A SYNTHETIC METHODOLOGY TO PRODUCE TAILORED DEUTERATION PATTERNS IN BUILDING BLOCK MOLECULES WITH HIGH ISOTOPOMER SPECIFICITY VERIFIED BY MOLECULAR ROTATIONAL SPECTROSCOPY

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Building block molecules with precisely controlled deuteration patterns are needed for several applications in chemistry including mechanistic studies and the production of deuterated active pharmaceutical ingredients with improved efficacy and safety. The Harman group recently reported an organometallic chemistry methodology to add deuterium to benzene with high stereoselectivity providing access to a wide range of deuteration patterns in the cyclohexene reaction product. This methodology provides access to 52 unique isotopic variants of cyclohexene covering 10 isotopologues. Establishing the stereoselectivity of the synthesis is a challenge, especially for highly deuterated substrates, and requires a technique that can quantitatively analyze both the isotopologue and isotopomer distribution in a potentially complex mixture of deuterated reaction products. Molecular rotational resonance (MRR) spectroscopy is well-suited for this analysis challenge. The application of MRR analysis to understand the stereoselectivity in the different reaction steps of the conversion of benzene to target deuterated cyclohexene reaction products is the focus of the current work. In one example, the availability of a routine, rapid isotopologue/isotopomer analysis technique is used to gain insight on the mechanistic chemistry and, subsequently, to improve the selectivity for the synthesis of cis-3,4-cyclohexene-d2. Optimization of the reaction conditions leads to the production of the target species with less than 0.1% over-deuteration and low levels of underdeuteration (mainly from the 3-cyclohexene-d1 isotopomer). The stereoselectivity of the synthesis is demonstrated by the low levels of the anti-3,4-cyclohexene-d2 isotopomer that is present at below 0.3%.