

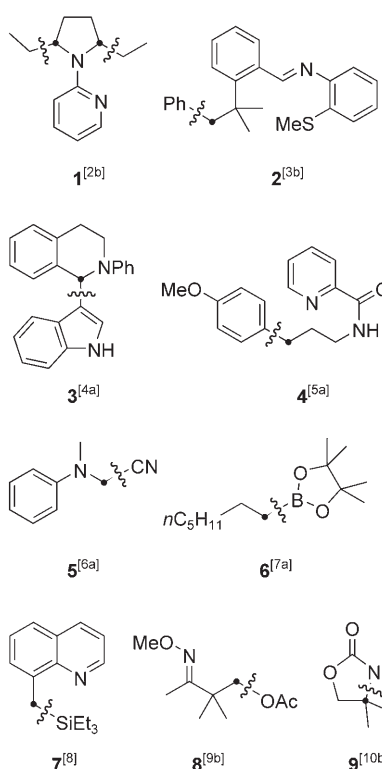
A Catalytic Approach for the Functionalization of C(sp³)–H Bonds

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The development of methodology for the direct functionalization of relatively unreactive C–H bonds has now become a major topic of research.^[1] The recent rapid growth of this area is not surprising, since such methodology facilitates the direct formation of C–C and C–Z bonds (Z = O, N, B, Si, etc.) without utilizing prefunctionalized C–X bonds (X = halogens, OTf (F₃CSO₃[−]), etc.). Although the pioneering studies on the activation of inert C–H bonds by stoichiometric amounts of transition-metal complexes appeared in the early 1960s, it was more than 20 years later that *catalytic* reactions involving the cleavage of C–H bonds were achieved.^[1a]

Since these ground-breaking discoveries, a number of catalytic C–H bond functionalization processes have been reported. Until recently, the majority of the catalytic processes reported were applicable to only C(sp²)–H bonds. The functionalization of C(sp³)–H bonds is still a particularly difficult challenge owing to the strength of C(sp³)–H bonds. However, in the last few years, some promising catalytic systems for the selective functionalization of C(sp³)–H bonds have been developed (Scheme 1).^[2–10]

Since these processes require the direct interaction between the metal catalyst and the C–H bond to be activated, the steric environment around the reaction center is a critical factor in determining whether the process is fea-



Scheme 1. Selected examples of catalytic functionalization of C(sp³)–H bonds.

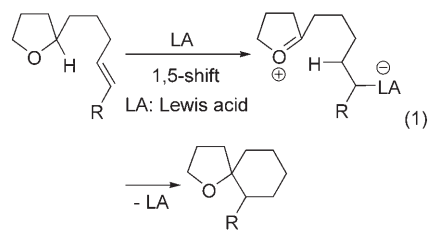
sible. Indeed, the compounds shown in Scheme 1 were synthesized through the functionalization of less hindered primary or secondary C(sp³)–H bonds with the exception of oxazolidinone **9**, which

Keywords:

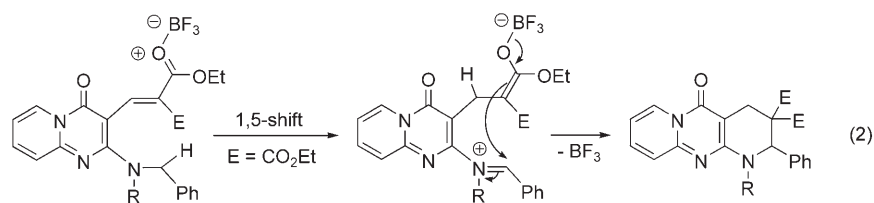
1,5-hydride shift · C–H activation · catalysis · Lewis acids

was formed by the metal–nitrenoid insertion into a tertiary C–H bond.^[10]

The transition-metal-mediated activation of unreactive C–H bonds proceeds by several mechanisms, which include oxidative addition to low-valent metal centers, substitution by electro-

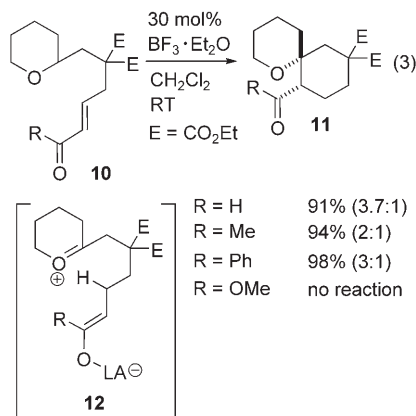


philic metal complexes, and metal–carbenoid insertion.^[11] A new approach was recently reported by Sames and co-workers.^[12] Their proposal includes the initial activation of the unsaturated moiety by an electrophilic metal catalyst, cleavage of a C–H bond in the context of a 1,5-hydride shift, and subsequent ring closure [Eq. (1)].^[13] This strategy eliminates the metal-mediated C–H bond-activation step and thus may be applicable to sterically hindered C(sp³)–H bonds. Although Lewis acid catalyzed and thermal cyclizations based on a similar concept have already been reported, the applicable substrates are limited to those that contain an extended π system [Eq. (2)].^[14]



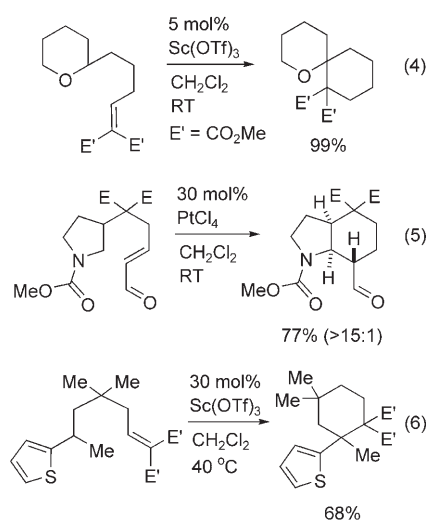
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Sames and co-workers realized the concept shown in Equation (1) by utilizing well-designed tetrahydropyran-based substrates **10**, which, in the presence of a catalytic amount of $\text{BF}_3 \cdot \text{Et}_2\text{O}$, afforded the expected spirocycles **11** [Eq. (3)]. The reaction presumably pro-



ceeds via the zwitterionic intermediate **12**, which is formed by a 1,5-hydride shift. α,β -Unsaturated aldehydes and ketones were suitable as hydride acceptors in this conversion, while α,β -unsaturated esters were not reactive under the reaction conditions. Although other Lewis acids, such as $\text{Sc}(\text{OTf})_3$, GaCl_3 , TiF_4 , and PtCl_4 , were also active for the reaction of **10**, undesired by-products resulted for this particular substrate.

In contrast, the reactions of α,β -unsaturated malonates proceeded effectively under the influence of the $\text{Sc}(\text{OTf})_3$ catalyst [Eq. (4)]. The reaction



can be applied not only to tertiary C–H bonds but also to secondary C–H bonds that are adjacent to heteroatoms such as nitrogen or oxygen [Eq. (5)]. A pseudo-benzylic $\text{C}(\text{sp}^3)\text{--H}$ bond lacking an α -heteroatom can also participate in the catalytic reaction [Eq. (6)]. The current limitation of the reaction is the requirement of a 1,5-relationship between the C–H bond and the electrophilic site.

The new approach for $\text{C}(\text{sp}^3)\text{--H}$ bond functionalization reported by Sames et al. represents a potentially powerful method for constructing a quaternary center directly from a tertiary C–H bond in a catalytic manner. Although the underlying concepts are the classical Lewis acid activation of α,β -unsaturated carbonyl compounds, a 1,5-hydride shift, and enolate alkylation, the use of well-designed substrates leads to an unprecedented methodology for the functionalization of sterically congested $\text{C}(\text{sp}^3)\text{--H}$ bonds. The methodology is currently limited to substrates containing a $\text{C}(\text{sp}^3)\text{--H}$ bond adjacent to a heteroatom or a tertiary benzylic C–H bond as a hydride donor and an electron-deficient alkene as a hydride acceptor. Further applications of this methodology can be expected.^[15]

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