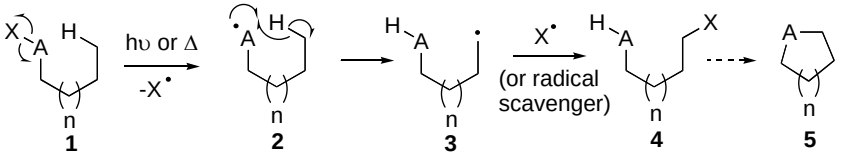
OXYGEN AND NITROGEN CENETERED RADICALS IN REMOTE FUNCTIONALIZATION REACTIONS

Reported by Erik M. Stang April 14, 2008

INTRODUCTION

The regioselective transposition of a radical center from oxygen or nitrogen to a remote position on a non-activated carbon atom represents a new synthetic methodology which fundamentally differs from the classical introduction of functional groups. [i,ii] Of the possible intramolecular hydrogen atom transfer reactions, 1,5 homolytic substitutions are the most prevalent.[iii] The general mechanism (**Scheme 1**) involves homolytic cleavage of a weak heteroatom-X bond (**1**) to produce the heteroatom-centered radical (**2**) that can abstract an appropriately located hydrogen (**3**). Radical trapping of the carbon-centered radical produces compound **4,** which can go on to cyclize (**5**) depending on the reaction conditions.[iv] Given the number of carbon- hydrogen bonds present in organic compounds, selective hydrogen abstraction is crucial. There are three main factors that control site-selectivity: strain in the transition state, bond dissociation energy, and polarity effects. These three themes will be seen in different forms throughout this discussion.

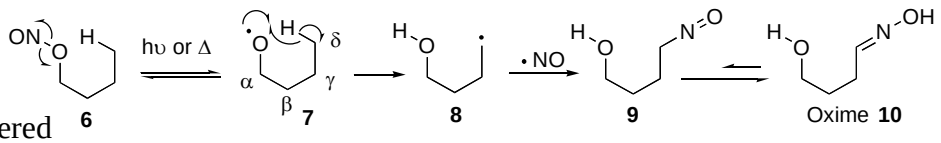
Scheme 1. General Hydorgen Abstraction Mechanism.



THE BARTON REACTION

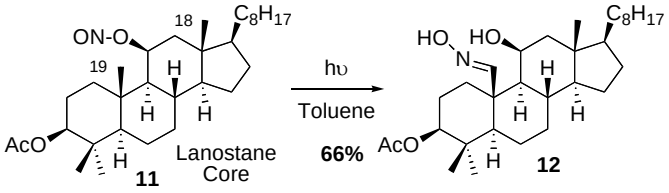
Scheme 2. General Barton Raction Mechanism.

In 1961 Barton and co-workers discovered



that photolysis of a nitrite ester (**6**) produced an alkoxyl radical (**7**), which abstracts a hydrogen from the δ-carbon (1,5-hydrogen abstraction reaction).[v] This carbon radical (**8**) is captured by nitric oxide liberated from the photolysis to produce, after tautomerization, an oxime product (**10**, **Scheme 2**). It was found that rigid carbon skeletons, like those found in steroids, were well suited for this transformation. A Lanostane nitrite ester (**11**) was photolyzed to provide an oxime on the C-19 methyl group (**12**, **Scheme 3**).[vi] Interestingly, no other functionalized products were seen even in the presence of another δ-methyl group at C-18, due to proximity.[vii]

Scheme 3. Barton Raction In Steroid Synthesis.

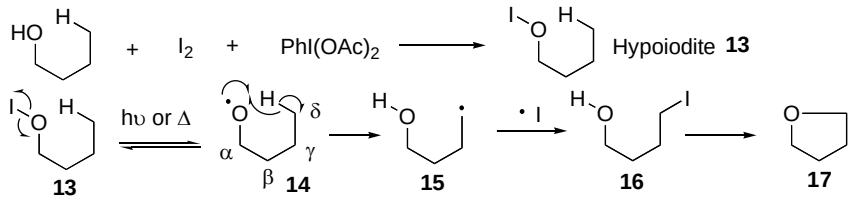


HYPOIODITE REACTIONS

Iodobenzene Diacetate Promoted Radicals

Huesler and Kalvoda popularized the term "hypoiodite reaction" to describe the homolytic cleavage of an alkyl hypoiodite. The major advance made with this methodology is the ease of preparation; hypoiodites are generated *in situ* from the free alcohol. Free alcohols in the presence of iodine and $PhI(OAc)_2$ produces a hypoiodite (**13**, **Scheme 4**). Photolytic cleavage of the O-I bond forms the alkoxyl radical (**14**). Subsequent 1,5 hydrogen abstraction produces the δ-carbon radical, which is immediately captured by iodine, thus forming an intermediary 1,4-iodohydrin (**16**). Nucleophilic or radical ring closure then provides the cyclic ether (**17**).[viii,ix,x]

Scheme 4. General $PhI(OAc)_2$ Promoted Functionalization.



Recent work in the Suarez group has focused on oxygen and nitrogen centered radicals in hydrogen abstraction reactions in carbohydrate systems. Early experiments with both alkoxyl and carbamoyl radicals showed that the majority of oxidized products arose from 1,5- hydrogen abstraction processes (**Table 1**).[xi]

In a separate study, 1,5-hydrogen abstraction reactions of amidyl radicals were studied in monosaccaride models (**Table 2**). It was found that varying the hard-soft character of the oxocarbenium ion, generated from the hydrogen abstraction, afforded different products. The amide- oxygen was the nucleophile for the harder oxocarbenium ions (**Entry 2**),

Table 1. 1,5 Hydrogen Transfer in Carbohydrate Systems.

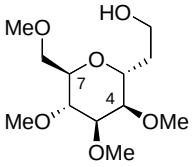
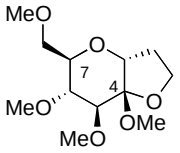
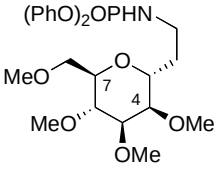
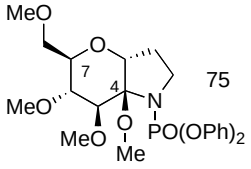
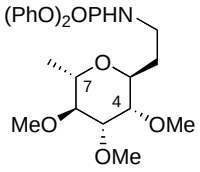
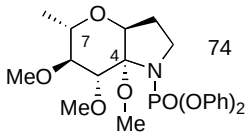
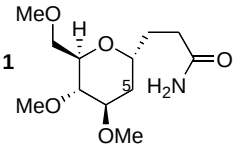
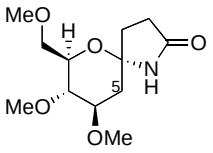
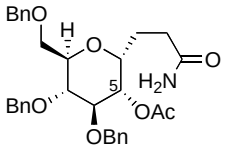
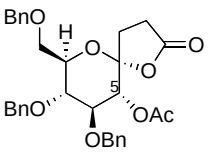
Entry	Substrate	$PhI(OAc)_2$ (eq)	Time (h)	Products	Yield (%)
1		1.3	1.25		70
2		2.2	3		75
3		2.1	5		74

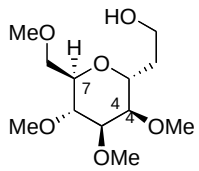
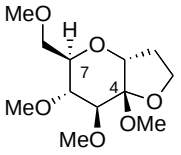
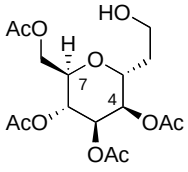
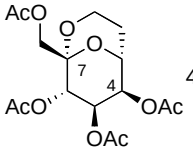
Table 2. 1,5 Hydrogen Transfer with Ambident Amides.

Entry	Substrate	$PhI(OAc)_2$ (eq)	Time (h)	Products	Yield (%)
1		2.5	0.5		70
2		2.5	0.5		67

whereas the amide- nitrogen was nucleophilic for softer oxocarbeniums ions (**Entry 1**). Thus varying the electron-withdrawing capability of the C-5 substituent can switch the reaction pathway to afford spirolactams or lactones.[xii]

1,6 hydrogen abstraction reactions are traditionally difficult. Thus, the Suarez group aimed to control the reaction course using polarity effects to favor 1,6 hydrogen abstraction products.[xiii] The results in **Table 3** show that varying the electron withdrawing character of the oxygen at the C-4

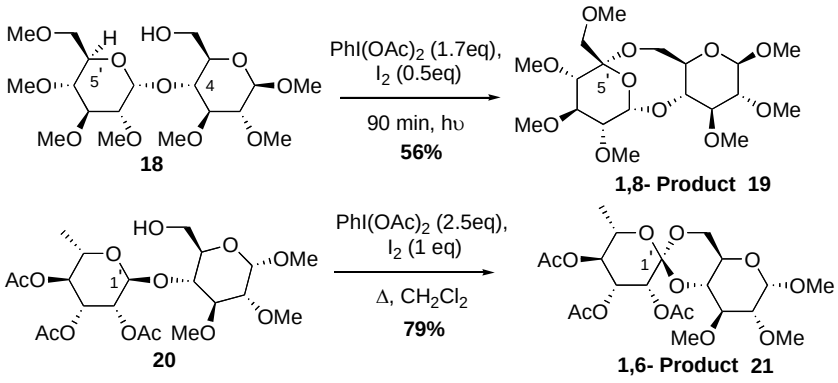
Table 3. The Polarity Effect: 1,6 Hydrogen Transfer Tuning.

Entry	Substrate	$PhI(OAc)_2$ (eq)	Time (h)	Products	Yield (%)
1		1.3	1.25		70
2		1.6	2.75		48

position greatly influences the reaction pathway. A withdrawing group at the C-4 position (**Entry 2**) forces the abstraction to occur from the less favored position (1,6- hydrogen abstraction), while electron donating or neutral positions at C-4 allow regioselective 1,5- hydrogen abstraction reactions exclusively (**Entry 1**).

Attempting to push the reaction further, the Suarez group looked at the formation of 1,8- HAT reactions in disaccharide models. It was reasoned that a compound with restricted conformational mobility could undergo hydrogen abstraction through a 9-membered transition state. The D-maltose analogue (**18**) was chosen because crystal structures showed that the reactive alkoxyl radical would be located at a favorable 2.5 Å from the hydrogen to be abstracted at C-5′. Treatment of compound **18** with $PhI(OAc)_2$ gave the 1,8- hydrogen abstraction product (**19**) as the only oxidized compound (**Scheme 5**).[xiv] It was later found that the stereochemistry of both saccharides played a crucial role in the 1,8- abstraction process. Other stereochemical analogues (**20**) gave exclusive 1,6- hydrogen abstraction products (**21**).[xv]

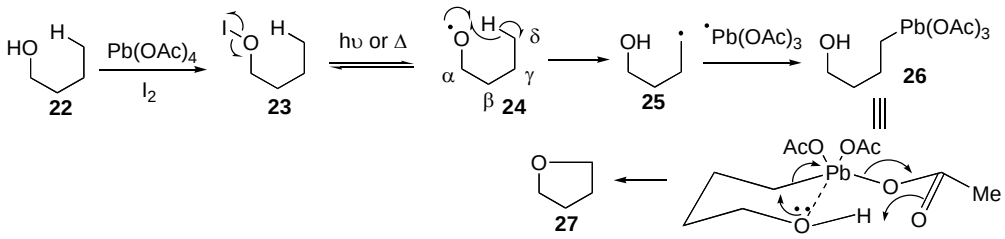
Scheme 5. 1,8 Hydrogen Transfer in Disaccharide Models.



Lead(IV) Tetraacetate (LTA) Promoted Radicals

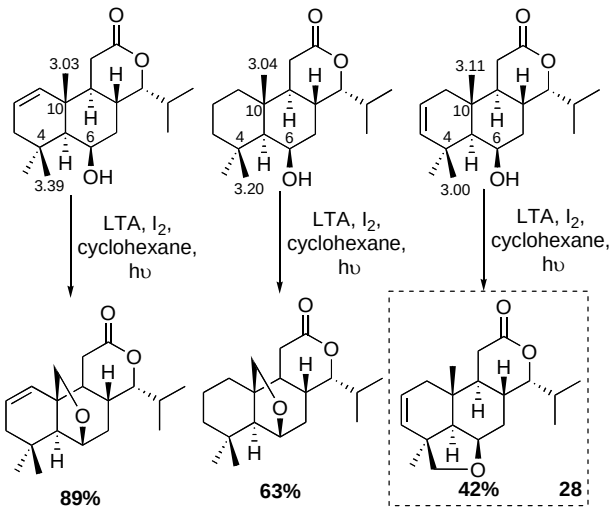
The use of lead tetraacetate and iodine is an extremely powerful method for the oxidative cyclization of alcohols to form tetrahydrofuran derivatives (**Scheme 6**). The mechanism is similar to $PhI(OAc)_2$ except the carbon radical (**25**) obtained from hydrogen abstraction is in a tight ion pair with the lead species (**26**). The tight radical pairing is one advantage of this

Scheme 6. General $Pb(OAc)_4$ Promoted Functionalization.



system over others. From the carbon-lead species, intramolecular ligand transfer and five-membered ring closure takes place (**27**).

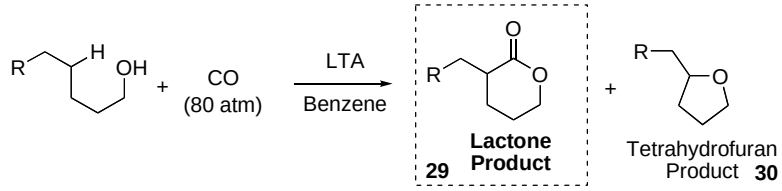
Scheme 7. Synthesis of Nagilactone F



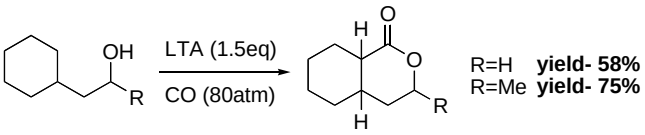
Much like the $PhI(OAc)_2$ promoted remote functionalizations, the $Pb(OAc)_4$ system has been most commonly applied to steroid and terpenoid structures to rigidify the reacting groups.[xvi] The total synthesis of Nagilactone F united the $Pb(OAc)_4$ promoted hydrogen abstraction method with computational analysis (**Scheme 7**). Studies showed that the distance of the methyl group for desired functionalization could be brought closer to the reacting alkoxyl radical by simply changing the double bond position. This allowed the formation of the desired oxidized product (**28**) and the completion of Nagilactone F.[xvii]

Despite the efforts of many research groups, the selective introduction of carbon monoxide into non-activated alkyl chains remained elusive for many years. Sonada and co-workers found a clever solution; they introduced a carbon radical via 1,5- hydrogen transfer with $Pb(OAc)_4$, and trapping it with CO, to form δ-lactones (**29**) after oxidative cyclization (**Scheme 8**).[xviii] The major hurdle in this process is to favor the carbonylation of the carbon radical rather than the normal mechanism with the carbon-lead radical pair to generate THF derivatives (**30**). The solution was using high levels of CO. Carbonylation occurs from both primary and secondary alcohols onto both

Scheme 8. Carbonylation via Hydrogen Transfer



Scheme 9. $Pb(OAc)_4$ Promoted Carbonylation.

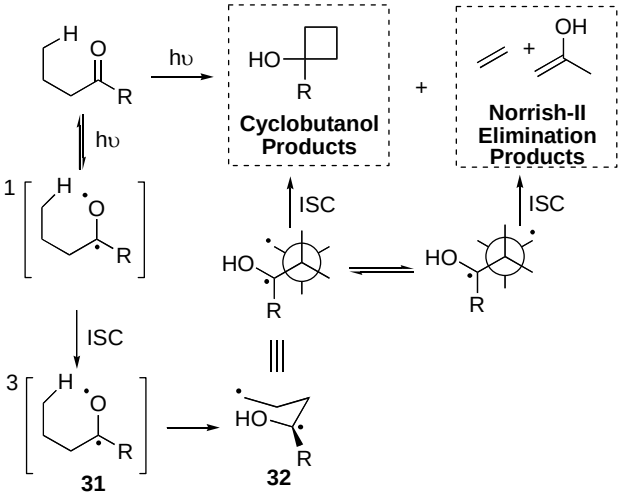


primary and secondary δ-carbons (**Scheme 9**). Secondary alcohols resulted in higher product yields than primary alcohols, due to lower levels of THF products.

NORRISH-YANG CYCLIZATION

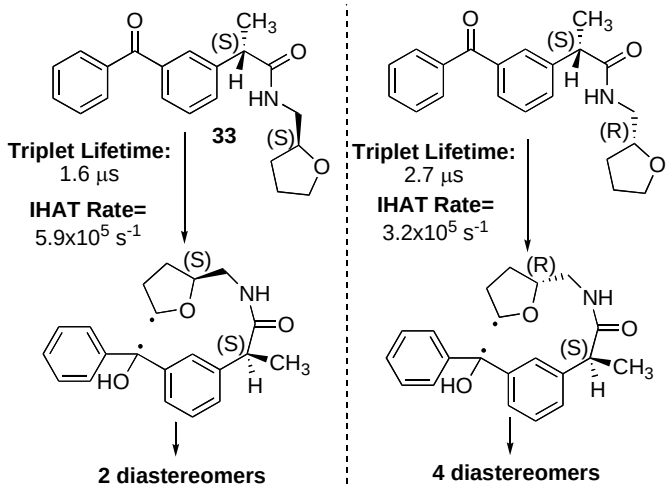
The Norrish-Yang cyclization involves the irradiation of a ketone to an excited triplet state (**31**, **Scheme 10**). The oxygen-centered radical can now abstract a hydrogen to produce a triplet biradical (**32**). The biradical can then undergo C-C bond forming radical recombination to produce cyclobutanols (in the case of 1,5- hydrogen abstraction reactions).[xix,xx,xxi,xxii,xxiii]

Scheme 10. General Norrish-II Yang Cyclization



A recent study of the remote functionalization process involved studying the triplet reactivity and the stereo/regioselectivity in the macrocyclization of diastereomeric ketoprofen conjugates (**Scheme 11**).[xxiv] The study found a remarkable diastereodifferentiation, expressed in the triplet lifetimes of the carbonyl chromophore. The diastereomer with the fastest hydrogen abstraction also exhibited the shortest triplet lifetime (**33**). This study is a good example of the subtle effects a minor stereochemical change can have on the rate/efficiency of hydrogen abstraction.

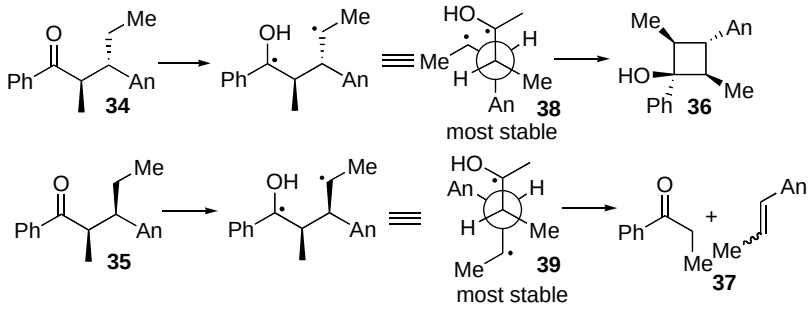
Scheme 11. Diastereodifferentiation in Ketoprofen Conjugates.



A recent publication by the Moorthy group showed another example of diastereo-differentiating photochemistry of β-

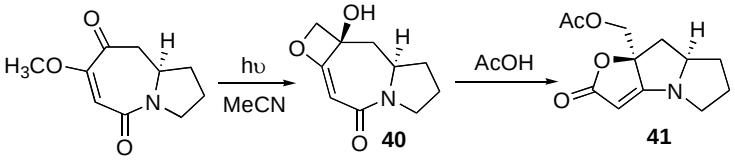
arylbutyrophenones (**Scheme 12**).[xxv] The diasteroemers of ketones **34** and **35** are shown to exhibit distinct photochemical reactivities due to conformational preferences; the anti isomer undergoes efficient yang cyclization to afford cyclobutanol **36** in high yield with remarkable diastereoselectivity. The syn isomer, on the other hand, resulted in only β-scission to produce Norrish type II elimination products (**37**). The divergent reaction pathways are presumed to result from the relative stabilities of the diastereomeric relationship between the two 1,4 triplet biradicals; the anti diastereomer favors a cisoid 1,4 triplet biradical (**38**) and thus undergoes yang cyclization whereas the syn diastereomer favors a transoid 1,4 triplet biradical (**39**). The diastereomeric discrimination in the product profiles of ketones **34** and **35** can both be linked to conformational differences as imposed by the different relative stereochemistry.

Scheme 12. Diastereoselective Norrish-Yang Cyclization.



A recent application of the Norrish-Yang cyclization was performed in the synthesis of aza-fused tricyclic lactones (**Scheme 13**). A Norrish-Yang cyclization followed by an acid catalyzed rearrangement of the cyclobutanol intermediate (**40**) resulted in the targeted aza-fused tricyclic core structure (**41**). [xxvi]

Scheme 13. Norrish-Yang Cyclization Strategy for Tricyclic Lactones.



CONCLUSION

The remote functionalization process offers a new tool for synthetic chemists that fundamentally differs from the classical introduction of functional groups. The transposition of functionality to remote, non-activated positions on organic molecules is a powerful disconnection. High site-selectivity is required for useful intramolecular hydrogen abstraction reactions. Several guidelines for selectivity have been established over the years involving transition state ring strain, bond dissociation energy, and polarity

effects. Following these guidelines, along with improved computational methods, will allow for more accurate selectivity predictions in the future. A major disadvantage of this method is the stereochemistry at the carbon radical position. Future directions for remote functionalization reactions will likely try to solve the stereochemical problems associated with long-lived free carbon radicals.

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