## Cascade Reactions

## Design of Leaving Groups in Radical C—C Fragmentations: Through-Bond 2c–3e Interactions in Self-Terminating Radical Cascades

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**Abstract:** Radical cascades terminated by  $\beta$ -scission of exocyclic C–C bonds allow for the formation of aromatic products. Whereas  $\beta$ -scission is common for weaker bonds, achieving this reactivity for carbon–carbon bonds requires careful design of radical leaving groups. It has now been found that the energetic penalty for breaking a strong  $\sigma$ -bond can be compensated by the gain of aromaticity in the product

and by the stabilizing two-center, three-electron "half-bond" present in the radical fragment. Furthermore, through-bond communication of a radical and a lone pair accelerates the fragmentation by selectively stabilizing the transition state. The stereoelectronic design of radical leaving groups leads to a new, convenient route to Sn-functionalized aromatics.

## Introduction

The alkyne group is a high-energy carbon-rich functionality that can serve as a perfect starting point for the preparation of conjugated molecules and materials.<sup>[1]</sup> For example, controlled cascade transformations<sup>[2]</sup> featuring alkyne cyclizations<sup>[3]</sup> provide practical means for the preparation of graphene nanoribbons.<sup>[1,4]</sup> On the other hand, alkenes, the reduced chemical cousins of alkynes, cannot serve as direct precursors for conjugated systems, as alkenes cyclize to products that require an extra oxidizing step for aromatization.

Recently, we amplified the subtle chemical differences between alkenes and alkynes by utilizing dynamic covalent chemistry<sup>[5]</sup> for the development of a regio- and chemoselective radical transformation of aromatic enynes into indenes.<sup>[6]</sup> Although both alkyne and alkene  $\pi$  bonds are indiscriminately attacked by Bu<sub>3</sub>Sn radicals, the pool of four equilibrating isomeric radical intermediates is selectively depleted ("kinetically self-sorted") through the "matched" *5-exo-trig* cyclization of the most reactive of the four radicals at the more reactive alkene  $\pi$  bond.

While investigating the scope of enyne cyclizations, we observed that alkyl substitution at the alkene changes the regioselectivity of the cyclization, by directing the formation of 6endo product **2** in 65% yield (Scheme 1).<sup>[7]</sup> This process does not provide a conjugated product, because it is terminated by hydrogen-atom abstraction. However, we also observed

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**Scheme 1.** Kinetic self-sorting of the pool of equilibrating radicals and change in reaction path on alkene substitution.

a small amount of naphthalene byproduct **3**, aromatized by the loss of an alkyl group (Scheme 1). Inspired by the observation that such  $\beta$ -scission of a C–C bond is a viable alternative to H-atom abstraction as the final step, we envisaged a route to aromatic products in which the alkene moiety potentially serves as a synthetic alkyne equivalent. If this cyclization cascade can be efficiently extended by incorporating the fragmentation step, this route leads to aromatization without an external oxidizing agent or radical. We tested the possibility of promoting this minor reaction path through the rational design of radical leaving groups.

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## **Results and Discussion**

#### Design of radical leaving groups

To break unstrained C–C bonds under relatively mild conditions, both thermodynamics and kinetics of this process must be optimized.<sup>[8]</sup> In the present example, the energetic penalty for the homolytic cleavage of a strong C–C bond is partially compensated by the aromatic stabilization gained in the product. However, the other product (the propyl radical) is a highenergy, unstable species. We envisioned that stabilization of the alkyl radical would further promote the fragmentation (Figure 1). To accelerate this reaction, this stabilization should



Figure 1. C-C bond homolysis facilitated by product stabilization.

develop early and become sufficiently large in the transition state (TS).  $\ensuremath{^{[9]}}$ 

Radical fragmentations provide a valuable option for the termination of cascade transformations.<sup>[10]</sup> The reactivity of radicals formed in the fragmentation step dictates the outcome of the competition between propagation and termination of radical cascades (Scheme 2). In particular, reactive radicals (i.e., alkyl or thiyl) can react further to propagate the chain process.



Scheme 2. Selected examples of radical fragmentations in synthesis. Left: Scission of a weak C–S is used to shift the equilibrium for an unfavorable rearrangement.<sup>[10b-d]</sup> Center: Rare example of  $\beta$ -scission of a C–C bond, reported by Zard et al.<sup>[10f,g]</sup> Right: Self-terminating radical cascades with the expulsion of NO<sub>2</sub>, reported by Wille et al.<sup>[10e]</sup>

This can be useful. For example, electrophilic (S-centered) Et<sub>3</sub>SiS radicals formed in a fragmentation-driven  $O \rightarrow C$  transposition sequence<sup>[10b-e]</sup> can be utilized for polarity-reversal catalysis.<sup>[11]</sup> However, in the case of sensitive substrates, the departing radicals can also induce undesired side reactions.

In self-terminating cascades, introduced by Wille et al., stable fragmenting radicals exit the reaction without participating in subsequent transformations.<sup>[10f]</sup> Only a few such processes involve C–C bond scission with the formation of C-centered radicals.<sup>[10g-j]</sup>

Our design of stabilized radical leaving groups was guided by the electronic structure of super-stable radicals such as molecular oxygen, nitric oxide, and 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO), in which a half-filled orbital is stabilized by an adjacent lone pair. In the extreme, such strong two-center, three-electron (2c-3e) interactions correspond to a bond order of  $\frac{1}{2}$  and can be referred to as half-bonds.

Stabilization provided by the 2c–3e interactions depends on the relative electronegativity of the heteroatom (Figure 2).



**Figure 2.** 2c-3e interactions (middle) stabilize half-bonds in many important compounds (left). Radical stabilizations calculated at the UM06-2X/LanL2DZ level by using the isodesmic equation are shown on the right.

When electronegativities of the interacting atoms are closer, stabilization is greater.  $NMe_2$  substitution provides about 10 kcal mol<sup>-1</sup> stabilization to the departing radical, whereas OR groups account for about one-half of that value (ca. 5 kcal mol<sup>-1</sup>). Phenyl substitution also provides substantial radical stabilization (> 10 kcal mol<sup>-1</sup>).

We expected that such strong stabilization through incorporation of heteroatoms adjacent to the radical center would increase the efficiency of the self-terminating fragmentation and also render the fragmented radical relatively inert, preventing undesirable side reactions. Allylic oxygen, nitrogen, and aromatic substituents can be easily incorporated at the ene terminus by using well-established C–C coupling procedures (Figure 3) to afford the requisite set of substrates. Indeed, heteroatom incorporation completely switched the selectivity in favor of the self-terminating fragmentation (Figure 4). Furthermore, the fragmentation is sufficiently fast to compete with 6*exo-dig* radical cyclization (Figure 4, bottom).

The self-terminating nature of the fragmentation is supported by the need to use a stoichiometric amount of initiator (0.5 equiv of 2,2'-azobisisobutyronitrile (AIBN) produces 1 equiv of isobutyronitrile radical) for full conversion (Table 1). Whereas

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Figure 3. Synthesis of starting materials (see the Supporting Information for further details).



**Figure 4.** Top: Switch from H abstraction to fragmentation promoted by 2c–3e bonds. Bottom: Loss of CH<sub>2</sub>OR group successfully competes with 6-*exo* cyclization.

e 1. Optimization of equivalents of AIBN. <sup>(a)</sup>								
	Bu₃SnH [equiv]	AIBN [equiv]	<i>t</i> [h]	Yield [%] <sup>[b]</sup>	USM [%] <sup>[b]</sup>			
	1.2	0.1	12	11	42			
	1.2	0.2	12	31	19			
	1.2	0.2	12	10 <sup>[c]</sup>	24			
	1.2	0.4	12	65	9			
	1.2	0.5	12	78	0			

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[a] See Figure 4 for reaction conditions. [b] Unconverted starting material, determined by  $^{1}H$  NMR spectroscopy with Ph<sub>3</sub>CH as internal standard. [c] With 0.2 equiv PhSH.

bond dissociation energies (BDE) suggest propagation through hydrogen abstraction by 'CH<sub>2</sub>X from Bu<sub>3</sub>SnH to be a thermodynamically favorable process (H–CH<sub>2</sub>OH, BDE=96 kcal mol<sup>-1</sup> versus Bu<sub>3</sub>Sn–H, BDE=74 kcal mol<sup>-1</sup>),<sup>[12]</sup> kinetics of such a process may be relatively slow, as both species are nucleophilic.

We envisioned that the fragmented radical could be coerced into propagating the radical chain through polarity-reversal catalysis.<sup>[11]</sup> In such processes, H-atom transfer between two nucleophilic radicals is promoted by an "H-shuttle" with an electrophilic radical. However, our attempt to increase the efficiency of propagation steps using thiophenol as the H-shuttle decreased the naphthalene yield (Table 1, entry 3). Although 10% of **3** was formed, we also obtained significant amounts of reduced acyclic products (along with 24% of the reactant). Product **3** is derived from the least stable of the equilibrating radicals, which suggests the radical pool can be depleted if the more stable radicals (incapable of cyclization) find a suitable reaction path. This is consistent with the previous reports of polarity-reversal catalysts prematurely terminating radical cascades by trapping relatively unreactive intermediates.<sup>[119,13]</sup>

Another possibility for preventing propagation is the facility of further fragmentation of the CH<sub>2</sub>XR radical.<sup>[14]</sup> We are currently investigating the mechanistic details in hopes of obtaining fragmented species and finding conditions for efficient propagation.

#### **Computational analysis**

Further insights into electronic factors responsible for the facile fragmentations came from DFT calculations. Free energies  $\Delta G$  of fragmentation were negative due to a combination of radical stabilization and the favorable entropic contribution. Because nitrogen is a better donor than oxygen<sup>[15]</sup> and because lone pairs are better donors than C-H/C-C bonds,<sup>[16]</sup> we expected reaction energies to reflect the importance of the donor abilities of lone pairs in the stabilization of the fragmented radical in an order analogous to that in Figure 2:  $CH_2NMe_2 > CH_2OMe/CH_2OH > CH_2Alkyl.$  However, the calculated exergonicities for the fragmentation of O-containing substrates (CH<sub>2</sub>OMe/CH<sub>2</sub>OH) were lower than that for the propyl-substituted substrate (Figure 5). This unexpected observation suggests the presence of a new remote electronic effect that stabilizes the benzylic reactants containing a  $\beta$ -C–X bond and thus decreases the exergonicity of their fragmentation. We suggest that this effect is a through-bond (TB) coupling of the

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Figure 5. Calculated energy profiles [kcalmol<sup>-1</sup>] for the fragmentation at the UM06-2X/LanL2DZ level of theory.  $\Delta G$  calculated at 384 K.

two nonbonding orbitals populated with three electrons (see below).

#### TB interactions in odd-electron systems

Such electronic effects are well-known when both of the nonbonding orbitals are singly occupied (e.g., in 1,4-diradicals). In these systems, TB coupling of radical centers<sup>[17]</sup> increases the population of the  $\sigma^*$  bridge orbital, which ultimately leads to fragmentation into two 2c-2e bonds. The same effect is responsible for rendering the Bergman cyclization a symmetry-allowed reaction<sup>[18]</sup> and providing about 3–5 kcal mol<sup>-1</sup> stabilization to *p*-benzyne.<sup>[19]</sup> Symmetry-enforced TB interactions play



**Figure 6.** Top: Transformation of TB electronic coupling between nonbonding orbitals in 1,4-diradicals and  $\beta$ -heteroatom-substituted radicals in a C–C bond fragmentation. Bottom: Energy penalty for inclusion of an additional electron in the fragmenting system.

an important role in "aborted" sigmatropic shifts, an unusual class of pericyclic reactions in which the geometry corresponding to the cyclic TS is more stable than the acyclic reactants.<sup>[9c]</sup> However, the role of TB coupling between radical centers and lone pairs in 2c–3e systems is not commonly recognized, perhaps due to the decreased driving force for the fragmentation of monoradicals, whereby one of the formed bonds is the 2c–3e half-bond (Figure 6).<sup>[20]</sup>

Comparison of data in Figures 2 and 5 provides a way to evaluate the magnitude of three-electron TB stabilization. For X=OH, the  $\Delta\Delta E_{rxn}$  (relative to X=propyl) is about 5–6 kcal mol<sup>-1</sup> less negative than one would expect from stabilization energies provided by Figure 2 (see Supporting Information for the full analysis).

#### Increased TB interaction in the fragmentation TS

Reactant stabilization is a potentially counterproductive factor in the design of fragmentations. However, the surprisingly large magnitude of kinetic effects in the calculated activation energies in Figure 5 suggest that these stabilizing interactions become even more important in the transition state and facilitate the fragmentation.<sup>[9]</sup>

To differentiate thermodynamic contributions to the barrier (the consequence of the increased stability of reaction products) from stabilizing effects intrinsic to the transition state, we turned to Marcus theory.<sup>[21]</sup> This approach dissects reaction energy as a combination of intrinsic energy and thermodynamic contribution [Eq. (1)].

$$\Delta E^{\ddagger} = \Delta E_0^{\ddagger} + \frac{1}{2} \Delta E_{\rm rxn} + \Delta E_{\rm rxn}^2 / 16 \Delta E_0^{\ddagger}$$
<sup>(1)</sup>

Stereoelectronic differences in the TS can be identified by examining the intrinsic barrier  $\Delta E_0^{\frac{1}{4}}$ , that is, the barrier of a thermoneutral process lacking the thermodynamic contributions.<sup>[22]</sup> The intrinsic barrier can be estimated if both the activation and reaction energies are known (Figure 7).

From the Marcus model, one would expect that the effect on the activation barrier should be significantly smaller than effect on the reaction energy ( $\Delta\Delta G^{+} \approx \frac{1}{2}\Delta\Delta G$ ). Contrary to these expectations, the effect on  $\Delta G^{+}$  rivals the effect on  $\Delta G$ in the case of X = CH<sub>2</sub>NMe<sub>2</sub>. The relatively small and sometimes negative activation entropies are surprising for a fragmentation reaction and suggest an increased degree of structural organization in the TS. To eliminate the complication associated with the difference in the entropic penalties, we focused our attention on reaction energies  $\Delta E$  and discovered even more striking trends (e.g.,  $\Delta\Delta E^{+} = 22.0$  with  $\Delta\Delta E = 21.4$  kcal mol<sup>-1</sup> for **1 A** versus **1 E**, respectively; see Supporting Information). These surprising observations suggest that the stabilizing effect of the heteroatom starts to manifest itself before a radical center is fully developed at the adjacent carbon atom.

The intrinsic reaction barriers are given in Figure 7. Clearly, when thermodynamic contributions to the barrier are removed, significant differences in the transition-state energies remain (1–2 kcal for  $X = CH_2OR$  and ca. 6 kcal mol<sup>-1</sup> for  $X = CH_2NMe_2$ ). These large effects on the fragmentation barrier

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Figure 7. Stereoelectronics of the fragmentation viewed through the window of Marcus theory. Top inset: Summary of differences in reaction and activation free energies imposed by the substituents. Bottom inset: Intrinsic reaction barriers for the fragmentation. Energies in kcal mol<sup>-1</sup>.



stretch C-A bond

Figure 8. Electronic coupling between nonbonding orbitals in 1,4-diradicals and  $\beta\text{-heteroatom-substituted}$  radicals strengthens in the TS and facilitates C-C bond fragmentation. Additional stabilization due to TB coupling through a breaking bridging bond is shown as  $\Delta \textit{E}.$  The  $\sigma$  and  $\sigma^*$  energies in the starting radical are shown in gray.

originate from electronic communication between the nonbonding orbitals, which weakens the bridging  $\sigma$  bond in the TS (Figure 8).

To test whether the long-range communication between nonbonding orbitals in the three-electron systems facilitates the fragmentation, we performed intrinsic reaction coordinate (IRC) analysis of the fragmentation step for the least sterically encumbered substrate, the allylic alcohol, in which stereoelectronic aspects of the fragmentation can fully develop (see Supporting Information). The evolution of the IRC geometries illustrates that molecular geometry in the CCOH group changes to



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Figure 9. Left: Optimized geometry for the fragmentation TS ( $X = CH_2OH$ ). Right: Orbital alignment with the  $\sigma^*$  orbital of the bridge facilitates TB coupling between the nonbonding orbitals leading to the fragmentation.

adopt the coplanar arrangement between the radical center and the *p*-type lone pair on the oxygen atom (Figure 9).

The final computational evidence was provided by natural bond orbital (NBO) analysis of the initial radical, transition state, and half-bonded radical fragments, which revealed the presence of very strong stabilizing interactions between the radical, the lone pair of the oxygen atom, and the bridge orbitals (Table 2). Although communication through the  $\sigma$  bridge is present in the radical, the effects become much larger in the TS. The increased interactions can be understood from the second-order perturbation energies  $E^{(2)}$  provided by NBO analysis [Eq. (2)]

$$E^{(2)} = q_i \frac{F_{ij}^2}{\varDelta E_{ij}} \tag{2}$$

where  $q_i$  is the donor orbital occupancy,  $\Delta E_{ij}$  is the energy difference between interacting orbitals, and  $F_{ij}$  is the off-diagonal NBO Fock matrix element.

<b>Table 2.</b> NBO analysis at the UM062X/LanL2DZ level of theory. Interaction energies in $kcalmol^{-1}$ .									
	Si	SM		TS <sup>[a]</sup>					
Interaction	$\alpha$ spin	$\beta$ spin	lpha spin	$\beta$ spin					
$n_{C} \rightarrow \sigma^{*}_{C-C}$	5.9	1.7	89.6	13.4					
$n_0 \rightarrow \sigma^*_{C-C}$	3.9	4.9	2.7	30.7					
$\sigma_{c-c}{\rightarrow}n_{c}$	_ <sup>[b]</sup>	5.0	_ <sup>[b]</sup>	79.9					
[a] The given Lewis structure was obtained using the SCHOOSE keyword									

(see the Supporting Information). [b] Below the threshold of 0.5 kcal  $mol^{-1}$ 

During fragmentation the energy of the  $\sigma$ -bonding orbital is raised as that of the  $\sigma^*$  orbital is lowered, and the  $\Delta E_{ii}$  term for interactions with nonbonding orbitals (i.e., the radical and lone pair) is decreased. In addition, as fragmentation progresses, the approximately  $sp^3 \sigma$  bond is transformed into two p orbitals (one  $\pi$ -bonded in naphthalene and the other in a 2c–3e half-bond), and this increases overlap between interacting orbitals. Together, these interactions are responsible for selective TS stabilization for the fragmentation process (see Supporting Information for full analysis).

### Conclusion

We have described a radical cascade that self-terminates by expulsion of primary C-centered radicals. Even though the ener-

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getic penalty for the homolytic cleavage of a strong C–C bond is significant, the combination of two stabilizing effects (the aromatic stabilization gained in the product and stabilization of radical leaving groups by 2c–3e bonds) can compensate for the cost of C–C bond cleavage. In the reaction sequence, a radical center is relocated to a position where it can communicate with a donor lone pair through a C–C bridge (TB interaction). Such communication leads to selective TS stabilization for the C–C bond cleavage. This work illustrates the potential of 2c–3e interactions in the design of radical leaving groups. Incorporation of C–C bond cleavage into self-terminating radical cascades allows the use of alkenes as alkyne equivalents for the preparation of aromatic structures.

## **Experimental Section**

#### Cyclization

The starting enyne (0.34 mmol) was degassed in 4 mL of toluene and heated to reflux. Separate solutions of AlBN (0.5 equiv) and  $Bu_3SnH$  (1.2 equiv), each in 3 mL of toluene, were added by syringe pump through the top of a condenser over 4 h to the refluxing solution. The reaction mixture was allowed to stir at reflux. Reaction progress was monitored by TLC. After completion, the solvent was evaporated and the product was dissolved in 20 mL of  $CH_2Cl_2$  and washed with 1 M HCl. The product was purified on silica gel by using a gradient of ethyl acetate/hexane as eluent.

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# **FULL PAPER**



Half-bonds to halve bonds: Cyclization followed by fragmentation allows the use of alkenes as alkyne equivalents. The energetic penalty for breaking a strong C–C bond is compensated by the gain of aromaticity in the product and by stabilizing 2c–3e half-bonds in the radical fragments. Kinetic acceleration of the fragmentation is provided by selective transition-state stabilization through 2c–3e through-bond interactions (see scheme).

## Cascade Reactions

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Design of Leaving Groups in Radical C-C Fragmentations: Through-Bond 2c-3e Interactions in Self-Terminating Radical Cascades