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Effect of Lewis acids and low temperature initiators on the allyl transfer reaction involving phthalimido-*N*-oxyl radical

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ABSTRACT

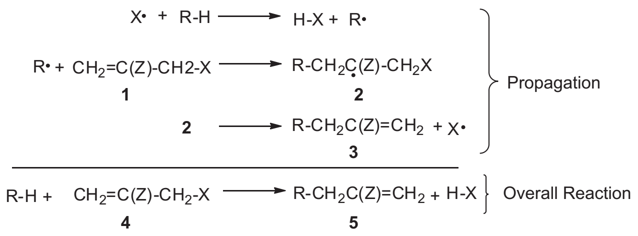
Previously, we reported allyl transfer reactions of allyl bromide and allyl phthalimido-*N*-oxyl substrates with hydrocarbons that result in C—C bond formation. In both cases, efficient chain transfer processes along with high reaction yields were observed. Since PINO· chemistry leads to an environmentally friendly method of hydrocarbon functionalization, additional studies were performed in order to improve the process. To expand the utility of this reaction, we carried out experiments to optimize reaction conditions and tested the effect of Lewis acids and low temperature initiators. Although allyl-PINO substrates reacted slightly slower than the bromides, the reactions were cleaner with little or no side products. The chain lengths for these reactions were compromised at lower temperatures, attributable to the high activation energy required for the hydrogen atom abstraction by PINO·. The addition of a Lewis acid catalyst ($AlCl_3$) improves the product yield and reaction rate, possibly due to the formation of a PINO·/$AlCl_3$ complex which lowers the activation energy for hydrogen abstraction step.

Introduction

A new free radical-based condensation reaction that achieves hydrocarbon functionalization and C—C bond formation in a single step was previously reported.[1–3] Utilizing an appropriately substituted allyl bromide or allyl phthalimido-*N*-oxyl (allyl-PINO) substrate as the key reactant, the net result of this transformation is the transfer of an allyl group to the hydrocarbon: $RH + CH_2{=}C(Z)CH_2X \rightarrow RCH_2C(Z){=}CH_2 + HX$ (X = Br, PINO). This allyl transfer reaction was especially fascinating because unlike other methods that effect this transformation, this functionalization was accomplished without the use of heavy metals such as tri-*n*-butyl tin hydride, distannanes, or alkyl mercuric halides,[4] which are often needed in radical-based synthetic methods. Similarly, strong acidic or basic reaction conditions which are needed in electrophilic or nucleophilic methods are not required. This method demonstrates that high chemical yields do not necessarily have to be compromised with the adoption of green chemical technologies.[5–7]

The mechanism of this reaction is depicted in Scheme 1. The chain carrier (X·) abstracts a hydrogen atom from hydrocarbon R–H such as toluene (which has a relatively weak, benzylic, C—H bond) generating an intermediate benzyl radical, R·. Addition of R· to the alkene of allyl substrate **1** generates a radical **2**, which undergoes subsequent β-cleavage to form the final product **3** and regenerates X·. Both Br· and PINO· proved particularly effective as X· in this reaction because they abstract a hydrogen atom from the benzylic position with high selectivity,[8,9] and the intermediate β-radicals readily undergo β-cleavage. Reaction yields and kinetic chain lengths (i.e., the rate of product formation relative to the rate of initiator disappearance) are both improved when the substituent Z was electron withdrawing, and the relative rates for radical addition were found to be 180 (Z = CN) > 110 (Z = CO_2R) > 65 (Z = Ph) >> 1 (Z = H) when X = Br.[2] This reactivity order parallels the relative rates of addition of $PhCH_2$ to substituted alkenes.[10]

More importantly, as a hydrogen atom abstractor, PINO· has been shown to be even less reactive and more selective than the bromine atom.[11] Allyl-PINO compounds **8** and **9** (Fig. 1) are excellent substrates for this chemistry (Scheme 2), offering several



Scheme 1. Propagation steps and overall allyl transfer reaction.

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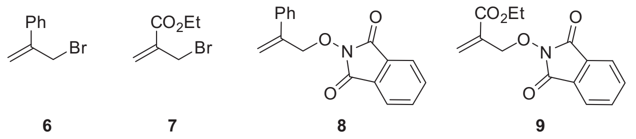
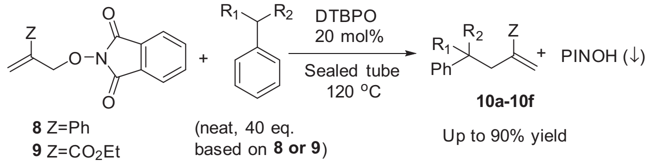


Figure 1. Substrates used for allyl transfer reaction.



Scheme 2. DTBPO (Di-*tert*-butyl peroxide) initiated reactions of allyl-PINO substrates (**8**,**9**) with benzylic hydrocarbons (For Z = Ph, **10a** $R_1 = R_2 = H$; **10b**- $R_1 = H$, $R_2 = CH_3$, **10c** $R_1 = R_2 = CH_3$, For $Z = CO_2Et$, **10d**- $R_1 = R_2 = H$; **10e**- $R_1 = H$, $R_2 = CH_3$, **10f** $R_1 = R_2 = CH_3$).

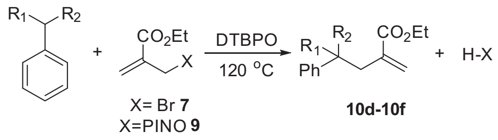
advantages over the corresponding allyl bromides.[3] This paper discusses our efforts to lower the temperature of this reaction and the results provide insight into the issues related to the propagation step/s (e.g., a hydrogen abstraction by PINO$^\cdot$ etc.) in the allyl transfer process.

Comparison of allyl bromides and allyl-PINO substrates

To confirm whether the replacement of PINO$^\cdot$ with Br$^\cdot$ leads to cleaner and more efficient reactions, reactions of allyl bromide and allyl-PINO substrate with hydrocarbons were studied. Results are summarized in Table 1. For each of these experiments, the reaction conditions were identical with regard to time, temperature, etc. High mass balances were observed for the reactions of **7** and **9** with hydrocarbons. Overall, the reactions utilizing the allyl-PINO substrates were considerably cleaner than the analogous reactions with allyl bromides. Although allyl bromides tended to react faster under comparable conditions, the mass balances were lower and undesirable side-products were formed.

To probe this further, kinetic chain lengths (i.e., the rate of product formation relative to the rate of initiator disappearance, $-(\partial[\text{product}]/\partial t)/(2\partial[\text{DTBPO}]/\partial t)$)[12] were determined by following product yields as a function of time for $Z = CO_2Et$. Although the initial chain lengths for the allyl-PINO compounds were consistently lower than for the allyl bromides, the reduced chain lengths for the allyl-PINO substrates do not have a deleterious effect on the product yields or mass balance of the reaction. These results and others (vide infra) lead to the suspicion that for X = PINO, the hydrogen abstraction or β-fragmentation step may not be as efficient as is the case for X = Br.

Table 1
Comparison: Reactions of allyl-PINO and allyl bromide substrates with hydrocarbons



Entry	R_1	R_2	X = Br			X = PINO		
			% **7**	% **10d–f**	Mass balance (%)	% **9**	% **10d–f**	Mass balance (%)
1[a]	H	H	0	35	35	21	48	69
2[b]	H	CH_3	0	70	70	44	56	100
3[b]	CH_3	CH_3	41	36	77	75	20	95

Reactions performed at 120 °C using 20 mol % DTBPO (di-*tert*-butyl peroxide) in neat hydrocarbons. %Mass balance = %**9** or **7** + %**11**.

[a] Reaction time 42 h.

[b] Reaction time 3 h (Hydrocarbon: 6.0 M, **7** or **9**: 0.15 M, DTBPO 0.03 M), ($Z = CO_2Et$, **10d** $R_1 = R_2 = H$, **10e** $R_1 = H$, $R_2 = CH_3$, **10f** $R_1 = R_2 = CH_3$).

As noted, one of advantages of using di-*tert*-butyl peroxide (DTBPO) as an initiator was that *tert*-butoxyl radical does not readily add to double bonds and is an excellent hydrogen atom abstractor. On the other hand, the drawback is the high temperature (120 °C) required for initiation which does not allow exploring regio- and stereoselectivity. To address this issue, initiators which work effectively at low temperatures such as triethylborane and di-*tert*-butylhyponitrite (DTBHN) were considered for allyl transfer reactions at low temperatures.

Low temperature reactions using triethylborane/O_2 (TEB)

The primary goal behind performing the allyl transfer reaction at low temperature was to investigate the regio- and stereoselectivity of the radical addition step. As observed in various cases, stereoselectivity depends directly on the temperature of the reaction and is generally found to be enhanced at lower temperatures.[13–16] In case of allyl transfer processes, low reaction temperatures might provide an opportunity to achieve an enantioselective radical addition if a prochiral radical or chiral auxiliary on the electrophile is used,[17,18] but the biggest challenge for the radical processes at low temperatures is finding an initiator which works efficiently at those temperatures. There are a few reported initiators like triethylborane/O_2[19] and dimethylzinc/O_2[20] which have been successfully used at very low temperatures. Triethylborane (a precursor of Et$^\cdot$ and/or EtOO$^\cdot$) was selected for allyl transfer reactions at low temperature owing to its established use in free radical reactions at low temperatures.[19,21–25]

In this section, we discuss the reactions of allyl-PINO substrates with hydrocarbons using triethylborane/O_2 as an initiator. Allyl-PINO substrates **8** and **9** and allyl-bromide substrate **6** were allowed to react with neat toluene, ethyl benzene, and cumene in the presence of triethylborane.

The low temperature reactions were first performed with allyl-bromide substrate **6** and hydrocarbons at varying concentrations of initiator and reaction temperature (Table 2). The reaction of toluene with **6** (entry 1) using 20 mol % of initiator at 0 °C led to no formation of product **10b**. Increasing the temperature of this reaction to room temperature led to a negligible 1% product formation (entry 2). Similarly, gradually increasing the concentration of initiator and reaction temperature (entries 2–4) led to a slight improvement in product yield (up to 10%). Finally, increasing the reaction temperature to 80 °C led to a respectable yield of product (entry 5). Use of ethyl benzene and cumene (entries 6 and 7) showed similar results, which led to the conclusion that a respectable product yield could only occur at high temperatures (80 °C).

The data in Table 3 show results of reactions of the allyl-PINO substrates **8** and **9** with hydrocarbons. However, even in this case, no product formation was observed at −78 °C, 0 °C or room temperature. Similar to the results in Table 2, a significant increase in product yields was observed only at high temperatures.

Since Et_3B/O_2 generates an Et$^\cdot$ and EtOO$^\cdot$,[25,26] it was conceivable that the mediocre results obtained with this initiator were because of the possibilities; (1) either Et$^\cdot$ and/or EtOO$^\cdot$ does not abstract a hydrogen (or add to the double bond) at the rate sufficient enough to efficiently initiate the reaction, (2) hydrogen atom abstraction by PINO$^\cdot$ is very slow at low temperature, or (3) the radical addition step is slow at low temperature. Based on the hypothesis that a Lewis acid could be used to activate the substrate (especially **9**)