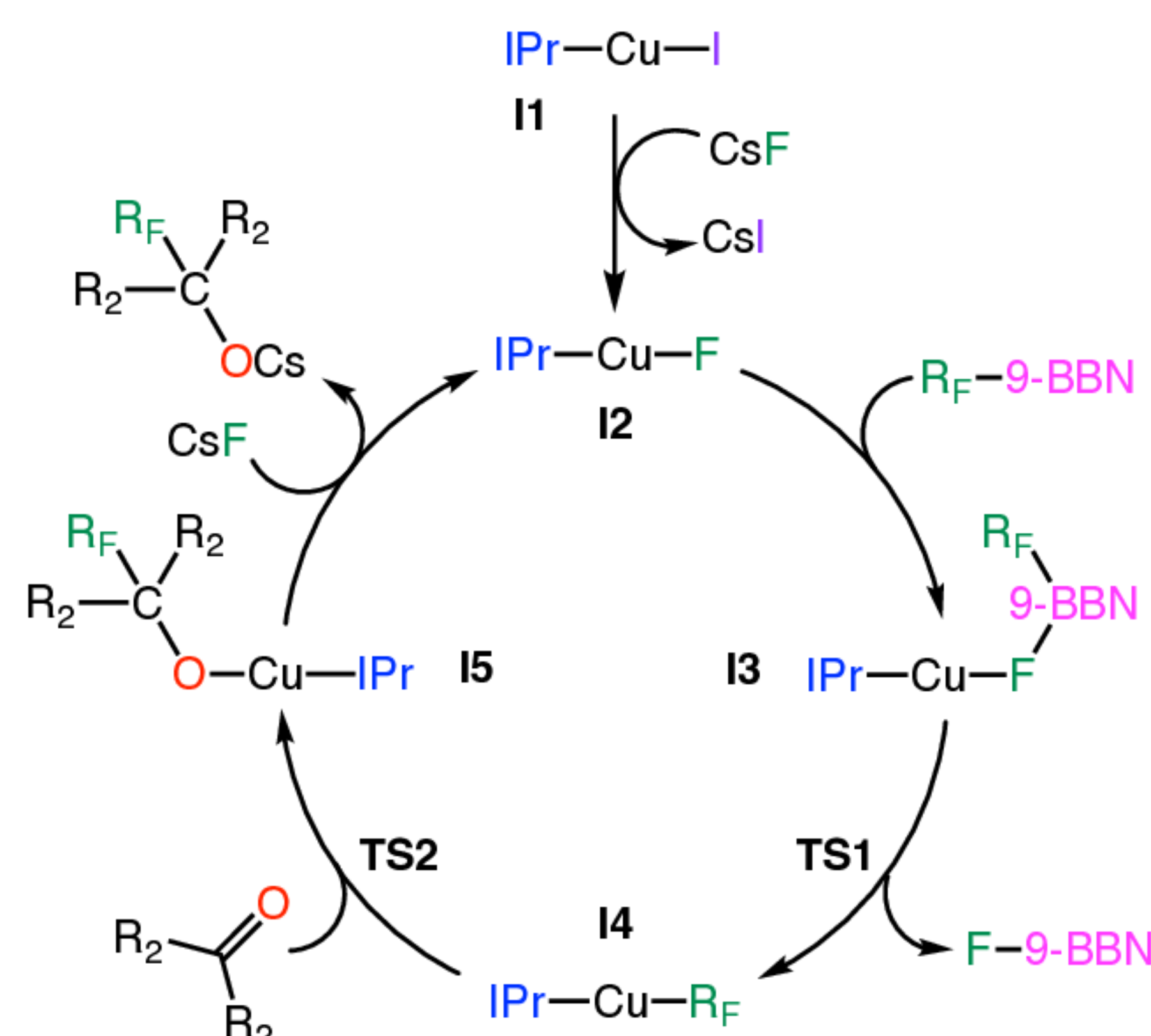


Computational Study of a Copper-Catalyzed Synthesis of Fluoroalcohols from Alkylboranes and Symmetric Ketones



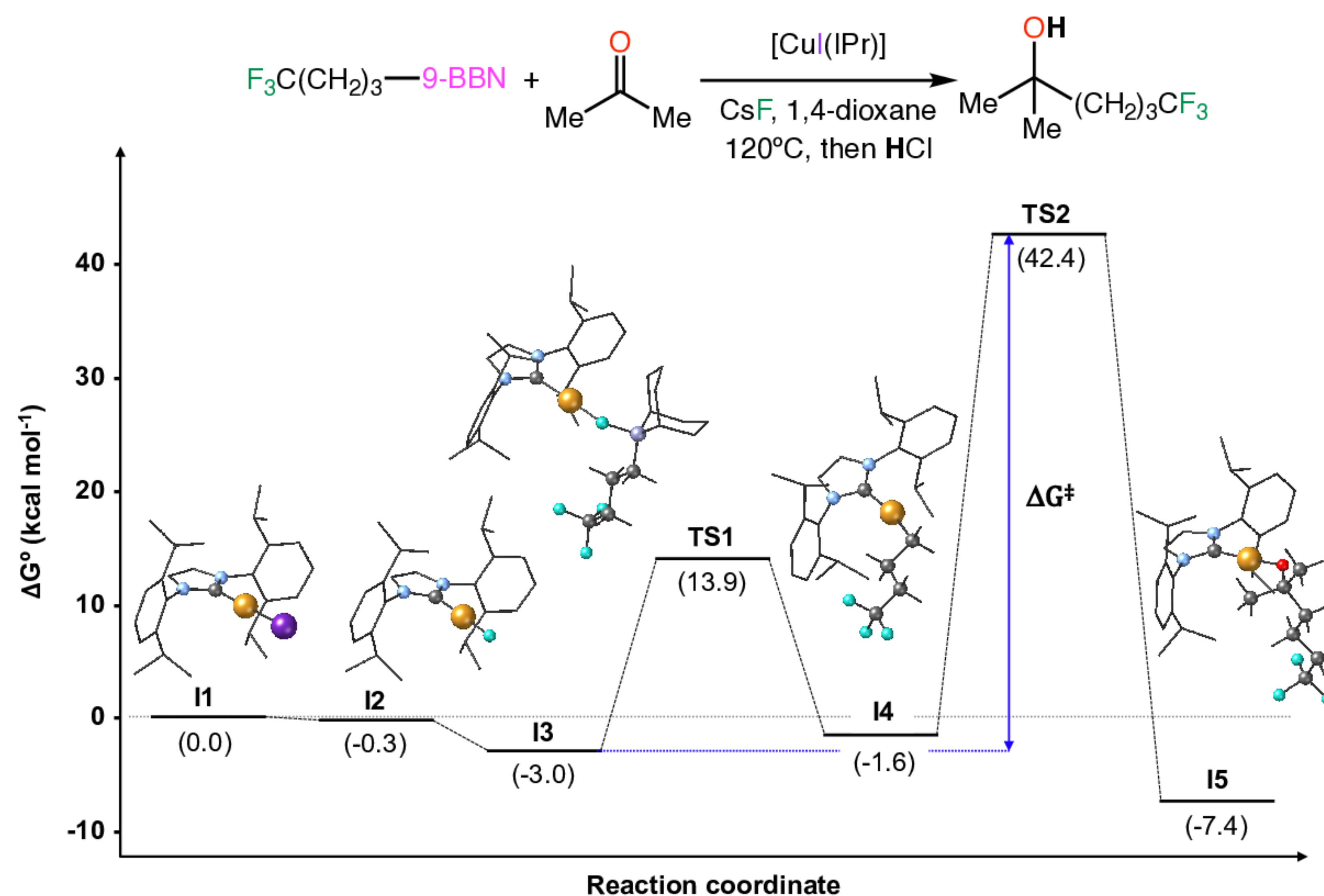
INTRODUCTION

Fluoroalcohols are organic compounds with both hydroxyl and fluorine atoms. Due to the high electronegativity of fluorine, they show special properties like high polarity, thermal stability, and weak hydrogen bonding. These features make them useful in medicine, batteries, imaging, and advanced materials.¹⁻³ However, traditional synthetic methods are often toxic and complex, so safer and more efficient synthesis routes are needed.



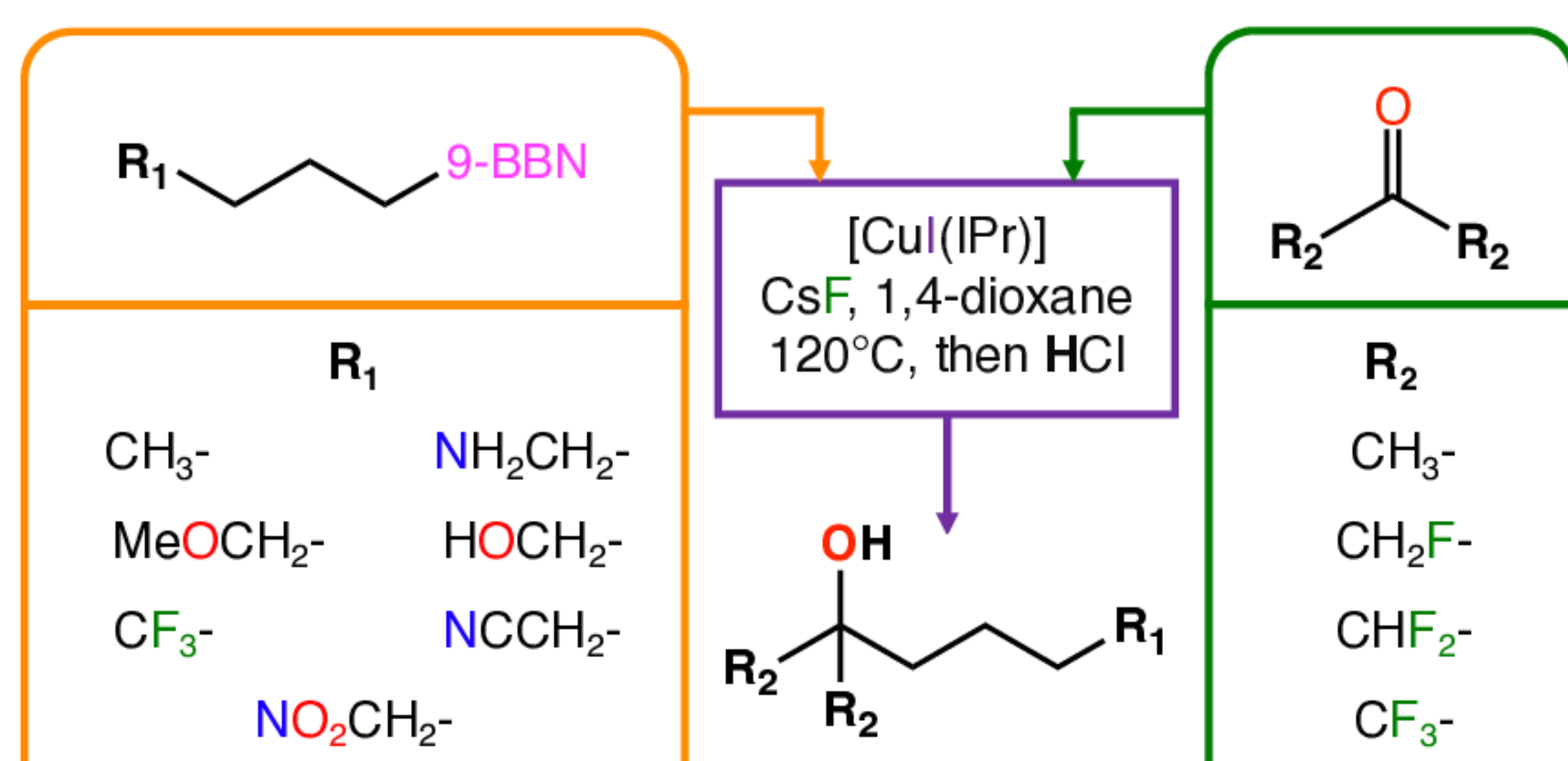
- [1] G. M. C. Silva, J. Justino, P. Morgado, M. Teixeira, L. M. C. Pereira, L. F. Vega and E. J. M. Filipe, *J. Mol. Liq.*, 2020, **300**, 112294.
[2] E. Hequet, C. Henoumont, R. N. Muller and S. Laurent, *Future Med. Chem.*, 2019, **11**, 1157–1175.
[3] Y.-J. Chen, R.-D. Wang, Y.-L. Shih, H.-Y. Chin and A. Y.-C. Lin, *Environ. Sci. Technol.*, 2024, **58**, 1648–1658

REACTION MECHANISM

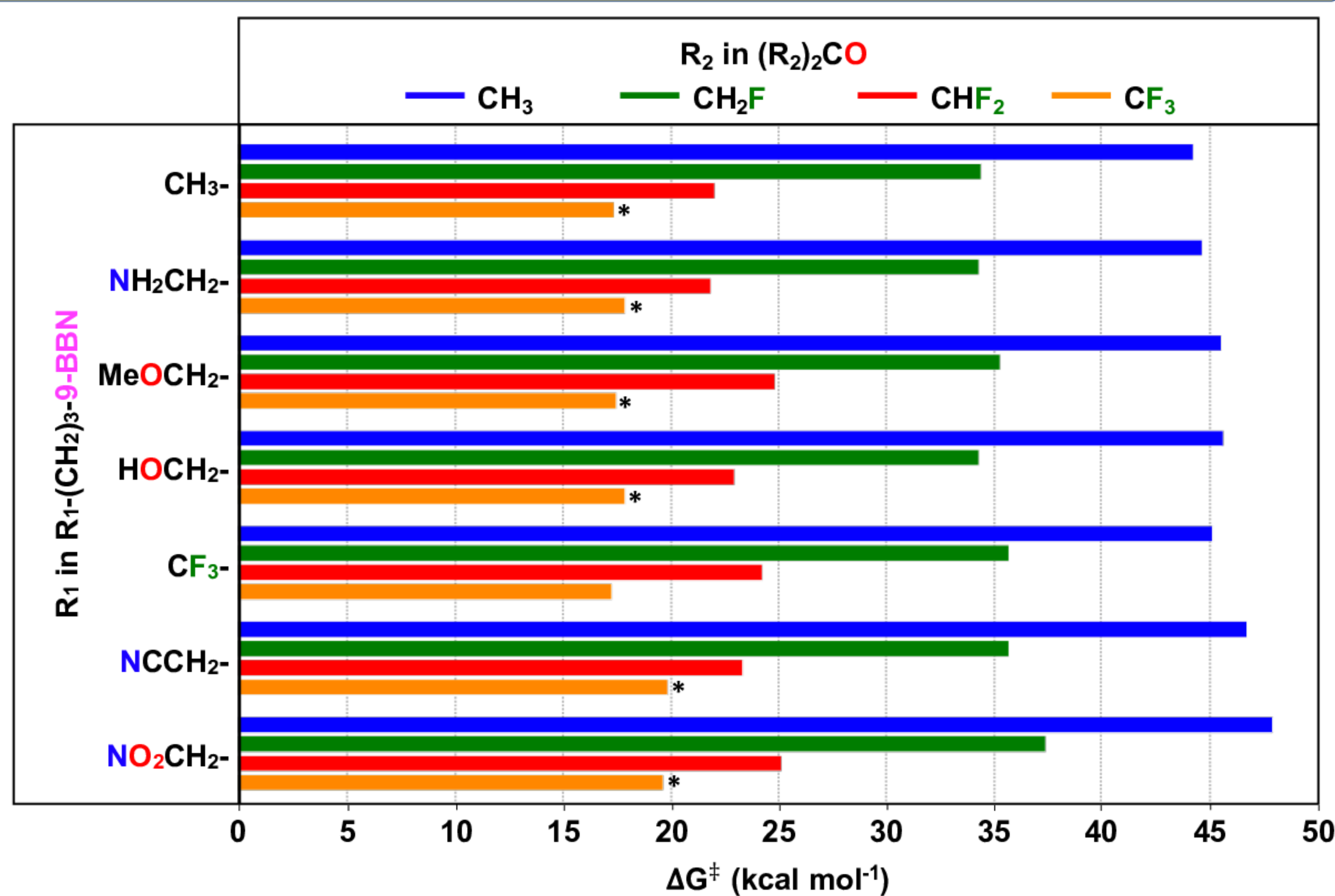


The reaction starts with halide exchange between [Cu(I)Pr] and CsF. The formed Cu-F complex reacts with an alkylborane, generating an organocopper intermediate. Transmetalation transfers the alkyl group to Cu, which then attacks the ketone (rate determining step). Catalyst regeneration and protonation yield the final fluoroalcohol.

DFT CALCULATIONS



A total of 28 combinations of 7 alkylboranes and 4 different ketones were evaluated using DFT calculations. The results show that ketones have a much stronger impact on the activation barrier than alkylboranes. In particular, highly fluorinated ketones, such as hexafluoroacetone, reduce the activation energy by over 25 kcal/mol. This is due to the strong electrophilicity of the carbonyl group, which stabilizes the transition state by facilitating the nucleophilic attack of the alkyl group. On a molecular level, this corresponds to a lower LUMO energy, which enhances interaction with the nucleophile.



However, in some reactions marked with “*”, the transmetalation becomes the slowest step. This shift occurs with highly electrophilic ketones like hexafluoroacetone, which accelerate the C–C bond formation and alter the overall energy profile.

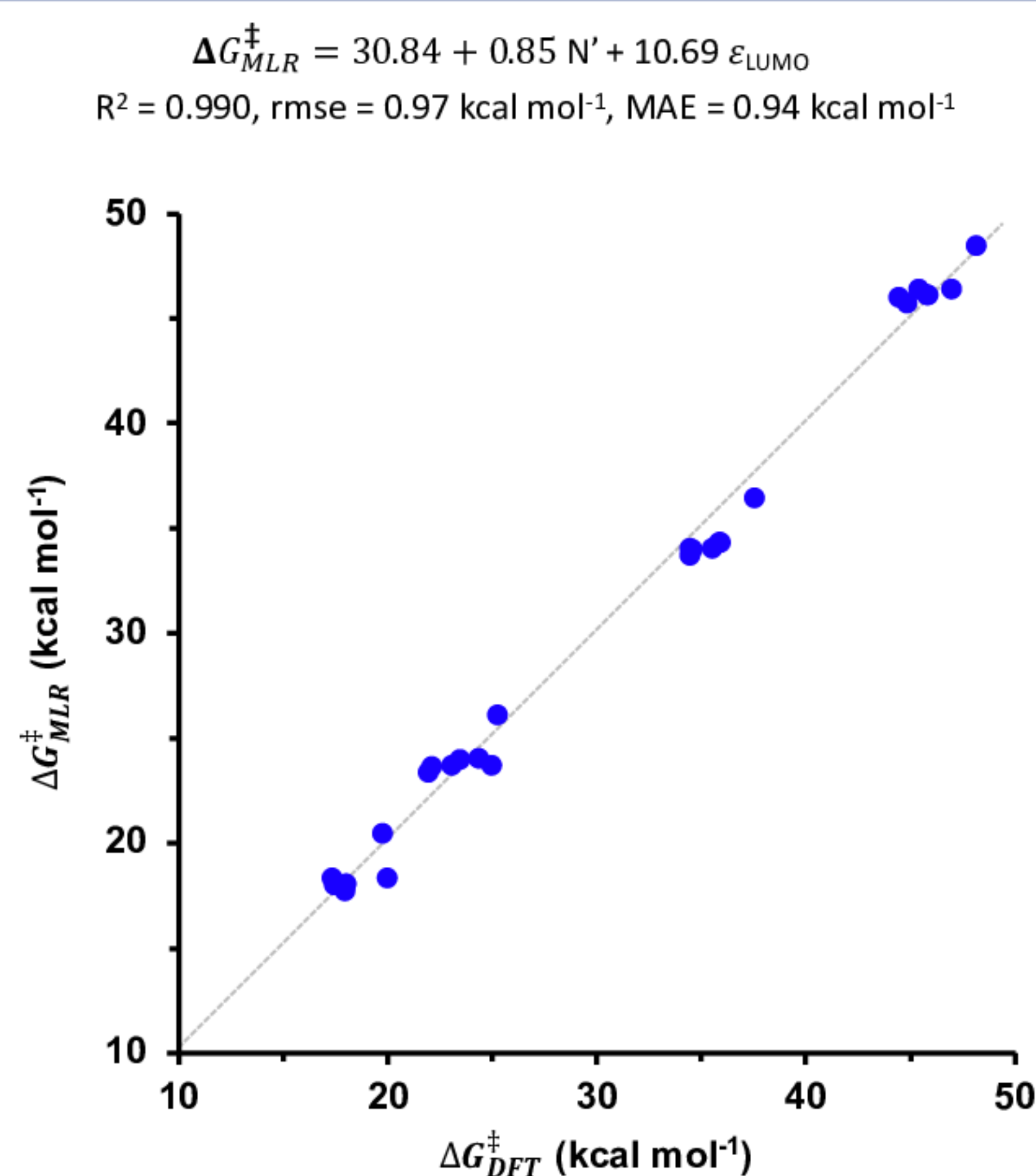
MLR MODEL

The standardized MLR model quantifies the influence of each descriptor on the barrier: ketone electronics (ϵ_{LUMO}) have ~ 11× more impact than alkylborane nucleophilicity index (N').

Energy barriers can be estimated without full mechanism calculations, using only the descriptors of the ketone and alkylborane.

METHODOLOGY

DFT calculations (Gaussian16, B3LYP-D3, PCM/SMD in 1,4-dioxane) with ultrafine grids and tight convergence. TZVP for all atoms, def2SVP+ECP for Cs and I; Gibbs energies (25 °C) from single points with def2-TZVPPD.



CONCLUSIONS

A mechanism is proposed for the Cu-catalyzed synthesis of fluoroalcohols from alkylboranes and ketones, and rate-limiting is strongly influenced by ketone electronics.

Fluorinated, electron-poor ketones are key for reactivity; electron-rich alkylboranes offer moderate enhancement.

A regression model enables fast prediction of barriers, help us to select substrate for future experiments.

FUNDING

Ayuda PRE2019-091164 financiada por MCIN/AEI 10.13039/501100011033 y por FSE invierte en tu futuro

Structures of Excellence María de Maeztu program (CEX2021-001202-M)

