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Pd-Catalyzed Arylation of Hydantoins with Aryl Chlorides Enabled by Ylide-Functionalized Phosphines (YPhos)

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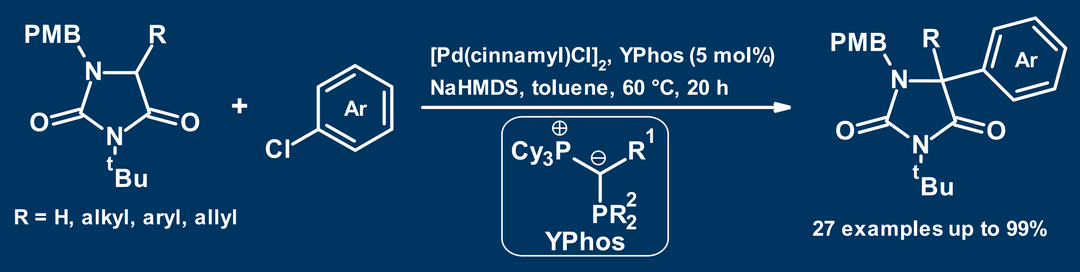
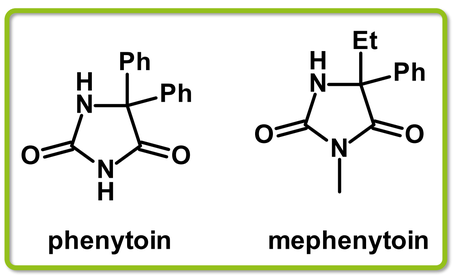
Abstract:

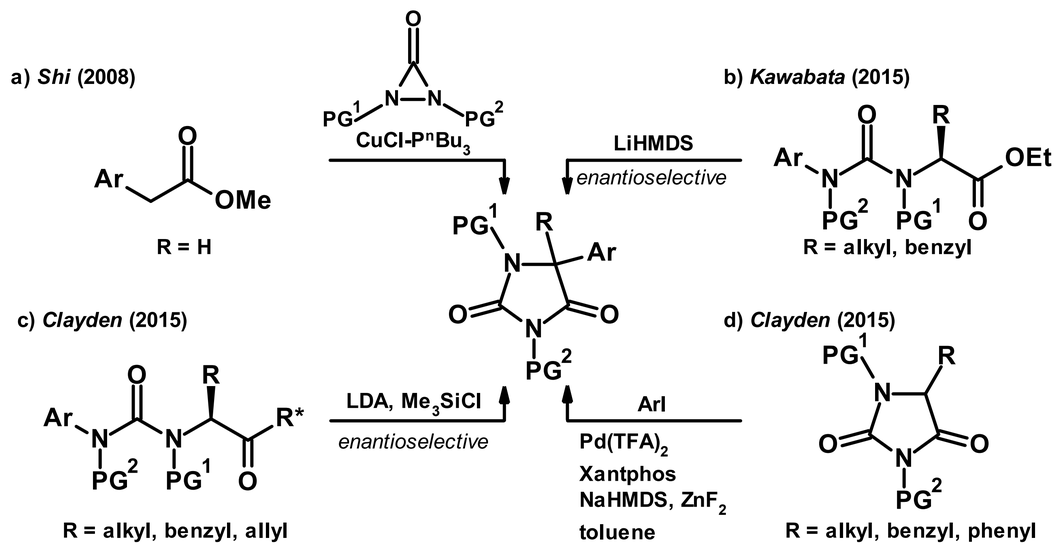
The hydantoin moiety is an important structural motif present in various pharmaceuticals. Palladium complexes bearing electron-rich, bulky ylide-functionalized phosphine (YPhos) ligands were found to catalyze the arylation of *N*-protected hydantoins with broadly available aryl chlorides. Selective monoarylations, sequential diarylations and arylation-alkylation sequences have been achieved. In combination with stepwise deprotection strategies, this opens up an expedient access to a wide variety of hydantoins, including derivatives of the anticonvulsant drugs phenytoin and mephenytoin.



5-Aryl Hydantoins

5-Aryl Hydantoins are common motifs in pharmaceuticals, especially in anti-convulsant drugs like phenytoin. Classical routes include for example Bucherer-Bergs chemistry. Modern syntheses of 5-aryl hydantoins include Shi's Cu-catalyzed α-amination of esters with diaziridinones.[1] Moreover, rearrangements discovered by Kawabata and Clayden are asymmetric pathways to enantiopure 5-aryl hydantoins.[2] However, the most straightforward method is the arylation of preformed hydantoins. In 2015, the Pd-catalyzed arylation of hydantoins was discovered by the Clayden group, but only using aryl iodides and not including a selective monoarylation leading to tertiary centers in the 5-position.[3]

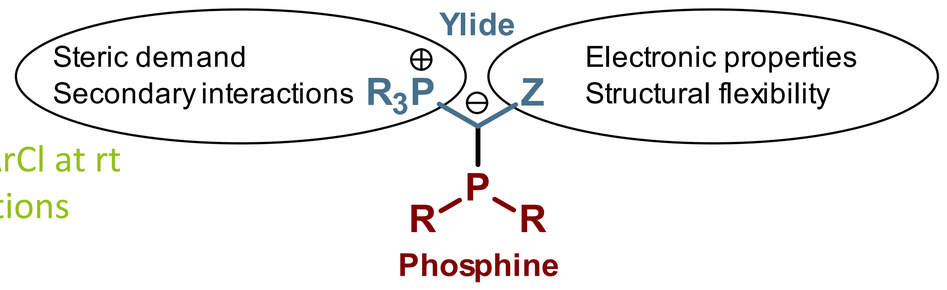




YPhos Ligands[4]

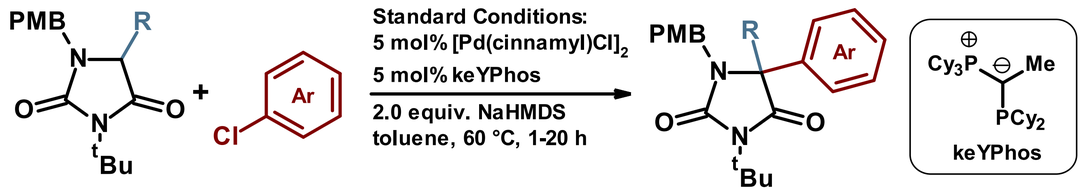
- ✓ Electron-rich
- ✓ Bulky
- ✓ Flexible
- ✓ Tunable

→ Ox. Addition of ArCl at rt
→ Multiple Applications

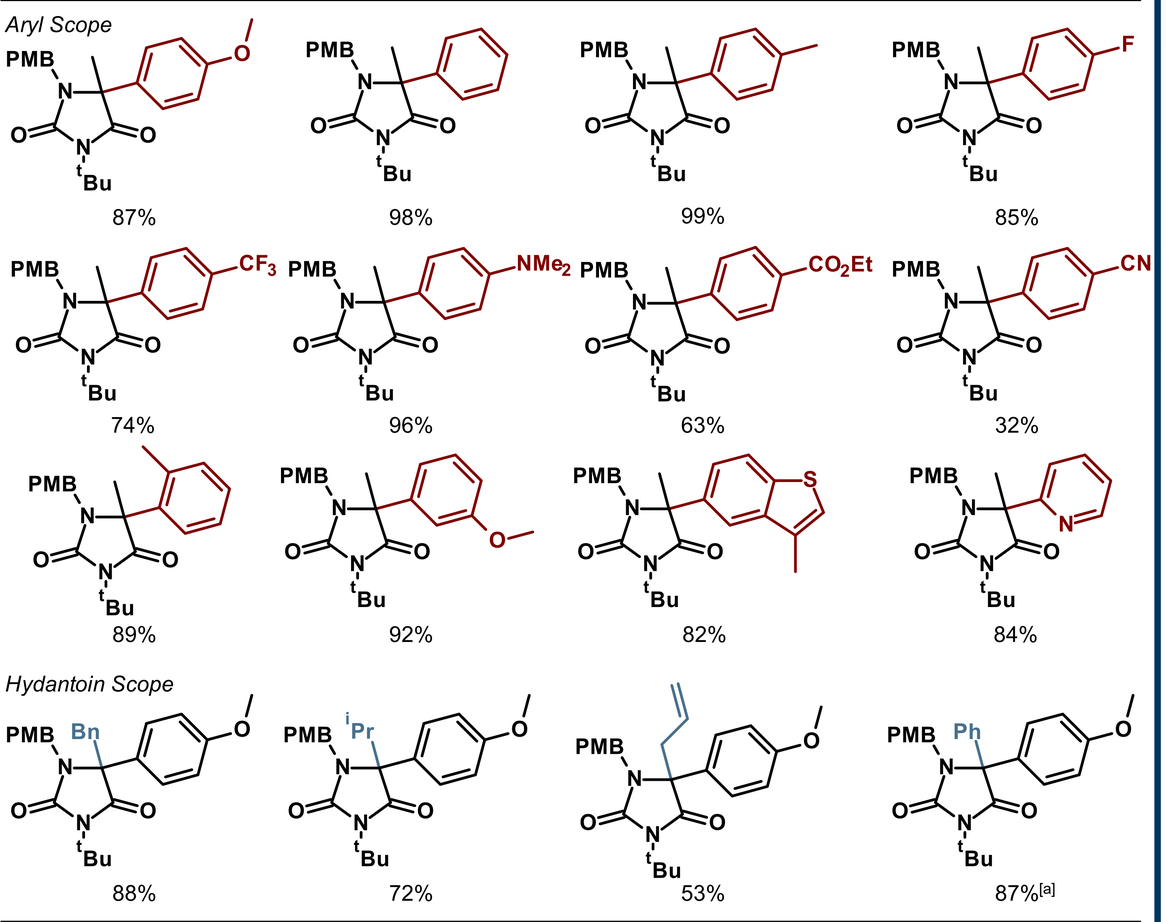


Broad Ligand Screening
→ Best Ligands in Arylation of Hydantoins
→ Enable Challenging Transmetalation
→ Enable Selective Monoarylation

Scope of Aryl Chlorides and Hydantoins



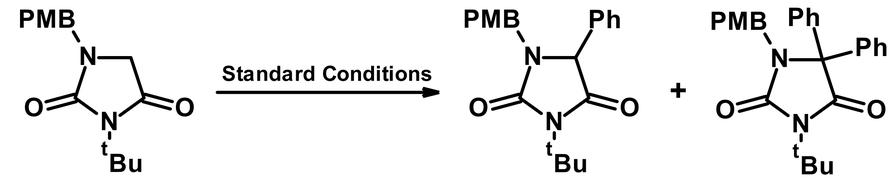
Aryl Scope

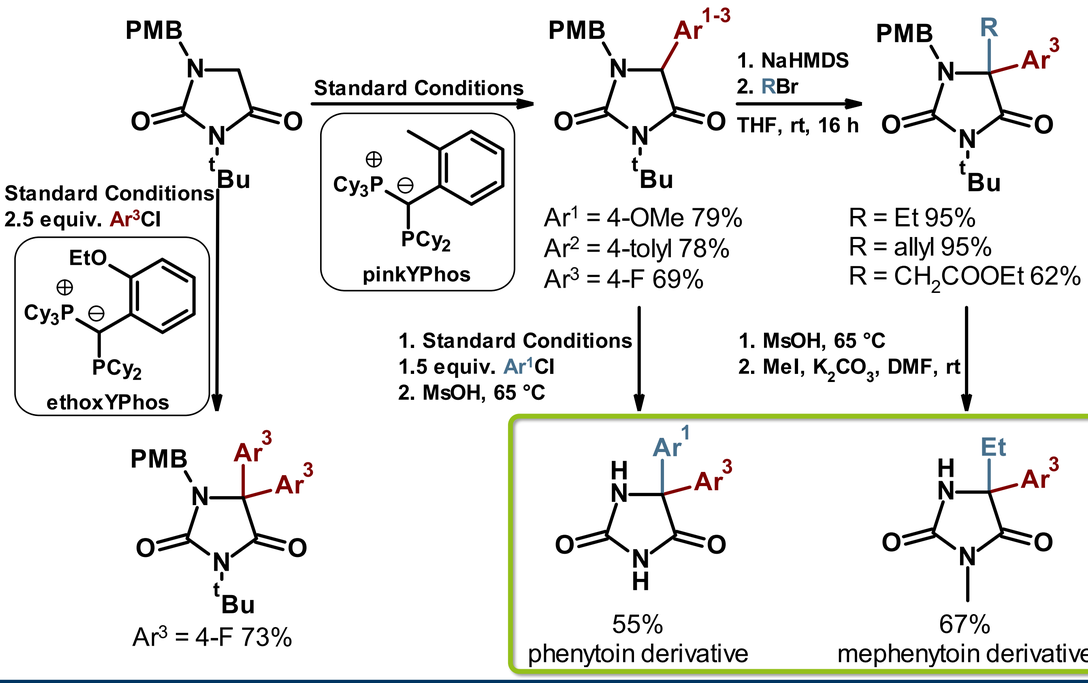


Hydantoin Scope

Conditions: 0.50 mmol hydantoin, 1.5 equiv. ArCl, 2.5 mol% $[Pd(cinnamyl)Cl]_2$, 5 mol% keYPhos, 2.0 equiv. NaHMDS, toluene, 60 °C, 1 h for aryl scope, 20 h for hydantoin scope. Isolated yields. Only selected examples presented.
[a] 25 mol% $ZnCl_2$ used as additive. Instead of 1.5 equiv., 2.0 equiv. ArCl were used.

Monoarylation and Further Applications





Conclusion and Outlook

Pd-complexes with YPhos ligands efficiently promote the so far elusive monoarylation of unsubstituted hydantoins with, enabling sequential double arylations, and combination of alkylations and arylations. This provides access to a wide range of drug-like molecules from easily available aryl chlorides.

References

[1] B. Zhao, H. Du, Y. Shi, *JACS,* **2008**, *130*, 7220–7221; [2] a) K. Tomohara, T. Yoshimura, R. Hyakutake, P. Yang, T. Kawabata, *JACS,* **2013**, *135*, 13294–13297; b) R. C. Atkinson, F. Fernández-Nieto, J. Mas Roselló, J. Clayden, *ACIE*, **2015**, *54*, 8961–8965; [3] F. Fernández-Nieto, J. Mas Roselló, S. Lenoir, S. Hardy, J. Clayden, *Org. Lett.* **2015**, *17*, 3838–3841. [4] S. Lapointe, A. Sarbajna, V. H. Gessner, *Acc. Chem. Res.,* **2022**, *55*, 770–782; [5] F. Papp, D. Sowa Prendes, S. Manna, A.-K. Seitz, S. Kostiukovska, J. Löffler, V. H. Gessner, Lukas J. Gooßen, *ACS Catalysis*, **2023**, *13*, 6846–6850.

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