# ORGANIC CHEMISTRY

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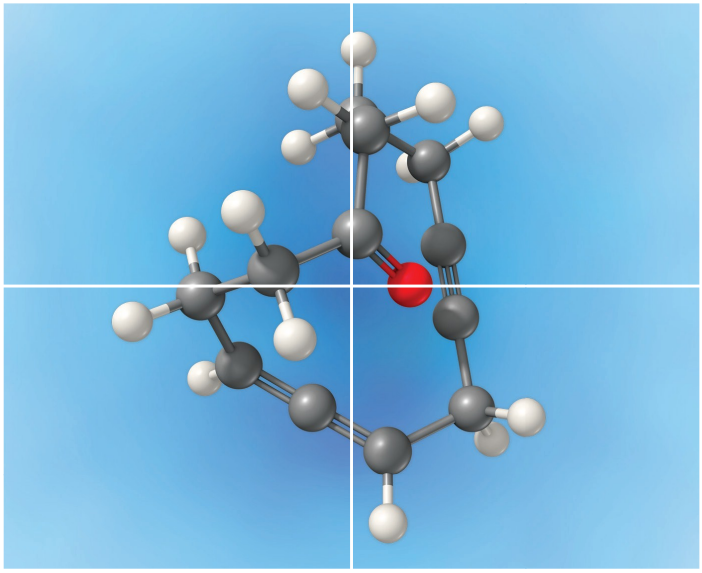

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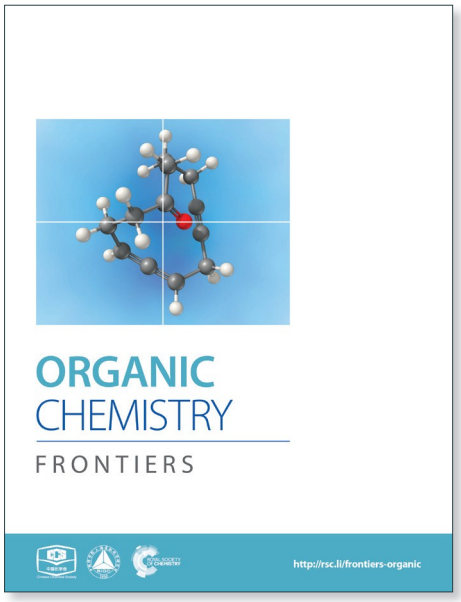


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Organic Chemistry Frontiers

HIGHLIGHT

# C(sp$^3$)–H Bond Functionalization by Sequential Hydride Transfer/Cyclization: Electronic Effect and Steric Effect Controlled Regioselectivity**

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The electron effect and steric effect had dramatic impact on the fascinating cascade [1,n]-hydride transfer/cyclization. The regioselectivity of two potential hydrogen donors could be perfectly tuned to construct different skeletons.

Although cascade [1,n]-hydride transfer/cyclization was identified more than one hundred years ago,[1] this internal redox process was largely overlooked until the beginning of this century. Inspired by the pioneering works from the groups of Sames,[2] Seidel,[3] and Akiyama,[4] the recent decade has witnessed a vigorous renaissance of this area as an intriguing avenue for C(sp$^3$)-H bond functionalization.

It is well known that cleavage of C(sp$^3$)-H bond is the rate-determining step in C(sp$^3$)-H bond functionalization and the hydride transfer dramatically relies on the substituent effects. The presence of heteroatoms, such as nitrogen and oxygen, will facilitate the hydride migration due to the following three factors. Firstly, heteroatoms with high electronegativities will polarize the C-X bond, causing the weakening of the C(sp$^3$)-H bond. Secondly, the hyperconjugation effect of $\sigma^*$C-H orbital with a neighbouring heteroatom lone pair or π-orbital promotes the hydride shift (Figure 1).[5] This effect not only weakens the C(sp$^3$)-H bond but also increases the negative charge density of the hydrogen atom. Thirdly, the carbocationic intermediate generated upon hydride migration, can be stabilized by adjacent heteroatoms, aromatic or alkyl substituents via p-p conjugation, π-p conjugation or σ-p hyperconjugation, respectively. Consequently, the rate of C(sp$^3$)-H bond cleavage is closely associated with the stability of cationic intermediate, thus any factor which can stabilize this intermediate will dramatically promote this process, while the groups

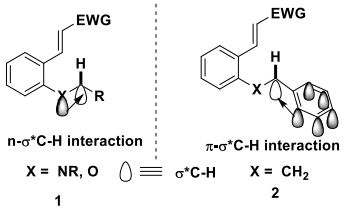
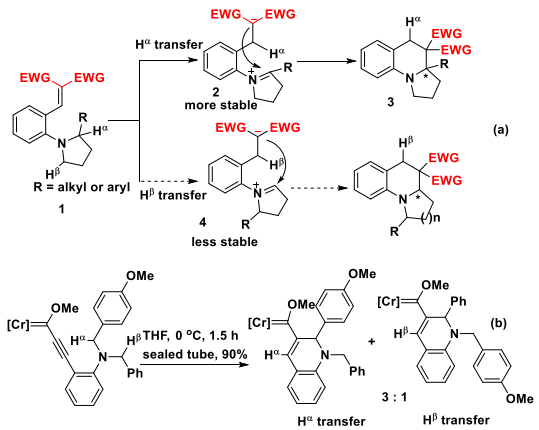



Figure 1. The electronic assistance from heteroatom and aryl group.

destabilizing it will retard the proximal C(sp$^3$)-H bond cleavage. Notably, without the electronic assistance, highly electrophilic hydride acceptors and harsh conditions are always required to get decent yields.

Electronic effect also has drastic influence on the regioslectivity. When two potential hydrides, $H^\alpha$ and $H^\beta$, were available in substrate **1**, $H^\alpha$ would migrate to create the more stable iminium intermediate **2** preferentially over migration of $H^\beta$ to furnish intermediate **4**.[6] Subsequent barrier-less and swift intramolecular nucleophilic attack on the iminium subunit resulted in the cyclized product **3**, even though the electrophilic moiety was more sterically hindered (Scheme **1a**).[7] Similarly, if two methylene moieties served as potential hydride donors, the methylene substituted with an electron-rich group would be more reactive (Scheme **1b**).[8] Consequently, the electron-donating substituents significantly facilitated its proximal C(sp$^3$)-H bond cleavage. In this case, the regioselectivity was dominated by the electronic effect instead of the steric effect of hydride donors.




Scheme 1. The electronic effect on the regioselectivity.

In addition to the electronic effect, this cascade reaction can also be strongly impacted by the distance between hydride donors and acceptors, and any factors rendering them closer to each other will drastically promote this process. Barluenga and Ballesteros et al. demonstrated that even a comparatively inert non-benzylic

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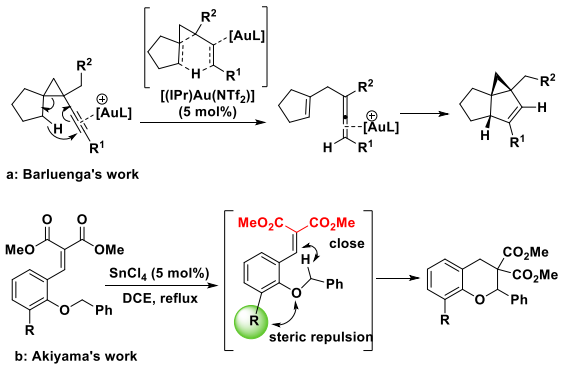
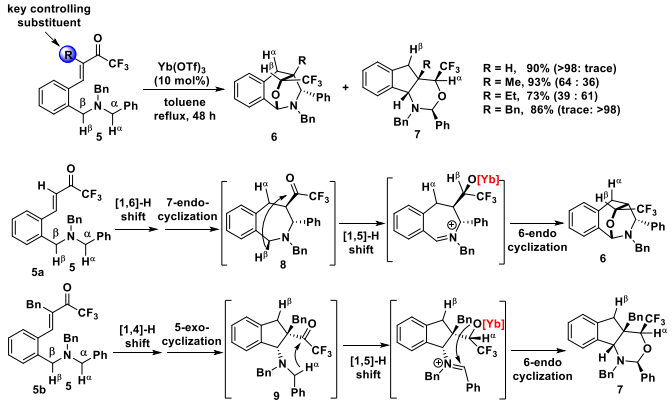
secondary C($sp^3$)-H bond, could be functionalized directly with a vicinal gold(III)-activated alkyne serving as a hydride acceptor, without electronic assistance from a heteroatom (Scheme **2a**).[9] Akiyama et al also observed an intriguing ortho-substituent acceleration effect in cascade [1,5]-hydride transfer/cyclization reaction (Scheme **2b**).[4a]




Scheme 2. Steric effect on the cascade hydride transfer/cyclization.

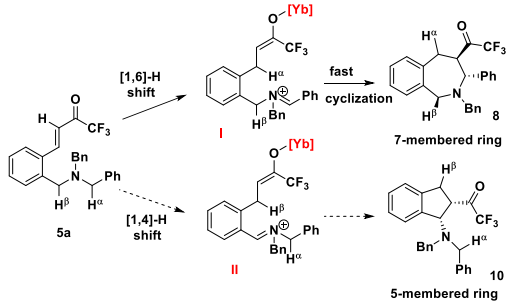
The precise regioselectivity-controlling effect of initial C($sp^3$)-H functionalization was elegantly demonstrated by Akiyama and coworkers, who recently reported a fascinating $Yb(OTf)_3$-catalyzed double C($sp^3$)–H bond functionalization of benzylamine derivative **5** through a sequential hydride shift/cyclization process (Scheme 3).[4e] Both electronic-effect and steric effect were exploited to precisely manipulate the sequence of two possible hydride migrations in Akiyama's work. In this reaction, the initial hydride shift ([1,4]- or [1,6]-hydride shift) was completely controlled by the steric effect of the α substituent of trifluoromethyl ketone (Scheme 4). By tuning the $R^1$ group of ketone, the sequence of functionalization of two potential hydrogen donors was totally reversed. A bicyclo[3.2.2]nonane skeleton **6** was provided from substrate **5a** ($R^1$ = H) through a sequential [1,6]- and [1,5]-hydride shift process. In sharp contrast, when a benzyl group was substituted at the α position of trifluoroacetyl group, a [1,4]- and [1,5]-




Scheme 3. Double C($sp^3$)–H bond functionalization of benzylamine derivative.

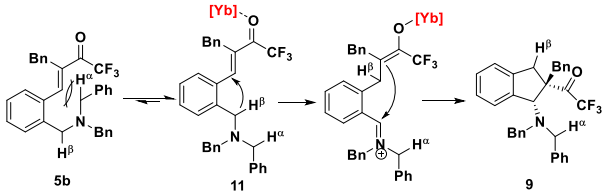
hydride shift occurred successively in substrate **5b**, resulting in the formation of fused bicyclic product **7**. Surprisingly, in the absence of a bulky $R^1$ group, the sterically disfavored 7-membered ring **8** was preferentially generated rather than the sterically favored 5-membered ring **9**. DFT calculation and theoretical studies revealed that the resonance stabilization in the benzylidene carbonyl moiety and the steric repulsion of the α-substituent ($R^1$) were the key points driving the reaction course.

In addition to the rationalization proposed by Akiyama et al, the regioselectivity can be interpreted in an intuitive way (Scheme 4). In substrate **5a**, $C^{\alpha}$-$H^{\alpha}$ is linked with a normal phenyl group, while $C^{\beta}$-$H^{\beta}$ is substituted with the electron-deficient phenyl group, the σ*C-H orbital of $C^{\alpha}$-$H^{\alpha}$ bond is impacted to a larger extent than that of $C^{\beta}$-$H^{\beta}$ bond through hyperconjugation, rendering $C^{\alpha}$-$H^{\alpha}$ bond much easier to be cleaved. Consequently, $H^{\alpha}$ will migrate preferentially to furnish intermediate **I** which undergoes a low-barrier and swift cyclization to afford 7-membered intermediate **8**, instead of formation of 5-membered **10**. It is a remarkable fact that formation of a sterically disfavored 7-membered ring rather than a sterically favored 5-membered ring. Once again, the regioselectivity is thoroughly governed by the electronic effect rather than steric effect.




Scheme 4. Electronic effect controlled regioselectivity.

When the bulky benzyl group was put at the position α to a trifluoroacetyl group as in substrate **5b**, the situation is thoroughly reversed. The sterically demanding benzyl group would induce a large steric repulsion between the hydrogen acceptor (α and β carbon of the ketone) and the methylene on which $H^{\alpha}$ is located, pushing the sterically hindered $H^{\alpha}$ moiety away, leading to the conformer **11**. As the reactivity of hydrogen donor is quite sensitive to the distance between donor and acceptor, the vicinal $H^{\beta}$ would shift preferentially, followed by a fast intramolecular nucleophilic attack to afford the intermediate **9**



Scheme 5. Steric effect controlled regioselectivity.

(Scheme 5). In this case, the steric effect dominated the sequence of hydride migration rather than electronic effect.

In summary, we have highlighted the key role of the electronic effect and steric effect in controlling the regioselectivity of [1,n]-hydride transfer/cyclization. The origin of this phenomenon has been rationalized and summarized. The recent double cascade [1,n]-hydride transfer/cyclization elegantly demonstrated the great power of this strategy, in which the regioselectivity of two potential hydrogen donors could be perfectly tuned with the aid of the "two hands", electronic effect and steric effect, to construct structurally diverse molecules in an atom-economic manner. The chemistry of [1,n]-hydride transfer/cyclization is of high significance, which, however, is still under development. We believe this useful strategy has a brilliant future and will inspire more application for construction of complex architectures.

## Acknowledgements

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