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Advancing selectivity control with highly reactive organometallic reagents

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English Summary

C-C bond forming reactions are fundamental tools in organic synthesis. Among the various protocols available for such transformation, Pd-catalyzed cross-couplings and Cu-catalyzed allylic alkylations represents highly versatile and valuable methods. Pd-catalyzed cross-couplings enable the connections of a wide array of carbon units and became one of the most applied C-C bond forming reactions in chemistry. Cu-catalyzed allylic alkylations serve to install alkyl units on allylic systems, a transformation that has been strongly applied, in its asymmetric variant, to the construction of enantioenriched α -chiral olefins. Both of these fundamental reactions are generally based on the use of an organometallic coupling partner. Among them, hard organometallic reagents represented a challenge in the past, and continue to be a present challenge as organic reactions involving these compounds are, in a positive or either a negative manner, strongly influenced by the high reactivity of this class of reagents. The review on the more recent advances on organolithium compounds chemistry (a class of organometallic among the most reactive ones) presented in Chapter 1 is meant to illustrate the effort that the chemical community has dedicated to the control of selectivity while using hard organometallics.

Grignard compounds are also among the most reactive organometallics. Nevertheless several catalytic protocols are described, dealing successfully with the control of selectivity using these organometallic reagents. In Chapter 2 the development of a Cu-catalyzed asymmetric allylic alkylation (AAA) protocol with Grignard reagents is reported. The choice of allylic *gem*-dichlorides as substrates leads to a process that, in addition to enantioselectivity, regioselectivity and chemoselectivity, affords internal olefins with high selectivity toward the formation of the thermodynamically disfavoured *Z*-isomer. This is a remarkable extension of the scope of Cu-catalyzed AAA as generally the preparation of internal olefins with this methodology is complicated by the lack of selectivity toward the geometry of the double bond. The enantioenriched *Z*-vinyl chlorides obtained with this methodology are versatile building blocks that *via* Suzuki coupling can be readily converted into a variety of disubstituted *cis* olefins.

In Chapter 3 a methodology toward catalyst induced reverse selectivity is presented. While commonly Cu-catalyzed allylic alkylations with hard organometallic reagents are inherently γ -selective, the corresponding α -selective protocols have been scarcely reported and are mostly based on the use of Grignard reagents. The choice of the ligand allows for a facile inversion of the regioselectivity in Cu-catalyzed allylic alkylation with organolithium reagents enabling a concise synthetic route toward α -alkylated product. This is a remarkable example of selectivity control dictated solely by the choice of the ligand.

In Chapter 4 and 5 the use of organolithium compounds in Pd-catalyzed cross-coupling is reported. Remarkably this class of organometallic reagents, often used as precursors for the preparation of the softer organometallics commonly applied in cross-coupling, have been overlooked after seminal reports in 1979. The potential of organolithium compounds in cross-coupling is highlighted by the short reaction times and mild conditions usually required to afford full conversion. High selectivity is achieved through careful choice of catalyst and conditions that allow a complete inhibition of common side reactions (halogen/lithium exchange, homocoupling) that commonly plague the cross-coupling of organolithium reagents. Alkylolithium compounds reacts without the occurrence of the notorious β -hydride elimination, even when challenging secondary alkyl units are coupled. Aryllithium compounds, rapidly prepared by halogen/lithium exchange and *ortho*-metallation also participate efficiently the cross-coupling with both aryl bromides and chlorides.

In Chapter 6 the observed tendency of organolithium to participate a fast transmetallation step is exploited in one of the more challenging coupling protocols: the combination of two *ortho*-substituted aryl units to generate highly congested tri- and tetra-*ortho* substituted systems. This is one of the few examples of such reactions performed under ambient conditions and the faster protocol to day to access highly hindered biaryls in Pd-catalyzed cross-couplings.

Finally in Chapter 7 the first example of a one-pot 1,2-addition/cross-coupling reaction of Weinreb amides and organolithium reagents is presented for the synthesis of alkyl- and aryl-ketones. This procedure allows the formal reaction of a ketone (masked as the 1,2-adduct intermediate) containing molecule with organolithiums compounds without needing a protection/deprotection sequence. The one-pot approach represent a short-cut compared with the usual two steps sequence and allows for a modular choice of the organolithium compounds. Different ketones with different substitution patterns can be prepared rapidly starting from a common starting material.

