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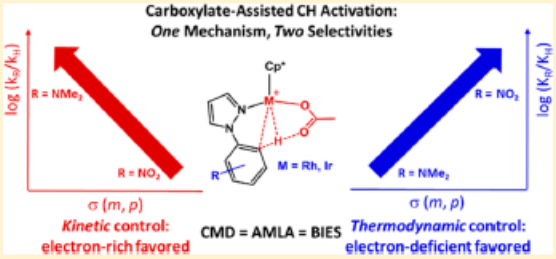
The Importance of Kinetic and Thermodynamic Control when Assessing Mechanisms of Carboxylate-Assisted C−H Activation

Raed A. Alharis,[†,§] Claire L. McMullin,[‡,∥] David L. Davies,*[,†] Kuldip Singh,[†] and Stuart A. Macgregor*[,‡]

[†]Department of Chemistry, University of Leicester, Leicester, United Kingdom
[‡]Institute of Chemical Sciences, Heriot-Watt University, Edinburgh EH14 4AS, United Kingdom

Supporting Information

ABSTRACT: The reactions of substituted 1-phenylpyrazoles (phpyz-H) at $[MCl_2Cp^*]_2$ dimers (M = Rh, Ir; Cp* = C_5Me_5) in the presence of NaOAc to form cyclometalated Cp*M(phpyz)-Cl were studied experimentally and with density functional theory (DFT) calculations. At room temperature, time-course and H/D exchange experiments indicate that product formation can be reversible or irreversible depending on the metal, the substituents, and the reaction conditions. Competition experiments with both para- and meta-substituted ligands show that the kinetic selectivity favors electron-donating substituents and correlates well with the Hammett parameter giving a negative slope consistent with a cationic transition state. However, surprisingly, the thermodynamic selectivity is completely opposite, with substrates with electron-withdrawing groups being favored. These trends are reproduced with DFT calculations that show C−H activation proceeds by an AMLA/CMD mechanism. H/D exchange experiments with the meta-substituted ligands show ortho-C−H activation to be surprising facile, although (with the exception of F substituents) this does not generally lead to ortho-cyclometalated products. Calculations suggest that this can be attributed to the difficulty of HOAc loss after the C−H activation step due to steric effects in the 16e intermediate that would be formed. Our study highlights that the use of substituent effects to assign the mechanism of C−H activation in either stoichiometric or catalytic reactions may be misleading, unless the energetics of the C−H cleavage step and any subsequent reactions are properly taken into account. The broader implications of our study for the assignment of C−H activation mechanisms are discussed.



INTRODUCTION

The use of carboxylate salts, particularly acetate and pivalate, to effect stoichiometric and catalytic C−H activation is now well-established.[1−4] However, several different terms are used to describe the mechanism of the C−H activation step, with, for aromatic substrates, S_EAr,[5] concerted metalation deprotonation (CMD),[6−8] ambiphilic metal ligand activation (AMLA),[9,10] and internal electrophilic substitution (IES)[11] being the most commonly cited. Electronic effects on reaction rates are often used to provide evidence to assign a particular C−H activation mechanism. For example, the observation of enhanced reactivity with more electron-rich substrates or with electron-donating substituents is often cited as evidence for an S_EAr process[12−16] or, if an internal base is involved, AMLA or a base-assisted IES (BIES).[17−20] Alternatively, rate enhancement with more electron-deficient substrates, or with more electron-withdrawing substituents, is often assigned to a CMD C−H activation mechanism.[21−25] We show here that such a strategy may be flawed, unless a full understanding of the details of the C−H activation process under study are taken into account. Specifically, we will show below that the same cyclometalation reaction can give opposite substituent effects depending on whether the reaction is under kinetic or thermodynamic control. The implications of these observations in terms of distinguishing between S_EAr, AMLA, CMD, and BIES are also discussed.

Early studies of substrate and substituent electronic effects on carboxylate-assisted C−H activation focused primarily on Pd. In the original experimental work by Ryabov on the cyclometalation of dimethylbenzylamines at $[Pd(OAc)_2]$ faster reactions were observed with electron-donating groups on the phenyl being activated.[26] He proposed an S_EAr mechanism with deprotonation by a coordinated acetate ligand. Our 2005 computational study in fact showed the mechanism involved an agostic interaction of the C−H bond with the electron-deficient metal center with simultaneous H-bonding to the free oxygen of a metal-bound acetate.[10] These calculations also reproduced the substituent effects observed by Ryabov, and we later termed this process AMLA.[9] More recently an electrospray ionization−mass spectrometry (ESI-MS) study of the kinetics of C−H activation of substituted acetanilides by $[Pd(OAc)_2]/CF_3CO_2H$ reached similar conclusions.[27]

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