), 1.49 (s, 3 H) ppm. ^{1}H NMR (400 MHz, $CDCl_3$, *Z* isomer): δ = 2.62 (d, *J* = 6.4 Hz, 1 H), 2.42 (d, *J* = 8.4 Hz, 1 H), 2.01 (s, 1 H), 1.61 (d, *J* = 7.2 Hz, 3 H), 1.54 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, *E* isomer): δ = 145.08, 136.10, 130.44, 128.82, 128.82, 125.11, 124.75, 124.75, 73.52, 47.20, 29.99, 20.95, 18.06 ppm. ^{13}C NMR (100 MHz, $CDCl_3$, *Z* isomer): δ = 144.97, 135.99, 128.82, 128.82, 128.20, 125.99, 124.77, 124.77, 74.29, 41.18, 29.82, 20.95, 13.05 ppm. HRMS (ESI): calcd. for $C_{13}H_{18}ONa$ [M + Na]$^+$ 213.1256; found 213.1256.

2p: Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, *E* isomer): δ = 7.68 (d, *J* = 7.6 Hz, 1 H), 7.35 (d, *J* = 7.6 Hz, 1 H), 7.27–7.16 (m, 2 H), 5.66–5.53 (m, 1 H), 5.22–5.10 (m, 1 H), 3.07–2.77 (m, 2 H), 2.80

(dd, J = 14.4, J = 8.4 Hz, 1 H), 2.55 (s, 1 H), 1.71 (s, 3 H), 1.63 (d, J = 6.0 Hz, 3 H) ppm. ^{1}H NMR (400 MHz, $CDCl_3$, *Z* isomer): δ = 3.18–3.13 (m, 1 H), 2.57–2.51 (m, 1 H), 2.59 (s, 1 H), 1.67 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, *E* isomer): δ = 143.84, 131.34, 130.93, 128.38, 128.24, 128.02, 126.81, 124.88, 75.02, 38.04, 27.24, 13.02 ppm. ^{13}C NMR (100 MHz, $CDCl_3$, *Z* isomer): δ = 144.01, 131.30, 130.78, 130.55, 128.19, 128.05, 126.81, 125.82, 74.22, 43.95, 27.17, 18.03 ppm. HRMS (ESI): calcd. for $C_{12}H_{15}ClONa$ $[M + Na]^+$ 233.0709; found 233.0719.

2q: Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, *E* isomer): δ = 7.38 (t, J = 8.4 Hz, 2 H), 7.30 (d, J = 8.4 Hz, 2 H), 5.69–5.53 (m, 1 H), 5.27–5.16 (m, 1 H), 2.65–2.52 (m, 2 H), 2.02 (s, 1 H), 1.60 (d, J = 6.8 Hz, 3 H), 1.54 (s, 3 H) ppm. ^{1}H NMR (400 MHz, $CDCl_3$, *Z* isomer): δ = 2.42–2.32 (m, 1 H), 2.12 (s, 1 H), 1.65 (d, J = 6.8 Hz, 3 H), 1.49 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, *E* isomer): δ = 146.37, 132.38, 128.78, 128.20, 128.20, 126.42, 126.42, 124.49, 74.15, 41.14, 29.80, 13.03 ppm. ^{13}C NMR (100 MHz, $CDCl_3$, *Z* isomer): δ = 146.50, 132.29, 131.06, 128.20, 128.20, 126.40, 126.40, 125.40, 73.38, 47.14, 29.92, 18.07 ppm. HRMS (ESI): calcd. for $C_{12}H_{15}ClONa$ $[M + Na]^+$ 233.0709; found 233.0689.

Supporting Information (see footnote on the first page of this article): Copies of the ^{1}H NMR and ^{13}C NMR spectra for compounds **2a**–**q**.

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[1] a) S. K. Woo, M. S. Kwon, E. Lee, *Angew. Chem.* **2008**, *120*, 3286; *Angew. Chem. Int. Ed.* **2008**, *47*, 3242–3244; b) C. L. Pereira, Y. H. Chen, F. E. McDonald, *J. Am. Chem. Soc.* **2009**, *131*, 6066–6067; c) M. R. Gesinski, K. Tadpetch, S. D. Rychnovsky, *Org. Lett.* **2009**, *11*, 5342–5345; d) P. Srihari, B. Kumaraswamy, J. S. Yadav, *Tetrahedron* **2009**, *65*, 6304–6309; e) H. M. Ko, C. W. Lee, H. K. Kwon, H. S. Chung, S. Y. Choi, Y. K. Chung, E. Lee, *Angew. Chem.* **2009**, *121*, 2400; *Angew. Chem. Int. Ed.* **2009**, *48*, 2364–2366; f) S. K. Woo, E. Lee, *J. Am. Chem. Soc.* **2010**, *132*, 4564–4565; g) M. Traore, M. Maynadier, F. Souard, L. Choisnard, H. Vial, Y. S. Wong, *J. Org. Chem.* **2011**, *76*, 1409–1417.

[2] a) A. Yanagisawa, H. Kageyama, Y. Nakatsuka, K. Asakawa, Y. Matsumoto, H. Yamamoto, *Angew. Chem.* **1999**, *111*, 3916; *Angew. Chem. Int. Ed.* **1999**, *38*, 3701–3703; b) R. A. Batey, A. N. Thadani, D. V. Smil, A. J. Lough, *Synthesis* **2000**, 990–998; c) T. Ishiyama, T. Ahiko, N. Miyaura, *J. Am. Chem. Soc.* **2002**, *124*, 12414–12415; d) M. Yasuda, K. Hirata, M. Nishino, A. Yamamoto, A. Baba, *J. Am. Chem. Soc.* **2002**, *124*, 13442–13447; e) A. V. Malkov, L. Dufkova, L. Farrugia, P. Kocovsky, *Angew. Chem.* **2003**, *115*, 3802; *Angew. Chem. Int. Ed.* **2003**, *42*, 3674–3677; f) L. Tang, L. Ding, W. X. Chang, J. Li, *Tetrahedron Lett.* **2006**, *47*, 303–306; g) A. V. Malkov, P. Ramirez-Lopez, L. Biedermannova, L. Rulisek, L. Dufkova, M. Kotora, F. Zhu, P. Kocovsky, *J. Am. Chem. Soc.* **2008**, *130*, 5341–5348; h) P. Jain, J. C. Antilla, *J. Am. Chem. Soc.* **2010**, *132*, 11884–11886; i) H. Kim, S. Ho, J. L. Leighton, *J. Am. Chem. Soc.* **2011**, *133*, 6517–6520; j) I. Sancho-Sanz, D. Miguel, A. Millan, R. E. Estevez, J. L. Oller-Lopez, E. Alvarez-Manzaneda, R. Robles, J. M. Cuerva, J. Justicia, *J. Org. Chem.* **2011**, *76*, 732–735; k) A. V. Malkov, M. Barlog, Y. Jewkes, J. Mikusek, P. Kocovsky, *J. Am. Chem. Soc.* **2011**, *133*, 4800–4804; l) A. Millan, A. G. Campana, B. Bazdi, D. Miguel, L. Alvarez de Cienfuegos, A. M. Echavarren, J. M. Cuerva, *Chem. Eur. J.* **2011**, *17*, 3985–3994.

[3] a) Y. Yamamoto, N. Asao, *Chem. Rev.* **1993**, *93*, 2207–2293; b) S. E. Denmark, J. Fu, *Chem. Rev.* **2003**, *103*, 2763–2793.

[4] a) S. Matsukawa, Y. Funabashi, T. Imamoto, *Tetrahedron Lett.* **2003**, *44*, 1007–1010; b) G. Bartoli, A. Giuliani, E. Marcantoni, M. Massaccesi, P. Melchiorre, S. Lanari, L. Sambri, *Adv. Synth. Catal.* **2005**, *347*, 1673–1680; c) G. Li, G. Zhao, *J. Org. Chem.* **2005**, *70*, 4272–4278.

[5] a) T. P. Loh, K. T. Tan, Q. Y. Hu, *Angew. Chem.* **2001**, *113*, 3005; *Angew. Chem. Int. Ed.* **2001**, *40*, 2921–2922; b) J. Nokami, K. Nomiyama, S. M. Shafi, K. Kataoka, *Org. Lett.* **2004**, *6*, 1261–1264; c) C. K. Lee, C. A. Lee, K. T. Tan, T. P. Loh, *Org. Lett.* **2004**, *6*, 1281–1283; d) A. V. Malkov, M. A. Kabeshov, M. Barlog, P. Kocovsky, *Chem. Eur. J.* **2009**, *15*, 1570–1573; e) S. Kobayashi, T. Endo, U. Schneider, M. Ueno, *Chem. Commun.* **2010**, *46*, 1260–1262; f) M. Chen, W. R. Roush, *Org. Lett.* **2010**, *12*, 2706–2709; g) X. Gao, I. A. Townsend, M. J. Krische, *J. Org. Chem.* **2011**, *76*, 2350–2354.

[6] a) K. T. Tan, S. S. Chng, H. S. Cheng, T. P. Loh, *J. Am. Chem. Soc.* **2003**, *125*, 2958–2963; b) P. V. Ramachandran, D. Pratihar, D. Biswas, *Chem. Commun.* **2005**, 1988–1989.

[7] a) U. Schneider, S. Kobayashi, *Angew. Chem.* **2007**, *119*, 6013; *Angew. Chem. Int. Ed.* **2007**, *46*, 5909–5912; b) M. Yamaguchi, N. Morita, U. Schneider, S. Kobayashi, *Adv. Synth. Catal.* **2010**, *352*, 1461–1465.

[8] a) S. Hayashi, K. Hirano, H. Yorimitsu, K. Oshima, *J. Am. Chem. Soc.* **2006**, *128*, 2210–2211; b) M. Iwasaki, S. Hayashi, K. Hirano, H. Yorimitsu, K. Oshima, *J. Am. Chem. Soc.* **2007**, *129*, 4463–4469; c) M. R. Medeiros, J. L. Wood, *Tetrahedron* **2010**, *66*, 4701–4709; d) R. Wakabayashi, D. Fujino, S. Hayashi, H. Yorimitsu, K. Oshima, *J. Org. Chem.* **2010**, *75*, 4337–4343.

[9] L. M. Zhao, H. S. Jin, L. J. Wan, L. M. Zhang, *J. Org. Chem.* **2011**, *76*, 1831–1837.

[10] E. Estevez, J. Justicia, B. Bazdi, N. Fuentes, M. Paradas, D. Choquesillo-Lazarte, J. M. Garcia-Ruiz, R. Robles, A. Gansauer, J. M. Cuerva, J. E. Oltra, *Chem. Eur. J.* **2009**, *15*, 2774–2791.

[11] a) T. Daskapan, *Tetrahedron Lett.* **2006**, *47*, 2879–2881; b) T. Daskapan, F. Yesilbag, S. Koca, *Appl. Organomet. Chem.* **2009**, *23*, 213–218.

[12] T. Mukhopadhyay, D. Seebach, *Helv. Chim. Acta* **1982**, *65*, 385–391.

[13] a) J. Nokami, K. Yoshizane, H. Matsuura, S. Sumida, *J. Am. Chem. Soc.* **1998**, *120*, 6609–6610; b) J. Nokami, L. Anthony, S. Sumida, *Chem. Eur. J.* **2000**, *6*, 2909–2913; c) S. Sumida, M. Ohga, J. Mitani, J. Nokami, *J. Am. Chem. Soc.* **2000**, *122*, 1310–1313; d) J. Nokami, M. Ohga, H. Nakamoto, T. Matsubara, I. Hussain, K. Kataoka, *J. Am. Chem. Soc.* **2001**, *123*, 9168–9169.

[14] G. Courtois, L. Miginiac, *J. Organomet. Chem.* **1974**, *69*, 1–44.

[15] a) P. J. Battye, D. W. Jones, *J. Chem. Soc., Chem. Commun.* **1986**, 1807–1808; b) D. M. Birney, X. Xu, S. Ham, *Angew. Chem.* **1999**, *111*, 147; *Angew. Chem. Int. Ed.* **1999**, *38*, 189–193; c) Y. Kato, K. Miki, F. Nishino, K. Ohe, S. Uemura, *Org. Lett.* **2003**, *5*, 2619–2621.

[16] Zinc powder was activated by using acetic acid in MeOH. After stirring for 20 min, the metal was filtered, washed and dried under high vacuum for 3 h.

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