JOC The Journal of Organic Chemistry
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Regioselectivity of Intermolecular Pauson−Khand Reaction of Aliphatic Alkynes: Experimental and Theoretical Study of the Effect of Alkyne Polarization

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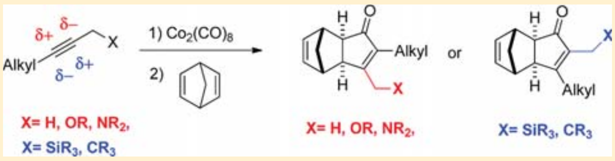
Ⓢ *Supporting Information*



ABSTRACT: Generally judged poor electronic regioselectivity of alkyne insertion in intermolecular Pauson−Khand reaction (PKR) has severely restricted its synthetic applications. In our previous rational study concerning diarylalkynes (Fager-Jokela, E.; Muuronen, M.; Patzschke, M.; Helaja, J. *J. Org. Chem.* **2012**, *77*, 9134−9147), both experimental and theoretical results indicated that purely electronic factors, i.e., alkyne polarization via resonance effect, induced the observed modest regioselectivity. In the present work, we substantiate that the alkyne polarization via inductive effect can result notable, synthetically valuable regioselectivity. Computational study at DFT level was performed to disclose the electronic origin of the selectivity. Overall, the NBO charges of alkynes correlated qualitatively with regioisomer outcome. In a detailed computational PKR case study, the obtained Boltzmann distributions of the transition state (TS) populations correlate closely with experimental regioselectivity. Analysis of the TS-structures revealed that weak interactions, e.g., hydrogen bonding and steric repulsion, affect the regioselectivity and can easily override the electronic guidance.

■ INTRODUCTION

The Pauson−Khand reaction, the carbonylative cycloaddition between an alkyne and an alkene promoted by cobalt carbonyl complexes, is one of the most reliable methodologies for the construction of cyclopentenone rings.[1] The intramolecular version of the reaction has been used widely in the synthesis of complex polycyclic compounds.[2] Although less common, the intermolecular version can efficiently provide key intermediates that have been used in several total syntheses of biologically active compounds.[3] The main advantages of the intermolecular version are the rapid construction of the cyclopentenone ring from simple fragments and the existence of reliable asymmetric versions.[4] However, its use is hampered by the small range of reactive olefins and, in the case of internal alkynes, by the difficult prediction of the regioselectivity.

It has been established that the regiochemistry of the alkyne fragment is controlled by both steric and electronic factors: large and electron donating groups (EDG) tend to favor cyclopentenone *α*-position, while small and electron withdrawing groups (EWG) have a preference for the *β*-position.[5] The pioneering work of Gimbert and co-workers showed several examples in which the initial C−C bond is formed with the more electron rich alkyne carbon according to the NBO charges.[6] In the case of functionalized diarylalkynes, we have shown that in certain cases the electronic effects had been overestimated although they can induce a clear regioselectivity that can be predicted quantitatively from *α*-alkyne NBO charges.[7] In the case of aliphatic internal alkynes, the regioselectivity is in some cases surprisingly high: Ethyl butynoate,[8] trifluoromethyl[3a] and silyloxymethylacetylenes[3f] have proved to react with norbornene, norbornadiene or ethylene in a completely regiolective manner (Figure 1).

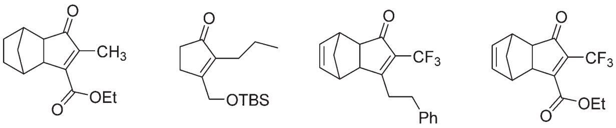


Figure 1. Literature examples of PK adducts of completely regioselective intermolecular PK reactions of internal alkynes.

Encouraged by these results, we decided to undertake a systematic study of the regioselectivity of internal aliphatic alkynes on intermolecular PKR to find out the rules that could allow us to predict such regiochemistry. We report herein that several internal alkynes gained substantial regioguidance in intermolecular PKR due to electronic factors. We also show

Received: September 3, 2014
Published: October 16, 2014

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