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Full Paper

Polarization-Induced Regioselectivity

Polarization Effect on Regioselectivity of Pd-Catalyzed Cyclization of 2-Alkynylbenzaldehydes

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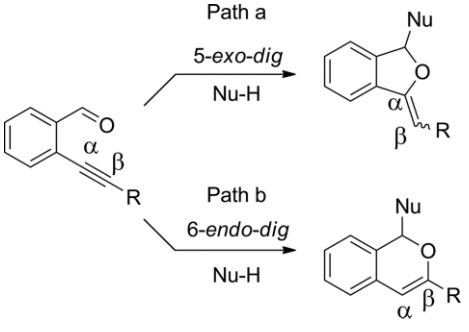
Abstract: We report a study on the relationship between the polarization of C≡C bond in a series of 2-alkynylbenzaldehydes and the regioselectivity of their Pd-catalyzed annulation reactions. The electrophilic and nucleophilic character of the triple bond carbon atoms was examined using ^{13}C and HMBC NMR experiments. The direction of polarization is determined only by the formyl group and its position on an aromatic ring. On the other hand, the strength of the polarization expressed through chemical shift difference $\Delta\delta$ of acetylenic carbon atoms is a result of electron-withdrawing or electron-donating ability of the other substituent. Out of two possible regioisomers, the Pd-catalyzed cyclization reactions of 2-alkynylbenzaldehydes that were studied predominantly afforded 1*H*-isochromenes suggesting that the polarization of a triple bond is one of the contributing factors in the regioselectivity of this process.

Introduction

The abundance of isochromene-containing natural products that exhibit a wide spectrum of interesting and valuable biological properties[1] has propelled extensive effort to design synthetic routes that would compete with the cost of isolation of these heterocycles from their natural sources. We note that intramolecular cyclization of 2-alkynylaryl aldehydes stands today as one of the simplest, atom-economical and highly effective approach towards 1*H*-isochromenes and structurally related cyclic ethers. A considerable amount of progress has been achieved in the development of efficient strategies for this particular transformation. Among currently available methods, the majority relies on using transition metal complexes, namely those of Pd[2] and Au.[3] Reactions catalyzed by Ag,[4] Cu,[5] Pt,[6] In,[7] and W[8] are studied and reported as well but to lesser extent. Moreover, Pd and Au catalyzed tandem reactions in the presence of a C-, O- or N-based nucleophile allowed synthesis of isochromenes and structural equivalents with higher molecular complexity. In a similar manner, cyclization of 2-alkynyl benzyl alcohols catalyzed by Pd,[9] Au[10] or Ru[11] also serve as a method for construction of cyclic alkenyl ethers. Other methods for synthesis of isochromene compounds include base promoted iodocyclization of 2-alkynylbenzaldehydes[12] or 2-alkynyl benzyl alcohols,[13] intramolecular Michael cyclization of nitroalkenes,[14] intramolecular Wittig reaction,[15] and intramolecular oxa-Michael reaction.[16] Although highly reliable, the above-mentioned methods often suffer from poor regioselectivity. In principle, cyclization of 2-alkynylbenzaldehydes in the presence of an external nucleophile can proceed via two pathways and as a result, two regioisomers can be formed. The benzofuran product is derived from 5-*exo-dig* cyclization (path a, Scheme 1), while 6-*endo-dig* cyclization favors the formation of 1*H*-isochromene (path b, Scheme 1).



Scheme 1. Two possible pathways for the cyclization of 2-alkynylbenzaldehydes.

It is generally accepted that the regioselectivity mainly depends on the basicity of a reaction medium. In the absence of a base, the reaction is believed to proceed via domino annulation/addition sequence (Scheme 2a). In the first step the metal catalyst coordinates to the triple bond of the alkynyl aldehyde **A**, thus activating it for the subsequent 6-*endo-dig* attack of the carbonyl oxygen atom and the formation of the isobenzopyrylium intermediate **B**. Next, the nucleophilic addition leads to the intermediate **C**, which upon proto-demetallation gives the isochromene product **D**. On the other hand, addition/annulation sequence is favored in the base-promoted reaction, independently of the metal catalyst. First, the deprotonated nucleophile attacks the carbonyl carbon atom, thus forming the hemiacetal anion intermediate **E**. The following annulation and protonation of the formed alkenyl anion predominantly gives the benzofuran product **F** via 5-*exo-dig* process (Scheme 2b).

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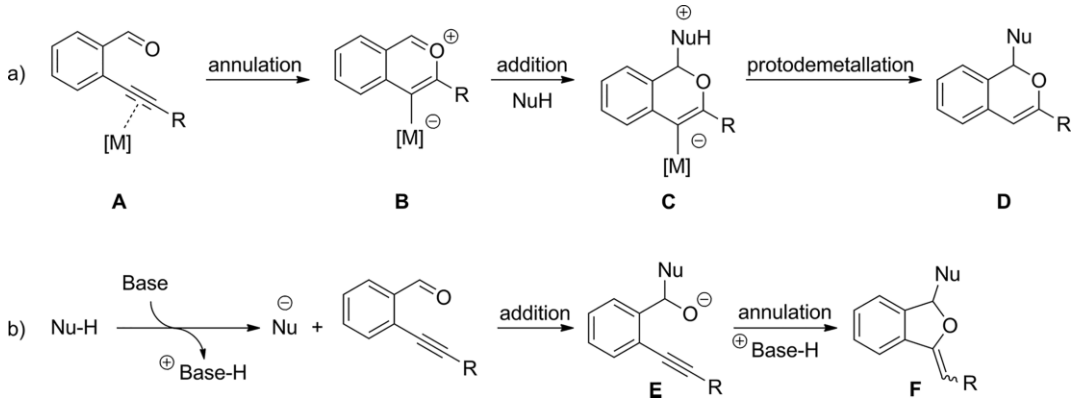


Scheme 2. Proposed mechanisms for the cyclization of 2-alkynylbenzaldehydes.

According to the literature, in addition to the basicity of the reaction medium, as stated before,[17] additional factors that affect the regioselectivity of this process are; i) nature of the carbonyl group,[18] ii) nature of the metal catalyst,[5a,19] and iii) the polarization of the acetylenic portion of the molecule.[3i] The latter effect, that is, the correlation between the regioselectivity and the polarization has not been extensively studied.[20] In accordance with the proposed mechanisms, we believe that the regiochemistry could be highly affected by the electron distribution (polarization) of the alkyne moiety of *ortho* alkynylbenzaldehydes. Regardless of the mechanism, the nucleophilic carbonyl oxygen atom in the isobenzopyrilium pathway, or the oxygen atom in the hemiacetal anion pathway should bond to the more electrophilic acetylenic carbon atom. The presence of an electron-withdrawing group (EWG) on the β-atom of the alkyne should favor the 5-*exo*-*dig* cyclization and the formation of the benzofuran products, while the 6-*endo*-*dig* cyclization, initiated by the presence of the electron-donating group (EDG), would lead to 1*H*-isochromenes. The correlation between electron properties of the alkyne moiety and regioselectivity in cyclization of *ortho* alkynyl benzylic alcohols has been studied,[21] but to the best of our knowledge, the same study has not been performed for 2-alkynylbenzaldehydes. Yamamoto's seminal work on $Pd(OAc)_2$-catalyzed cyclization of alkynyl aldehydes in the presence of alcohol has shown that the regiochemistry of the heteroannulation step is affected to some extent by the EDG or EWG on the alkyne portion of the molecule.[2b] In the case of carbon-tethered alkynyl aldehydes bearing an EDG on the alkyne, a mixture of five and six-membered heterocycles was obtained, while only the five-membered cyclic ether was obtained in cyclization of acetylenic aldehydes bearing the EWG. On the other hand, the cyclization of 2-alkynylbenzaldehydes with an EDG afforded only 1*H*-isochromene products, while the same reactions with EWG on the alkyne were not reported. As there is a lack of information on the correlation between the polarization of C≡C bond and regioselectivity of the Pd-catalyzed cyclization of 2-alkynylbenzaldehydes in the presence of an external oxygen-containing nucleophile, the purpose of this work is to investigate: i) how the electron-donating and electron-withdrawing ability of a substituent on the β-carbon atom affects the polarization, ii) the additional factors that influence the electron density of acetylenic portions of these compounds, and iii) how the unequal electron distribution is translated to the regioselectivity of this process.

Results and Discussion

To analyze the polarization-regioselectivity correlation, a series of *ortho* substituted alkynylbenzaldehydes was prepared. The other substitution patterns (*meta* and *para*) were intentionally avoided to exclude any potential steric effect on the regioselectivity. The electronic distribution, that is, the electrophilic and nucleophilic character of the acetylenic carbon atoms can be easily deduced from the chemical shift of the corresponding signals in the ^{13}C NMR spectra.[22] The signal that appear downfield in the spectra would correspond to the electrophilic carbon atom while the signal of the nucleophilic carbon atom would have an upfield chemical shift value. Also, the strength of the triple bond polarization can be characterized by the chemical shift difference between the acetylenic carbon atoms. If polarization is influenced only by the substituent on the β-carbon atom, we assumed that 2-alkynylbenzaldehydes carrying an electron-donating substituent would exert such a polarization where the electron density would be higher on the α-carbon atom. On the other hand, the β-carbon atom should be more nucleophilic if the substituent is an electron withdrawing group. In that manner, with the aid of ^{13}C and HMBC NMR experiments, the partial charges were assigned to the corresponding carbon atoms of the triple bond.[23] The observed electron distribution (polarization) was identical in all cases and the nucleophilicity (δ^-) resides mostly on the α-carbon atom (the benzaldehyde side) while the β-carbon atom is electrophilic (δ^+) (Figure 1).

These results indicate that the electron distribution is weakly affected by the substituent on the β-carbon atom of the triple bond and that the nature of the aldehyde group plays a key role in its polarization. The most intriguing result was the polarization in **1c**. Although the cyano group is a stronger EWG compared to the formyl, the electron density is higher on the α-carbon atom of the triple bond. That implies that the position of the substituents might be also one of the factors that determines the polarization. It is worth mentioning that the value of the chemical shift difference $\Delta\delta$ ranges from 1.6 ppm for

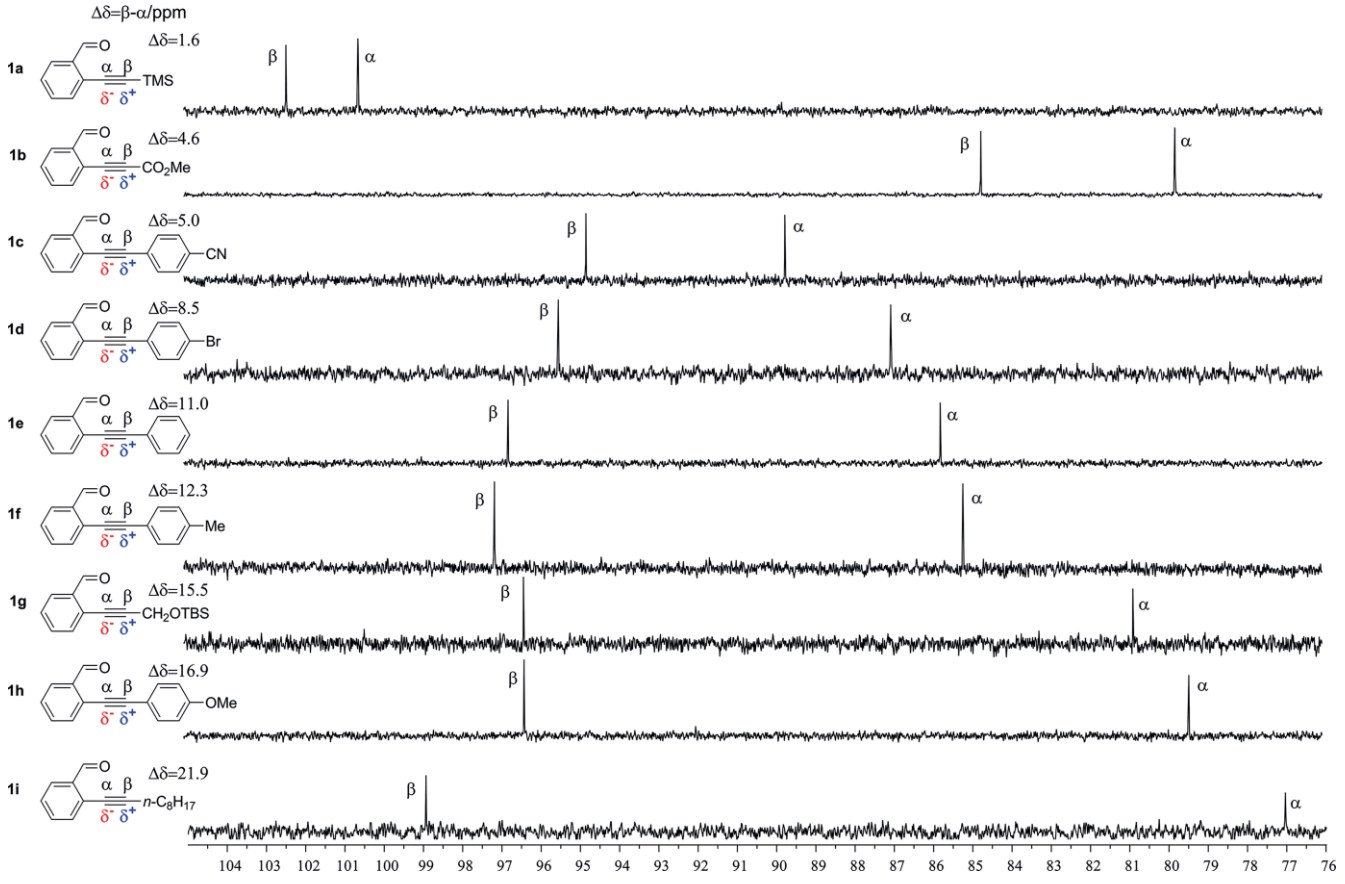


Figure 1. Polarization of the triple bond in 2-alkynylbenzaldehydes **1a**–**1i**.

trimethylsilyl substituent in **1a** to 21.9 ppm in the case of octyl substituent on the β-carbon atom as in **1i**. The observed trend shows that the polarization is stronger when the substituent exhibits electron-donating properties.

As benzaldehydes **1c**–**1f** and **1h** are essentially diphenylacetylenes with an *ortho*-positioned formyl group on one aromatic ring and *para*-positioned substituent on the other, relative to the triple bond, we assumed that by allocating the formyl group to *para* and *meta* positions we could directly observe its influence on the polarization. To test this assumption, the 4-alkynylbenzaldehyde **1j** and 3-alkynylbenzaldehyde **1k** were prepared and the polarization was determined on the basis of ^{13}C NMR chemical shifts of the α- and β-carbon atoms (Figure 2).

The observed electron distribution in **1k** was the opposite compared to its regioisomer **1c** with the value of the chemical shift difference changing from 5.0 ppm to –2.9 ppm, respectively. The direction of polarization in **1j** was reversed as well with respect to **1c** but the direct "push-pull" system created by placing the aldehyde group in *para* position resulted in weaker polarization where the chemical shift difference dropped to only –1.2 ppm. These results suggest that the position of the

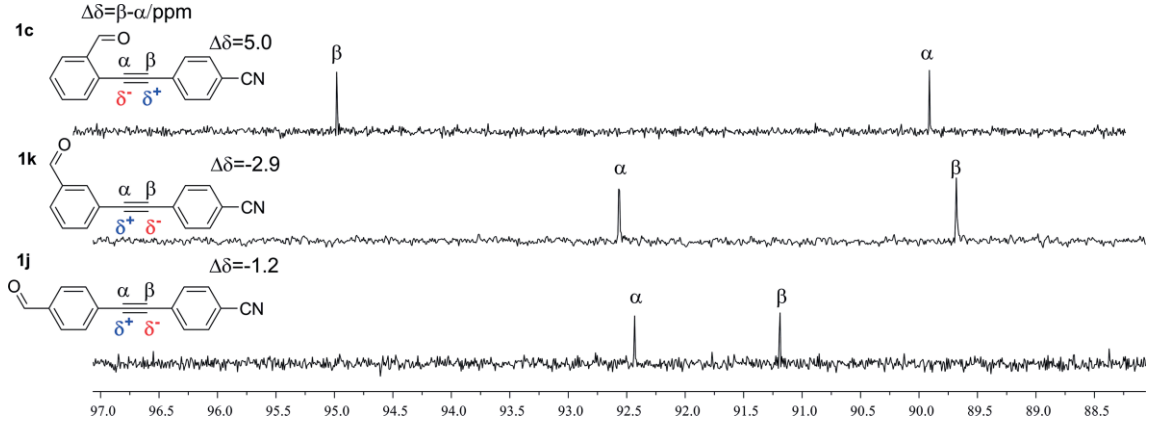


Figure 2. Polarization of the triple bond in alkynylbenzaldehydes **1c**, **1k**, and **1j**.

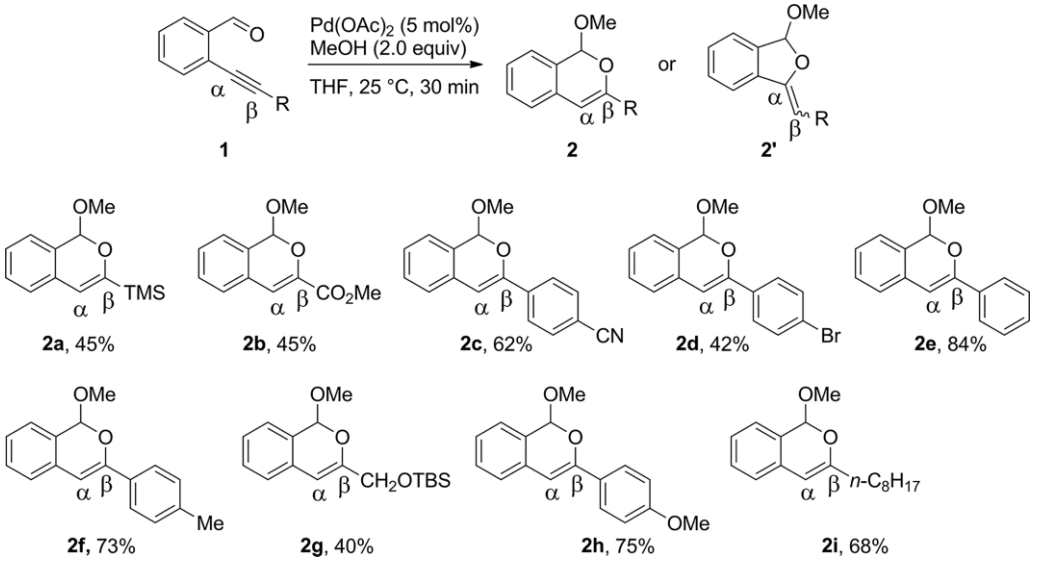
formyl group exhibits a crucial effect on the polarization of the triple bond and overshadows the influence of the substituents on the β-carbon atom. This phenomenon could be explained by the effect of substituents on the electron density of carbon atoms within an aromatic ring and how π-charges and substituent effect are transferred through highly polarizable C≡C bond. The π-electron population at the *ortho* and *para* positions is depleted for the case of an EWG but not equally. The *ortho* position is more affected than the *para* position. The cyano group is a stronger EWG than *para*- and *meta*-positioned formyl group and as a result it affects the polarization of the alkyne bond as expected. However, when in *ortho* position, formyl group becomes a stronger EWG than *para*-positioned cyano group and the polarization is reversed. Moreover, the study on the transmission of electronic substituent effects through the C≡C bond in substituted phenylacetylenes shows that *ortho*- or *para*-positioned π-acceptor interacts through conjugation with the C≡C π-bond that is orthogonal to the π-system of the aromatic ring, thus greatly affecting its polarization.[24]

With 2-alkynylbenzaldehydes in hand, we proceeded with Pd-catalyzed cyclization reactions in the presence of methanol as the external nucleophile. If there is a correlation between polarization of the triple bond and the regioselectivity of this process, then the nucleophilic oxygen atom of the formyl group in all prepared 2-alkynylbenzaldehydes should bond itself to the electrophilic β-carbon atom, thus providing only products with a 1*H*-isochromene core. In that sense, the $Pd(OAc)_2$-catalyzed cyclization reactions in THF with two equivalents of MeOH were carried out as described previously and the results are summarized in Scheme 3. All reactions provided the expected six-membered cyclic alkenyl ethers while the formation of benzofuran products was not observed indicating the close correlation between the polarization and the regioselectivity. The rather modest yields in some cases can be attributed to the problems encountered during the isolation of the products from the remaining Pd-catalyst and unreacted starting material. The structures of the obtained regioisomers were confirmed by HSQC and HMBC NMR experiments (see Supporting Information).

Driven by the above-mentioned results, which suggest the prevalent role of the formyl group on the direction of the polarization in 2-alkynylbenzaldehydes, we aimed to investigate the extent of that effect. By placing the EDG or EWG on one or both of the aromatic rings we might be able to influence the polarization of the C≡C bond that could translate to the regioselectivity of the cyclization reactions. For that purpose, several 2-alkynylbenzaldehydes with *para* substitution on the aldehyde ring relative to the alkynyl moiety were prepared. The type of substituent and the substitution pattern was selected in such a way to create the "push-pull" effect between the substituents on both aromatic rings or between the substituent and the formyl group. Again, the partial charges were assigned to the acetylenic carbon atoms in the same manner as previously, (Figure 3).

The observed polarization was identical as in the previous cases, even though the substituent effect was expected to be the strongest in **1l**. We assumed that the combination of electron-donating methoxy group and electron-withdrawing nitrile would result in strong polarization of the C≡C bond where the negative charge would reside on the β-carbon atom. However, in this case the observed strength of the triple bond polarization is the weakest with a chemical shift difference reduced to only 3.5 ppm. Once again, these results provide evidence that the *ortho* positioned formyl group in 2-alkynylbenzaldehydes has yet the greatest influence on the triple bond polarization.

With respect to the observed polarization in **1l**–**1q**, cyclization reactions should proceed in such a manner where again the aldehyde oxygen atom would bond to the β-carbon atom of the triple bond, thus providing the 1*H*-isochromene products. Indeed, only one regioisomer, the six-membered cyclic ether, was obtained as a sole product upon cyclization of 2-alkynylbenzaldehydes **1m**–**1n** and **1p**–**1q** (Scheme 4). Cyclization of **1o** gave a complex mixture, from which it was not possi-



Scheme 3. Products of cyclization of 2-alkynylbenzaldehydes **1a**–**1i**.

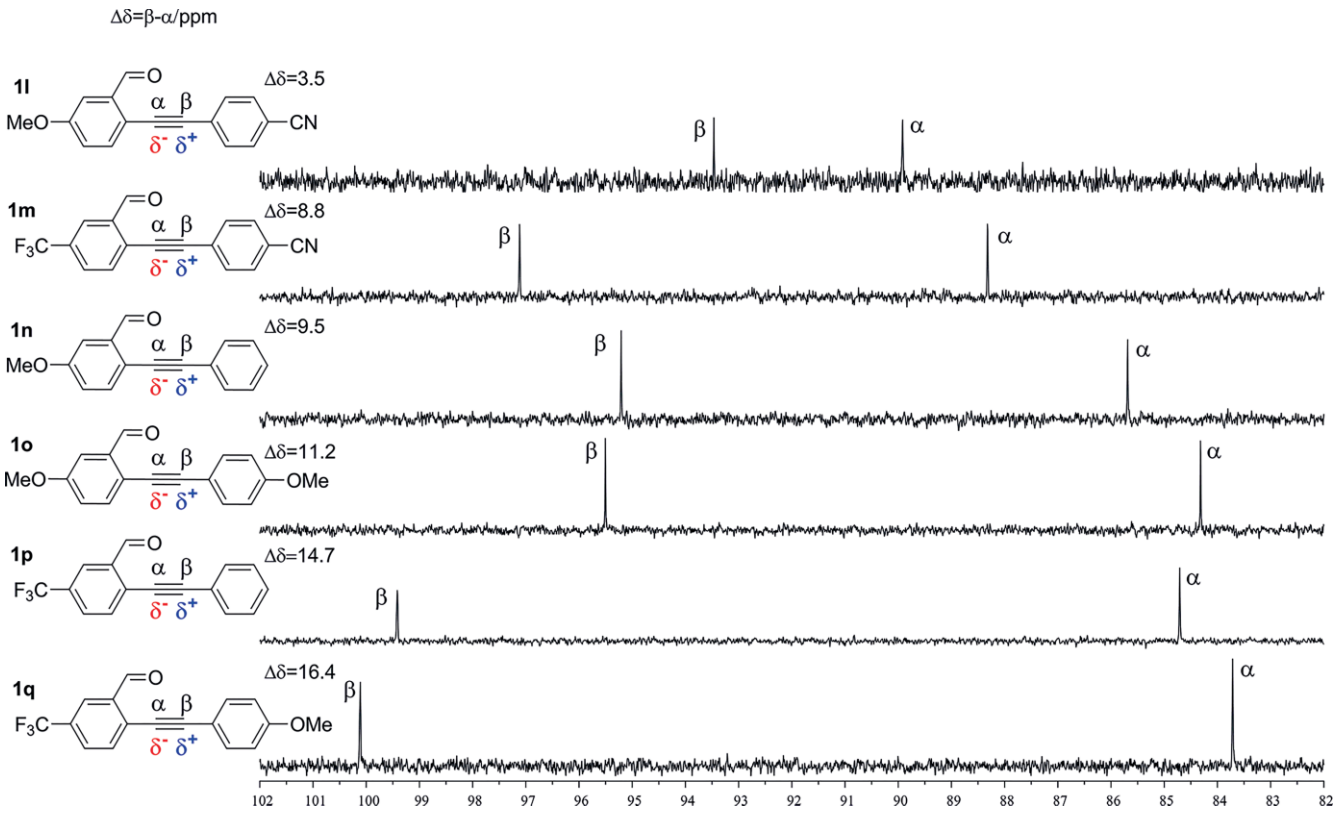
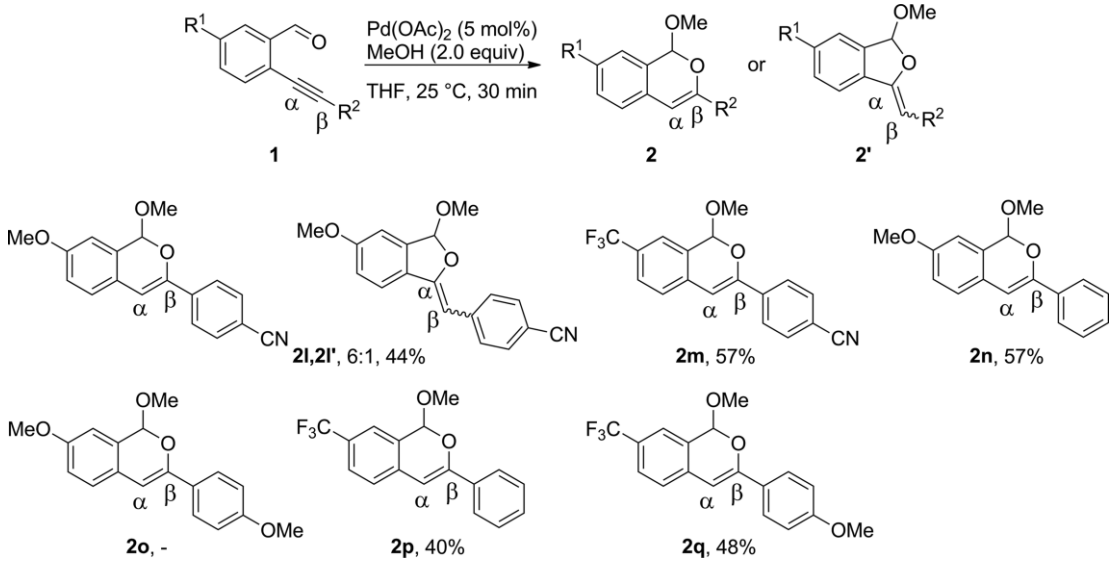


Figure 3. Polarization of the triple bond in 2-alkynylbenzaldehydes **1l**–**1q**.



Scheme 4. Products of cyclization of 2-alkynylbenzaldehydes **1l**–**1q**.

ble to isolate and characterize any products by ^{1}H and ^{13}C NMR analysis although mass spectrometry of the crude reaction mixture showed a mass peak (298.1199) that matched the expected product.

On the other hand, the cyclization of **1l** provided a mixture of two products: 1*H*-isochromene **2l** and benzofuran **2l′** in a 6:1 ratio. This result implies either a different course of the reaction or the polarization of the triple bond being reversed during the reaction. The proposed mechanism for the cyclization of carbon-tethered- and 2-alkynylbenzaldehydes in the presence of MeOH suggests the formation of a hemiacetal as the first step. Even if hemiacetal is formed during the course of the reaction, the hydroxyl oxygen atom would still attack the more electrophilic carbon atom of the triple bond. Nevertheless, the transformation of the electron-withdrawing formyl group to the electron-donating hemiacetal might affect the polarization it-

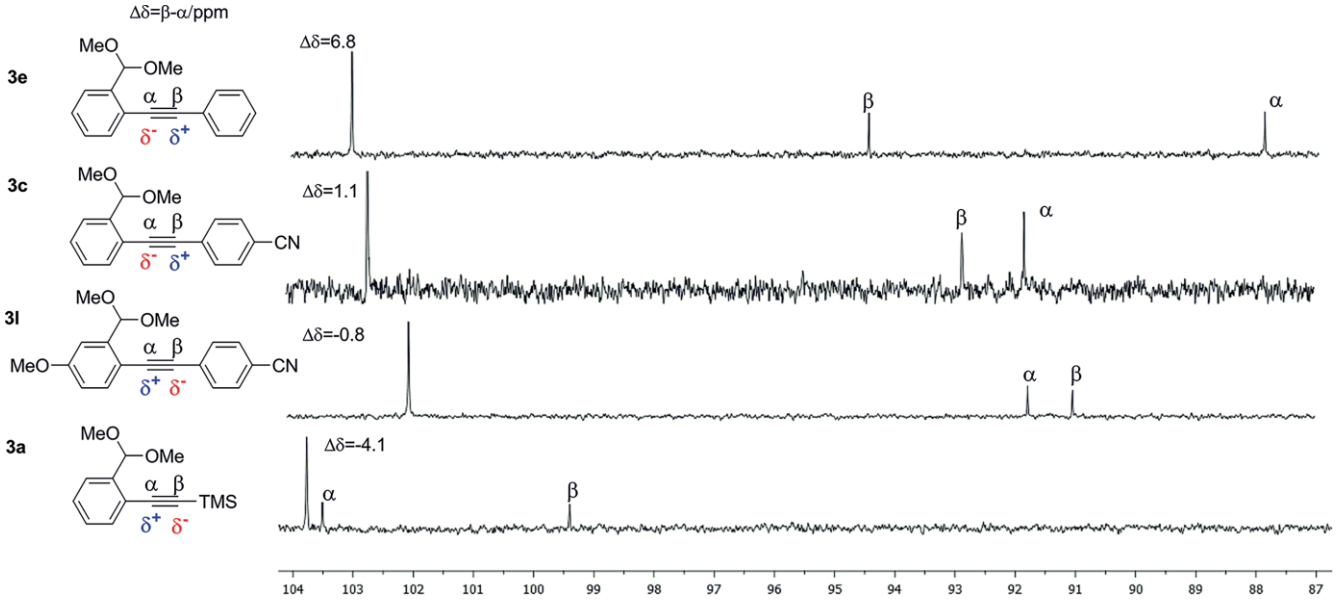


Figure 4. Polarization of the triple bond in acetals **3e**, **3c**, **3l**, and **3a**.

self, thus favoring the formation of the regioisomer opposite from the one expected with respect to the polarization in 2-alkynylbenzaldehyde **1l**. Since monitoring the change in polarization using NMR would be rather difficult, to get better insight into the polarization of the triple bond during the course of cyclization, the stable counterparts, which would mimic the hemiacetal formed in the first step had to be prepared. In that sense, reactions of **1e**, **1c**, and **1l** with trimethyl orthoformate afforded the corresponding acetals **3e**, **3c**, and **3l** respectively. In addition, acetal **3a** was prepared from **1a** given the fact that this substrate has the weakest polarized bond, (Figure 4). The NMR analysis of the formed acetals **3e** and **3c** revealed that the polarization is the same compared to the 2-alkynylbenzaldehydes **1e** and **1c**.

Without change in polarization, the cyclization would still provide the 1*H*-isochromene products **2e** and **2c** as observed. On the other hand, the electron distribution around the triple bond in acetals **3l** and **3a** is the opposite to their aldehyde counterparts **1l** and **1a**. This shows that when the polarization of the triple bond is weak enough ($\Delta\delta$ = 3.5 ppm for **1l** and 1.6 ppm for **1a**) the formation of hemiacetals during the reaction could flip the polarization thus giving a product mixture as observed in cyclization of **1l**. However, cyclization of alkynylbenzaldehyde **1a** provided only 1*H*-isochromene regioisomer **2a** despite the reversed polarization in acetal **3a**. Formation of only one regioisomer could be attributed to the steric effect posed by the bulky TMS group. Regardless of the mechanism, 5-*exo*-*dig* cyclization would result in the sterically hindered vinylpalladium intermediate **4**, (Figure 5). Conversely, a pathway towards six-membered cyclic ether would include intermediate **5** where the palladium atom bonded to the α-carbon atom is more distant from the TMS group, thus reducing the steric hindrance and allowing for the formation of product **2a**.

Although these results are based on approximate correlation between the formed acetals and the mechanistically proposed hemiacetals, the change in polarization that might occur during the course of the reaction could account for or substantially contribute to the observed regioselectivity.

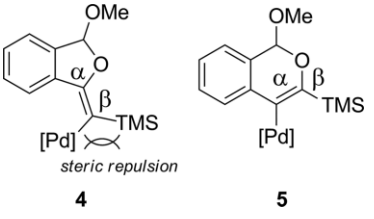


Figure 5. Possible intermediates formed during cyclization of **1a**.

Conclusions

We have described the factors that affect the electron distribution (polarization) around the triple bond in 2-alkynylbenzaldehydes and their correlation with the regioselectivity of the Pd-catalyzed cyclization reaction. The polarization is not the direct result of the electron-donating or electron-withdrawing ability of the substituent on the alkynyl moiety, but rather it is a consequence of the influence of a formyl group and its position on the aromatic ring. Furthermore, the Pd-catalyzed annulation reactions of the compounds studied provided predominantly 1*H*-isochromene heterocycles, therefore suggesting the close correlation between the polarization of the triple bond and the regioselectivity of these processes.

Experimental Section

General procedure for the cyclization of 2-alkynylbenzaldehydes 1: Under an argon atmosphere, a 25 mL, flame-dried Schlenk flask was charged with 2-alkynylbenzaldehyde **1** (0.50 mmol, 1.0 equiv.) and $Pd(OAc)_2$ (0.025 mmol, 5.0 mol-%). THF (1.0 mL) and MeOH (1.0 mmol, 2.0 equiv.) were added sequentially and the resulting reaction mixture was stirred at 25 °C. After 30 minutes,

the reaction mixture was filtered through a plug of silica gel and concentrated under reduced pressure.

(1-Methoxy-1*H*-isochromen-3-yl)trimethylsilane (**2a**): Column chromatography of the residue on silica gel (hexanes/EtOAc, 40:1) yielded 0.053 g (45 %) of **2a** as a colorless oil. ^{1}H NMR ([D$_6$]acetone, 600 MHz): δ = 7.33 (td, J = 6.6, 2.4 Hz, 1H), 7.27–7.24 (m, 2H), 7.14 (d, J = 7.2 Hz, 1H), 6.31 (s, 1H), 5.97 (s, 1H), 3.46 (s, 3H), 0.23 (s, 9H); ^{13}C NMR ([D$_6$]acetone, 151 MHz) δ = 159.7, 129.9, 129.7, 128.9, 127.7, 127.1, 124.4, 114.2, 99.0, 55.1, –2.4; IR (neat): $\tilde{\nu}$ = 2920, 2851, 1462, 1375, 1247, 1057, 958, 842, 752 cm^{-1}; HRMS (EI) *m/z* calcd. For $C_{13}H_{18}O_2Si$ [M]$^+$: 234.1076, found 234.1076. R_f (hexanes/EtOAc, 40:1) = 0.25.

Acknowledgments

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Keywords: Homogeneous catalysis · Cyclization · Isochromenes · Polarization · Regioselectivity

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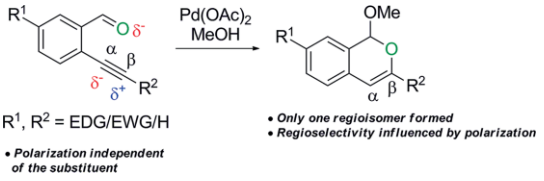

The influence of C≡C bond polarization on the regioselectivity of Pd-catalyzed cyclization of 2-alkynylbenzaldehydes is described.

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