Magnesium-Catalyzed Electrophilic Trifluoromethylation: Facile Access to All-Carbon Quaternary Centers in Oxindoles

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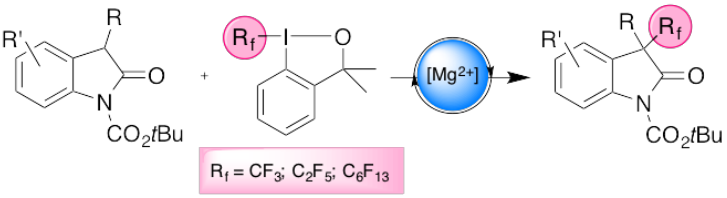
3,3-Difunctionalized oxindoles are widely recognized as valuable synthetic intermediates which form the core of many natural products and synthetic analogues. As part of ongoing research in our laboratory towards the development of novel methodologies to access organofluorine compounds via electrophilic trifluoromethylation [1,2], we anticipate that the introduction of fluoroalkyl groups into the oxindole moiety will provide access to new drug candidates with unique biological properties.



$R_f = CF_3; C_2F_5; C_6F_{13}$

Benefits:
- *low-cost catalyst*
- *no external base required*
- *mild & simple protocol*
- *broad substrate scope: 27 examples*
- *high chemical efficiency: up to 92% yield*

Figure 1. Magnesium-catalyzed perfluoroalkylation of 3-substituted oxindoles.

Herein we describe the first example of direct electrophilic trifluoromethylation of 3-substituted oxindoles under $MgBr_2 \cdot Et_2O$ catalysis using hypervalent iodine reagents as the source of the fluoroalkyl group (Figure 1) [3]. $MgBr_2 \cdot Et_2O$ plays a dual activation role, activating both the trifluoromethylation reagents and the oxindole substrates. Furthermore, this Lewis acid is commercially available, inexpensive, and generates non-toxic by-products. We have also demonstrated an asymmetric variant of the reaction through the use of a chiral ligand, and in addition to trifluoromethylation, other perfluoroalkyl groups could be introduced with a similar level of efficacy. An investigation of the reaction mechanism points towards the involvement of radical species as the likely reactive intermediates. This synthetically valuable transformation constructs challenging perfluoroalkylated quaternary carbon centers under very mild reaction conditions and demonstrates excellent functional group tolerance. The discovery that simple magnesium salts can effectively activate hypervalent iodine-based compounds provides new routes towards the realization of novel perfluoroalkylation methodologies. The introduction of other functional groups through the use of hypervalent iodine reagents in combination with Lewis acid catalysis is currently under investigation.

[1] D. Katayev, V. Matoušek, R. Koller, and A. Togni, *Org. Lett.* **2015**, *17*, 5898-5901.
[2] D. Katayev, J. Václavík, F. Brüning, B. Commare and A. Togni, *Chem. Commun.* **2016**, *52*, 4049-4052.
[3] D. Katayev, H. Kajita and A. Togni, *Chem. Eur. J.* **2017**, doi/10.1002/chem.201700851.