

BREAKING THE REACTIVITY TREND WITH COOPERATIVELY-CATALYZED
(4K) REACTION

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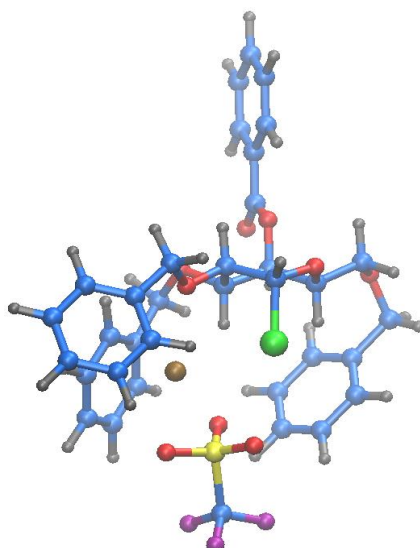
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The classical Koenigs-Knorr glycosidation of bromides or chlorides promoted with Ag₂O or Ag₂CO₃ works well only with reactive substrates, ideally both reactive (armed) donor and reactive acceptor [1]. This reaction was found to be practically ineffective with unreactive (disarmed) per-*O*-benzoylated halides and sugar alcohols. Recently, it was discovered that the addition of catalytic (Lewis) acids to a silver salt-promoted reaction has a dramatic effect on the reaction rate and yield [2]. A tentative mechanism for this cooperatively-catalyzed glycosylation reaction has been proposed, and the improved understanding of the reaction led to more efficient protocols and broader applications to a variety of glycosidic linkages [3]. Since Ag₂O-mediated activation was introduced by German chemists Koenigs and Knorr, and “cooperatively catalyzed” is Kooperativ Katalysiert in German, we refer to this new reaction as “the 4K reaction”[4].

Remarkably, the reactivity order of differentially substituted glycosyl halides changes dramatically under these cooperatively catalyzed reaction conditions [3]. For instance, we have observed reactivity trends wherein the reaction rates of the expectedly more reactive armed glycosyl halides were surpassed by their expectedly less reactive disarmed counterparts. Described herein is our investigation into the peculiar reactivity trends of the 4K reaction through synthetic, computational, and theoretical reasoning.

**References:**

1. Y. Singh, S. Geringer and A. V. Demchenko, *Chem. Rev.* **2022**, 122, 11701-11758.
2. Y. Singh and A. V. Demchenko, *Chem. Eur. J.* **2019**, 25, 1461-1465.
3. Y. Singh and A. V. Demchenko, *Chem. Eur. J.* **2020**, 26, 1042-1051.
4. A. V. Demchenko and C. De Meo, *Carbohydr. Res.* **2024**, 538, 109102.