

RESEARCH ARTICLE

View Article Online

View Journal | View Issue



Cite this: *Org. Chem. Front.*, 2019, **6**, 1796

Radical addition of ketones and cyanide to olefins via acid catalyzed formation of intermediate alkenyl peroxides†

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A Brønsted acid catalyzed method was developed for the synthesis of γ -cyanoketones from sulfonyl cyanides, olefins and ketones. The reaction is believed to proceed *via* intermediate formation of alkenyl peroxides by condensation of ketones with *tert*-butylhydroperoxide. These unstable compounds decompose by homolytic O–O bond cleavage, generating ketone-derived radicals which add to the olefins and generate the final products after reaction with the sulfonyl cyanide, thereby forming two new C–C bonds. A range of different ketones and olefins can be used, including steroidal ketones and simple alkyl olefins. The products can be further transformed to substituted lactones and piperidines, including a tetracyclic one. This reaction can thus be utilized to gain access to complex molecules from simple starting materials in only a few synthetic steps.

Received 28th March 2019,
Accepted 17th April 2019

DOI: 10.1039/c9qo00447e

rsc.li/frontiers-organic

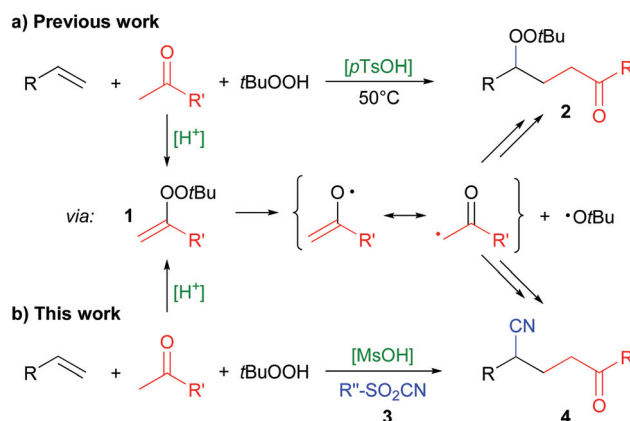
Introduction

Radical addition reactions enable the double functionalization of olefins with heteroatom- and carbon-residues, thus much effort is put into their development.¹ We have recently developed a method for the acid-catalyzed generation of radicals from ketones and hydroperoxides *via* the intermediate formation of alkenyl peroxides **1** (Scheme 1a).² Alkenyl peroxides are highly unstable and can generally not be isolated at ambient temperature.³ Using this strategy, simple ketones can be utilized in radical reactions, for example towards the synthesis of γ -peroxyketones **2**^{2a} and heterocycles.⁴

The generation of radicals in the α -position of ketones can be achieved by alternative means,⁵ but often it is only effective with 1,3-dicarbonyl compounds,⁶ at temperatures above 100 °C,⁷ with α -bromo-ketones as substrates⁸ and larger amounts of metal reagents,⁹ respectively. Their formation *via* alkenyl peroxides (**1**) by condensation with hydroperoxides, on the other hand, is particularly effective with plain ketones and only requires simple acids as catalysts. We were thus interested to extend the radical addition of ketones *via* this mechanism

to the twofold addition of carbon-radicals instead of the carboxypoxidation as in the synthesis of **2**. Here, we report our results of the addition of ketones and cyanide to olefins (Scheme 1b).

We tested a variety of additional reagents to introduce a carbon residue instead of the peroxide group, but the peroxyketones **2** were always formed as major products. Overriding this preference was finally possible by employing sulfonyl cyanides **3** which led to formation of cyanoketones **4**. Sulfonyl cyanides are well-known reagents for the transfer of a cyano group to carbon-radicals.¹⁰ For example, the Landais group used *para*-toluenesulfonic cyanide (*p*TsCN, **3a**) in the radical



Scheme 1 Radical addition reactions *via* intermediate alkenyl peroxides (**1**) formed by acid catalysis.

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†Electronic supplementary information (ESI) available: Detailed experimental and computational results. CCDC 1878410. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c9qo00447e

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addition of ester, thioester or amide residues to olefins, requiring the use of stoichiometric organometallic reagents and pre-functionalized substrates, respectively.^{10g-i} Radical trifluoromethylation with hypervalent iodine reagents together with cyanation has been reported by several groups.¹¹ The groups of Liu and Zhu reported an intramolecular CN-transfer after radical addition, requiring special olefin substrates.¹² The strategy of an intramolecular CN-transfer had previously been employed by the groups of Kalvoda, Watt and Nikishin to synthesize γ -cyanoketones.¹³ However, the yield in those reactions was typically rather low. Zhu *et al.* also described such products *via* a radical ring-opening reaction of cyclobutanols in the presence of *p*TsCN.^{10f}

γ -Cyanoketones can also be prepared in a single step by conjugate addition reactions of ketones to vinyl nitriles and of nitriles to enones, respectively, generally requiring strong bases or complex catalysts.¹⁴ Applying chiral catalysts, this can allow the stereoselective synthesis of the products, but at the same time requiring nitriles with electron-withdrawing groups in the α -position.¹⁵

The method we have developed could be complementary to those known cases. It uses readily available ketones and olefins and can be catalyzed by simple Brønsted acids. Directly adding ketone and cyanide radicals to an olefin could also allow the synthesis of γ -cyanoketones not easily accessible by the aforementioned methods.

Results and discussion

During the optimization of the method, we screened many different conditions, *e.g.* solvents, acids, cyanide reagents and concentrations. Full details can be found in the ESI,[†] and exemplary results are shown in Table 1. The desired product **4aa** was formed in good yields from *p*TsCN (**3a**), styrene (**5a**) and acetone (**6a**) in polar aprotic solvents (entries 1–3). Slightly better results were achieved when using ethyl- or methyl-

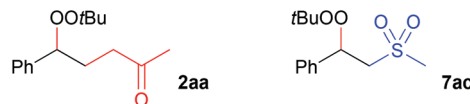


Fig. 1 Characterized byproducts of the reaction.

sulfonyl cyanides **3b** and **3c** (entries 4 and 5),[§] which can easily be synthesized by oxidation of the thiocyanates.^{10h} We achieved the best results with **3c** in dichloromethane (entry 5).

In those reactions, two byproducts could be characterized (Fig. 1). Peroxyketone **2aa** – the product formed in the absence of sulfonyl cyanides^{2a} – was found in low amounts of up to 10% only. Peroxy-sulfone¹⁶ **7ac** was formed in comparable, but generally lower yields than cyanoketone **4aa**. In order to achieve good yields of the desired products, the olefin therefore has to be used in excess. Generally, sulfones **7** can easily be separated from nitriles **4** by column chromatography.

Using the conditions as of Table 1, entry 5, we investigated this method in the reactions of different ketones with styrene (Scheme 2). Simple open-chain and cyclic alkyl ketones gave the expected products **4aa–4ag**. With methyl isopropyl ketone, the new bond was exclusively formed at the methyl group (**4ab**). Methyl aryl ketones afforded products **4ah–4al** in similar yields. The successful utilization of phenolic ketone **6l** in the synthesis of **4al** is interesting, as many phenols are known as radical inhibitors. Two steroids, epiandrosterone **6m** and pregnenolone **6n** could be used as ketone component, giving the products **4am** and **4an**. The presence of a free hydroxyl group and an olefin in the ketone **6n** did not hamper the yield significantly, as **4an** was formed in a relatively good yield of 43%.

With pinacolone (**6c**) as a model ketone, we also tested the reaction with a variety of different aryl olefins (Scheme 3). A range of products **4bc–4nc** with different aryl-substituents were formed in mostly good yields above 50%, with the exception of the strongly electron-withdrawing and -donating substituents CF₃, CN and OMe (**4fc–4hc**). A methyl substituent in the *ortho*-position also gave a good yield of 60% of **4lc**, but the *ortho*-bromide product **4nc** gave a lower yield. Using indene (**5q**) as olefin gave the products **4qc** and **4qe** (using cyclohexanone) in good yields, which are remarkable for their high *trans*-selectivity. For **4qc**, a diastereomeric ratio of >19 : 1 was determined in the crude reaction mixture, but after purification, we received the pure *trans*-product. In the case of **4qe**, two diastereomers were isolated which differ in the configuration at the α -position of the cyclohexanone residue.

We also investigated the reaction between acetone or pinacolone and non-aryl olefins which on average gave lower yields than with styrene derivatives (Scheme 4). This is possibly due to the nature of the ketone-derived radicals, as this had also been observed during the synthesis of γ -peroxyketones.^{2a} Noteworthy exceptions were the use of 1-octene (**8b**) and 6-cyano-1-hexene (**8e**), providing yields above 50%. A natural product, limonene

Table 1 Effect of reagents on the reaction outcome^a

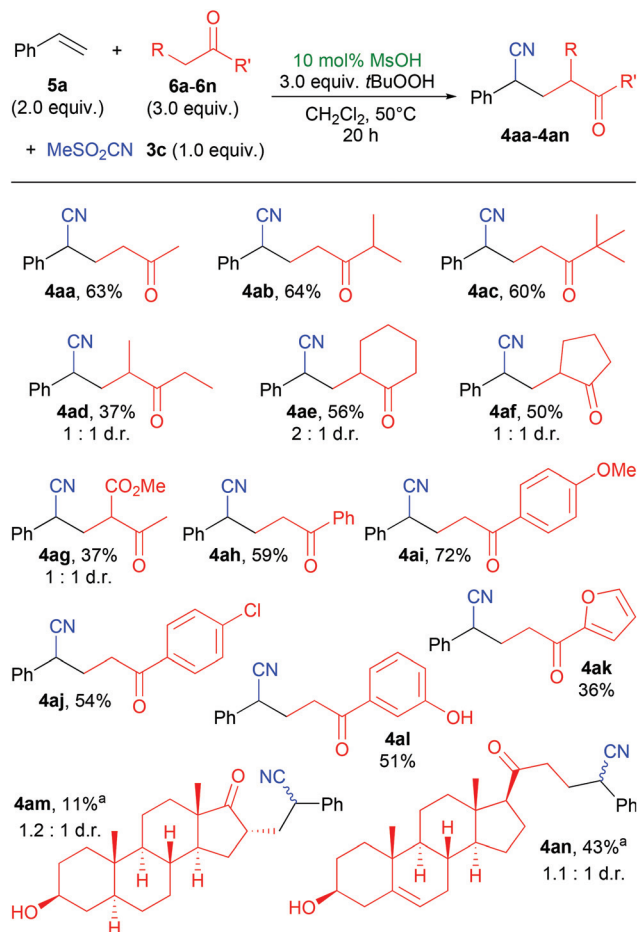
Entry	R (3)	Solvent	Yield ^b /%
1	<i>p</i> Tol (3a)	EtOAc	60
2	<i>p</i> Tol (3a)	CHCl ₃	48
3	<i>p</i> Tol (3a)	CH ₂ Cl ₂	61
4	Et (3b)	CH ₂ Cl ₂	64
5	Me (3c)	CH ₂ Cl ₂	69 (63) ^c

^a Screening reactions were typically performed with 0.5 mmol **5a**, 1.25 mmol **6a**, 0.25 mmol **3**, 1.0 mmol *t*BuOOH and 0.025 mmol acid in 0.2–1.0 ml solvent under an argon atmosphere at 50 °C.

^b Determined by ¹H-NMR. ^c Isolated yield, reaction at a scale of 0.5 mmol **3**, 1.5 mmol **6a**, 1.5 mmol *t*BuOOH and 1.0 ml of CH₂Cl₂.

[§] The superiority of MsCN (**3c**) over *p*TsCN (**3a**) had already been noted before, see ref. 10c.



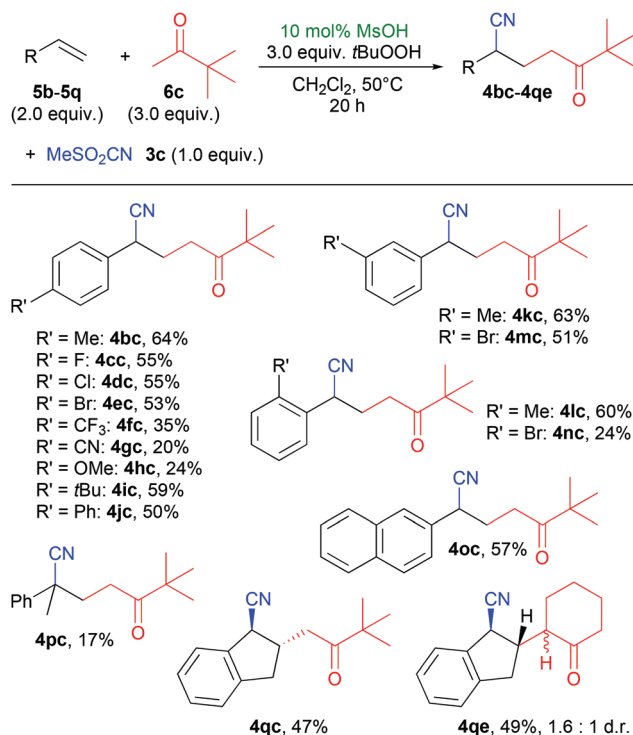


Scheme 2 Radical addition utilizing different ketones. ^a Using 1.5 equivalents of ketone.

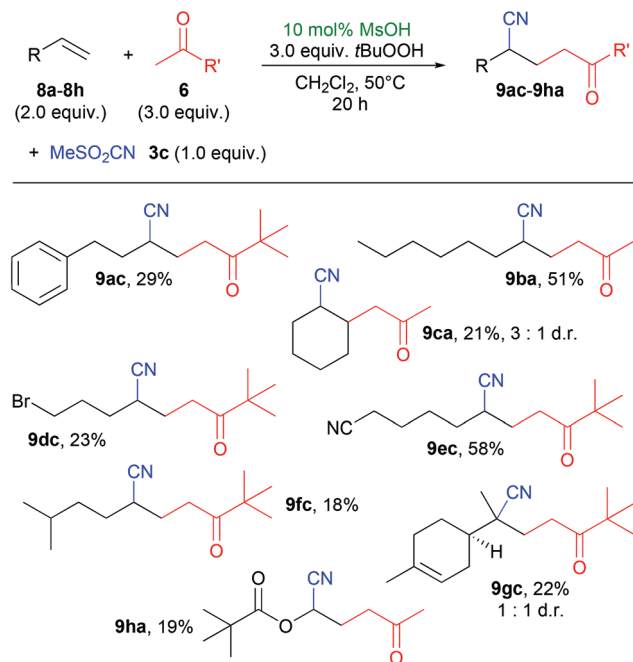
(8g) could be used as olefin component, albeit with only a rather low yield of 22% of product 9gc. Interestingly, in the reactions with these olefins, the sulfonyl peroxide byproducts 7 were observed in traces only and could not be isolated.

Cyanoketones have previously been utilized as valuable synthetic intermediates that can be converted to lactones and piperidines, respectively, by reduction and subsequent cyclization.^{14a,15c-e,17} We have also applied these strategies to selected products, without purification after the first step (Scheme 5). A substituted δ -valerolactone 10 was formed from product 4aa in a 1 : 1 mixture of diastereomers. Reduction of the nitrile group by hydrogenation in the presence of RANEY® Nickel and subsequent protection with a Boc-group gave piperidines 11 and 12 from cyanoketones 4ai and 4qe, respectively.

Interestingly, the major diastereomer of 11 was found to obtain a solution conformation with both aryl groups in axial position, as shown in Scheme 5 (determined by NMR coupling constants and an NOESY experiment, see the ESI† for details). This at first surprising result was supported by DFT calculations:¹⁸ this conformation was indeed found to be more stable than the one with both aryl groups in equatorial position by 3.3 kJ mol⁻¹ and also more stable than alternative boat



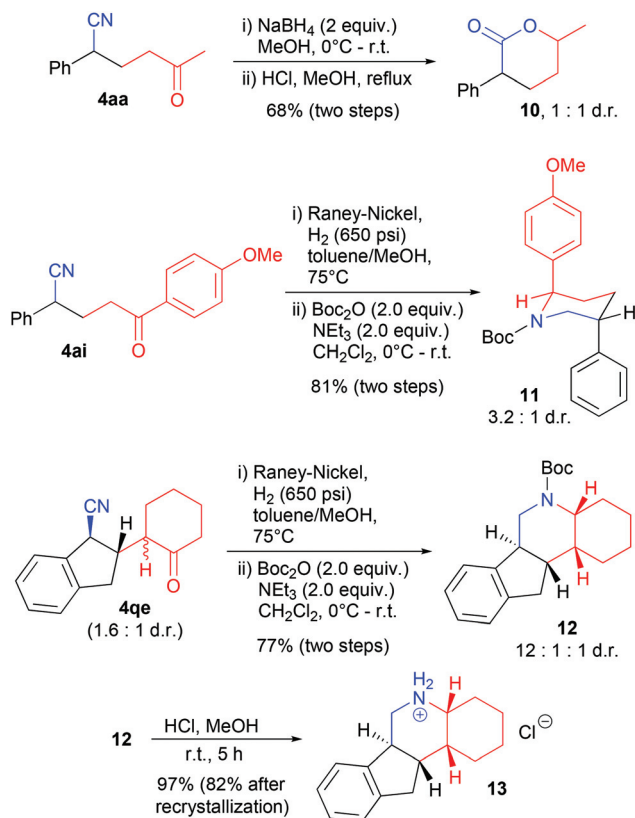
Scheme 3 Radical addition utilizing different aryl olefins.



Scheme 4 Radical addition utilizing other olefins.

conformations. This results presumably from the avoidance of steric repulsion between the *p*-methoxyphenyl and the Boc group¹⁹ and from a favorable orbital interaction between the nitrogen lone pair and the σ^* -bond of the C-aryl bond (see the ESI† for further details).

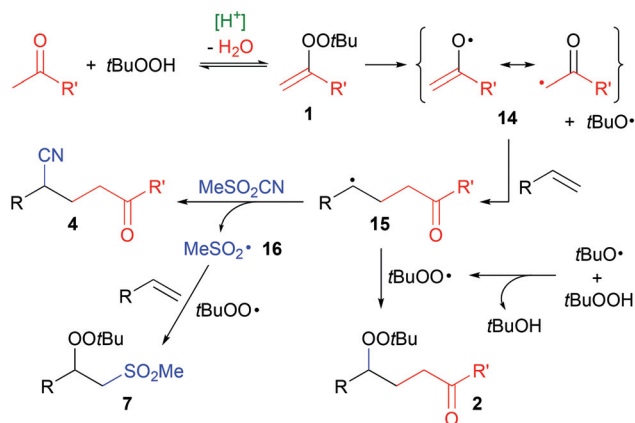




Scheme 5 Further transformations of selected products.

Tetracyclic piperidine **12** was formed with a high preference for one diastereomer, as depicted in Scheme 5. The structure of the major one was confirmed by NMR spectroscopy and X-ray crystallography of the corresponding ammonium salt **13**, which was isolated diastereomerically pure after recrystallization (see the ESI† for further details).

In accordance with our earlier mechanistic studies of alkenyl peroxide formation^{2b} and based on the observation of byproducts **2** and **7**, a radical mechanism appears reasonable (Scheme 6).

Scheme 6 Suggested reaction mechanism including formation of byproducts **2** and **7**.

Alkenyl peroxides **1** are formed by acid-catalyzed condensation of ketones and *t*BuOOH. Rapid homolytic O–O cleavage generates a *tert*-butoxy radical and resonance-stabilized radical **14**, which adds to an olefin, forming the intermediate C-radical **15**. Reaction with MeSO₂CN^{10c} generates the cyanoketones **4** and a sulfonyl radical **16**. Rapid H-atom transfer from *t*BuOOH to the oxyl radical generates the *tert*-butyl peroxy radical²⁰ which can attack **15**, forming peroxyketone **2** as minor byproduct. Major byproduct **7** is formed by subsequent attack of a sulfonyl and peroxy radical on an alkene.^{16,21}

Conclusions

In summary, we have developed a Brønsted-acid catalyzed synthetic method for the radical addition of ketones and cyanide to olefins, achieving the formation of two new C–C bonds. A variety of ketones can be added to styrene derivatives but also to various alkyl olefins, giving a range of structurally diverse γ -cyanoketones. Selected products were further converted to a lactone and two piperidines, including the case of a tetracyclic piperidine that was thus synthesized in three steps only from simple starting materials.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We thank the DFG (KL 2221/7-1 and KL 2221/4-2, Heisenberg scholarship to M.K.) and the Max-Planck-Institut fuer Kohlenforschung for funding. We are grateful to the Regional Computing Center of the University of Cologne for providing computing time of the DFG-funded High Performance Computing (HPC) System CHEOPS as well as for their support. Open Access funding provided by the Max Planck Society.

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