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C–H Bond Functionalization with the Formation of a C–C Bond: A Free Radical Condensation Reaction Based on the Phthalimido-*N*-oxyl Radical

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The development of a new chemical process that effects the conversion RH + C=C–C–X → R–C–C=C + HX, in which X is the phthalimido-*N*-oxyl radical (PINO·), is reported. The reaction yields are high, mass balances are excellent, and C–H bond functionalization and C–C bond formation are achieved in a single transformation. The byproduct of the reaction, *N*-hydroxyphthalimide, precipitates from solution and can be easily removed by simple filtration (and recycled). The kinetic chain lengths are shorter and the reaction times are longer (relative to those of the analogous reactions of allyl bromides), most likely because PINO· is a less-reactive hydrogen-atom abstractor. There appears to be no significant difference in efficiency in the addition–elimination steps. Competition experiments reveal that Br· and PINO· are comparable in leaving group ability.

Introduction

C–H bond functionalization catalyzed by *N*-hydroxyphthalimide has received a great deal of attention in the past decade as a simple, environmentally benign method to oxidize organic compounds.[1] The key player in this chemistry is the phthalimido-*N*-oxyl radical (PINO·, **1**), which serves as a hydrogen-atom abstractor in these systems.[2] PINO· is more reactive than dialkyl nitroxyl radicals such as 2,2,6,6-tetramethylpiperidine *N*-oxide (TEMPO), because the lone pair of electrons on the nitrogen atom is tied up in resonance with the carbonyl groups, and this diminishes the contribution of resonance form **2** (Figure 1) and effectively localizes the spin density on the oxygen atom.[3]

As a hydrogen-atom abstractor, PINO· exhibits low reactivity and high selectivity. For example, the relative reactivity of the benzylic C–H bonds of cumene, ethyl benzene, and toluene towards PINO· are 3° (26) > 2° (9) > 1° (1) on a per hydrogen basis.[4] These values are remarkably similar to the relative reactivity trend of these substrates towards Br·: 3° (59) > 2° (25) > 1° (1).[5] It was this similarity to Br· that led us to wonder whether the chemistry of PINO· could be extended in such a way to achieve C–H bond functionalization and C–C bond formation in a single chemical process.

Carbon-centered radicals, typically generated from organic halides or organometallic compounds, can be allylated by using allyl compounds with suitable homolytic leaving groups (halogen, SnR_3, SiR_3, SR, etc.) through an addition–elimination process.[6] (These and related allyl compounds are also useful as chain-transfer agents in free radical polymerizations.)[7] In small molecule synthesis, there has been particular interest, and success, in developing synthetically useful radical-based allyl transfer reactions that do not involve toxic metals such as tin and mercury.[6c,8]

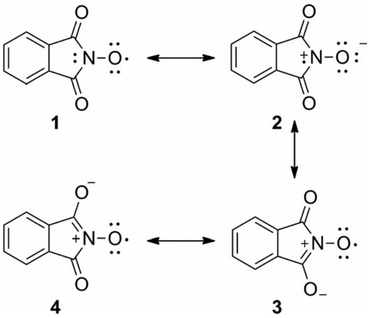

Figure 1. Some of the resonance contributors in the phthalimido-*N*-oxyl radical.

In 1999, we reported a bromine atom based method that achieves hydrocarbon functionalization and allyl transfer in a single step: R–H + $CH_2{=}C(Z)CH_2Br \rightarrow RCH_2C(Z){=}CH_2$ + HBr.[9] The mechanism for this reaction is summarized in Scheme 1 (X = Br). The bromine atom abstracts a hydrogen atom from a hydrocarbon such as toluene (which has relatively weak, benzylic C–H bonds) to generate an intermediate benzyl radical R·. Addition of R· to the alkene generates β-bromo radical **5**, which undergoes β-cleavage to form the final product with the regeneration of X·. The bromine atom is the key to this reaction, because Br· is sufficiently reactive that it can abstract a hydrogen atom with high

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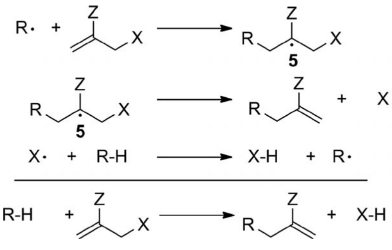
selectivity yet sufficiently stable that β-bromo radicals readily undergo fragmentation. This balance is not achieved with other halogen atoms: Cl˙ and F˙ are not selective in H-atom abstractions; I˙ is a good leaving group for β-fragmentation, but it does not abstract hydrogen at a reasonable rate. Consequently, because of the parallels between Br˙ and PINO˙, it seemed possible that a similar allyl transfer reaction could be developed on the basis of PINO˙ chemistry, if PINO˙ was a suitable leaving group for β-cleavage.



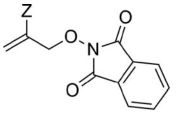
Scheme 1. Propagation steps in the allyl transfer reaction.

Results and Discussion

In this manuscript, we report a newly developed free radical reaction that achieves all of these objectives, C–H bond functionalization and C–C bond formation in a single reaction on the basis of PINO˙ chemistry through a process that proceeds by the same mechanism as that shown in Scheme 1. This chemistry is compared and contrasted to the analogous chemistry of Br˙ in terms of reaction yields, mass balance, kinetic chain lengths, and leaving group effects (Br˙ vs. PINO˙).

Generally, the "allyl-PINO" compounds that would be needed as substrates for this new reaction would be synthesized directly through the condensation of *N*-hydroxyphthalimide with the corresponding allyl alcohols.[10] For our work, however, we elected to synthesize the allyl-PINO substrates from the corresponding allyl bromides, because the latter were also needed for comparison purposes in this study. (Many of the allyl bromides are hygroscopic and thus more difficult to handle.)

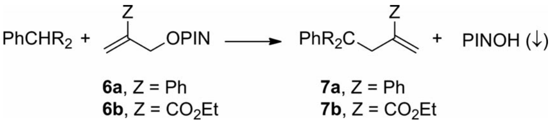
Allyl-PINO compounds **6a** and **6b** (Figure 2) were prepared by following modified literature procedures[11] and allowed to react with toluene, ethyl benzene, and cumene under standard conditions (Table 1). Optimized product yields ranged from 50 to 90%, and as the high mass balances show, the reactions were exceptionally clean. Moreover, the obligatory reaction byproduct, *N*-hydroxyphthalimide (PINOH), precipitated from solution and could be easily separated by filtration at the end of the reaction. (In contrast, the Br-based reaction produces HBr as a byproduct and requires the use of a base or epoxide as a scavenger.)



6a: Z = Ph
6b: Z = CO_2Et

Figure 2. Substituted allyl-PINO substrates.

Table 1. Results for the reactions of **6a** and **6b** with hydrocarbons.[a]

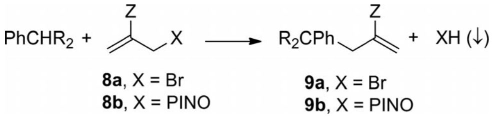


$PhCHR_2$[b]	Z	Time [h]	% **7a** or **7b**	% **6a** or **6b**
$PhCH_3$	Ph	24	77	23
$PhCH_3$	CO_2Et	42	48, 43[c]	21, 30[c]
$PhCH_2CH_3$	Ph	29	89	9
$PhCH_2CH_3$	CO_2Et	17	85	7
$PhCH(CH_3)_2$	Ph	29	76	22
$PhCH(CH_3)_2$	CO_2Et	24	91	9

[a] Reactions performed at 120 °C by using di-*tert*-butyl peroxide (DTBPO, 20 mol-%) as the initiator. [b] Neat. [c] Time: 24 h.

Overall, the reactions utilizing the allyl-PINO substrates were considerably cleaner than the analogous reactions with allyl bromides. This is illustrated by the results summarized in Table 2. For each of these experiments, the reaction conditions were identical with regard to time, temperature, and so on; the difference was the use of an allyl bromide versus an allyl-PINO substrate. Although the allyl bromides tended to react faster under comparable conditions, the mass balances were lower and undesirable side products were formed.

Table 2. Comparison of the reactions of allyl bromides and allyl-PINO substrates with hydrocarbons.[a]



X = Br				X = PINO		
$PhCHR_2$	% **8a**	% **9a**	Mass balance [%]	% **8b**	% **9b**	Mass balance [%]
$PhCH_3$[b]	0	35	35	21	48	69
$PhCH_2CH_3$[c]	0	70	70	44	56	100
$PhCH(CH_3)_2$[c]	41	36	77	75	20	95

[a] Reactions performed at 120 °C by using DTBPO (20 mol-%) as the initiator in neat hydrocarbons. [b] Reaction time: 42 h. [c] Reaction time: 3 h.

To probe this chemistry further, kinetic chain lengths {i.e., the rate of product formation relative to the rate of initiator disappearance, $-(\partial[\text{product}]/\partial t)/(2\partial[\text{In}_2]/\partial t)$} were determined by following product yields as a function of time for Z = CO_2Et as described previously.[9a] The initial chain lengths for the allyl-PINO compounds were consistently lower than those for the allyl bromides (Table 3), although the reduced chain lengths for the allyl-PINO substrates did not have a deleterious effect on either the product yield or mass balance for the reaction. The longer reaction times and shorter kinetic chain lengths suggest that for X = PINO, one of the propagation steps (hydrogen abstraction, addition, or β-fragmentation) may not be as efficient as is the case for X = Br.

Table 3. Kinetic chain lengths for the reactions of hydrocarbons with $CH_2=C(CO_2Et)CH_2X$ (X = Br, PINO).[a]

X	$PhCH_3$	$PhCH_2CH_3$	$PhCH(CH_3)_2$
Br[b]	800	–	60
PINO[c]	270	130	12

[a] Reactions performed at 120 °C by using DTBPO (20 mol-%) as initiator and neat hydrocarbon. [b] Ref.[7] [c] Current work with same initiator loading.

Given that the elimination of PINO· by β-cleavage was unprecedented, experiments were designed to determine the relative leaving group ability of Br versus PINO. In principle, this could be achieved through competition experiments by pitting an allyl bromide versus an allyl-PINO for the benzyl radical (Figure 3). As both substrates would produce the same organic product if $Z^1 = Z^2$, indirect competition experiments were undertaken by using various Z^1, Z^2, and leaving group combinations. The results are summarized in Table 4.

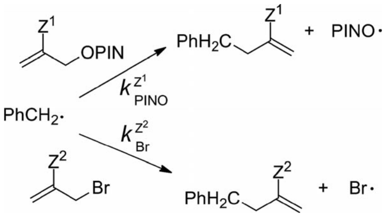


Figure 3. Competition experiment for the determination of rate constants for the addition–elimination process in the allyl transfer reaction. In any given competition $Z^1 \neq Z^2$.

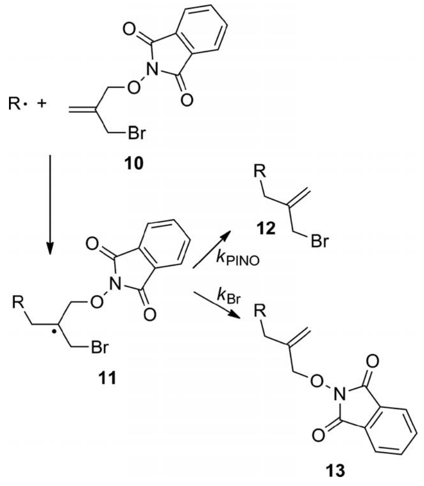
From the data in Table 4, the relative rate constants for the addition–elimination of benzyl radical $CH_2=C(Z)CH_2X$ for the same Z substituent could be derived (last three entries in Table 4). The relative rate constants for the allyl bromides were only slightly higher than those for the allyl-PINOs. Notably, the relative rate constants are for addition–elimination, and it is not known which of these steps is rate limiting. Rather than differences in leaving group ability, it may be that the allyl bromides are slightly more reactive towards addition. Nonetheless, the results do not suggest any major differences in reactivity between allyl-PINOs and allyl bromides in the addition–elimination sequence that leads to product formation.

To address the intrinsic relative leaving group ability of Br· versus PINO· directly, compound **10** (Scheme 2), which incorporates both leaving groups into a single substrate, was synthesized. The reaction of **10** with toluene (initiated with DTBPO and conducted to low percent conversion to avoid further reaction of the products) allowed the leaving group abilities of PINO and Br to be directly determined: $k_{PINO}/k_{Br} = 3\ (\pm 1)$.

Table 4. Relative rate constants for the reaction of $PhCH_2^{\cdot}$ with various allyl bromides and allyl-PINOs.

Rate constant ratio	Related rate constant
$k_{Br}^{CO_2Et}/k_{PINO}^{Ph}$	3.40 (0.03)[a]
$k_{Br}^{Ph}/k_{PINO}^{CO_2Et}$	1.20 (0.01)[a]
$k_{Br}^{CO_2Et}/k_{PINO}^{CN}$	2.60 (0.02)[a]
$k_{Br}^{CN}/k_{PINO}^{CO_2Et}$	1.10 (0.01)[a]
$k_{Br}^{CN}/k_{PINO}^{Ph}$	2.70 (0.02)[a]
$k_{Br}^{Ph}/k_{PINO}^{CN}$	2.30 (0.05)[a]
$k_{Br}^{CO_2Et}/k_{PINO}^{CO_2Et}$	1.1 (0.3)[b]
$k_{Br}^{Ph}/k_{PINO}^{Ph}$	3.6 (1.5)[b]
$k_{Br}^{CN}/k_{PINO}^{CN}$	2.5 (1.0)[b]

[a] Measured directly. [b] Calculated from other rate constant ratios in this table.



Scheme 2. Experiment for relative leaving group abilities of PINO· versus Br·.

The data in Table 4 also provide information about the relative rate of the reaction of the benzyl radical with the allyl-PINO substrate as a function of Z: CO_2Et (3.0) > CN (1.3) > Ph (1). These are comparable to allyl bromides: CN (2.8) > CO_2Et (1.6) > Ph (1.0). As noted in our earlier work, these trends parallel rates of addition of $PhCH_2^{\cdot}$ to alkenes,[12] which suggests the ordering reflects relative rates of addition. In total, the results suggest that (1) PINO is a slightly better leaving group than Br and (2) the allyl bromides are slightly more reactive towards radical addition. (One possibility that explains this is that the β-bromo alkyl radicals are stabilized by β-bridging interactions).[13] However, these differences appear minor and for the most part inconsequential.

It therefore seems most likely that the differences in reaction times and chain lengths for the allyl-PINOs versus allyl bromides are attributable to the hydrogen-atom abstraction step. The absolute rate constant for hydrogen abstraction from toluene by Br is $10^{5}\ \mathrm{M}^{-1}\,\mathrm{s}^{-1}$.[5] In contrast, for PINO, the absolute rate constant is several orders of magnitude lower, $0.38\ \mathrm{M}^{-1}\,\mathrm{s}^{-1}$.[4]

Conclusions

In summary, the results reported herein demonstrate that allyl-PINO compounds are excellent substrates for the free radical based allylation of hydrocarbons; this allows C–H functionalization and C–C bond formation to be achieved in a single reaction through the mechanism outlined in Scheme 1. The reaction yields are high and the mass balances are excellent. Compared to allyl bromides, allyl-PINO compounds are much easier to handle. Moreover, the byproduct of the reaction, *N*-hydroxyphthalimide, precipitates from solution and can be easily removed by simple filtration (and recycled). Chain lengths are shorter and reaction times are longer (relative to those of the analogous reactions of allyl bromides), most likely because PINO is a less-reactive hydrogen-atom abstractor. There appears to be no significant difference in efficiency of the addition–elimination steps.

Supporting Information (see footnote on the first page of this article): Experimental details, characterization data, and copies of the ^{1}H NMR and ^{13}C NMR spectra of all key intermediates and final products.

Acknowledgments

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