

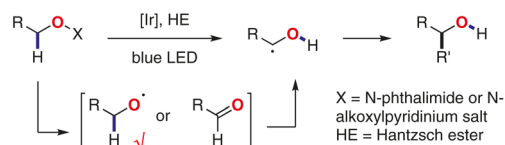
Investigations on the 1,2-Hydrogen Atom Transfer Reactivity of Alkoxy Radicals under Visible-Light-Induced Reaction Conditions

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a series of mechanistic investigations to validate the 1,2-HAT of alkoxy radicals

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Abstract The alkoxy radicals have demonstrated superior hydrogen atom transfer reactivity in organic synthesis due to the strong oxygen–hydrogen bond dissociation energy. However, only the intermolecular hydrogen atom transfer (HAT) and intramolecular 1,5-HAT have been widely studied and synthetically utilized for C(sp³)–H functionalization. This Account summarizes our investigations on the unusual 1,2-HAT reactivity of alkoxy radicals under visible-light-induced reaction conditions for the α -C–H functionalization. Various mechanistic investigations were discussed in this Account to address three key questions to validate the 1,2-HAT reactivity of alkoxy radicals.

- 1 Introduction
- 2 Could Aldehydes/Ketones Be the Sole Reaction Intermediate for the α -C–H Alkylation? NO
- 3 Is the Alkoxy Radical Absolutely Involved in the Reaction? YES
- 4 Does the 1,2-HAT of Alkoxy Radicals Irrefutably Exist? YES
- 5 Conclusion

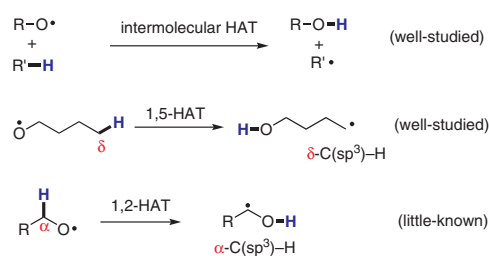
Key words alkoxy radical, 1,2-HAT, C–H functionalization, photoredox catalysis, N-alkoxyphthalimide, N-alkoxy pyridinium salt

1 Introduction

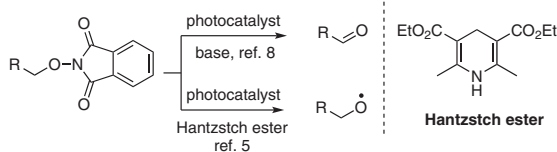
The alkoxy radicals are reactive intermediates in organic chemistry and are useful for the inert chemical bonds functionalization with the hydrogen atom transfer (HAT) reactivity.¹ The selective intermolecular HAT by alkoxy radicals is challenging to differentiate C–H bonds with various bond-dissociation energies due to the strong oxygen–hydrogen bond-dissociation energy ($E_{\text{bond(O-H)}} = \text{ca. } 105 \text{ kcal/mol}$).² In contrast, the intramolecular 1,5-HAT is useful for the selective δ -C–H activation with the preferred six-membered-ring transition state involving the alkoxy radical and the δ -C–H (Scheme 1a).³ To date, the selective intramolecular HAT for C–H functionalization other than the δ -C–H is less known and little synthetically used, especially

for the new C–C bond formations.⁴ We describe our journey in this Account on the 1,2-HAT reactivity discovery for the selective α -C–H functionalization by alkoxy radicals, which have spanned over several years in retrospect when we first discovered alkoxy-radical generation under visible-light-induced reaction conditions in 2015.⁵ We have performed various mechanistic investigations to validate the existence of alkoxy-radical 1,2-HAT reactivity, and will describe them in detail in this Account.

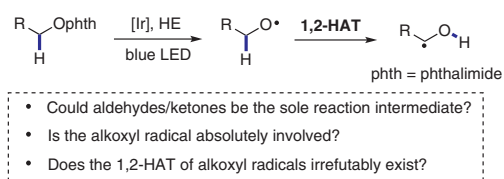
a) Hydrogen-atom transfer by the alkoxy radical: intermolecular HAT, 1,5-HAT (well-studied), and 1,2-HAT (little-known)



b) Visible-light-induced reactions of N-alkoxyphthalimides



c) Three key questions on the 1,2-HAT reactivity of alkoxy radicals



Scheme 1 The investigation of the alkoxy-radical HAT reactivity

N-Alkoxyphthalimides are stable on the benchtop and can be easily prepared from alcohols or alkyl halides.⁶ The traditional heating conditions with azodiisobutyronitrile/tributyltin hydride generated alkoxy radicals from *N*-alkoxyphthalimides,^{6,7} however, the relatively harsh reaction conditions limited the functional group compatibility and further synthetic applications. The first attempt to generate alkoxy radicals from *N*-alkoxyphthalimides under visible-light-induced reaction conditions was conducted in 2011, however, only the aldehydes were obtained by the intramolecular redox fragmentations, and the alkoxy radical was not observed (Scheme 1b).⁸ In 2015 the first alkoxy-radical generation under visible-light-induced reaction conditions from *N*-alkoxyphthalimides was reported by our group, and the use of Hantzsch ester (HE) was critical for the alkoxy-radical generation.⁵ The alkoxy radicals generated under visible-light-induced reaction conditions from *N*-alkoxyphthalimides and HE have demonstrated various 1,5-HAT and β -fragmentation reactivity with excel-

lent chemoselectivity and functional group compatibility,⁹ which are suitable for the late-stage functionalization of complex alcohol molecules with excellent regioselectivity.

In 2019, our group reported the first regioselective α -C(sp³)-H allylation of *N*-alkoxyphthalimides under visible-light-induced reaction conditions, and the 1,2-HAT of alkoxy radicals was proposed as the reaction mechanism.¹⁰ However, some key questions remained to be conclusively addressed in the preliminary communication. In this Account, we will discuss three key questions regarding the proposed reaction mechanism (Scheme 1c): 1) May the aldehyde/ ketone be the sole reaction intermediate? 2) Is the alkoxy radical absolutely involved? 3) Does the 1,2-HAT of alkoxy radical irrefutably exist? As the reaction optimization and substrate scopes have been revealed in the previous communication,¹⁰ we will briefly summarize them and will not report the whole dataset in detail (Scheme 2). In brief, the α -carbonyl, α -cyano, α -trifluoromethyl, and ben-

Biographical Sketches



Dan Liu was born in 1993 in Yangzhou, P. R. of China. She received her Bachelor's degree in

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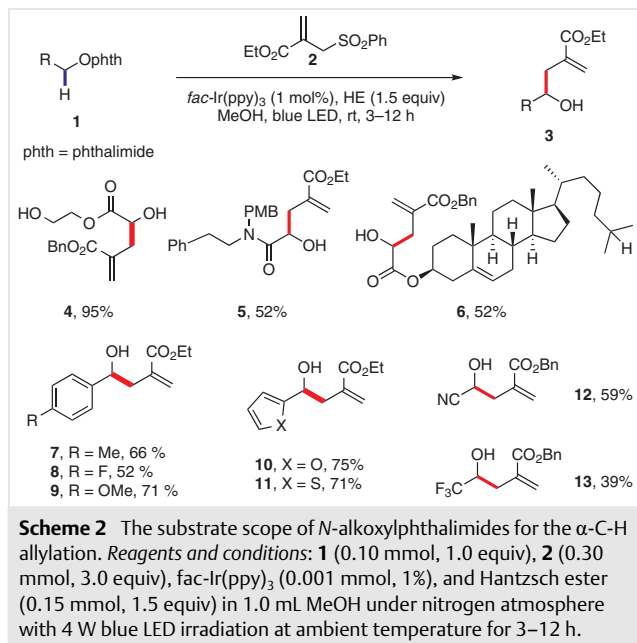


Dr. Yiyun Chen received his Bachelor's degree in chemistry at Peking University (P. R. of China) in 2002 and earned his PhD degree in organic chemistry at Princeton University (USA) in 2007. After postdoctoral studies at Harvard University (USA) and Howard Hughes Med-

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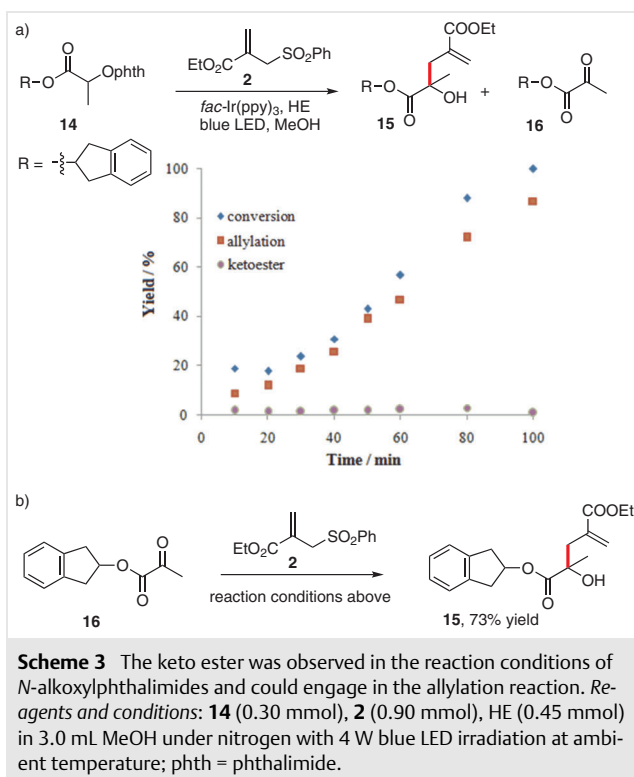
zylc *N*-alkoxyphthalimides were suitable substrates for the α -C–H allylation (**4–13**), and the photocatalyst in combination with HE was required for the reaction.



2 Could Aldehydes/Ketones Be the Sole Reaction Intermediate for the α -C–H Allylation? NO

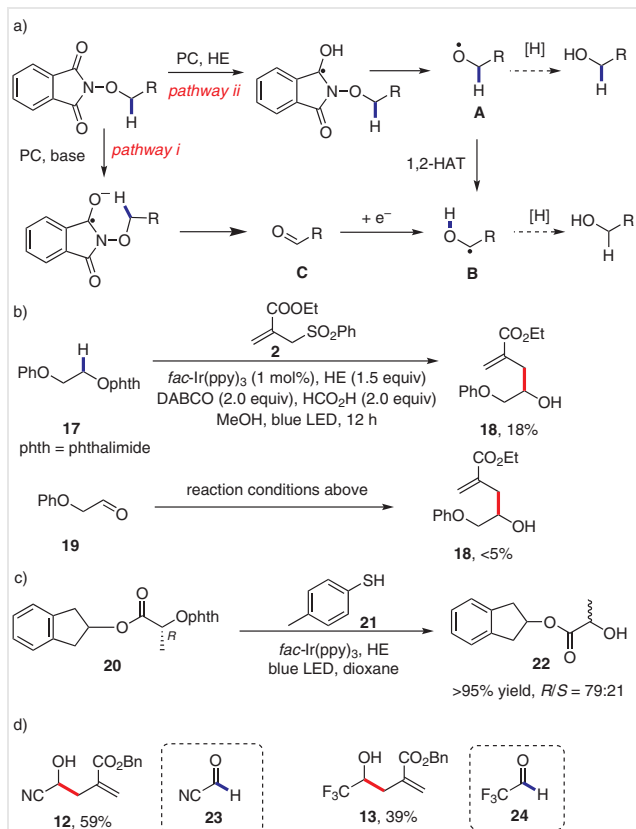
The initial mechanistic investigation on the 1,2-HAT of alkoxy radicals was complicated by the NMR analysis on the reaction mixture of *N*-alkoxyphthalimide **14**, in which the formation of keto ester **16** was observed (Scheme 3a). With the consumption of *N*-alkoxyphthalimide **14** and the formation of allylation product **15**, the keto ester **16** was detected as well, however, in less than 5% yield. This observation raised the question if the keto ester **16** was the sole reaction intermediate leading to the α -C–H allylation product **15** and the alkoxy-radical intermediate was not involved. In fact, our group had previously reported the polarity-reversed allylation of aldehydes or ketones under similar visible-light-induced reaction conditions.¹¹ To add more convolution to the mechanistic investigation, the injection of keto ester **16** to the reaction conditions above resulted in the formation of **15** in 73% isolated yield (Scheme 3b). All these results brought the first key question to the table: May the aldehyde/ketone be the sole reaction intermediate for the α -C–H allylation without involving the 1,2-HAT of alkoxy radicals?

Based on the literature and our own mechanistic studies, there are two mechanistic scenarios for *N*-alkoxyphthalimides upon the single-electron reduction of *N*-alkoxyphthalimides under visible-light-induced reaction condi-



tions (Scheme 4a): *i*) in the presence of bases, the concerted intramolecular elimination of benzyl-substituted *N*-alkoxyphthalimide yields the aldehyde **C**;⁸ and *ii*) in the presence of Hantzsch ester, the single-electron reduction and protonation by HE yields the alkoxy radical **A**.⁵ The paradox lies upon if the α -C-centered radical **B** is the result of the single-electron reduction from the aldehyde **C** or the 1,2-HAT adduct from the alkoxy radical **A**. To address this, we have synthesized *N*-alkoxyphthalimide **17** and subjected it to the reaction conditions (Scheme 4b). The α -C–H allylation adduct **18** was obtained in 18% yield with 1,4-diazabicyclo(2,2,2)octane (DABCO) and formic acids addition to accelerate the reaction. In contrast, no allylation product was obtained from aldehyde **19**, which confirmed that the carbonyl compound was not the sole reaction intermediate leading to the α -C–H radical formation and the alkoxy radical had to be involved. The enantiopure (*R*)-*N*-alkoxyphthalimide **20** was also subjected to the reaction conditions with thiophenol **21** as the hydrogen donor to obtain the alcohol, and the reduced alcohol adduct **22** was obtained with the *R/S* ratio = 79:21 in >95% yield (Scheme 4c). This result suggested the keto ester **16** was not the sole reaction intermediate which would lead to the achiral alcohol product, and the alkoxy radical need to be involved for the chiral alcohol formation. In addition, the α -cyano- or α -trifluoromethyl-substituted *N*-alkoxyphthalimides afforded the α -C–H allylation products **12** and **13** in 59% and 39% yields, respectively (Scheme 4d). In contrast, their counterpart

formyl cyanide **23** and trifluoromethyl aldehyde **24** were extremely unstable molecule moieties to be synthetically utilized. Taken together, a negative answer is obtained for the aldehyde/ketone as the sole reaction intermediate for the α -C–H allylation and the presence of the alkoxy radical is required.

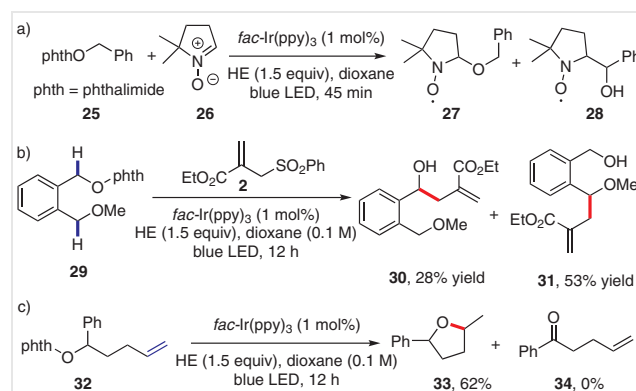


Scheme 4 The experimental evidence to exclude the aldehyde/ ketone as the sole reaction intermediate for the α -C–H allylation

3 Is the Alkoxy Radical Absolutely Involved in the Reaction? YES

The second question is if the presence of alkoxy radicals could be experimentally validated in the reaction conditions. In fact, the electron paramagnetic resonance (EPR) experiment with 5,5-dimethyl-pyrroline *N*-oxide (DMPO) **26** as the radical spin trap detected both the O-centered radical trapping adduct **27** and the α -C-centered radical trapping adduct **28**, which directly confirmed the existence of the alkoxy radical (Scheme 5a).¹⁰ The presence of the alkoxy radical could also be validated by the well-studied reactivity of alkoxy radicals by the probe molecules **29** and **32**. The *N*-alkoxyphthalimide **29** has both the δ -C–H and α -C–H that are prone to the intramolecular HAT, and the δ -C–H allylation adduct **31** could be obtained in 53% yield, together with the α -C–H allylation adduct **30** in 28% yield

(Scheme 5b). With the pendent alkene at the δ -position of the *N*-alkoxyphthalimide, the 5-*exo*-cyclization adduct **33** was obtained in 62% yield, while the ketone **34** was not observed (Scheme 5c). These results from EPR experiments and probe molecules validated the existence of alkoxy radicals in the reaction conditions and excluded the aldehyde/ketones as the sole reaction intermediates.

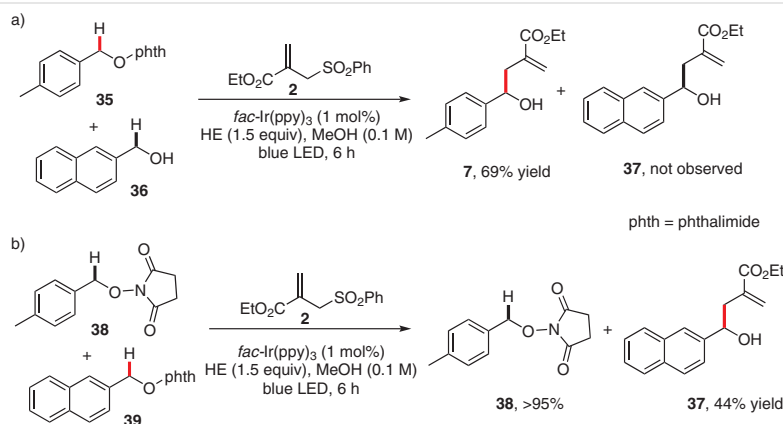


Scheme 5 The evidence of the presence of alkoxy radicals in the reaction conditions

The intermolecular HAT pathway to afford the α -C-centered radical was next evaluated by the crossover experiments (Scheme 6). The naphthalenylmethanol **36** and the structurally similar *N*-alkoxyphthalimide **35** were subjected to the standard reaction conditions with allylsulfone **2** (Scheme 6a). The homoallylic alcohol **7** from **35** was obtained in 69% yield, while the homoallylic alcohol **37** from **36** was not observed. This result excluded the alcohol formation from the hydrogenation of the alkoxy radical and the subsequent intermolecular HAT on the α -C–H of the alcohol. The *N*-alkoxysuccinimide **38** was further tested which succinimide moiety has the similar electronic property as the phthalimide moiety. As a result, only the formation of **37** from **39** was obtained in 44% yield, and the *N*-alkoxysuccinimide **38** was recovered in >95% yield. Taken together, the intermolecular HAT does not contribute to the α -C–H allylation of *N*-alkoxyphthalimides.

4 Does the 1,2-HAT of Alkoxy Radicals Irrefutably Exist? YES

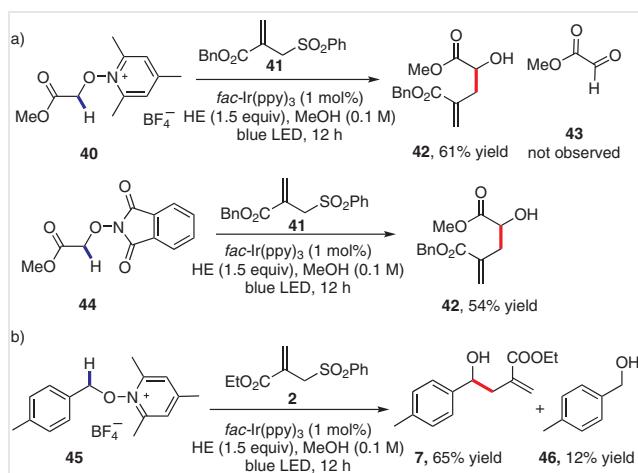
With the negative answer for the carbonyl compound as the sole reaction intermediate and the positive answer for the alkoxy-radical presence in the reaction conditions, the final and most essential question is if the 1,2-HAT of alkoxy radical irrefutably exists? While the 1,2-HAT of alkoxy radicals under visible-light-induced reaction conditions was first revealed with *N*-alkoxyphthalimides as radical precursors,^{10,12} the carbonyl compound formation in the reaction conditions complicated the mechanistic analysis. We envi-



Scheme 6 The experimental evidence to exclude the intermolecular HAT reaction

sion the demonstration of 1,2-HAT reactivity from other alkoxy-radical precursors, especially in the absence of the carbonyl intermediate, will irrefutably validate the unusual 1,2-HAT reactivity of alkoxy radicals. The *N*-alkoxypyridinium salt has been shown to generate alkoxy radicals under visible-light-induced reaction conditions, and there were no redox fragmentation pathways to form aldehydes or ketones.¹³ In addition, various 1,5-HAT or alkene addition reactivity of *N*-alkoxypyridinium salts have been reported to validate the alkoxy-radical generation.¹⁴

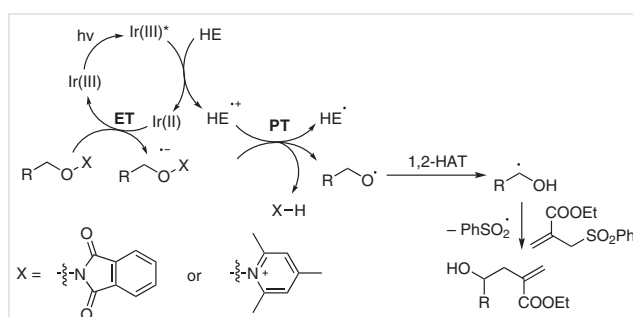
We then synthesized the *N*-alkoxypyridinium salt **40** derived from the α -hydroxyl ester and subjected it to the standard reaction conditions (Scheme 7a). While the use of HE was not required for the previous alkoxy-radical generation from *N*-alkoxypyridinium salts, it has been proved useful for the reductive coupling reactions with allyl sulfones.^{5,9b,11,15} Throughout the reaction courses, no methyl 2-oxoacetate **43** was observed, in sharp contrast to the reactions using *N*-alkoxyphthalimides. Instead, the α -C–H al-



Scheme 7 The alkoxy-radical 1,2-HAT reactivity from *N*-alkoxypyridinium salts

lylation adduct **42** was obtained in 61% yield, which was comparable to the 54% yield from *N*-alkoxyphthalimide **44** derived from the same α -hydroxyl ester. The *N*-alkoxypyridinium salt derivatives of benzyl alcohol **45** also afforded the α -C–H allylation adduct **7** in 65% yield together with the hydrogenation adduct **46** in 12% yield (Scheme 7b), which were comparable to the reactions of *N*-alkoxyphthalimides to obtain 66% yield of **7** in Scheme 2. These results collectively suggested the 1,2-HAT of alkoxy radicals universally existed and was independent on the radical precursors used.

From the mechanistic investigations on the above three key questions, we propose the reaction is initiated from the reductive quenching of the photoexcited Ir(III)* to Ir(II) by Hantzsch ester, and Ir(II) subsequently reduces the *N*-alkoxyphthalimide or the *N*-alkoxypyridinium salt to the radical anion (Scheme 8). The radical anion then undergoes proton transfer with Hantzsch ester radical cation and subsequent N–O bond cleavage to form the alkoxy radical, which subsequently undergoes 1,2-HAT and allylation reaction. In the case of *N*-alkoxyphthalimides, the carbonyl compound intermediate cannot be excluded; however, the alkoxy radical irrefutably exists with the 1,2-HAT reactivity. In the case of *N*-alkoxypyridinium salts, the 1,2-HAT reactivity of the



Scheme 8 The mechanistic proposal of the alkoxy-radical 1,2-HAT reactivity

alkoxyl radical is the only irrefutable reaction pathway leading to the C–H allylation products.

5 Conclusion

In conclusion, we have investigated the 1,2-HAT reactivity of alkoxyl radicals under visible-light-induced reaction conditions and unambiguously addressed three key questions for the reaction mechanism: i) The aldehydes/ketones as the sole reaction intermediate was excluded by the α -C–H allylations on substrates requiring the alkoxyl-radical intermediates and the retention of the chiral information from the enantiopure substrate. ii) The presence of alkoxyl radicals in the reaction conditions was experimentally validated by EPR studies with the radical spin trap and the signature reactivity of alkoxyl radicals; and the intermolecular HAT pathways were excluded by the crossover experiments. iii) The α -C–H allylation by *N*-alkoxypyridinium salts suggested the alkoxyl-radical 1,2-HAT reactivity was independent on the alkoxyl-radical precursors and irrefutably validated its existence.

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Supporting Information

Supporting information for this article is available online at <https://doi.org/10.1055/a-1300-3453>.

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