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Computationally Designed and Experimentally Confirmed Diastereoselective Rhodium-Catalyzed Pauson−Khand Reaction at Room Temperature

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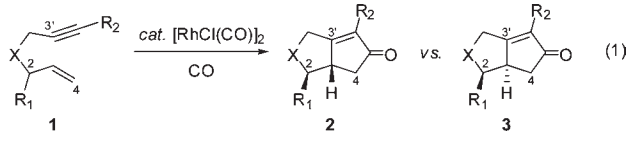
Supporting Information

ABSTRACT: The computational analysis of the rhodium-catalyzed Pauson−Khand reaction indicates that the key transition state is highly charge-polarized, wherein different diastereoisomers have distinctively different charge polarization patterns. Experimental studies demonstrate that chloroenynes provide the optimal σ-electron-withdrawing group to promote polarization and thereby reduce the activation barrier to provide a highly diastereoselective reaction at room temperature.

A critical feature in the development of transition metal-catalyzed higher-order [*m*+*n*+*o*] carbocyclization reactions is the ability to control the assembly of the individual π-components in a chemo-, regio-, and stereoselective manner.[1] A fundamental objective in this area is the ability to predict the outcome of a specific transformation without having to revert to extensive experimentation.[2] In this context, we recently described a combined theoretical and experimental study on the rhodium-catalyzed Pauson−Khand (PK) reaction, which delineated the impact of the coordination number of the metal center on diastereocontrol.[3−5] Nevertheless, a critical limitation with this transformation remains the variance in diastereoselectivity that is exhibited for a range of tethered 1,6-enynes, which impacts its synthetic utility.[6,7] We envisioned that this limitation could be overcome by preferentially lowering the activation barrier for the favored metallacycle, which is known to be rate-determining, through the manipulation of the stereoelectronics of the π-components. Herein, we now describe the theoretical impact of modifying the stereoelectronics of the 1,6-enyne **1** in the rhodium-catalyzed PK carbocyclization to provide the bicyclopentenones **2**/**3**, and we experimentally support this hypothesis with a highly stereoselective room-temperature reaction that favors **2** (eq 1).[8]



(1)

Although we previously demonstrated that the oxidative addition to provide the metallacycle intermediate for **1a** (X = O, R_1 = Me, R_2 = H) is rate determining,[5] a more detailed analysis of the

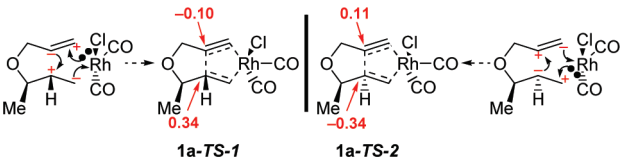


Figure 1. Computed partial charges at the oxidative addition transition states (in red) and a conceptual view of the oxidative addition invoking heterolytic π-bond cleavage.

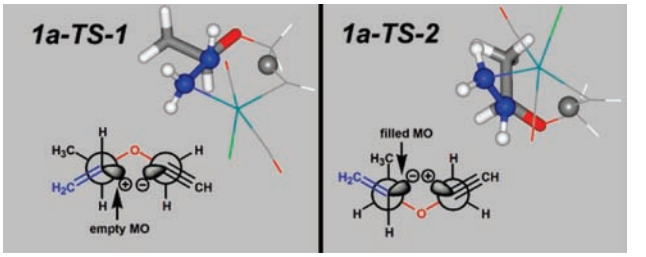


Figure 2. Structures of **1a-TS-1** and **1a-TS-2**.

transition states **1a-TS-1** and **1a-TS-2** that furnish the major and minor isomers **2a** and **3a**, respectively, reveals an interesting electronic feature. *Although both transition states are highly charge polarized, they are polarized in opposite directions at the distal carbon atoms in the metallacycle intermediates, as indicated by the partial charges in the transition states (Figure 1).* The computed partial charge[9] for the C3-position is positive for **1a-TS-1** (+0.34) and negative for **1a-TS-2** (−0.34). Furthermore, the C3′ in **1a-TS-1** and **1a-TS-2** is polarized with opposite signs, −0.10 and +0.11, respectively, which suggests that the oxidative addition is best conceptualized as a heterolytic cleavage of the π-bonds followed by an electronic reorganization (Figure 1).[10−13]

Figure 2 provides insight into the origin of stereocontrol in this process. As illustrated by the Newman projections, the methyl group at the C2-position is in a *trans* disposition relative to the sp^2-hybridized orbital on C3, which will form a new σ-bond with the C3′-carbon in **1a-TS-1**. This orientation is necessary for obtaining **2a**, since it provides the necessary *syn* orientation of the C3-hydrogen relative to the C2-methyl group. Similarly, the forma-

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Table 1. Effect of the C4′ Substituent on the Computed Barrier for Metallacycle Formation (eq 1; 1, X = O, R_1 = Me)[a]

		$\Delta G^{\ddagger}_{calc}$ (kcal/mol)	
entry	R_2	*syn* **2**	anti **3**
1	H	28.4	31.1
2	Cl	24.5	29.3
3	Br	24.5	29.5
4	I	25.7	30.3

[a] Jaguar 7.0, Schrödinger, LLC, New York, NY, 2007.

tion of the *anti* product **3a** results from the sp^2-hybridized orbital becoming *syn* to the C2-methyl in **1a-TS-2** (Figure 2). Considering the structural requirements in the transition state, the electronic consequences are evident. In **1a-TS-1**, hyperconjugation amplifies the +I effect of the methyl group, which stabilizes the developing positive charge on C3. Alternatively, in **1a-TS-2**, the methyl group is approximately orthogonal to the sp^2 orbital on C3, which reduces the electronic communication between the methyl group and the C3 sp^2 orbital. With the charge-directing effect of the methyl group reduced by this structural arrangement, the −I effect of the methylene moiety (blue in Figure 2) stabilizes the developing negative charge on the sp^2 orbital on C3. This in turn causes a reversal of the charge polarization in the metallacycle **1a-TS-2** compared to **1a-TS-1** (Figure 1). Leveraging this conceptual understanding, we envisioned that prepolarization of the enyne substrate to resemble the charge polarization in **1a-TS-1** should increase the chemical reactivity and improve the level of stereocontrol.

Theoretical analysis of several electron-withdrawing groups (R_2 = aryl, ester, and halide groups) indicates that the addition of a halogen to the terminal alkyne position should induce a positive partial charge at the C4′-position and thereby decrease the barrier for the rate-determining step significantly to provide the requisite conditions for a spontaneous room-temperature reaction. This is illustrated by the ability of the chloride-substituted terminal alkyne to lower the activation barrier by 4 kcal/mol for the *syn* diastereoisomer **2aj** (Table 1, entry 2 vs 1).[14] Interestingly, the addition of a halogen not only reduces the barrier for both diastereoisomers but also amplifies the preference for the *syn* diastereoisomer **2** significantly.

Table 2 outlines the examination of the C4′-halogenated 1,6-enynes in the rhodium-catalyzed PK reaction. In accord with our hypothesis, preliminary studies clearly demonstrated the necessity of the halogen in order to facilitate the room-temperature reaction (entry 2 vs 1). Additional studies explored the suitability of various halogens and their ability to promote the reaction compared to the theoretical predictions. This study demonstrates that chloride is optimal for this transformation (entries 2−4), which is somewhat consistent with the calculations (Table 1).[14] Moreover, this effect is quite general, since the PK reaction using carbon- and nitrogen-based tethers also proceeds at room temperature in high yield (entries 5 and 6).[8] In light of these promising results, we elected to reexamine the diastereoselectivity for the sulfonamide and ether tethers, since there was a large discrepancy between the levels of stereocontrol under the previously reported conditions.[6,7] Gratifyingly, the reactions with the C2-substituted 1,6-haloenynes **1ag**−**al** demonstrates excellent diastereocontrol in each case (entries 7−12), thereby circumventing the problems previously encountered with the sulfonamide tethers.[7] Moreover, the latent vinyl chloride provides a useful functional handle to facilitate an array of

Table 2. Scope of the Rhodium-Catalyzed Pauson−Khand Reaction with C4′-Halogenated 1,6-Enynes (eq 1)[a]

	1,6-enyne **1**					
entry	X	R_1	R_2		yield (%)[b]	ratio of **2**:**3**[c]
1	O	H	H	**aa**	NR	−
2	O	H	Cl	**ab**	74	−
3	O	H	Br	**ac**	39	−
4	O	H	I	**ad**	NR	−
5	$C(CO_2Me)_2$	H	Cl	**ae**	74	−
6	NTs	H	Cl	**af**	81	−
7	NTs	Me	Cl	**ag**	80	97:3
8	NTs	CH_2OBn	Cl	**ah**	73	98:2
9	NTs	Bn	Cl	**ai**	84	≥99:1
10	O	Me	Cl	**aj**	82	98:2
11	O	CH_2OBn	Cl	**ak**	84	≥99:1
12	O	Bn	Cl	**al**	87	≥99:1

[a] All reactions were carried out on a 0.2 mmol scale utilizing 5 mol % $[RhCl(CO)_2]_2$ in p-xylene (0.1 M) at 25 °C. [b] Isolated yields. NR = no reaction. [c] Ratios of diastereoisomers were determined by HPLC or GC analysis of the crude products.

well-established cross-coupling reactions that enhance the synthetic utility of this process in the context of target-directed synthesis.[15]

In conclusion, computational analysis of the diastereoselective rhodium-catalyzed Pauson−Khand reaction reveals that the key transition state is highly charge-polarized, with the different diastereoisomeric transition states having distinctively different charge polarization patterns. The rationalization of this computational observation utilizing a heterolytic bond-cleavage in the oxidative addition indicated that σ-electron-withdrawing moieties on the alkyne terminus, such as halogens, prepolarize the enyne and lower the activation barrier for oxidative addition. Experimental studies confirmed this hypothesis, with a chloride substituent providing the optimal functionality on the alkyne to reduce the activation barrier for this transformation. Finally, this approach enables diastereoselectivity to be garnered in a PK reaction that was previously unselective.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures and spectral data for the preparation of **1**/**2aa**−**al**, along with computational details and Cartesian coordinates for all structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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