JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

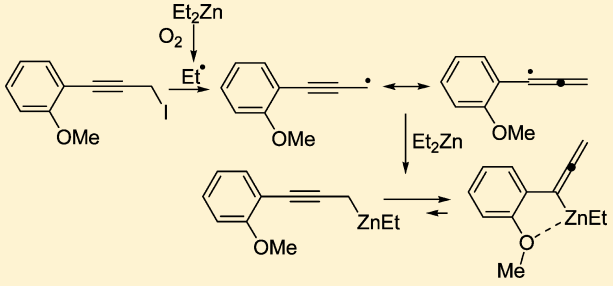
Theoretical Support for the Involvement of a Radical Pathway in the Formation of Allenylzincs from Propargyl Iodides and Dialkylzincs: Influence of Zinc Coordination

Suribabu Jammi,[†] Dominique Mouysset,[†] Didier Siri,*[,‡] Michèle P. Bertrand,*[,†] and Laurence Feray*[,†]

Aix-Marseille Université, CNRS, Institut de Chimie Radicalaire, UMR 7273, Equipes [†]CMO and [‡]CT, 13397 Cedex 20, Marseille, France

Supporting Information

ABSTRACT: Propargyl iodides are good precursors for allenylzincs via reaction with diethylzinc, even in nondegassed medium. These reactions proceed via zinc/iodine exchange. Owing to the previously reported detection of propargyl radical by ESR experiments, in this process a radical mechanism was suspected. Calculations of the C−Zn BDEs in allenyl- and propargylzinc species were performed with the CBS-QB3 method to demonstrate that propargyl radicals could undergo homolytic substitution at zinc. The stabilization of allenylzinc derivatives by chelation, made possible by the selection of appropriate ortho-substituted 3-phenylalkynyl iodides as precursors, was shown to influence the regioselectivity of their addition to aldehydes and ketones. The more stabilized the chelated allenylzinc intermediate, the higher the ratio of homopropargylic alcohols.



INTRODUCTION

The reactivity of allenylzincs and other allenyl metals, stimulated by the synthetic potential of acetylenic and allenic linkages, has widely been investigated.[1] Little rationale can help in predicting the reactivity of these organometallic species with electrophiles.

Different methodologies have been explored for the specific production of organozinc compounds:[2,3] transmetalation of organo-lithiated derivatives in the presence of ZnX_2,[4] boron/Zn exchange from boronates,[5] palladozincation of propargyl benzoates or mesylates,[6] direct zincation of propargyl halides,[7] Zn-mediated Barbier reactions[8] and Brook rearrangement.[9] Comparatively, procedures involving iodine/Zn exchange from the corresponding propargyl iodides[10] or allenyl iodides have scarcely been exploited.[11] Closely related In-mediated reactions have also been reported.[12] In most of these reactions, allenylzinc derivatives, supposed to be in equilibrium with the isomeric propargylzincs, behave as propargylation reagents when reacting with aldehydes or ketones via six-membered ring transition states.[13] This behavior affords valuable stereoselective synthetic routes to homopropargyl alcohols.[2,4−6,9,10] However, the regioselectivity of reactions of allenylmetal compounds with electrophiles depends on numerous parameters like the nature of the substituents at the α- and γ- positions in the alkynyl system, the metal, and the nature of the electrophile. It is often related to steric effects. As an example allenylzinc reagents derived from TMS and most of all TIPS and TBDMS protected alkynes lead to the quasi exclusive formation of homopropargyl alcohols.[2,4,14]

Our group has been involved in radical reactions promoted by dialkylzincs over the past decade.[15] The generation and the reactivity of propargyl radicals have scarcely been investigated, and little synthetic applications have been developed for these short-lived species.[16] The treatment of propargyl iodides with diethylzinc in the presence of a catalytic amount of oxygen was recently shown to produce propargyl radical on the ground of electron paramagnetic resonance (EPR) experiments.[17] As a consequence, a radical chain mechanism might be proposed for the formation of allenylzincs which would imply homolytic displacement at diethylzinc by propargyl radical. However, owing to the great sensitivity and specificity of EPR technique in detecting free radicals, the detection of propargyl radicals is necessary but not sufficient to demonstrate that the formation of allenylzinc derivatives follows a radical pathway. Theoretical calculations were undertaken to better understand the driving force for this homolytic reaction. Such a displacement should be facilitated by the coordination of zinc atom with a basic directing group.[18]

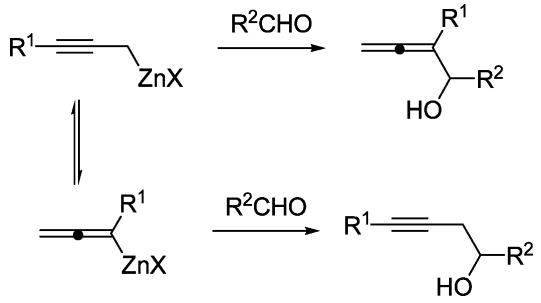
Chelation is known to influence the stereochemical outcome of reactions of alkylzinc derivatives.[19] This is the reason why we decided to investigate the possibility to initiate by oxygen the formation of chelated allenylzinc species, and to explore the impact of a coordinated directing group on the competition between propargylation and allenylation of electrophiles like aldehydes and ketones. It is generally admitted that a S_E2' mechanism is operative (Scheme 1).[2]

Chelated allenylzincs of variable ring-size were prepared from *o*-substituted 3-phenylpropargyl iodides of type **1b−d** and

Received: December 12, 2012
Published: January 13, 2013

   dx.doi.org/10.1021/jo302704g | J. Org. Chem. 2013, 78, 1589−1603

Scheme 1. General Reaction of Allenylzincs with Aldehydes



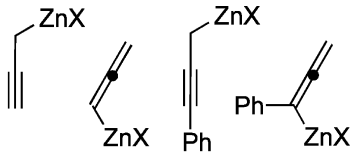
8a–c. The influence of the basic oxygen atom of ether and ester groups on the regioselectivity of their reactions with selected electrophiles is discussed in the following (Schemes 4, 5, 6).

RESULTS AND DISCUSSION

Theoretical calculations of the C–Zn bond dissociation enthalpy (BDE) in isomeric propargyl- and allenylzinc derivatives were performed at the CBS-QB3 level of theory.[20,21]

An equilibrium promoted by a metallotropic rearrangement is often used to represent allenylzinc and propargylzinc species (Scheme 1). In the absence of substituent on the allenyl moiety, allenylzinc species are reputedly thermodynamically more stable than their propargylic isomers. Unsubstituted propargylzinc-, 3-phenylpropargylzinc-, and the corresponding isomeric allenylzinc species, were taken as models for this theoretical study. The bond dissociation enthalpy of the C–Zn bond in each of these monomeric species was calculated, and the relative stability of the two regio-isomers was compared in both cases. The data are reported in Table 1.

Table 1. C–Zn BDEs in Propargylzinc and Allenylzinc Species, Calculated at the CBS-QB3 Level of Theory

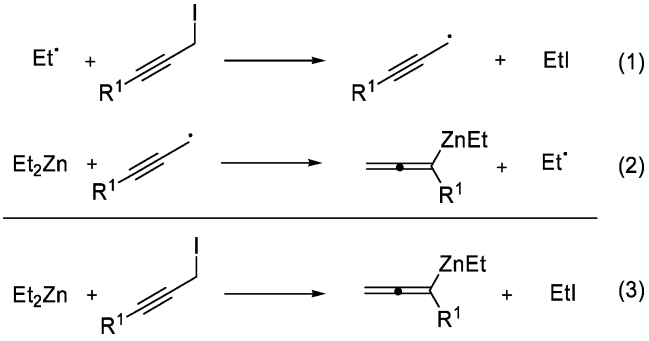


C-ZnX BDE (kJ mol^{-1})	X= Et	256	272	250	261
	X= OEt	271	285	266	271

In a process initiated with oxygen, X can either be an ethyl group or an ethoxy group in RZnX species (Scheme 2). Even though the former is more likely in the presence of a catalytic amount of oxygen,[22] the C–Zn BDEs were calculated for both types of monomeric propargyl- and allenylzinc species. These values clearly indicate that the C–Zn bond is stronger in the allenylzinc derivative. When X = Et, allenylzincs are more stable by 16 kJ mol^{-1} (bare allenyl frame) and 11 kJ mol^{-1} (phenylsubstituted allene), than the corresponding propargylzincs. At room temperature, the equilibrium between propargyl- and allenylzinc derivatives, postulated in Scheme 1, should be completely, or quasi completely, shifted toward the latter.

It must be noted that the C–Zn bond (Table 1) is either lower by 5 kJ.mol^{-1} (R = CH=C=CH$_2$) or 16 kJ.mol^{-1} (R = C(Ph)=C=CH$_2$) in allenylzinc derivatives than the C–Zn bond in Et$_2$Zn (277 kJ mol^{-1} at the same level of theory). This means that the transfer of EtZn group should be endothermic.

The global exchange in eq 3 implies the simultaneous formation of ethyl iodide through iodine atom transfer from the



propargylic iodide to ethyl radical (eq 1). As the C–I bond is much stronger in ethyl iodide than in propargyl iodide, the iodine atom transfer favors the generation of propargyl radical (ΔH = −50.9 kJ mol^{-1} when R^1 = H, according to experimental C–I BDE values).[23] Therefore the exothermicity of the first propagation step largely counter-balance the endothermicity of the second one (eq 2). Enthalpic factors are therefore favorable to the formation of allenylzincs through two successive S_H2 processes (global exothermicity −45.9 kJ mol^{-1} when R^1 = H).

Both reversible and irreversible tautomerization of metal η^1-allenyl species, are known.[24] The theoretical studies were completed by investigating the isomerization of monomeric ethyl propargylzinc into the corresponding allenylzinc (Scheme 3).

As stated above, the optimization of both species led to two distinct stable structures.[25] The less stable propargylzinc readily converts into its isomer via a concerted pathway. The reaction profiles were calculated in three cases. The transition states were located at the level of theory used in the optimization step of the CBS-QB3 procedure (B3LYP/6-311G(2d,d,p)) and confirmed by the Intrinsic Reaction Coordinate (IRC) approach. The calculations of their free energy performed at the CBS-QB3 level allowed the estimation of reaction barriers and of approximate reaction rates.

Theoretical calculations at the CBS-QB3 level of theory show that the rearrangement of monomeric propargylzinc into allenylzinc has an activation barrier ranging between 30 (iii) to 33.5 kJ mol^{-1} (ii) for X = Et. The structures of the transition states are shown in Scheme 3.

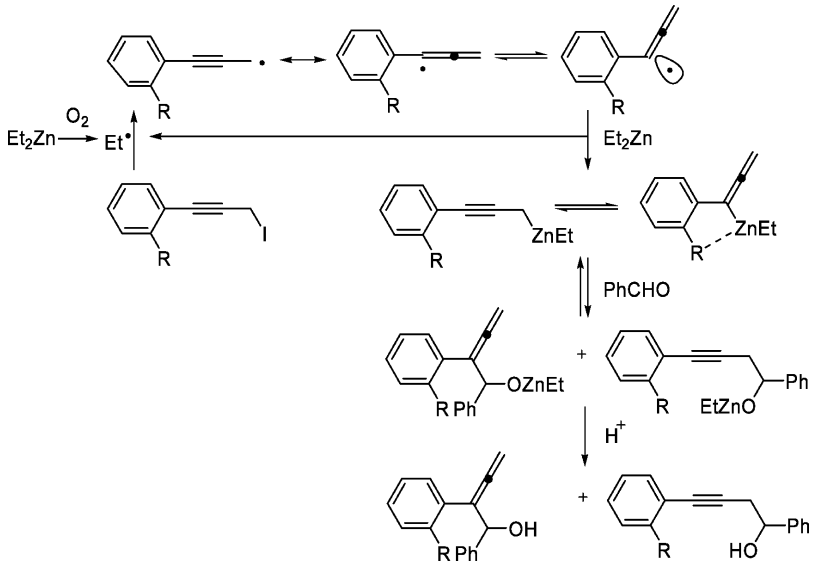
As expected when the stabilization of the allenylzinc increases with chelation, the activation barrier for the reverse reaction reaches 70 kJ mol^{-1}. Therefore, in the case of allenylzinc **B** (Figure 1), the reverse process should be dramatically slowed down. According to the calculated values, the rate constant for the rearrangement of propargylzinc derivatives in the isomeric allenylzincs would be extremely fast, ranging between 9 to 17 × 10^5 s^{-1} at 298 K.

The rate constant for the reverse isomerization would be nearly 2 orders of magnitude slower in cases (i) and (ii), that is, k_- = 4–20 × 10^3 s^{-1} (which still remains very fast), whereas in the case of the chelated enolate **B** (iii), the conversion of the allenylzinc back to the propargylzinc would be 5 orders of magnitude slower (k_-= 1.3 s^{-1}). This should influence the reactivity of these organometallic species with respect to electrophiles.

Ether Oxygen Atoms as Intramolecular Coordinating Agents. Our goal was to investigate how coordinating substituents in position ortho on the aromatic ring might influence the regioselectivity of the trapping of allenylzinc species by electrophiles. To this end, a series of 3-phenylpropargyl iodides

dx.doi.org/10.1021/jo302704g | J. Org. Chem. 2013, 78, 1589–1603

Scheme 2. Radical Route to Allenylzincs and Subsequent Trapping by Benzaldehyde



bearing methoxy or ω-methoxyalkyl groups in position ortho relative to the triple bond were prepared and reacted with diethylzinc in the presence of benzaldehyde in nondegassed medium. The results compared to those obtained from 3-phenylpropargyl iodide are given in Scheme 5. Blank experiments performed in the absence of aldehyde by simply quenching the reaction with aqueous NH_4Cl, led to the data reported in Scheme 4. A trace amount of the alkyne resulting from nucleophilic substitution of the iodine atom by an ethyl group, was detected in the case of iodide **1b**. This is consistent with iodide becoming a better leaving group as regard to nucleophilic displacement, owing to the electronic effect of the *o*-methoxy group.

Clearly no incidence of the possible chelation of allenylzinc intermediates **B**–**D** (Figure 1) was detected on the regioselectivity of the protonation. This is in good agreement with the lack of significant difference in Mulliken net atomic charges on the two extreme carbons of the allenyl (or propargyl) system in the isomeric metalated derivatives (Table 2).

The formation of allenylzincs was monitored by ^{1}H NMR (nondegassed solvent).[26] As shown in Figure 2, in the case of iodide **1b**, nearly no evolution was detected unless the NMR tube was shaken so that the two reagents interact with each other. Only the starting material was detected (the methylene protons and the methyl protons gave rise to two singlets at 3.95 and 3.80 ppm, respectively).

After shaking the solution, which clearly evidenced the influence of the nondegassed medium (Figure 2), the signal of EtI grew regularly while new signals appeared that were assigned to allenylzinc **B** (☆) (1:1 ratio with respect to EtI; the $=CH_2$ group was assigned the singlet at 4.31 ppm and the protons in the CH_3O group exhibited a singlet at 3.89 ppm). It is to be noted that trace amount of **2b** (▲) and **3b** (■) together with the alkyne resulting from the nucleophilic substitution of iodine by an ethyl group ($ArC{\equiv}CCH_2CH_2CH_3$) were detected. After completion, the quenching of the reaction by addition of a drop of water led to the disappearance of the signals corresponding to allenylzinc **B**, and concomitantly to the increase of the signals of both **2b** and **3b** (60:40 ratio) resulting from its protonation. Only trace amount of signals corresponding to ethoxy groups could be detected at 3.70 ppm under these conditions.

It is worth noting that the role of oxygen was even more striking when more oxygen was allowed to interact with the solution by several cycles of shaking/reopening the NMR tube just before registering the spectrum (Figure 2). The formation of allenylzinc **B** and EtI became quasi instantaneous.[27] The formation of allenylzinc **C** exhibited the very same behavior. A closely related behavior was also observed when monitoring the reaction of diethylzinc with **1d**. (see Supporting Information).

It was interesting to compare the reactivity of iodide **1a** to that of **1b**. In the case of **1a** (Figure 3), no clearly distinct signals could be assigned to the protons of either allenylzinc **A** or its propargylic isomeric form, even though the signals corresponding to EtI were strong. Only a hardly visible very broad singlet appeared at 2.65 ppm. That signal gradually increased with the amount of EtI in the reaction medium. However, the quenching of the reaction led to clean signals corresponding to the expected allene and alkyne in a 55:45 ratio, exactly matching the amount of EtI, as in the other experiments.

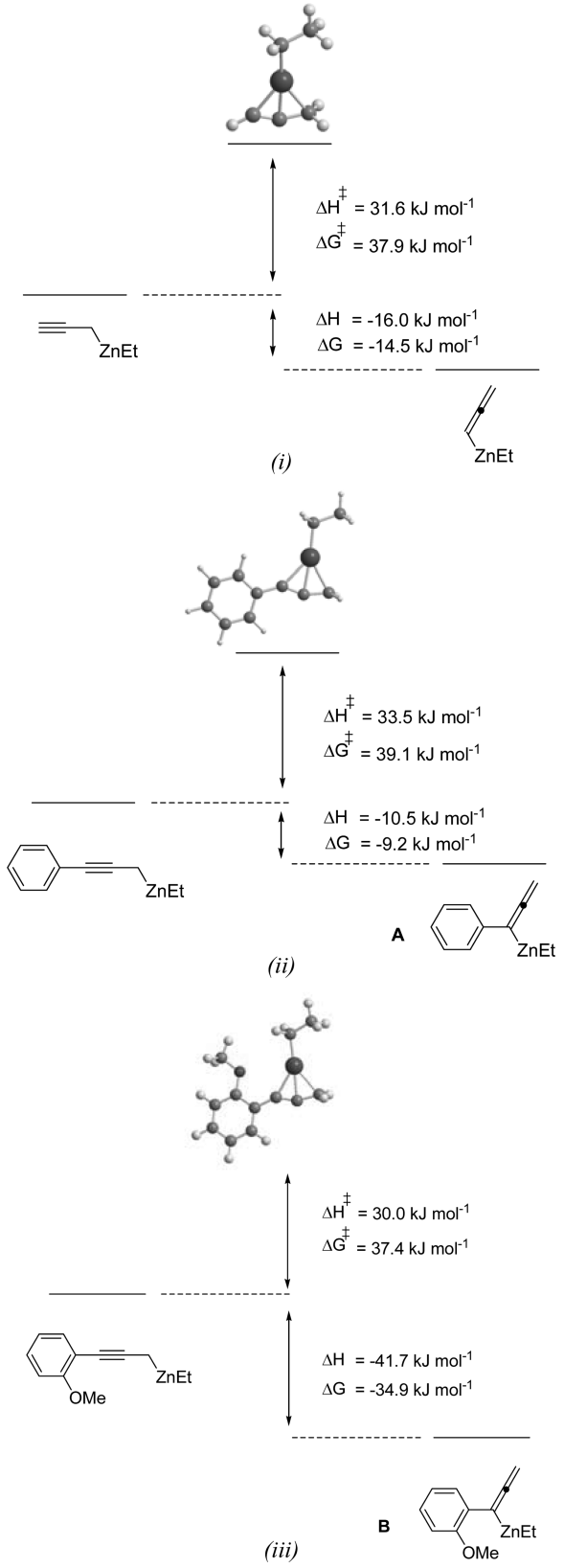
This observation would be consistent with a polymeric nature of these organozinc species, as suggested by Utimoto, who reported that the depolymerization of the latter could be induced by the addition of diethyl ether to the reaction medium.[10] The involvement of a radical mechanism in alkenes carbozincation has already been proposed.[28] However, covalent bonding is not necessarily implied in the formation of polymeric species, coordination of Zn(II) with π bonds has already been demonstrated.[29] The broadening of the signal suggests an alternative rationale, it might result of a dynamic process with allenyl- and propargylzinc species fastly interconverting at room temperature at an intermediate rate with respect to the NMR time-scale.

As expected from the estimate of the isomerization rate constant, the coordinated methoxy group in **B** (and in all likelihood in **C**) would slow down the interconversion process so that only the most stable allenylzinc species are detected by NMR. The rate of interconversion would be too fast in the case of **A**. No effect was observed on the ^{1}H NMR spectrum by lowering the temperature down to 200 K.

The reaction of diethylzinc with oxygen is likely to promote a radical chain reaction, as proposed in Scheme 2. Propargyl radical can be represented by the contribution of two canonical forms. It should rapidly interconvert into the slightly geometrically

dx.doi.org/10.1021/jo302704g | J. Org. Chem. 2013, 78, 1589–1603

Scheme 3. Isomerization of Propargylzinc Derivatives in Isomeric Allenylzincs



different allenyl radical. This vibrational motion is accompanied by the rehybridation of the initially sp hybridized carbon atom into a sp^2 carbon. The calculated bending frequencies of the

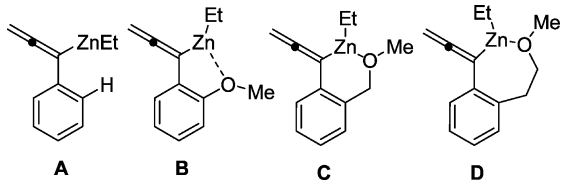
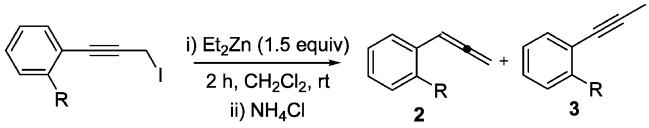


Figure 1. Structure of allenylzincs **A**–**D**.

Scheme 4. Protonation of Allenylzincs A–D



1a	R= H	57%	58:42
1b	R= OMe	48%	52:48
1c	R= CH_2OMe	66%	51:49
1d	R= $(CH_2)_2OMe$	87%	46:54

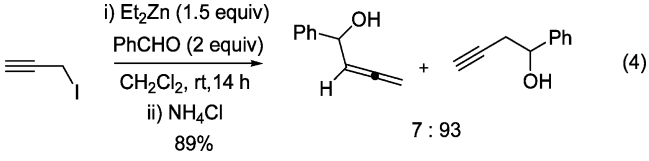
C–H and the C–C_{ar} bonds are 467 and 257 cm^{-1}, in propargyl and phenylpropargyl radicals, respectively, which indicates a very low barrier to the geometrical change.[30] As already stated, owing to the substitution of Et–Zn bond by a slightly weaker C–Zn bond and the replacement of the propargyl-I bond by a much stronger C–I bond, the allenyl radical can displace an ethyl group from diethylzinc. This displacement is even more favored in the presence of a coordinating substituent on the aromatic ring.

Visualization of Natural Bond Orbitals[31] (performed on geometries calculated at the B3LYP/6-31+G(d,p)) showing the orbital overlaps that probes the interaction between the oxygen lone pair and zinc in the chelated allenylzincs **B** and **D** is given in Figure 4. Even in the case of the most flexible arm in position ortho (-$(CH_2)_2$OMe) (**D**), the NBO analysis shows that the overlap of the lone pair of the oxygen atom with the vacant *p* orbital at zinc contributes to the stabilization of the allenylzinc species (by approximately 18 and 17 kcal mol^{-1}, respectively).

The influence of the chelating arms on the aromatic ring on the relative stabilities of allenylzincs **B**, **C**, **D**, as compared to the corresponding propargylzinc species, was calculated. The results of these theoretical calculations are given in Table 3. It must be noted that the stability of the most stable conformers of the chelated allenylzinc species shown in Figure 5 was found superior by 26–30 kJ mol^{-1} to that of the nonchelated, torsionless, released conformers. This supports the easy formation of chelated species.

The presence of coordinating agents in the medium strongly influences the reactivity of alkylzinc species.

The reactions reported in Scheme 5, performed in the presence of benzaldehyde, were compared to the reaction performed with propargyl iodide which can be used as standard (eq 4). Under completely similar experimental conditions, the

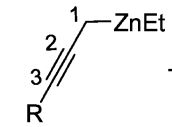
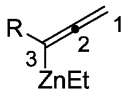


(4)

allenylzinc formed from propargyl iodide led to the highly regioselective formation of the expected homopropargyl alcohol. This result is obviously different from the data obtained from nonsubstituted 3-phenyl-propargyl iodide **1a** which led to a

dx.doi.org/10.1021/jo302704g | J. Org. Chem. 2013, 78, 1589–1603

Table 2. Mulliken Net Atomic Charges in Propargyl and Allenylzinc Species Calculated at B3LYP/6-311G(2d,d,p)

	R=H			R=Ph			R=*o*-MeO-Ph		
	C1	C2	C3	C1	C2	C3	C1	C2	C3
	-0.6	+0.1	-0.1	-0.6	+0.1	-0.1	-0.6	+0.1	+0.1
	-0.1	+0.1	-0.6	-0.1	+0.1	-0.8	-0.1	+0.1	-0.8

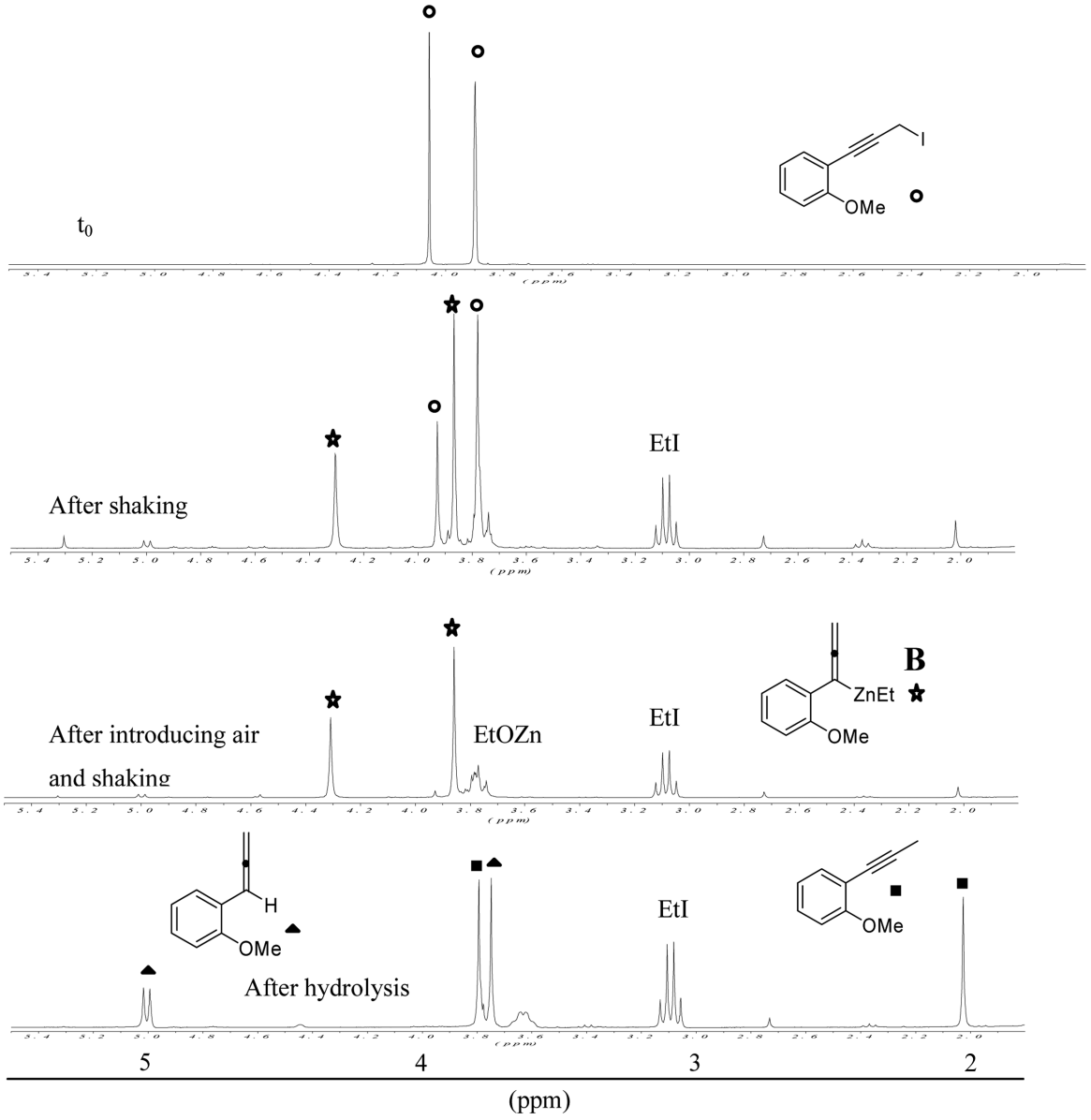


Figure 2. ^{1}H NMR monitoring (between 2.0 and 5.4 ppm) of the formation of organometallic species from **1b**.

52:48 ratio of allenylation to propargylation (Scheme 5). This experimental observation correlates with the relative stabilities of propargyl/allenylzinc species in both cases. However, no assumption could be made about the rate constant for the bimolecular reaction of each species with benzaldehyde.

In the presence of benzaldehyde, a clear influence of the nature of the substituent in position ortho on the aromatic ring is observed. The size of the intermediate chelated allenylzinc governs the regioselectivity and the overall yield of the reaction (Scheme 5).

It must be noted that reactions were performed under inert atmosphere but without degassing the solvent in order for a catalytic amount of oxygen to be present in the medium to initiate a radical chain process. Very good yields could be reached

dx.doi.org/10.1021/jo302704g | *J. Org. Chem.* 2013, 78, 1589−1603

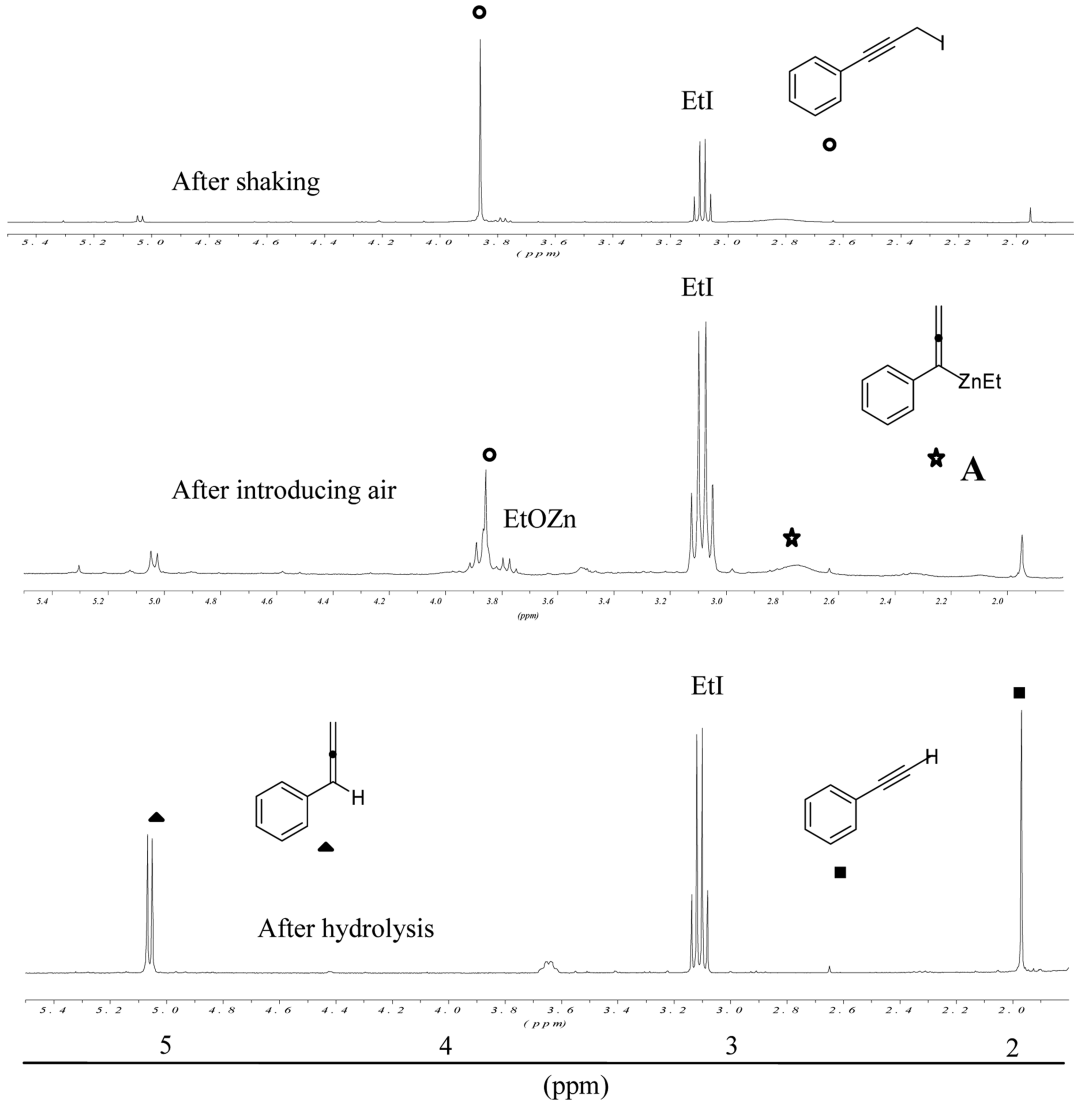


Figure 3. ^{1}H NMR monitoring (between 2.0 and 5.4 ppm) of the formation of organometallic species from **1a**.

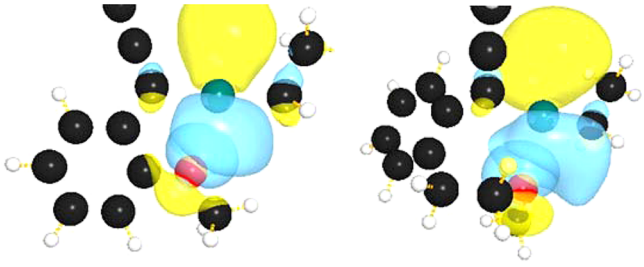


Figure 4. NBO visualization of the interaction between the oxygen lone pair and the metal in **B** and **D**.

despite the presence of oxygen.[9,32] Even when air was added (20 mL) to the reaction medium in dichloromethane, the overall yield from iodide **1d** was only lowered to 78%. The ratio of isomeric products was essentially the same, and trace amount of propargylic alcohol was detected. This argues in favor of a radical mechanism for the formation of the reactive species, whatever the experimental conditions.

It is noteworthy that the lack of regioselectivity in the reaction of **1a** (Scheme 5) is completely different from that

Table 3. Relative Energies of Propargylzinc and Chelated Allenylzinc Species Calculated at the CBS-QB3 Level of Theory

	Relative energies in kJ mol^{-1}			
R	H	OMe	CH_2OMe	$(CH_2)_2OMe$
ZnEt, R	0	0	0	0
ZnEt, R	-10.5	-40.7 (**B**)	-39.9 (**C**)	-12.3 (**D**)

observed in the In(0)-mediated reaction (97:3 in favor of the allenylation product), however, the latter experiment was performed at room temperature in the presence of a chiral amino-alcohol.[11d] A completely different ratio was also reported by Tamaru and co-workers for the Pd-catalyzed zincation of **1a** which led to a 18:82 ratio in favor of the homopropargylic alcohol at the same temperature.[6a] It is hardly believable that

dx.doi.org/10.1021/jo302704g | J. Org. Chem. 2013, 78, 1589−1603

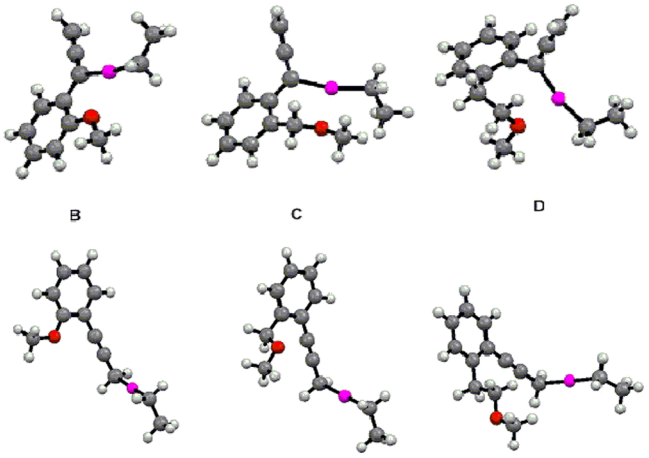
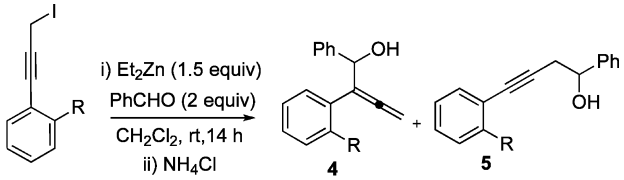


Figure 5. Calculated most stable conformers of chelated allenyl species **B**, **C**, and **D** and the corresponding propargylzincs.

Scheme 5. Reaction of Allenylzincs A–D with Benzaldehyde



1a	R= H	56%	52:48[a]
1b	R= OMe	72%	35:65[a]
1c	R= CH_2OMe	75%	44:56[a]
1d	R= $(CH_2)_2OMe$	90%	72:28[a]

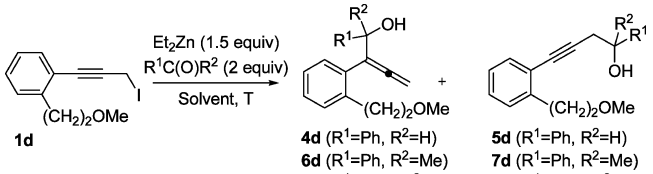
the same type of reactive intermediate could be involved in these reactions.

The presence of the ortho-substituent influences the ratio of allenylation to propargylation. Increasing the size of the ring in the chelated allenylzincs, which are likely to be involved in these reactions, contributes to increase the ratio of allenyl alcohol. It is generally admitted that propargyl- and allenylzincs react through six-membered transition states to give allenylation and propargylation products, respectively.[2] Therefore the more stabilized is the allenylmetal, the higher the ratio of homopropargyl versus allenyl alcohol should be. The frame giving rise to the most stabilized chelate leads to the highest relative amount of homopropargyl alcohol (Figure 1). Nevertheless, it is difficult to exclude from these data, the participation of a S_E2 mechanism in these reactions. Only the determination of the activation barriers of S_E2' reactions of allenyl- and propargylzinc species with aldehydes would help in clarifying this point. The knowledge of thermodynamic data is not sufficient to predict the kinetics of competitive reactions.

Since most methods involving organozincs, as reminded above, are selective in the formation of homopropargyl alcohols, we tried to displace the reaction in the opposite direction. We searched how to improve the amount of allenylation by testing various experimental conditions in the most favorable case, that is, taking **1d** as substrate. The influence of parameters like the solvent, the temperature, and the nature of the electrophile are reported in Table 4.

No significant change in the regioisomers ratio was detected when changing the nature of the solvent (entries 1–3). However, yields were lower in toluene and THF than in DCM. Temperature has a large incidence on the ratio of the two regioisomers.

Table 4. Parameters Influencing the Ratio of Allenyl/Homopropargyl Alcohol Starting from 1d



4d (R^1=Ph, R^2=H) **5d** (R^1=Ph, R^2=H)
6d (R^1=Ph, R^2=Me) **7d** (R^1=Ph, R^2=Me)
8d (R^1=*n*-Pr, R^2=H) **9d** (R^1=*n*-Pr, R^2=H)
10d (R^1=Me, R^2=Me) **11d** (R^1=Me, R^2=Me)

entry	*T* (° C)	solvent	time	yield	products	ratio
1	25	CH_2Cl_2	14 h	90%	**4d:5d**	72:28
2	25	Toluene	14 h	56%	**4d:5d**	75:25
3	25	THF	14 h	51%	**4d:5d**	75:25
4	25	DMF	14 h	84%	**4d:5d**	74:26
5	−10	CH_2Cl_2	16 h	64%	**4d:5d**	72:28
6	80	$(CH_2Cl)_2$	40 min	96%	**4d:5d**	7:93
7	25	CH_2Cl_2	14 h	87%	**6d:7d**	<1:>99
8	25	CH_2Cl_2	14 h	70%	**8d:9d**	66:34
9	25	CH_2Cl_2	14 h	73%	**10d:11d**	9:91[a]

[a]Trace amount of the propargylic alcohol corresponding to the starting material was detected from the ^{1}H NMR spectrum of the crude mixture.

The lowering of the temperature down to −10 °C did not increase the amount of allenyl alcohol (entry 5). Conversely, increasing the temperature up to 80 °C led to a 7:93 regioisomers ratio in favor of the homopropargylic alcohol (entries 6) which is the thermodynamic product. When an isolated 69:31 mixture of allenyl- and homopropargyl- alcohols **4d** and **5d** was allowed to react with diethylzinc at 80 °C, **5d** was isolated as the only product in quantitative yield. This is an additional evidence for the reversibility of the addition reaction that had previously been assumed.[2a] Conversely allenyl alcohol **4a** prepared in 72% from **1a** by the indium methodology (In(0), AcOH, in DMF)[11] was recovered unchanged after treatment by diethylzinc at room temperature. This demonstrated that the reaction is irreversible at room temperature.

Theoretical calculations of the zinc alkoxides, precursors of **4a** and **5a** were performed to confirm that homopropargylic alkoxides were more stable than the isomeric allenyl alkoxides (Figure 6). The homopropargylic zinc alkoxide is more stable

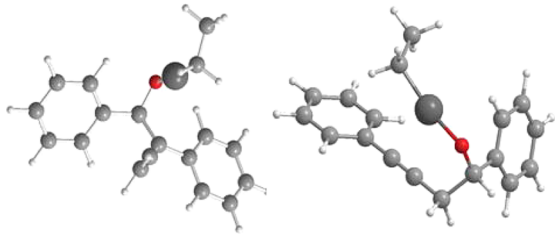


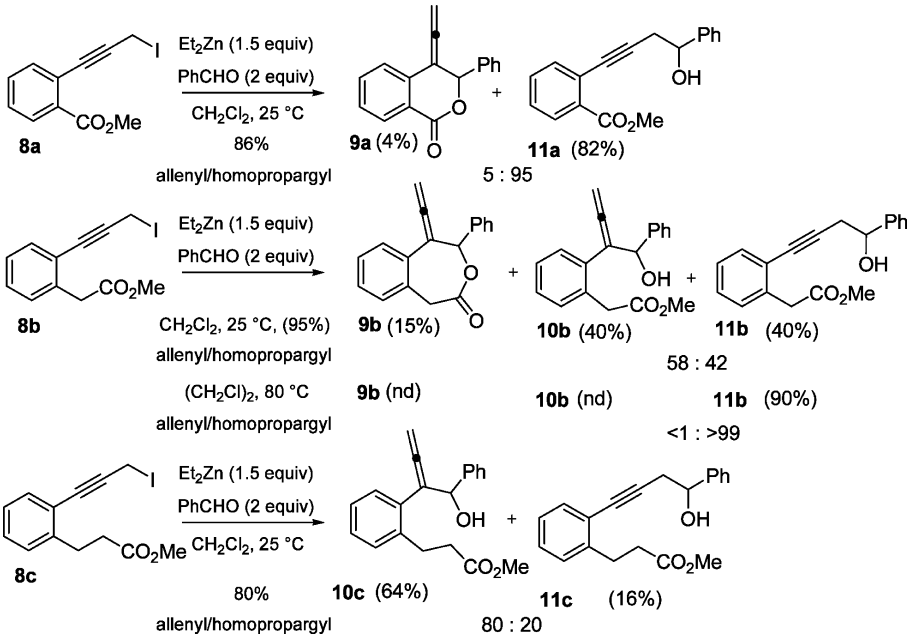
Figure 6. Relative stability of the most stable conformers of the zinc alkoxides precursors of **4a** and **5a** in (CBS-QB3 level).

by 20.3 kJ mol.$^{-1}$ than the isomeric allenyl zinc alkoxide. Alcohol **5a** is clearly the thermodynamic product.

Finally it can be noted that replacing benzaldehyde by the more crowded and less reactive acetophenone led to the exclusive formation of the corresponding propargylation product

dx.doi.org/10.1021/jo302704g | J. Org. Chem. 2013, 78, 1589–1603

Scheme 6. Reaction of Allenylzincs E−G with Benzaldehyde



7d (entry 7). Propanaldehyde led to a 66:34 ratio of **8d** to **9d** (entry 8), while acetone, as acetophenone, led to the quasi exclusive formation of homopropargylic alcohol **11d** (entry 9). This clearly confirms the incidence of steric hindrance which slows down the rate of formation of allenyl alcohol.

Ester Carbonyl Groups as Intramolecular Coordinating Agents. The introduction of a methyl carboxylate as coordinating group in position ortho relative to the triple bond was also investigated starting from iodides **8a−c**. The results of their reaction with diethylzinc in the presence of benzaldehyde at room temperature are given in Scheme 6.

In this case varying the alkyl chain spacer induces the possibility to compare the reactivity of 6-, 7-, and 8-membered chelated allenyl zinc **E**, **F**, and **G**, respectively (Figure 7).

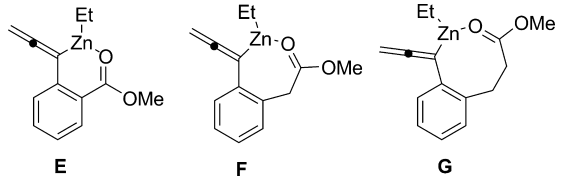
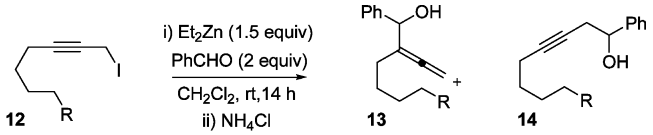


Figure 7. Structure of allenylzincs **E−G**.

Increasing the size of the ring in the chelated allenylzinc again favors the ratio of allenyl alcohols **10** (and (or) the resulting lactones **9**) to homopropargyl alcohols **11**. Again, rising the temperature of the reaction increased the ratio of the thermodynamic product **11b** formed from **8b** at 80 °C. This is in good agreement with the trend previously observed with the series of aromatic ethers. The difference resides in this case in further lactonization of the allenyl alcohol.

Behavior of Aliphatic Derivative 12. The reactivity of iodide **12a** was studied by comparison to **12b**. The results are given in Scheme 7. They confirm the absence of influence of the flexible methoxylated tether on the regioselectivity of the reaction with benzaldehyde. It must be noted that comparing **12a** to **1a** shows a dramatic influence of conjugation with the aromatic ring in **1a** on the ratio of regio-isomeric products.

Scheme 7. Reaction of Iodides 12a,b with Benzaldehyde



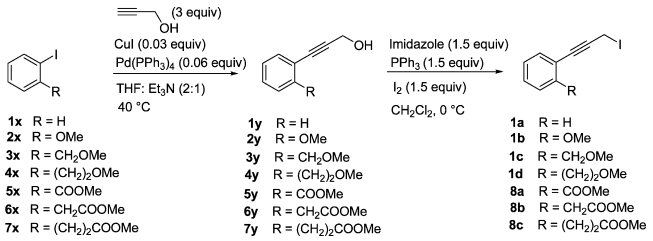
CONCLUSION

In conclusion, we have shown that the formation of allenylzincs could be promoted by diethylzinc, in the presence of oxygen, via the generation of propargyl radicals from propargyl iodides. The involvement of a radical chain mechanism had already been suspected from the detection of propargyl radicals by EPR.[16] Its validity was attested by theoretical calculations of dissociation enthalpies of C−Zn and C−I bonds, performed at the CBS-QB3 level. The relative stability of isomeric propargyl- and allenylzincs was also confirmed in this study. The reactivity of ortho-substituted 3-phenylpropargyl iodides clearly indicated that the possibility to stabilize allenylzincs by chelation influences the regioselectivity of their addition to aldehydes. Increasing the stability of the reactive allenylzinc intermediate by reducing the chelate ring size led to improve the ratio of homopropargyl-/allenyl- alcohols. However, the knowledge of thermodynamic data is only indicative. It does not allow the kinetics of competitive reactions to be predicted. Monitoring the formation of allenylzinc by ^{1}H NMR brought new evidence for the importance of ligation on the stabilization and on the reactivity of organozinc species and most of all for the acceleration of the formation of allenylzinc by oxygen.

EXPERIMENTAL SECTION

General. Commercially available dichloromethane (pure for synthesis and stabilized with ethanol 0.1−0.4% m/m) was stored on molecular sieves, and used without further purification. The commercially available dialkylzinc solutions were 1 M in heptane. Analytical thin layer chromatography was performed on precoated silica gel plates.

dx.doi.org/10.1021/jo302704g | J. Org. Chem. 2013, 78, 1589−1603



^{1}H and ^{13}C NMR spectra were recorded at 400 MHz (^{1}H) and 100 MHz (^{13}C) using $CDCl_3$ as the solvent. Chemical shifts (δ) are reported in ppm. Signals of the residual protonated solvent or of the deuterated solvent served as the internal standard to calibrate the spectra (^{1}H NMR, $CHCl_3$, 7.26 ppm; ^{13}C NMR, $CDCl_3$, 77.16 ppm). Multiplicity is indicated by one or more of the following abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), hept (heptuplet), m (multiplet), br (broad). The *J* values are given in Hz. High resolution MS experiments were performed with a mass spectrometer equipped with an electrospray ionization source operated in the positive ion mode. In this hybrid instrument, ions were measured using an orthogonal acceleration time-of-flight mass analyzer.

General Procedure for the Synthesis of Orthosubstituted 3-Phenylalkynyl iodides 1a–d and 8a–c. General Procedure A, Sonogashira Cross-coupling.[33] To a solution of orthosubstituted phenyl iodide (**2x–7x**) in a 2:1 mixture of dry tetrahydrofuran/triethylamine was added $Pd(PPh_3)_4$ (6 mol %) followed by CuI (3 mol %) and propargyl alcohol (3 equiv), under argon atmosphere. The above solution was stirred at 40 °C and the reaction progress was monitored by CCM. After completion, the reaction mixture was concentrated in *vacuo* and the crude residue was purified through flash column chromatography using a 1:1 pentane/diethylether mixture as the eluent, to obtain the cross-coupled products **2y–7y**.

*3-(2-Methoxyphenyl)prop-2-yn-1-ol (**2y**):*[34] 1-Iodo-2-methoxybenzene (**2x**) (1 g, 4.27 mmol, 1 equiv), propargyl alcohol (0.72 g, 12.81 mmol, 3 equiv), $Pd(PPh_3)_4$ (0.15 g, 0.13 mmol, 0.03 equiv), CuI (0.049 g, 0.26 mmol, 0.06 equiv), and THF/Et_3N (20:10 mL) were reacted under the conditions mentioned in the general procedure A for 12 h to obtain compound **2y** as a yellow oil in 79% yield (0.55 g).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.41 (dd, *J* = 7.5, 1.5, 1H), 7.30 (td, *J* = 8.2, 1.5, 1H), 6.95–6.83 (m, 2H), 4.54 (s, 2H), 3.81 (s, 3H), 1.72 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.1 (C), 133.9 (CH), 130.1 (CH), 120.6 (CH), 111.7 (C), 110.7 (CH), 91.5 (≡C), 82.1 (≡C), 55.9 (OCH_3), 52.03 (OCH_2).

HRMS: Calcd for $C_{10}H_{14}NO_2^+$ $(M + NH_4)^+$ 180.1019, Found 180.1021.

*3-(2-(Methoxymethyl)phenyl)prop-2-yn-1-ol (**3y**).* 1-Iodo-2-(methoxymethyl)benzene (**3x**) (3.20 g, 13.00 mmol, 1 equiv), propargyl alcohol (2.18 g, 39.00 mmol, 3 equiv), $Pd(PPh_3)_4$ (0.45 g, 0.39 mmol, 0.03 equiv), CuI (0.15 g, 0.78 mmol, 0.06 equiv), and THF/Et_3N (60:30 mL) were subjected to the conditions depicted in the general procedure A for 3 h to obtain compound **3y** as a yellow oil in 88% yield (2 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.43 (2xd, *J* = 7.7, 2H), 7.33 (t, *J* = 7.5, 1H), 7.24 (t, *J* = 7.5, 1H), 4.62 (s, 2H), 4.52 (d, *J* = 5.0, 2H), 3.43 (s, 3H), 2.41 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 140.0 (=C), 132.4 (=CH), 128.8 (=CH), 127.8 (=CH), 127.5 (=CH), 121.5 (=C), 92.0 (≡C), 83.3 (≡C), 72.8 (CH_2), 58.5 (CH_3), 51.7 (CH_2).

HRMS: Calcd for $C_{11}H_{12}O_2Na^+$ $(M + Na)^+$ 199.0729, Found 199.0729.

*3-(2-(2-Methoxyethyl)phenyl)prop-2-yn-1-ol (**4y**).* The compound **4y** was obtained from 1-Iodo-2-(2-methoxyethyl)benzene (**4x**) (1 g, 3.83 mmol, 1 equiv). Propargyl alcohol (0.643 g, 11.49 mmol, 3 equiv), $Pd(PPh_3)_4$ (0.128 g, 0.11 mmol, 0.03 equiv), CuI (0.044 g, 0.229 mmol, 0.06 equiv) in THF/Et_3N (20:10 mL) were mixed according to the general procedure A for 3 h to give **4y** as a yellow oil in 52% yield (0.378 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.43 (d, *J* = 7.3, 1H), 7.30–7.22 (m, 2H), 7.21–7.15 (m, 1H), 4.53 (s, 2H), 3.65 (t, *J* = 7.3, 2H), 3.39 (s, 3H), 3.09 (t, *J* = 7.3, 2H), 2.60 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 140.8 (=C), 132.8 (=CH), 129.5 (=CH), 128.7 (=CH), 126.4 (=CH), 122.5 (=C), 91.3 (≡C), 84.1 (≡C), 72.7 (CH_2), 58.7 (CH_3), 51.6 (CH_2), 34.8 (CH_2).

HRMS: Calcd for $C_{12}H_{15}O_2^+$ $(M + H)^+$ 191.1067, Found 191.1068.

*Methyl 2-(3-hydroxyprop-1-ynyl)benzoate (**5y**).* The compound **5y** was obtained from methyl 2-iodobenzoate (**5x**) (1 g, 3.8 mmol, 1 equiv) Propargyl alcohol (0.638 g, 11.49 mmol, 3 equiv), $Pd(PPh_3)_4$ (0.131 g, 0.11 mmol, 0.03 equiv), CuI (0.043 g, 0.229 mmol, 0.06 equiv) in THF/Et_3N (20:10 mL) were mixed according to the general procedure A for 3 h to give **5y** as a yellow oil in 66% yield (0.476 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.92 (d, *J* = 7.8, 1H), 7.54 (d, *J* = 7.8, 1H), 7.45 (t, *J* = 7.5 1H), 7.36 (t, *J* = 7.5 1H), 4.55 (s, 2H), 3.91 (s, 3H), 2.37 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.7 (O=C), 134.3 (=CH), 132.0 (=CH), 131.8 (C), 130.5 (=CH), 128.2 (=CH), 123.4 (C), 92.9 (≡C), 84.3 (≡C), 52.4 (CH_3), 51.8 (CH_2).

HRMS: Calcd for $C_{11}H_{14}NO_3^+$ $(M + NH_4)^+$ 208.0974, Found 208.0975.

*Methyl 2-(2-(3-hydroxyprop-1-ynyl)phenyl)acetate (**6y**).* Methyl 2-(2-iodophenyl)acetate (**6x**) (1 g, 3.63 mmol, 1 equiv), propargyl alcohol (0.60 g, 10.89 mmol, 3 equiv), $Pd(PPh_3)_4$ (0.125 g, 0.108 mmol, 0.03 equiv), CuI (0.041 g, 0.217 mmol, 0.06 equiv), and THF/Et_3N (20:10 mL) were subjected to the conditions mentioned in the general procedure A for 16 h to get compound **6y** as a yellow oil in 87% yield (0.650 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.43 (d, *J* = 7.5, 1H), 7.32–7.21 (m, 3H), 4.49 (s, 2H), 3.82 (s, 2H), 3.70 (s, 3H), 1.94 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 172.1 (O=C), 136.5 (=C), 132.1 (=CH), 130.0 (=CH), 128.9 (=CH), 127.3 (=CH), 123.0 (=C), 92.4 (≡C), 83.9 (≡C), 52.3 (CH_3), 51.7 (CH_2), 40.3 (CH_2).

HRMS: Calcd for $C_{12}H_{16}NO_3^+$ $(M + NH_4)^+$ 222.1125, Found 222.1125.

*Methyl 3-(2-(3-Hydroxyprop-1-ynyl)phenyl)propanoate (**7y**).* Methyl 3-(2-iodophenyl)propanoate (**7x**) (1.20 g, 4.13 mmol, 1 equiv), propargyl alcohol (0.69 g, 12.39 mmol, 3 equiv), $Pd(PPh_3)_4$ (0.147 g, 0.123 mmol, 0.03 equiv), CuI (0.047 g, 0.247 mmol, 0.06 equiv), and THF/Et_3N (20:10 mL) were subjected to the conditions depicted in the general procedure A for 21 h to obtain compound **7y** as a yellow oil in 91% yield (0.820 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.40 (dd, *J* = 7.5, 0.75, 1H), 7.27–7.15 (m, 3H), 4.52 (s, 2H), 3.68 (s, 3H), 3.10 (t, *J* = 7.8, 2H), 2.66 (t, *J* = 8.0, 2H), 2.20 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.0 (O=C), 142.7 (=C), 132.3 (=CH), 128.9 (=CH), 128.8 (=CH), 126.5 (=CH), 122.2 (=C), 92.0 (≡C), 83.9 (≡C), 51.9 (CH_3), 51.7 (CH_2), 35.0 (CH_2), 30.3 (CH_2).

HRMS: Calcd for $C_{13}H_{18}NO_3^+$ $(M + NH_4)^+$ 236.1281, Found 236.1281.

General Procedure B, Iodination Reaction.[35] To a light-protected solution (flask wrapped in an aluminum foil) of phenyl propargyl alcohol derivative (**1y–7y**) in dry CH_2Cl_2 under argon atmosphere at 0 °C, were added imidazole (1.5 equiv), triphenylphosphine (1.5 equiv) and iodine (1.5 equiv). The reaction mixture was stirred at 0 °C and monitored by CCM. After completion of the reaction, the excess of iodine was removed by washing with sat. aqueous $Na_2S_2O_3$ solution and the organic layer was dried with $MgSO_4$, filtered and concentrated in *vacuo*. The resultant residue was quickly purified through flash column chromatography using pentane/diethylether mixture (9:1) as the eluent to give the ortho-substituted 3-phenylalkynyl iodides (**1a-d and 8a-c**).

*1-(3-Iodoprop-1-ynyl)benzene (**1a**).* 3-Phenylprop-2-yn-1-ol (**1y**) (1 g, 7.6 mmol, 1 equiv), imidazole (0.772 g, 11.36 mmol, 1.5 equiv), triphenylphosphine (2.97 g, 11.36 mmol, 1.5 equiv) and iodine (2.87 g, 11.36 mmol, 1.5 equiv) were mixed in dry CH_2Cl_2 (40 mL) according to the general procedure B for 3 h to afford 74% of the titled compound **1a** as a yellow viscous liquid (1.4 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.44–7.41 (m, 2H), 7.33–7.29 (m, 3H), 3.96 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 139.9 (=CH), 128.8 (=CH), 128.4 (=CH), 122.7 (=C), 86.4 (≡C), 85.5 (≡C), −17.3 (CH_2).

HRMS: Calcd for $C_9H_7IAg^+$ $(M + Ag)^+$ 348.8638, Found 348.8633.

*1-(3-Iodoprop-1-ynyl)-2-methoxybenzene (**1b**).* 3-(2-Methoxyphenyl)prop-2-yn-1-ol (**2y**) (1 g, 3.67 mmol, 1 equiv), imidazole (0.375 g, 5.51 mmol, 1.5 equiv), triphenylphosphine (1.44 g, 5.51 mmol, 1.5 equiv) and iodine (1.39 g, 5.51 mmol, 1.5 equiv) were mixed in dry

dx.doi.org/10.1021/jo302704g | J. Org. Chem. 2013, 78, 1589–1603

CH_2Cl_2 (25 mL) according to the general procedure B for 3 h to afford compound **1b** as a yellow viscous liquid (71%, 1.06 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.39 (dd, J = 7.5, 1.5, 1H), 7.32 (td, J = 8.5, 1.5, 1H), 6.88 (td, J = 7.5, 0.8, 1H), 6.86 (d, J = 8.5, 1H), 4.05 (s, 2H), 3.90 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.3 (=C), 133.9 (=CH), 130.3 (=CH), 120.6 (=CH), 111.8 (=C), 110.8 (=CH), 90.3 (≡C), 82 (≡C), 56 (CH_3), −16.5 (CH_2).

HRMS: Calcd for $C_{10}H_{10}OI^+$ $(M + H)^+$ 272.9770, Found 272.9770.

*1-(3-Iodoprop-1-ynyl)-2-(methoxymethyl)benzene (**1c**).* The compound **1c** was obtained from 3-(2-(Methoxymethyl)phenyl)prop-2-yn-1-ol (**3y**) (2.00 g, 11.36 mmol, 1 equiv), imidazole (1.60 g, 22.80 mmol, 2 equiv), triphenylphosphine (6 g, 22.80 mmol, 2 equiv) and iodine (5.75 g, 22.80 mmol, 2 equiv) in dry CH_2Cl_2 (60 mL) according to the general procedure B. Compound **1c** was isolated after 3 h as a yellow oil in 92% yield (3 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.42 (m, 2H), 7.34 (dt, J = 1.3, 7.5, 1H), 7.23 (dt, J = 1.0, 7.5, 1H), 4.61 (s, 2H), 4.00 (s, 2H), 3.47 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 140.7 (=C), 132.2 (=CH), 129.0 (=CH), 127.7 (=CH), 127.4 (=CH), 121.2 (=C), 90.7 (≡C), 83.3 (≡C), 72.6 (CH_2), 58.7 (CH_3), −17.5 (CH_2).

HRMS: Calcd for $C_{11}H_{15}NOI$ $(M + NH_4)^+$ 304.0192, Found 304.0192.

*1-(3-Iodoprop-1-ynyl)-2-(2-methoxyethyl)benzene (**1d**).* 3-(2-(2-Methoxyethyl)phenyl)prop-2-yn-1-ol (**4y**) (2.20 g, 11.57 mmol, 1 equiv), imidazole (1.18 g, 17.35 mmol, 1.5 equiv), triphenylphosphine (4.50 g, 17.35 mmol, 1.5 equiv) and iodine (4.40 g, 17.35 mmol, 1.5 equiv) were mixed in dry CH_2Cl_2 (80 mL) under the general procedure B for 3 h to afford compound **1d** as a yellow oil (88%, 3 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.40 (d, J = 7.3, 1H), 7.30−7.22 (m, 2H), 7.18−7.14 (m, 1H), 4.00 (s, 2H), 3.64 (t, J = 7.2, 2H), 3.39 (s, 3H), 3.05 (t, J = 7.3, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 141.4 (=C), 132.5 (=CH), 129.7 (=CH), 128.9 (=CH), 126.4 (=CH), 122.3 (=C), 89.9 (≡C), 84.3 (≡C), 72.7 (CH_2), 58.8 (CH_3), 34.8 (CH_2), −17.2 (CH_2).

HRMS: Calcd for $C_{12}H_{14}OI^+$ $(M + H)^+$ 301.0083, Found 301.0085.

*Methyl 2-(3-Iodoprop-1-ynyl)benzoate (**8a**).* Methyl 2-(3-hydroxyprop-1-ynyl)benzoate (**5y**) (2.00 g, 10.52 mmol, 1 equiv), imidazole (1.07 g, 15.78 mmol, 1.5 equiv), triphenylphosphine (4.10 g, 15.78 mmol, 1.5 equiv) and iodine (4.00 g, 17.35 mmol, 2 equiv) were stirred in dry CH_2Cl_2 (40 mL) according to the general procedure B for 3 h to give compound **8a** as a yellow oil (90%, 2.83 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.94 (dd, J = 7.9, 1.6, 1H), 7.53 (dd, J = 7.5, 1.0, 1H), 7.46 (td, J = 7.5, 1.3, 1H), 7.37 (td, J = 7.5, 1.0, 1H), 4.02 (s, 2H), 3.96 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.5 (O=C), 134.2 (=CH), 132.0 (=C), 131.7 (=CH), 130.5 (=CH), 128.3 (=CH), 123.0 (=C), 91.1 (≡C), 84.0 (≡C), 52.4 (CH_3), −17.3 (CH_2).

HRMS: Calcd for $C_{11}H_{10}O_2I^+$ $(M + H)^+$ 300.9720, Found 300.9716.

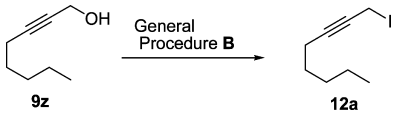
*Methyl 2-(2-(3-iodoprop-1-ynyl)phenyl)acetate (**8b**).* Methyl 2-(2-(3-hydroxyprop-1-ynyl)phenyl)acetate (**6y**) (0.63 g, 3.08 mmol, 1 equiv), imidazole (0.25 g, 3.69 mmol, 1.2 equiv), triphenylphosphine (0.96 g, 3.69 mmol, 1.2 equiv) and iodine (0.93 g, 3.69 mmol, 1.2 equiv) were stirred in dry CH_2Cl_2 (15 mL) according to the general procedure B for 2 h to give compound **8b** as a yellow oil (80%, 0.75 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.43 (d, J = 7.5, 1H), 7.32−7.21 (m, 3H), 3.97 (s, 2H), 3.82 (s, 2H), 3.73 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.6 (O=C), 136.7 (=C), 132.4 (=CH), 130.0 (=CH), 129.1 (=CH), 127.3 (=CH), 122.9 (=C), 90.8 (≡C), 83.6 (≡C), 52.3 (CH_3), 39.8 (CH_2), −17.8 (CH_2).

HRMS: Calcd for $C_{12}H_{12}O_2I^+$ $(M + H)^+$ 314.9877, Found 314.9871.

*Methyl 3-(2-(3-Iodoprop-1-ynyl)phenyl)propanoate (**8c**).* Methyl 3-(2-(3-hydroxyprop-1-ynyl)phenyl)propanoate (**7y**) (0.80 g, 3.66 mmol, 1 equiv), imidazole (0.37 g, 5.50 mmol, 1.5 equiv), triphenylphosphine (1.40 g, 5.50 mmol, 1.5 equiv) and iodine (1.40 g, 5.50 mmol, 1.5 equiv) were reacted in dry CH_2Cl_2 (15 mL) according to the general procedure B for 2 h to afford product **8b** as a yellow oil (56%, 0.75 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.39 (dd, J = 7.8, 1.0, 1H), 7.27−7.14 (m, 3H), 3.99 (s, 2H), 3.68 (s, 3H), 3.08 (t, J = 7.5, 2H), 2.68 (t, J = 8.3, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.4 (O=C), 143.1 (=C), 132.5 (=CH), 129.1 (=CH), 129.05 (=CH), 126.5 (=CH), 122.0 (=C), 90.4 (≡C), 83.9 (≡C), 51.8 (CH_3), 34.9 (CH_2), 29.9 (CH_2), −17.4 (CH_2).

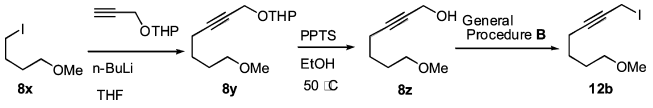
HRMS: Calcd for $C_{13}H_{14}O_2I^+$ $(M + H)^+$ 329.0033, Found 329.0025.

Synthesis of Aliphatic Propargyliodides 12a, 12b and Propargyliodides.



*1-Iodooct-2-yne (**12a**).* Oct-2-yn-1-ol (**9z**)[36] (2 g, 16 mmol, 1 equiv), imidazole (1.63 g, 24 mmol, 1.5 equiv), triphenylphosphine (6.28 g, 24 mmol, 1.5 equiv) and iodine (6.07 g, 24 mmol, 1.5 equiv) were reacted in dry CH_2Cl_2 (15 mL) according to the general procedure B for 2 h to afford product **12a** as a yellow liquid (68%, 2.6 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.70 (t, J = 2.5, 2H), 2.21−2.15 (m, 2H), 1.54−1.45 (m, 2H), 1.40−1.25 (m, 4H), 0.89 (t, J = 7.0, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 87.0 (≡C), 77.1 (≡C), 31.1 (CH_2), 28.2 (CH_2), 22.3 (CH_2), 19.2 (CH_2), 14.1 (CH_3), −16.5 (CH_2).

HRMS: Calcd for $C_8H_{13}IAg^+$ $(M + Ag)^+$ 342.9107, Found 342.9109.



*2-(7-Methoxyhept-2-ynyloxy)-tetrahydro-2H-pyran (**8y**):*[37] To a solution of THP protected propargyl alcohol (4.25g, 30.37 mmol, 1 equiv) in 50 mL of dry THF at −78 °C was added n-BuLi (13 mL, 30.37 mmol, 1 equiv, 2.34 M solution in hexane) over 30 min. After the completion of the addition, the mixture was warmed to room temperature and then substrate **8x**[38] (6.5g, 30.37 mmol, 1 equiv) was added over 10 min. The resulting mixture was heated at 55 °C for 24 h. The cooled mixture was diluted in ethylacetate and sequentially washed with ice−water, water and brine. The organic extract was dried over $MgSO_4$ and concentrated. The residue was purified through flash column chromatography to give product **8y** (5.5 g, 80% yield) as colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.79 (t, J = 3.3, 1H), 4.27 (dt, J = 15.3, 2.0, 1H), 4.17 (dt, J = 15.3, 2.0, 1H), 3.82 (m, 1H), 3.52 (m, 1H), 3.37 (t, J = 6.5, 2H), 3.31 (s, 3H), 2.24 (tt, J = 2.0, 7.0, 2H), 1.90−1.44 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 96.8 (CH), 86.4 (≡C), 76.2 (≡C), 72.3 (CH_2), 62.1 (CH_2), 58.7 (CH_3), 54.7 (CH_2), 30.4 (CH_2), 28.9 (CH_2), 25.5 (CH_2), 25.4 (CH_2), 19.3 (CH_2), 18.8 (CH_2).

HRMS: Calcd for $C_{13}H_{22}NaO_3^+$ $(M + Na)^+$ 249.1461, Found 249.1459.

*7-Methoxyhept-2-yn-1-ol (**8z**):*[39] To a solution of 2-(7-methoxyhept-2-ynyloxy)-tetrahydro-2H-pyran (**8y**) (2.42 g, 10.7 mmol) in 100 mL of ethanol was added pyridinium p-toluenesulfonate (2.68 g, 10.7 mmol) slowly at room temperature over 30 min. After addition completion, the reaction mixture was heated at 50 °C for 12 h. Ethanol was evaporated and the resulted residue was purified through flash column chromatography to get product **8z** as colorless liquid in 80% yield (1.2 g): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.19 (br s, 2H), 3.35 (t, J = 6.3, 2H), 3.29 (s, 3H), 2.21 (tt, J = 2.3, 7.0, 2H), 1.86 (br s, 1H), 1.67−1.60 (m, 2H), 1.57−1.50 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 86.2 (≡C), 78.8 (≡C), 72.4 (CH_2), 58.7 (CH_3), 51.4 (CH_2), 28.8 (CH_2), 25.4 (CH_2), 18.7 (CH_2).

HRMS: Calcd for $C_8H_{14}NaO_2^+$ $(M + Na)^+$ 165.0886, Found 165.0883.

*1-Iodo-7-methoxyhept-2-yne (**12b**).* 7-Methoxyhept-2-yn-1-ol (**8z**) (1.2 g, 8.45 mmol, 1 equiv), imidazole (0.86 g, 12.6 mmol, 1.5 equiv), triphenylphosphine (3.3 g, 12.6 mmol, 1.5 equiv) and iodine (3.18 g, 12.6 mmol, 1.5 equiv) were reacted in dry CH_2Cl_2 (15 mL) according to the general procedure B for 2 h to afford product **12b** as a yellow liquid (75%, 1.6 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.69 (t, J = 2.5, 2H), 3.38 (t, J = 6.0, 2H), 3.32 (s, 3H), 2.25−2.19 (m, 2H), 1.70−1.50 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 86.5 (≡C),

dx.doi.org/10.1021/jo302704g | J. Org. Chem. 2013, 78, 1589−1603

77.4 (≡C), 72.3 (CH_2), 58.7 (CH_3), 28.8 (CH_2), 25.2 (CH_2), 19.0 (CH_2), −16.7 (CH_2).

HRMS: Calcd for $C_8H_{13}INaO^+$ $(M + Na)^+$ 274.9903, Found 274.9903.

3-Iodoprop-1-yne:[40] Prop-2-yn-1-ol (2.5 mL, 43 mmol, 1 equiv), imidazole (4.4 g, 64.5 mmol, 1.5 equiv), triphenylphosphine (16.8 g, 64.5 mmol, 1.5 equiv) and iodine (16.3 g, 64.5 mmol, 1.5 equiv) were reacted in dry CH_2Cl_2 (100 mL) according to the general procedure B for 3 h to afford the expected product as a yellow liquid (43%, 3 g) together with trace amount of the isomeric allenyliodide. ^1H NMR (400 MHz, $CDCl_3$) δ: 3.64 (d, J = 2.5, 2H), 2.41 (t, J = 2.5, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 80.6 (≡C), 73.5 (≡C), −19.5 (−CH_2).

Characteristic signals of iodoallene: ^1H NMR (400 MHz, $CDCl_3$) δ:5.70 (t, J = 6.3, IH), 4.62 (d, J = 6.3, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 208.7 (=C=), 78.6 (=CH_2), 29.8 (=CH).

HRMS: could not be obtained owing to the volatility of the product.

General Procedure C, Radical Reactions with Diethylzinc. *Reactions of Propargyl Iodides with Diethylzinc.* Light-protected round-bottom flask (covered with an aluminum foil) was loaded with ortho-substituted 3-phenylalkynyl iodide (0.5 mmol, 1 equiv) and nondegassed dry CH_2Cl_2 (2.5 mL, 0.2 M) under argon atmosphere. Diethylzinc (0.75 mL, 1.5 equiv) (1 M solution in heptane) was added to the above solution and the resulting mixture was stirred at room temperature for 14 h. Then, the reaction was quenched with a saturated NH_4Cl aqueous solution. The two layers were separated and the aqueous layer was extracted twice with dichloromethane (2 × 5 mL) and the combined organic layers were evaporated *in vacuo*. The crude residue was purified through flash column chromatography using pentane/diethylether mixture as the eluant to give the products.

The NMR data of 1-(propa-1,2-dienyl)benzene (**2a**),[41] 1-(prop-1-ynyl)benzene (**2b**),[42] 1-methoxy-2-(propa-1,2-dienyl)benzene (**3a**),[43] and 1-methoxy-2-(prop-1-ynyl)benzene (**3b**)[44] are in agreement with those previously reported in the literature.

*1-(Methoxymethyl-2-(propa-1,2-dienyl)benzene (**2c**) and 1-(Methoxymethyl)-2-(prop-1-ynyl)benzene (**3c**).* 1-(3-Iodoprop-1-ynyl)-2-(methoxymethyl)benzene (**1c**) (0.143 g, 0.50 mmol, 1 equiv), diethylzinc (0.75 mL, 0.75 mmol, 1.5 equiv) (1 M solution in heptane) and nondegassed dry CH_2Cl_2 (2.5 mL, 0.2 M) were reacted according to the general procedure **C** to give the products **2c** and **3c** as colorless oil (overall yield 66%, 0.053 g). The two products could not fully separated from each other, pure isolated chromatographic fractions were used for NMR.

(**2c**): ^1H NMR (400 MHz, $CDCl_3$) δ: 7.40 (d, J = 7.5, 1H), 7.24−7.18 (m, 2H), 7.11 (dt, J = 1.0, 7.5, 1H), 6.39 (t, J = 6.8, 1H), 5.05 (d, J = 6.8, 2H), 4.44 (s, 2H), 3.32 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 210.6 (=C=), 134.5 (=C), 132.8 (=C), 129.6 (=CH), 128.4 (=CH), 127.7 (=CH), 126.9 (=CH), 90.6 (=CH), 78.3 (=CH_2), 73.0 (CH_2), 58.2 (CH_3).

HRMS: Calcd for $C_{11}H_{12}ONa^+$ $(M + Na)^+$ 183.0780, Found 183.0782.

(**3c**): ^1H NMR (400 MHz, $CDCl_3$) δ: 7.35−7.30 (m, 2H), 7.22 (dt, J = 1.3, 7.5, 1H), 7.13 (dt, J = 1.3, 7.5, 1H), 4.54 (s, 2H), 3.37 (s, 3H), 2.03 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 139.9 (=C), 132.2 (=CH), 127.9 (=CH), 127.4 (=CH), 127.3 (=CH), 122.8 (=C), 90.5 (≡C), 77.6 (≡C), 72.9 (CH_2), 58.6 (CH_3), 4.6 (CH_3).

HRMS: Calcd for $C_{11}H_{12}ONa^+$ $(M + Na)^+$ 183.0780, Found 183.0781.

*1-(2-Methoxyethyl)-2-(propa-1,2-dienyl)benzene (**2d**) and 1-(2-Methoxyethyl)-2-(prop-1-ynyl)benzene (**3d**).* 1-(3-Iodoprop-1-ynyl)-2-(2-methoxyethyl)benzene (**1d**) (0.150 g, 0.50 mmol, 1 equiv) and diethylzinc (0.75 mL, 0.75 mmol, 1.5 equiv) (1 M solution in heptane) were mixed in nondegassed dry CH_2Cl_2 (2.5 mL, 0.2 M) according to the general procedure **C** to give the products **2d** and **3d** as colorless oil (overall yield 86%, 0.075 g). The two products could not be fully separated from each other, pure isolated chromatographic fractions were used for NMR.

(**2d**): ^1H NMR (400 MHz, $CDCl_3$) δ: 7.34 (d, J = 7.5, 1H), 7.13−7.04 (m, 3H), 6.34 (t, J = 6.8, 1H), 5.04 (d, J = 6.8, 2H), 3.49 (t, J = 7.3, 2H), 3.29 (s, 3H), 2.89 (t, J = 7.5, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 210.6 (=C=), 135.6 (=C), 132.2 (=C), 130.5 (=CH), 127.8 (=CH), 127.1 (=CH), 126.9 (=CH), 91.0 (=CH), 78.2 (=CH_2), 73.1 (CH_2), 58.8 (CH_3), 33.7 (CH_2).

HRMS: Calcd for $C_{12}H_{14}ONa^+$ $(M + Na)^+$ 197.0936, Found 197.0932.

(**3d**): ^1H NMR (400 MHz, $CDCl_3$) δ: 7.30 (d, J = 7.5, 1H), 7.15−7.04 (m, 3H), 3.56 (t, J = 7.0, 2H), 3.31 (s, 3H), 2.99 (t, J = 7.3, 2H), 2.02 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 140.5 (=C), 132.4 (=CH), 129.4 (=CH), 127.8 (=CH), 126.3 (=CH), 123.9 (=C), 89.5 (≡C), 78.3 (≡C), 72.8 (CH_2), 58.7 (CH_3), 34.8 (CH_2), 4.6 (CH_3).

HRMS: Calcd for $C_{12}H_{14}ONa^+$ $(M + Na)^+$ 197.0936, Found 197.0929.

General Procedure D, Radical Reactions with Diethylzinc and Electrophiles. *Reactions of Propargyl Iodides, with Diethylzinc and Electrophiles.* Light-protected round-bottom flask (covered with an aluminum foil) was loaded with ortho-substituted 3-phenylalkynyl iodide (**1a−d** and **8a−c**) (0.25 mmol, 1 equiv), electrophile (aldehydes or ketones) (0.5 mmol, 2 equiv) and kept under argon atmosphere. The above reagents were dissolved in nondegassed solvent and diethylzinc was injected through a syringe in the solution (see the tables and schemes for the solvent and the number of equiv of diethylzinc). The reaction mixture was stirred at the temperature and during the time mentioned in tables and schemes. After that time, the reaction was quenched with saturated NH_4Cl aqueous solution. The two layers were separated, the aqueous layer was extracted with dichloromethane (2 × 5 mL) and the combined organic layers were evaporated *in vacuo*. The crude residue was then purified via flash column chromatography using pentane/diethylether mixtures to afford the products.

The NMR spectra of 1,4-diphenylbut-3-yn-1-ol (**4a**) and 1,2-diphenylbuta-2,3-dien-1-ol (**5a**)[45] were in agreement with the literature data.

*2-(2-Methoxyphenyl)-1-phenylbuta-2,3-dien-1-ol (**4b**) and 4-(2-Methoxyphenyl)-1-phenylbut-3-yn-1-ol (**5b**).* 1-(3-Iodoprop-1-ynyl)-2-methoxybenzene (**1b**) (0.068 g, 0.25 mmol, 1 equiv), benzaldehyde (0.053 g, 0.5 mmol, 2 equiv), diethylzinc (0.375 mL, 0.375 mmol, 1.5 equiv) (1 M solution in heptane) and nondegassed dry CH_2Cl_2 (1.25 mL, 0.2 M) were reacted according to the general procedure **D** to afford products **4b** and **5b** in a 35:65 ratio, as colorless oil (overall yield 72%, 0.045 g). The two products could not be fully separated from each other, a pure isolated chromatographic fraction of **5b** was used to assign the NMR signals of **4b**. The ratio was determined from the relative integration of the protons of the methoxy groups.

(**4b**): ^1H NMR (400 MHz, $CDCl_3$) δ: characteristic signals 6.93 (dd, J = 7.3, 1.5) 1H), 6.76 (td, J = 7.5, 1.0, 1H), 5.57 (br s, 1H), 4.93−4.85 (AB part of an ABX spectrum, J_{AB} = 11.6, 2H), 3.73 (s, 3H), 3.13 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 207.7 (=C=), 156.4 (=C), 142.5 (=C), 131.3 (=CH), 129.0 (=CH), 128.0 (=CH), 127.3 (=CH), 126.5 (=CH), 124.3 (=C), 121.1 (=CH), 111.2 (=CH), 108.2 (=C), 77.9 (=CH_2), 73.9 (CH), 55.7 (CH_3).

(**5b**): ^1H NMR (400 MHz, $CDCl_3$) δ: 7.36 (2 × d, J = 7.5, 2H), 7.29−7.08 (m, 5H), 6.81 (td, J = 7.5, 1.0, 1H), 6.79 (br d, J = 7.5, 1H), 4.93−4.85 (dd, J = 5.3, 7.5, 1H), 3.77 (s, 3H), 2.95 (br s, 1H) 2.85−2.74 (AB part of an ABX spectrum, J_{AB} = 16.8, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.2 (=C), 142.8 (=C), 133.2 (=CH), 129.5 (=CH), 128.5 (=CH), 127.9 (=CH), 125.9 (=CH), 120.6 (=CH), 112.4 (=C), 110.6 (=CH), 90.6 (≡C), 80.1 (≡C), 72.5 (CH), 55.8 (CH_3), 31.3 (CH_2).

HRMS: Calcd for $C_{17}H_{16}O_2Na$ $(M + Na)^+$ 275.1043, Found 275.1043.

*2-(2-(Methoxymethyl)phenyl)-1-phenylbuta-2,3-dien-1-ol (**4c**) and 4-(2-(Methoxymethyl)phenyl)-1-phenylbut-3-yn-1-ol (**5c**).* 1-(3-Iodoprop-1-ynyl)-2-(methoxymethyl)benzene (**1c**) (0.071 g, 0.25 mmol, 1 equiv), benzaldehyde (0.053 g, 0.5 mmol, 2 equiv), diethylzinc (0.375 mL, 0.375 mmol, 1.5 equiv) (1 M solution in heptane) and nondegassed dry CH_2Cl_2 (1.25 mL, 0.2 M) were mixed according to the general procedure **D** to give the products **4c** and **5c** in a 44:56 ratio isolated as colorless oil (overall yield 75%, 0.050 g). The two products could not be separated from each other. Their ratio was

dx.doi.org/10.1021/jo302704g | J. Org. Chem. 2013, 78, 1589−1603

determined from the relative integration of the protons of the methoxy groups.

(**4c**): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.45−7.20 (m, 8H), 6.90 (dd, J = 7.5, 1.5, 1H), 5.56−5.47 (m, 1H), 4.92 (d, J = 2.0), 4.46 (s, 2H), 4.02 (br m, 1H), 3.41 (s, 3H).

HRMS: Calcd for $C_{18}H_{18}O_2Na$ $(M + Na)^+$ 289.1199, Found 289.1197.

(**5c**): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.48−7.20 (m, 9H), 5.02−4.93 (m, 1H), 4.56 (AB part of an AB spectrum, J_{AB} = 12.5, 2H), 3.38 (s, 3H), 3.31 (br m, 1H), 2.93 (AB part of an ABX pattern, J_{AB} = 17.0, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) for the two products, δ: 205.1 (=C=), 142.7 (=C), 142.2 (=C), 139.7 (=C), 136.1 (=C), 134.4 (=C), 132.0 (=CH), 129.6 (=CH), 129.4 (=CH), 128.5 (=CH), 128.4 (=CH), 128.2 (=CH), 128.0 (=CH), 127.9 (=CH), 127.8 (=CH), 127.6 (=CH), 127.5 (=CH), 127.4 (=CH), 126.9 (=CH), 126.4 (=CH), 125.8 (=CH), 122.5 (=C), 107.2 (=C), 91.2 (≡C), 81.1 (≡C), 76.7 ($=CH_2$), 74.9 (CH), 73.1 (CH_2), 72.9 (CH_2), 72.6 (CH), 58.2 (CH_3), 57.9 (CH_3), 30.8 (CH_2).

HRMS: Calcd for $C_{18}H_{18}O_2Na$ $(M + Na)^+$ 289.1199, Found 289.1197.

*2-(2-(2-Methoxyethyl)phenyl)-1-phenylbuta-2,3-dien-1-ol (**4d**) and 4-(2-(2-Methoxyethyl)phenyl)-1-phenylbut-3-yn-1-ol (**5d**).* 1-(3-Iodoprop-1-ynyl)-2-(2-methoxyethyl)benzene (**1d**) (0.075 g, 0.25 mmol, 1 equiv), benzaldehyde (0.053 g, 0.5 mmol, 2 equiv), diethylzinc (0.375 mL, 0.375 mmol, 1.5 equiv) (1 M solution in heptane) and nondegassed dry CH_2Cl_2 (1.25 mL, 0.2 M) were reacted according to the general procedure **D** to afford products **4d** and **5d** in a 72:28 ratio as colorless oil (overall yield 90%, 0.063 g). The two products could not be fully separated from each other, a pure isolated chromatographic fraction of **5d** was used to assign the NMR signals of **4d**. Their ratio was determined from the relative integration of the protons of the methoxy groups. A pure sample of **5d** was obtained from this mixture upon reaction with diethylzinc at 80 °C, see below.

(**4d**): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.32−7.00 (m, 8H), 6.94 (d, J = 7.8, 1H), 5.39 (dt, J = 7.0, 2.5, 1H), 4.84 (AB part of an ABX spectrum, J_{AB} = 11.3, 2H), 3.45−3.36 (m, AA′ part of an AA′XX′ pattern, 2H), 3.34 (d, J = 4.5, 1H), 3.21 (s, 3H), 2.87−2.74 (m, XX′ part of an AA′XX′ pattern, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 205.7 (=C=), 142.3 (=C), 137.9 (=C), 134.8 (=C), 129.8 (=CH), 129.3 (=CH), 127.8 (=CH), 127.6 (=CH), 126.6 (=CH), 126.2 (=CH), 108.0 (=C), 78.0 ($=CH_2$), 75.2 (CH), 73.9 (CH_2), 58.7 (CH_3), 33.0 (CH_2).

(**5d**): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.36 (br d, J = 8.8, 2H), 7.29−7.04 (m, 8 H), 4.88 (t, J = 6.3, 1H), 3.54−3.45 (m, AA′ part of an AA′XX′ pattern, 2H), 3.23 (s, 3H), 3.11 (br s, 1H), 2.90−2.86 (m, XX′ part of an AA′XX′ pattern, 2H), 2.86−2.78 (AB part of an ABX spectrum, J_{AB} = 16.8, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 143.0 (=C), 141.1 (=C), 132.2 (=CH), 129.4 (=CH), 128.6 (=CH), 128.2 (=CH), 127.9 (=CH), 126.3 (=CH), 125.9 (=CH), 123.4 (=C), 90.1 (≡C), 81.8 (≡C), 73.2 (CH_2), 72.7 (CH), 58.8 (CH_3), 35.0 (CH_2), 30.9 (CH_2).

HRMS: Calcd for $C_{19}H_{20}O_2Na^+$ $(M + Na)^+$ 303.1356, Found 303.1355.

*4-(2-(2-Methoxyethyl)phenyl)-1-phenylbut-3-yn-1-ol (**5d**).* Mixture of **4d** and **5d** (100 mg, 0.35 mmol, 1 equiv, **4d**/**5d** 69:31) was dissolved in nondegassed dry 1,2-dichloroethane and kept under argon atmosphere. Diethylzinc (0.525 mL, 0.525 mmol, 1.5 equiv, 1 M solution in heptane) was injected to the above solution and stirred for 2 h at 80 °C. After this time, the reaction was quenched with saturated aqueous NH_4Cl solution. The layers were separated and the aqueous layer was washed with CH_2Cl_2 (2 × 5 mL) and the combined organic layers were evaporated *in vacuo*. The crude mixture showed that **5d** was the only product formed in quantitative yield.

*5-(2-(2-Methoxyethyl)phenyl)-2-phenylpent-4-yn-2-ol (**7d**).* 1-(3-Iodoprop-1-ynyl)-2-(2-methoxyethyl)benzene (**1d**) (0.075 g, 0.25 mmol, 1 equiv), acetophenone (0.060 g, 0.5 mmol, 2 equiv), diethylzinc (0.375 mL, 0.375 mmol, 1.5 equiv) (1 M solution in heptane) and nondegassed dry CH_2Cl_2 (1.25 mL, 0.2 M) were reacted according to the general procedure **D** to give product **7d** as a colorless oil (overall yield 87%, 0.063 g).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.50−7.43 (m, 2H), 7.33−7.24 (m, 3H), 7.23−7.02 (m, 4H), 3.51−3.39 (m, AA′ part of an AA′XX′ pattern, 2H), 3.22 (s, 3H), 3.04 (s, 1H), 2.97 (d, A part of an AB pattern, J_{AB} = 16.6, 1H), 2.86 (d, B part of an AB pattern, J_{AB} = 16.6, 1H), 2.87−2.74 (m, XX′ part of an AA′XX′ pattern, 2H), 1.60 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 147.0 (=C), 141.3 (=C), 132.3 (=CH), 129.4 (=CH), 128.4 (=CH), 128.2 (=CH), 127.1 (=CH), 126.3 (=CH), 125.0 (=CH), 123.4 (=C), 89.8 (≡C), 82.5 (≡C), 73.8 (C), 73.3 (CH_2), 58.8 (CH_3), 35.8 (CH_2), 35.0 (CH_2), 29.8 (CH_3).

HRMS: Calcd for $C_{20}H_{22}O_2Na^+$ $(M + Na)^+$ 317.1512, Found 317.1512.

*4-(2-(2-Methoxyethyl)phenyl)hexa-4,5-dien-3-ol (**8d**) and 6-(2-(2-Methoxyethyl)phenyl)hex-5-yn-3-ol (**9d**).* 1-(3-Iodoprop-1-ynyl)-2-(2-methoxyethyl)benzene (**1d**) (0.075 g, 0.25 mmol, 1 equiv), propionaldehyde (0.029 g, 0.5 mmol, 2 equiv), diethylzinc (0.375 mL, 0.375 mmol, 1.5 equiv) (1 M solution in heptane) and nondegassed dry CH_2Cl_2 (1.25 mL, 0.2 M) were kept under the general procedure **D** to furnish the products **8d** and **9d** in a 66:34 ratio, isolated as a colorless oil (overall yield 70%, 0.041 g). The two products could not be separated from each other. Their ratio was determined from the relative integration of the protons of the methoxy groups.

(**8d**): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.30−7.12 (m, 4H), 5.00−4.92 (AB part of an ABX spectrum, J_{AB} = 11.8, 2H), 4.29 (tt, J = 7.5, 2.5, 1H), 3.68−3.59 (t, J = 7.3, 2H), 3.32 (s, 3H), 3.12−3.02 (dt, J = 13.8, 7.0, 1H), 2.98−2.88 (dt, J = 13.8, 7.3, 1H), 2.45 (br s, 1H), 1.80−1.53 (m, 2H), 1.00 (d, J = 7.3, 3H).

(**9d**): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.40 (d, J = 7.5, 1H), 7.30−7.12 (m, 3H), 3.80−3.78 (m, 1H), 3.68−3.56 (m, AA′ part of an AA′XX′ pattern, 2H), 3.35 (s, 3H), 3.12−3.02 (m, 2H), 2.73 (dd, J = 4.5, 16.8, 1H), 2.59 (dd, J = 6.8, 16.8, 1H), 2.45 (br s, 1H), 1.80−1.53 (m, 2H), 1.00 (t, J = 7.3, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) for the two products, δ: 205.5 (=C=), 140.9 (=C), 137.6 (=C), 135.8 (=C), 132.2 (=CH), 129.8 (=CH), 129.4 (=CH), 129.1 (=CH), 128.1 (=CH), 127.7 (=CH), 126.5 (=CH), 126.3 (=CH), 123.5 (=C), 107.4 (=C), 90.4 (≡C), 81.5 (≡C), 77.8 ($=CH_2$), 74.0 (CH), 73.8 (CH_2), 73.2 (CH_2), 71.8 (CH), 58.8 (2xCH_3), 35.2 (CH_2), 33.2 (CH_2), 29.4 (CH_2), 28.7 (CH_2), 28.2 (CH_2), 10.3 (CH_3), 10.2 (CH_3).

HRMS: Calcd for $C_{15}H_{21}O_2^+$ $(M+H)^+$ 233.1536, Found 233.1538.

*3-(2-(2-Methoxyethyl)phenyl)-2-methylpenta-3,4-dien-2-ol (**10d**) and 5-(2-(2-Methoxyethyl)phenyl)-2-methylpent-4-yn-2-ol (**11d**).* 1-(3-Iodoprop-1-ynyl)-2-(2-methoxyethyl)benzene (**1d**) (0.075 g, 0.25 mmol, 1 equiv), acetone (0.029 g, 0.5 mmol, 2 equiv), diethylzinc (0.375 mL, 0.375 mmol, 1.5 equiv) (1 M solution in heptane) and nondegassed dry CH_2Cl_2 (1.25 mL, 0.2 M) were mixed according to the general procedure **D** to afford products **10d** and **11d** in a 9:91 ratio, isolated as a colorless oil (overall yield 73%, 0.042 g, products could not be separated from each other, and a trace amount of propargyl alcohol (**7y**) corresponding to the starting material (**1d**) was also detected in the mixture of the products).

(**10d**): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.23−7.04 (m, 4H), 4.76 (s, 2H), 3.24 (s, 3H), 3.01 (t, J = 7.0, 2H), 2.91 (t, J = 6.8, 2H), 2.48 (br s, 1H), 1.36 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 204.8 (=C=), 138.0 (=C), 135.5 (=C), 132.5 (=CH), 130.3 (=CH), 129.5 (=CH), 127.7 (=C), 126.0 (=CH), 110.8 (=C), 76.5 ($=CH_2$), 73.4 (CH_2), 71.2 (C), 58.7 (CH_3), 34.8 (CH_2), 29.8 (CH_3).

(**11d**): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.33 (d, J = 7.5, 1H), 7.23−7.04 (m, 3H), 3.55 (t, J = 7.0, 2H), 3.26 (s, 3H), 3.00 (t, J = 7.0, 2H), 2.56 (s, 2H), 2.48 (br s, 1H), 1.31 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 140.9 (=C), 132.3 (=CH), 129.4 (=CH), 128.1 (=CH), 126.4 (=CH), 123.5 (=C), 90.4 (≡C), 82.0 (≡C), 73.2 (CH_2), 70.3 (C), 58.8 (CH_3), 35.4 (CH_2), 35.2 (CH_2), 28.9 (CH_3).

HRMS: Calcd for $C_{15}H_{21}O_2^+$ $(M + H)^+$ 233.1536, Found 233.1538.

*3,4-Dihydro-3-phenyl-4-vinylideneisochromen-1-one (**9a**) and Methyl 2-(4-Hydroxy-4-phenylbut-1-ynyl)benzoate (**11a**).* Methyl 2-(3-iodoprop-1-ynyl)benzoate (**8a**) (0.108 g, 0.36 mmol, 1 equiv), benzaldehyde (0.078 g, 0.7 mmol, 2 equiv), diethylzinc (0.55 mL, 0.55 mmol, 1.5 equiv) (1 M solution in heptane) and nondegassed dry CH_2Cl_2 (1.25 mL, 0.2 M) were reacted according to the general

dx.doi.org/10.1021/jo302704g | J. Org. Chem. 2013, 78, 1589−1603

procedure **D** to give product **9a** (4 mg, 4% yield) isolated as a white solid and product **11a** (82 mg, 82% yield isolated as a colorless oil (overall yield 86%, overall allene:propargyl ratio, 5:95).

(**9a**): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.15 (dd, J = 7.8, 0.8, 1H), 7.59 (td, J = 7.8, 1.0, 1H), 7.46 (d, J=7.8, 1H), 7.42−7.29 (m, 6H), 6.18 (t, J = 3.0, 1H), 5.34−5.20 (AB part of an ABX spectrum, J_{AB} = 13.3, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 206.9 (=C=), 164.3 (O=C), 137.9 (=C), 134.6 (=C), 134.3 (=CH), 130.6 (=CH), 128.8 (=CH), 128.5 (=CH), 128.4 (=CH), 127.0 (=CH), 126.0 (=CH), 123.4 (=C), 100.1 (=C), 82.1 (=CH_2), 79.8 (CH).

HRMS: Calcd for $C_{17}H_{13}O_2^+$ $(M + H)^+$ 249.0910, Found 249.0910.

(**11a**): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.92 (dd, J = 7.8, 1.0, 1H), 7.57 (td, J = 7.8, 1.3, 1H), 7.49 (d, J = 7.3, 2H, plus superimposed td, J = 7.8, 1.3, 7.5, 1.3, 1H), 7.42−7.35 (m, 3H), 7.31 (tt, J = 7.3, 1.3, 1H), 5.07 (dd, J = 8.3, 4.0, 1H), 4.38 (br s, 1H), 3.85 (s, 3H), 2.93 (dd, J = 4.0, 16.8, A part of an ABX pattern, 1H), 2.85 (dd, J = 8.5, 16.8, B part of an ABX pattern,1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.7 (O=C), 142.9 (=C), 133.8 (=CH), 132.2 (=CH), 131.4 (=C), 130.7 (=CH), 128.5 (=CH), 127.8 (=CH), 127.7 (=CH), 125.8 (=CH), 124.5 (=C), 92.8 (≡C), 82.6 (≡C), 72.5 (CH), 52.6 (CH_3), 31.8 (CH_2).

HRMS: Calcd for $C_{18}H_{20}NO_3^+$ $(M + NH_4)^+$ 298.1438, Found 298.1438.

*4,5-Dihydro-4-phenyl-5-vinylidenebenzo[d]oxepin-2(1H)-one (**9b**), Methyl 2-(2-(1-Hydroxy-1-phenylbuta-2,3-dien-2-yl)phenyl)-acetate (**10b**) and Methyl 2-(2-(4-Hydroxy-4-phenylbut-1-ynyl)-phenyl)acetate (**11b**).* Methyl 2-(2-(3-iodoprop-1-ynyl)phenyl)-acetate (**8b**) (0.115 g, 0.37 mmol, 1 equiv), benzaldehyde (0.078 g, 0.74 mmol, 2 equiv), diethylzinc (0.55 mL, 0.55 mmol, 1.5 equiv) (1 M solution in heptane) and nondegassed dry CH_2Cl_2 (1.25 mL, 0.2 M) were mixed according to the general procedure **D** to give product **9b** (15 mg, 15% yield) isolated as a white solid and products **10b** and **11b** (85 mg, 80% yield) isolated as an unseparable mixture of colorless oils (overall yield 95%, overall allene/propargyl ratio, 58:42 (the ratio is based on the integration of the characteristic signals at 5.42 and 4.91 ppm)).

(**9b**): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.48 (dd, J = 1.3, 8.0, 1H), 7.38 (m, 2H), 7.33−7.25 (m, 3H), 7.21 (td, J = 7.8, 1.5, 1H), 7.16 (td, J = 7.8, 1.5, 1H), 7.09 (br d, J = 7.3, 1H), 6.39 (t, J = 2.8, 1H), 5.03−4.90 (AB part of an ABX spectrum, J_{AB} = 13.5, 2H), 4.56 (d, J = 15.3, 1H), 3.76 d, J = 15.3, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 210.5 (=C=), 171.0 (O=C), 137.4 (=C), 131.6 (=C), 131.3 (=CH), 129.1 (=CH), 128.6 (=CH), 128.3 (=CH), 128.2 (=CH), 128.2 (=CH), 128.0 (=C), 127.3 (=CH), 106.8 (=C), 81.7 (=CH_2), 79.4 (CH), 42.0 (CH_2).

HRMS: Calcd for $C_{18}H_{15}O_2^+$ $(M+H)^+$ 263.1067, Found 263.1067.

(**10b**): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.38−7.11 (m, 8H), 7.02 (d, J = 8.0, 1H), 5.42 (t, J = 2.8, 1H), 4.87−4.80 (AB part of an ABX spectrum, J_{AB} = 11.3, 2H), 3.58 (AB spectrum, J_{AB} = 16.3, 2H), 3.61 (s, 3H), 3.02 (br s, 1H).

(**11b**): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.38−7.11 (m, 9H), 4.91 (dd, J = 5.2, 7.3, 1H), 3.70 (AB spectrum, J_{AB} = 15.1, 2H), 3.61 (s, 3H), 3.29 (br s, 1H), 2.84 (dd, J = 5.2, 16.8, AB part of an ABX pattern, 1H), 2.85 (dd, J = 7.3, 16.8, AB part of an ABX pattern, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) mixture of the two products, δ: 205.5 (=C=), 172.9 (O=C), 172.2 (O=C), 142.8 (=C), 141.9 (=C), 136.1 (=C), 134.6 (=C), 133.0 (=C), 132.2 (=CH), 131.0 (=CH), 130.0 (=CH), 129.2 (=CH), 128.6 (=CH), 128.4 (=CH), 128.1 (=CH), 128.0 (=CH), 127.7 (=CH), 127.6 (=CH), 127.3 (=CH), 127.2 (=CH), 126.6 (=CH), 125.9 (=CH), 123.7 (=C), 107.9 (=C), 91.5 (≡C), 81.2 (≡C), 78.5 (=CH_2), 75.0 (CH), 72.6 (CH), 52.4 (CH_3), 52.3 (CH_3), 40.5 (CH_2), 38.8 (CH_2), 31.1 (CH_2).

HRMS: Calcd for $C_{19}H_{22}NO_3^+$ $(M + NH_4)^+$ 312.1594, Found 312.1596.

*Methyl 3-(2-(1-hydroxy-1-phenylbuta-2,3-dien-2-yl)phenyl)-propanoate (**10c**) and methyl 3-(2-(4-hydroxy-4-phenylbut-1-ynyl)-phenyl)propanoate (**11c**).* Methyl 3-(2-(3-iodoprop-1-ynyl)phenyl)-propanoate (**8c**) (0.082 g, 0.25 mmol, 1 equiv), benzaldehyde (0.053 g, 0.5 mmol, 2 equiv), diethylzinc (0.375 mL, 0.375 mmol, 1.5 equiv) (1 M solution in heptane) and nondegassed dry CH_2Cl_2 (1.25 mL, 0.2 M) were mixed according to the general procedure **D** to give products **10c** and **11c** in a 84:16 ratio isolated as colorless oil (overall yield 80%, 0.061 g). The two products could not be separated from each other. Their ratio was determined from the relative integration of the protons of the methoxy groups.

(**10c**): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.41−7.13 (m, 8H), 7.09 (dd, J = 1,0, 7.3, 1H), 5.47 (br s, 1H), 5.07−4.99 (AB part of an ABX spectrum, J_{AB} = 11.1, 2H), 3.67 (s, 3H), 2.95−2.84 (m, AA′ part of an AA′XX′ pattern, 2H), 2.71 (br s, 1H), 2.54−2.34 (m, XX′ part of an AA′XX′ pattern, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 205.2 (=C=), 173.8 (O=C), 141.8 (=C), 139.4 (=C), 134.1 (=C), 129.5 (=CH), 129.3 (=CH), 128.3 (=CH), 128.0 (=CH), 127.9 (=CH), 126.7 (=CH), 126.3 (=CH), 108.0 (=C), 78.9 (=CH_2), 75.2 (CH), 51.7 (CH_3), 35.3 (CH_2), 28.2 (CH_2).

(**11c**): ^{1}H NMR (400 MHz, $CDCl_3$) δ: characteristic signals 7.49−7.47 (m, 2H), 7.42−7.37 (m, 3H), 7.41−7.13 (m, 4H), 5.02−4.98 (m, 1H), 3.67 (s, 3H), 3.07 (t, J = 7.8, 2H), 3.05 (br s, 1H), 2.95−2.84 (m, 2H), 2.63 (pseudo t, J = 6.5, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.8 (O=C), 143.0 (=C), 142.4 (=C), 132.5 (=CH), 128.8 (=CH), 128.5 (=CH), 128.3 (=CH), 127.9 (=CH), 126.4 (=CH), 125.9 (=CH), 122.9 (=C), 90.6 (≡C), 81.2 (≡C), 72.7 (CH), 51.8 (CH_3), 35.0 (CH_2), 30.8 (CH_2), 30.2 (CH_2).

HRMS: Calcd for $C_{20}H_{20}O_3Na^+$ $(M + Na)^+$ 331.1304, Found 331.1304.

*1-Phenyl-2-vinylideneheptan-1-ol (**13a**) and 1-Phenylnon-3-yn-1-ol (**14a**).* 1-Iodooct-2-yne (**12a**) (0.059 g, 0.25 mmol, 1 equiv), benzaldehyde (0.053 g, 0.5 mmol, 2 equiv), diethylzinc (0.375 mL, 0.375 mmol, 1.5 equiv) (1 M solution in heptane) and nondegassed dry CH_2Cl_2 (1.25 mL, 0.2 M) were reacted according to the general procedure **D** to give products **13a** and **14a** in a 73:27 ratio isolated as a colorless oil (overall yield 89%, 0.048 g). The two products could not be separated from each other. Their ratio was determined from the relative integration of characteristic signals at 5.02 and 4.73 ppm.

(**13a**): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.32−7.18 (m, 5H), 5.02 (t, J = 2.2, 1H), 4.95−4.88 (m, 2H), 2.15 (br s, 1H), 1.80−164 (m, 2H), 1.44−1.10 (m, 6H), 0.76 (t, J = 6.8, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 204.2 (=C=), 142.3 (=C), 128.4 (=CH), 127.9 (=CH), 126.8 (=CH), 108.4 (=C), 79.9 (=CH_2), 74.2 (CH), 31.6 (CH_2), 28.0 (CH_2), 27.2 (CH_2), 22.6 (CH_2), 14.1 (CH_3).

(**14a**): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.30−7.18 (m, 5H), 4.73 (dd, J = 5.3, 7.6, 1H), 2.59−2.46 (m, 2H), 2.38 (br s, 1H), 2.08 (tt, J = 2.3, 7.0, 2H), 1.44−1.10 (m, 6H), 0.82 (t, J = 7.0, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 142.9 (=C), 128.5 (=CH), 127.8 (=CH), 125.9 (=CH), 83.8 (≡C), 76.0 (≡C), 72.7 (CH), 31.2 (CH_2), 30.2 (CH_2), 28.7 (CH_2), 22.3 (CH_2), 18.9 (CH_2), 14.1 (CH_3).

HRMS: Calcd for $C_{15}H_{20}ONa^+$ $(M + Na)^+$ 239.1406, Found 239.1405.

*8-Methoxy-1-phenyl-2-vinylideneoct-3-yn-1-ol (**13b**) and 8-Methoxy-1-phenyloct-3-yn-1-ol (**14b**).* 1-Iodo-7-methoxyhept-2-yne (**12b**) (0.063 g, 0.25 mmol, 1 equiv), benzaldehyde (0.053 g, 0.5 mmol, 2 equiv), diethylzinc (0.375 mL, 0.375 mmol, 1.5 equiv) (1 M solution in heptane) and dry CH_2Cl_2 (1.25 mL, 0.2 M) were reacted according to the general procedure **D** to afford products **13b** and **14b** in a 72:28 ratio, isolated as a colorless oil (overall yield 92%, 0.053 g). The two products could not be separated from each other. Their ratio was determined from the relative integration of characteristic signals at 5.03 and 4.71 ppm.

(**13b**): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.30−7.18 (m, 5H), 5.03 (br s, 1H), 4.95−4.85 (m, 2H), 3.21 (t, J = 6.3, 2H), 3.20 (s, 3H), 2.40 (br s, 1H), 1.82−1.69 (m, 2H), 1.49−1.32 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 204.3 (=C=), 142.2 (=C), 128.3 (=CH), 127.7 (=CH), 126.7 (=CH), 108.0 (=C), 79.8 (=CH_2), 74.3 (CH), 72.7 (CH_2), 58.6 (CH_3), 29.2 (CH_2), 27.6 (CH_2), 24.1 (CH_2).

(**14b**): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.30−7.18 (m, 5H), 4.71 (t, J = 6.3, 1H), 3.29 (t, J = 6.3, 2H), 3.24 (s, 3H), 2.59 (br s, 1H), 2.55−2.45 (m, 2H), 2.13−2.09 (tt, J = 7.0, 2.3, 2H), 1.59−1.52 (m, 2H), 1.49−1.32 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 143.0 (=C), 128.4 (=CH), 127.8 (=CH), 125.9 (=CH), 83.0 (≡C), 76.5 (≡C), 72.7 (CH), 72.3 (CH_2), 58.6 (CH_3), 30.1 (CH_2), 28.8 (CH_2), 25.6 (CH_2), 18.6 (CH_2).

dx.doi.org/10.1021/jo302704g | J. Org. Chem. 2013, 78, 1589−1603

HRMS: Calcd for $C_{15}H_{20}O_2Li^+$ $(M + Li)^+$ 239.1618, Found 239.1621.

NMR Experiment. The propargylic iodide (0.1 mmol) was put in a dry NMR tube closed with rubber septum. Nondegassed $CDCl_3$ (0.5 mL) was injected through septum using a syringe. Diethylzinc (0.15 mL of a 1 M solution in heptane) was injected into the above solution with a syringe through septum. After the addition, the septum was replaced with the NMR tube cap and the reaction was monitored using NMR spectroscopy. No evolution was observed unless the solution was shaken, so that reactants were mixed and the solution becomes homogeneous. After evolution, the reaction mixture was quenched with a drop of water.

The evolution was instantaneous when the NMR tube was reopened and shaken several times just before the spectrum was recorded.

COMPUTATIONAL DETAILS

All calculations were performed with Gaussian 09 package.[46] The geometries of all species were calculated with the CBS-QB3[19] composite method in order to obtain accurate thermodynamic data. During the CBS-QB3 procedure, vibrational frequencies were calculated and the nature of stationary points were confirmed (0 or 1 imaginary frequency for a minimum or a transition state, respectively). All transition state geometries were confirmed by intrinsic reaction coordinate (IRC) calculations at the B3LYP/6-311G(2d,d,p) level of theory. The NBO calculations for figure 4 were performed at the B3LYP/6-31+G(d,p) level of theory.

ASSOCIATED CONTENT

Supporting Information

EPR spectra for all new compounds, computational details. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*E-mail: michele.bertrand@univ-amu.fr; laurence.feray@univ-amu.fr; didier.siri@univ-amu.fr.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The authors thank Aix-Marseille Université for funding the post doctoral fellowship of Dr S. Jammi. Calculation facilities were provided by the "Centre Régional de Compétences en Modélisation Moléculaire" (Marseille, France).

REFERENCES

(1) For a review, see: Yamamoto, Y. In *Comprehensive Organic Synthesis*; Trost, B. M, Ed.; Pergamon Press: Oxford, 1991; Vol. 2, pp 81−98.

(2) For reviews, see: (a) Marshall, J. A.; Gung, B. W.; Grachan, M. L. Synthesis and Reactions of Allenyl Compounds. In *Modern Allene Chemistry*; Krause, N., Hashmi, A. S. K., Eds; WILEY-VCH: Weinheim, 2004; pp 493−592. (b) Marshall, J. A. In *The chemistry of Organozinc Compounds*; Rappoport, Z., Marek, I., Eds; WILEY: New-York, 2006; Vol. *1*, pp 421−455. (c) Botuha, C.; Chemla, F.; Ferreira, F.; Pérez-Luna, A.; Roy, B. *New. J. Chem.* **2007**, *31*, 1552−1567. For the propargylation of imines, see also: (d) Botuha, C.; Chemla, F.; Ferreira, F.; Louvel, J.; Pérez-Luna, A. *Tetrahedron: Asymmetry* **2010**, *21*, 1147−1153 and previous refs cited therein.

(3) For an exhaustive review on the generation and the reactivity of functionalized organozinc compounds, see: Knochel, P.; Millot, N.; Rodriguez, A. L.; Tucker, C. E. *Org. React.* **2001**, *58*, 417−731.

(4) For selected examples, see: (a) Poisson, J.-F.; Chemla, F.; Normant, J. F. *Org. Lett.* **2001**, *3*, 1889−1891. (b) Poisson, J.-F.; Normant, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 4639−4640. (c) Louvel, J.; Botuha, C.; Chemla, F.; Demont, E.; Ferreira, F.; Pérez-Luna, A. *Eur. J. Org. Chem.* **2010**, *16*, 2921−2926. (d) Voituriez, A.; Pérez-Luna, A.; Ferreira, F.; Botuha, C.; Chemla, F. *Org. Lett.* **2009**, *11*, 931−934. (e) Séguin, C.; Ferreira, F.; Botuha, C.; Chemla, F.; Pérez-Luna, A. *J. Org. Chem.* **2009**, *74*, 6986−6992.

(5) (a) Fandrick, D. R.; Fandrick, K. R.; Reeves, J. T.; Tan, Z.; Johnson, C. S.; Lee, H.; Song, J. J.; Yee, N. K.; Senayake, C. H. *Org. Lett.* **2010**, *12*, 88−91. (b) Fandrick, D. R.; Saha, J. S.; Fandrick, K. R.; Sanyal, S.; Ogikubo, J.; Lee, H.; Roschanger, F.; Song, J. J.; Senayake, C. H. *Org. Lett.* **2011**, *13*, 5616−5619.

(6) (a) Tamaru, Y.; Goto, S.; Tanaka, A.; Shimizu, M.; Kimura, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 878−880. (b) Marshall, A. J. *Chem. Rev.* **2000**, *100*, 3163−3185. (c) Marshall, J. A.; Adams, N. D. *J. Org. Chem.* **1999**, *64*, 5201−5204. (d) Marshall, J. A.; Chobanian, H. R. *J. Org. Chem.* **2000**, *65*, 8357−8360. (e) Marshall, J. A.; Mulhearn, J. J. *Org. Lett.* **2005**, *7*, 1593−1596. (f) Marshall, J. A.; Eidam, P.; Eidam, H. S. *J. Org. Chem.* **2006**, *71*, 4840−4844. (g) Hameury, T.; Guillemon, J.; Van Hifte, L.; Bellosta, V.; Cossy, J. *Org. Lett.* **2009**, *11*, 2397−2400. (h) Defosseux, M.; Blanchard, N.; Meyer, C.; Cossy, J. *Org. Lett.* **2003**, *5*, 4037−4040. (i) Monti, C.; Sharon, O.; Gennari, C. *Chem. Commun.* **2007**, 4271−4273. (j) Sakamoto, T.; Takahashi, K.; Yamazaki, T.; Kitazume, T. *J. Org. Chem.* **1999**, *64*, 9467−9474.

(7) For pioneering studies, see: Moreau, J. L.; Gaudemar, M. *Bull. Soc. Chim. Fr.* **1970**, 2171−2175.

(8) (a) Bieber, L. W.; Da Silva, M. F.; Da Costa, R. C.; Silva, L. O. S. *Tetrahedron Lett.* **1998**, *39*, 3655−3658. (b) Jögi, A.; Mäeorg, U. *Molecules* **2001**, *6*, 964−968.

(9) Unger, R.; Weisser, F.; Chinkov, N.; Stanger, A.; Cohen, T.; Marek, I. *Org. Lett.* **2009**, *11*, 1853−1856.

(10) Trost, B. M.; Ngal, M.-Y.; Dong, G. *Org. Lett.* **2011**, *13*, 1900−1903.

(11) (a) Shinokubo, H.; Miki, H.; Yokoo, T.; Oshima, K.; Utimoto, K. *Tetrahedron* **1995**, *51*, 11681−11692. (b) Lin, M. H.; Tsai, W. S.; Lin, L. Z.; Hung, S. F.; Chuang, T. H.; Su, Y. J. *J. Org. Chem.* **2011**, *76*, 8518−8523.

(12) It must be noted that Indium-mediated reactions and In(cat)/Ga-mediated reactions using propargyl bromides as the precursors of organometallic species have also been investigated, see: (a) Hirayama, L. C.; Dunham, K. K.; Singaram, B. *Tetrahedron Lett.* **2006**, *47*, 5173−5176. (b) Lee, P. H.; Kim, H.; Lee, K. *Adv. Synth. Catal.* **2005**, *347*, 1219−1222. (c) Lin, M.-J.; Loh, T.-P. *J. Am. Chem. Soc.* **2003**, *125*, 13042−13043. (d) Loh, T.-P.; Lin, M.-J.; Tan, K.-L. *Tetrahedron Lett.* **2003**, *44*, 507−509. (e) Hua, X.-G.; Mague, J. T.; Li, C.-J. *Tetrahedron Lett.* **1998**, *39*, 6837−6840. (f) Miao, W.; Lu, W.; Chan, T. H. *J. Am. Chem. Soc.* **2003**, *125*, 2412−2413. (g) Xu, B.; Hammond, G. B. *Chem.—Eur. J.* **2008**, *14*, 10029−10035. (h) Gu, C. Z.; Li, Q. R.; Yin, H. *Chin. Chem. Lett.* **2005**, *16*, 1573−1576. For the reactivity of related organoaluminum, see: (i) Daniels, R. G.; Paquette, L. A. *Tetrahedron Lett.* **1981**, *22*, 1579−1582. (j) Guo, L.-N.; Gao, H.; Mayer, P.; Knochel, P. *Chem.—Eur. J.* **2010**, *16*, 9829−9834.

(13) (a) Gung, B. W.; Xue, X.; Knatz, N.; Marshall, J. A. *Organometallics* **2003**, *22*, 3158−3163. (b) Bejjani, J.; Botuha, C.; Chemla, F.; Ferreira, F.; Magnus, S.; Pérez-Luna, A. *Organometallics* **2012**, *31*, 4876−4885.

(14) For copper-catalyzed silylpropargylation, see: Ohmiya, H.; Yokobori, U.; Makida, Y.; Sawamura, M. *Org. Lett.* **2011**, *13*, 6312−6315.

(15) (a) Bazin, S.; Feray, L.; Bertrand, M. P. *Chimia* **2006**, *60*, 260−265 and previous references cited therein. (b) Bazin, S.; Feray, L.; Vanthuyne, N.; Siri, D.; Bertrand, M. P. *Tetrahedron* **2007**, *63*, 77−85. (c) Cougnon, F.; Feray, L.; Bazin, S.; Bertrand, M. P. *Tetrahedron* **2007**, *63*, 11959−11964. (d) Feray, L.; Bertrand, M. P. *Eur. J. Org. Chem.* **2008**, 3164−3170.

(16) For examples of intramolecular trapping of propargyl radical or its canonical allenyl radical form, see: (a) Alameda-Angulo, C.; Quiclet-Sire, B.; Zard, S. Z. *Tetrahedron Lett.* **2006**, *47*, 913−916. (b) Wartenberg, F. H.; Junga, H.; Blechert, S. *Tetrahedron Lett.* **1993**,

34, 5251−5252. (c) Fantazier, R. M.; Poutsma, M. L. *J. Am. Chem. Soc.* **1968**, *90*, 5490−5498.
(17) Maury, J.; Jammi, S.; Vibert, F.; Marque, S. R. A.; Siri, S.; Feray, L.; Bertrand, M. P. *J. Org. Chem.* **2012**, *77*, 9081−9086.
(18) (a) Maury, J.; Feray, L.; Bertrand, M. P. *Org. Lett.* **2011**, *13*, 1884−1887. (b) Chemla, F.; Dulong, F.; Ferreira, M. P.; Nüllen, A.; Pérez-Luna, A. *Synthesis* **2011**, 1347−1360. (c) Pérez-Luna, A.; Botuha, C.; Ferreira, F.; Chemla, F. *Chem.—Eur. J.* **2008**, *14*, 8784−8788. (d) Chen, Z.; Zhang, Y.-X.; An, Y.; Song, X.-L.; Wang, Y.-H.; Zhu, L.-L.; Guo, L. *Eur. J. Org. Chem.* **2009**, 5146−5142.
(19) (a) Maury, J.; Mouysset, D.; Feray, L.; Marque, S. R. A.; Siri, D.; Bertrand, M. P. *Chem.—Eur. J.* **2012**, *18*, 3241−3247. (b) Maury, J.; Feray, L.; Perfetti, P.; Bertrand, M. P. *Org. Lett.* **2010**, *12*, 3590−3593.
(20) (a) Montgomery, J. A., Jr.; Frisch, M. J.; Ochterski, J. W.; Petersson, G. A. *J. Chem. Phys.* **1999**, *110*, 2822−2827. (b) Montgomery, J. A., Jr.; Frisch, M. J.; Ochterski, J. W.; Petersson, G. A. *J. Chem. Phys.* **2000**, *112*, 6532−6542.
(21) The composite CBS-QB3 method was used in order to obtain accurate energy values. This method is fitted to reproduce thermodynamic experimental data in vacuo. We did not try to take solvent effects into account as, with this method they may alter the quality of the results. Furthermore, all experiments were performed in dichloromethane, a solvent of low dielectric constant.
(22) For an estimate of the amount of oxygen dissolved in DCM see: Maury, J.; Feray, L.; Bazin, S.; Clément, J.-L.; Marque, S. R. A.; Siri, D.; Bertrand, M. P. *Chem.—Eur. J.* **2011**, *17*, 1586−1595.
(23) The experimental values for the C-I bond dissociation enthalpy is 233.5 kJ mol^{-1} in ethyl iodide and 184.6 kJ mol^{-1} in 3-iodo-prop-1-yne, see: *Handbook of Bond Dissociation Energies in Organic Compounds*; Luo, Y.-R., Ed.; CRC Press: Boca Raton, FL, 2007.
(24) (a) Chen, J.-T. *Coord. Chem. Rev.* **1999**, *190−192*, 1143−1168. (b) Guo, J.-N.; Gao, H.; Mayer, P.; Knochel, P. *Chem.—Eur. J.* **2010**, *16*, 9829−9834.
(25) For theoretical calculations of propargyl-allenyl indium systems, see: (a) Miao, W.; Chung, L. W.; Wu, Y.-D.; Chan, T. H. *J. Am. Chem. Soc.* **2004**, *126*, 13326−13334. For calculations of lithium derivatives, see: (b) Reich, H. J.; Thompson, J. L. *Org. Lett.* **2000**, *2*, 783−786.
(26) (i) The propargylic iodide (0.1 mmol) was put in a dry NMR tube closed with rubber septum. Nondegassed $CDCl_3$ (0.5 mL) was injected through septum using a syringe. Diethylzinc (0.15 mL of a 1 M solution in heptane) was injected into the above solution with a syringe through septum. After the addition, the septum was replaced with the NMR tube cap. No evolution was observed unless the solution was shaken, so that reactants were mixed and the solution becomes homogeneous. After evolution, the reaction mixture was quenched with a drop of water. (ii) The evolution was instantaneous when the NMR tube was reopened and shaken several times just before the spectrum was recorded.
(27) This observation must be connected with the report on the acceleration of Zn/iodine exchange leading to carbenoids in CH_2I_2/Et_2Zn-promoted cyclopropanation reactions in the presence of air. See: (a) Miyano, S.; Hashimoto, H. *J. Chem. Soc., Chem. Commun.* **1971**, 1418−1419. (b) Miyano, S.; Hashimoto, H. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 892−897. (c) Miyano, S.; Izumi, Y.; Fujii, H.; Hashimoto, H. *Synthesis* **1977**, 700−701. (c) Furukawa, J.; Kawabata, N.; Nishimura, J. *Tetrahedron* **1968**, *24*, 53−58.
(28) Cohen, T.; Gibney, H.; Ivanov, R.; Yeh, E. A.-H.; Marek, I.; Curran, D. P. *J. Am. Chem. Soc.* **2007**, *129*, 15405−15409.
(29) See: (a) Albright, M. J.; St Denis, J.; Oliver, J. P. *J. Organomet. Chem.* **1977**, *125*, 1−8. and previous refs cited therein. (b) St Denis, J.; Oliver, J. P. *Organomet. Chem* **1974**, *71*, 315−323. (c) Wooten, A.; Carroll, P. J.; Maestri, A. G.; Walsh, P. J. *J. Am. Chem. Soc.* **2006**, *128*, 4624−4631. (d) Wilson, E. E.; Oliver, A. G.; Hughes, R. P.; Ashfeld, B. L. *Organometallics* **2011**, *30*, 5214−5221.
(30) These data support the proposal of the ready formation of an allenyl radical to explain the lack of configurational stability of allenylzincs, see ref 10.
(31) For recent comprehensive reviews, see: (a) Weinhold, F. *J. Comput. Chem.* **2012**, *33*, 2363−2379. (b) Weinhold, F. *J. Comput. Chem.* **2012**, *33*, 2440−2449.
(32) Trost and co-worker (ref 9) have recently reported that in nondegassed medium, the yield of diethylzinc-mediated reaction of propargyl (or allenyl) iodide with cinnamaldehyde in the presence of chiral aminoalcohols was lowered due to the competition of radical pathways. In all likelihood, a radical mechanism is operative under both conditions in the formation of the organozinc species. A radical route initiated by SET mechanism might be operative under a strictly inert atmosphere.
(33) Grissom, J. W.; Klingberg, D.; Huang, D.; Slattery, B. J. *J. Org. Chem.* **1997**, *62*, 603−626.
(34) Bowman, R. M.; McCullough, J. J.; Swenton, J. S. *Can. J. Chem.* **1969**, *47*, 4503−4506.
(35) NMR data were in agreement with the data previously reported in the literature. Franks, M. A.; Schrader, E. A.; Pietsch, E. C.; Pennella, D. R.; Torti, S. V.; Welker, M. E. *Bioorg. Med. Chem.* **2005**, *3*, 2221−2233.
(36) Compound **9z** was prepared according to the literature procedure, see: Meyer, M. P.; Klinman, J. P. *J. Am. Chem. Soc.* **2011**, *133*, 430−439.
(37) Taber, D. F.; Herr, R. J.; Gleave, D. M. *J. Org. Chem.* **1997**, *62*, 194−198.
(38) Compound **8x** was prepared from a literature procedure, see: Cerichelli, G.; Luchetti, L. *Tetrahedron* **1993**, *49*, 10733−10738.
(39) Maji, M.; Mallick, D.; Mondal, S.; Anoop, A.; Bag, S. S.; Basak, A.; Jemmis, E. D. *Org. Lett.* **2011**, *13*, 888−891.
(40) Trost, B. M.; Ngai, M.-Y.; Dong, G. *Org. Lett.* **2011**, *13*, 1900−1903.
(41) Nishina, N.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 3314−3317.
(42) Tarasava, O. A.; Brandsma, L.; Nedilya, N. A.; Afonin, A. V.; Ushakov, I. A.; Klyba, L. V. *Russian J. Org. Chem.* **2003**, *39*, 1451−1457.
(43) Bolte, B.; Odabachian, Y.; Gagosz, F. *J. Am. Chem. Soc.* **2010**, *132*, 7294−7296.
(44) Cheng, C.-Y.; Minoru, I. *Tetrahedron* **2011**, *67*, 9957−9965.
(45) Nobuhito, K.; Kazuya, S.; Masao, T. *Tetrahedron* **2000**, *56*, 847−854.
(46) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery Jr., J. A.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *Gaussian 09*, Revision A.02; Gaussian, Inc.: Wallingford, CT, 2009.