Chemical Science

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Cite this: *Chem. Sci.*, 2026, **17**, 6507

All publication charges for this article have been paid for by the Royal Society of Chemistry

Received 8th October 2025
Accepted 30th January 2026

DOI: 10.1039/d5sc07764h

rsc.li/chemical-science

Visible-light-mediated synthesis of 2-oxetanes *via* Giese addition to α-oxy radicals

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Oxetanes have recently garnered large amounts of interest from synthetic chemists due to their unique structural and chemical properties. Despite substantial advances for the formation of 3,3-disubstituted oxetanes, its 2-functionalized counterparts remain a challenging synthetic motif. Furthermore, methods to form alkyl oxetanes remain underdeveloped. Herein, we disclose a novel protocol for the synthesis of various alkyl and aryl 2-oxetanes leveraging a Giese addition to α-oxy radicals, furnishing the desired products in up to 95% yield.

Introduction

Oxetanes are considered privileged motifs in modern drug discovery due to their unique ability to modulate key physicochemical properties, including lipophilicity, metabolic stability, and aqueous solubility.[1–6] Their incorporation into bioactive molecules holds the potential to improve pharmacokinetic profiles, making them attractive scaffolds for medicinal chemists.[1,5,7] As a result, there is growing interest in developing efficient strategies for the functionalization of oxetane scaffolds to enable structure–activity relationship (SAR) exploration and diversification of lead compounds.[7] Among the potential sites for derivatization, the 3-position of aryl-substituted oxetanes has been most extensively targeted,[8–17] in part due to the ability to generate stabilized benzylic radicals under photoredox-catalyzed conditions.[18] For example, visible-light-promoted decarboxylative alkylation of 3-aryl-oxetanes (**1**) enables the generation of benzylic radicals that engage efficiently in C–C bond-forming reactions, providing streamlined access to 3-functionalized oxetanes (**2**, Fig. 1). This reactivity is facilitated by radical stabilization from the adjacent aromatic ring, and multiple methods rely on this strategy to allow for alkylation and arylation at the 3-position (**3** to **4**, Fig. 1).[18]

In contrast, the functionalization of oxetanes at the 2-position remains a significant synthetic challenge. The lack of electronic stabilization at this site renders radical intermediates less accessible (**6**), and few methods have been developed to directly forge C–C bonds at the 2-position of oxetanes.[20–26] Recently, progress has been made by harnessing decarboxylative activation of 2-aryl-substituted oxetane carboxylic acids (**7**) to generate α-oxy radicals.[19] Under photoredox conditions, these intermediates can engage in bond-forming reactions, offering rare examples of direct substitution at the 2-

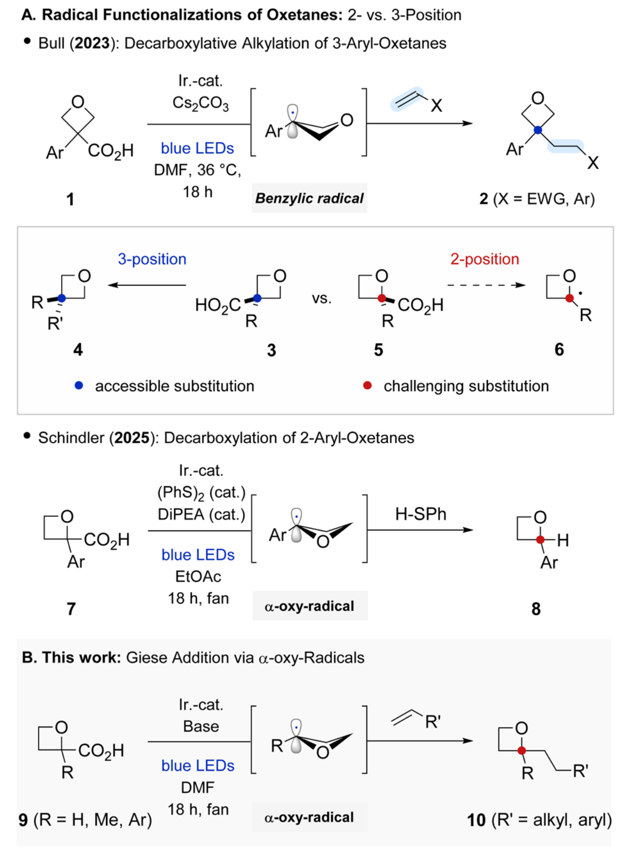

Fig. 1 Oxetane decarboxylation and functionalization. Previous reports and this study. (A) Previous work highlighting methods to functionalize oxetanes at the 3- and 2- position.[18,19] (B) Current work demonstrating the synthesis of various alkyl and aryl 2-oxetanes *via* a Giese addition to α-oxy radicals.

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position (**8**). However, such strategies remain limited in scope and are typically restricted to aryl-substituted systems.[19] To address this limitation, the present work establishes a general approach for the synthesis of 2-substituted oxetanes (**10**) *via* Giese-type addition of α-oxy radicals to electron-deficient alkenes. Notably, Mykhailiuk and co-workers recently successfully developed a Giese-addition approach from azetidine-2-carboxylic acids to access functionalized azetidines.[27] Using readily available oxetane carboxylic acids (**9**) to serve as radical precursors, and under visible-light irradiation, decarboxylation generates transient α-oxy radicals that can add to activated olefins to form C–C bonds at the 2-position (B. Fig. 1). This method proceeds under mild conditions, tolerates a variety of alkyl and aryl substituents, and provides a valuable platform for expanding the synthetic utility of oxetanes in the context of drug development.

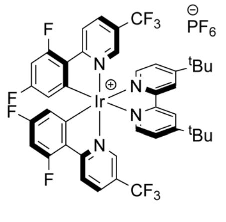
Results and discussion

To begin our studies towards the development of a novel protocol for the visible-light-mediated synthesis of various alkyl and aryl 2-oxetanes *via* a Giese addition to α-oxy radicals, oxetane-2-carboxylic acid (**9**) and 4-vinylpyridine (**10**) were chosen as model substrates and optimal conditions were explored (Table 1). Upon irradiating 2.0 equivalents of alkene (**10**) with oxetane-2-carboxylic acid (**9**) in conjunction with an excess of base in 0.2 M DMF, the desired product can be observed in 70% yield (entry 1 and Table 1). Varying the base used (entry 2 and Table 1) (see SI for additional details) revealed productive reactivity, although $LiOH \cdot H_2O$ was found to provide the best product yield. Importantly, evaluation of various photocatalysts revealed that both organic and metal-based photocatalysts were sufficient in providing reactivity, including **Ir1**, 4CzIPN, and **MesAcr1** (entry 4, 5 and Table 1). Subsequent efforts focused on varying the reaction solvent identified DMF as being superior, providing the highest product yield compared to other solvents, although reactivity was still observed with ethyl acetate and THF (59% and 62% product yield, respectively) (see SI for additional details). Furthermore, when increasing alkene loading to 2.5 equivalents, a slight increase in product yield was observed. Finally, decreasing reaction concentration from 0.2 M to 0.1 M highlighted an increase in product yield from 73 to 77% (entry 6, 7 and Table 1). By performing the reaction open to air, a noticeable decrease in product yield was observed (11% reduction in product yield) (see SI for additional information). Optimal reaction conditions using 2.5 mol% of **Ir1**, 2.5 equivalents of alkene **10**, 1.5 equivalents of $LiOH \cdot H_2O$, in 0.1 M DMF (degassed for 2 minutes) were found to furnish the desired product in up to 80% yield. Control experiments were also conducted, highlighting that both light and base were required to provide productive reactivity (entries 9, 10 and Table 1), with temperature playing no significant role in product yield with the absence of light (entry 11 and Table 1).

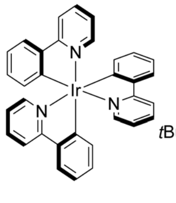
To demonstrate the utility of our protocol, we subjected various mono- and di-functionalized 2-oxetanes and alkene partners to optimized or modified conditions to assess their reactivity. For monofunctionalized 2-oxetanes (Fig. 2), acrylates such as phenyl- and benzyl acrylate gave the desired products **14** and **15** in in 89% and 74% yield, respectively. Styrene was also a viable radical acceptor, affording the desired oxetane **24**, albeit with lower yields (22%). Various styrene derivatives, including methyl 4-vinylbenzoate and 4-chlorostyrene also furnished the corresponding oxetane products **17** and **21** in 76% and 45% yield, respectively. Furthermore, α-methyl-substituted alkenes such as benzyl methacrylate and *N*-phenylmethacrylamide afforded products **18** and **19** in 73% and 50% yield, respectively. Importantly, heteroaryl substrates such as 4-vinyl- (**12**) and 2-vinylpyridine (**13**) were well tolerated, underscoring the method's applicability to late-stage functionalization of medicinally relevant compounds. Importantly, alkenes

Table 1 Reaction optimization. Conditions: reactions were performed with oxetane-2-carboxylic acid (**9**) (0.2 mmol), 4-vinylpyridine (**10**) (2.0–2.5 equiv.), base (1.1–1.5 equiv.), and photocatalyst (2.5 mol%) in DMF (0.1–0.2 M) under blue LED irradiation (456 nm) at ambient temperatures (fan cooling) for 18 h. All entries were degassed with N_2 for two minutes. Yield determined by quantitative ^1H NMR analysis. 1,3,5-trimethoxybenzene used as an internal standard. Optimal reaction conditions resulted in 80% oxetane, 33% styrene dimerization

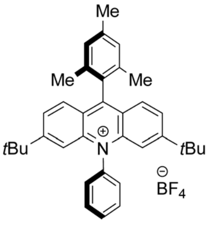
Entry	Photocat. (mol%)	Alkene (equiv.)	Base (equiv.)	Conc. (M)	Yield (%)
1	Ir1 PF_6 (2.5)	2.0	$LiOH \cdot H_2O$ (1.1)	0.2	70
2	Ir1 PF_6 (2.5)	2.0	Cs_2CO_3 (1.1)	0.2	68
3	Ir2 (2.5)	2.0	$LiOH \cdot H_2O$ (1.1)	0.2	n.r
4	MesAcr1 (2.5)	2.0	$LiOH \cdot H_2O$ (1.1)	0.2	21
5	4CzIPN (2.5)	2.0	$LiOH \cdot H_2O$ (1.5)	0.2	72
6	Ir1 PF_6 (2.5)	2.0	$LiOH \cdot H_2O$ (1.5)	0.2	73
7	Ir1 PF_6 (2.5)	2.0	LiOH H_2O (1.5)	0.1	77
8	Ir1 PF_6 (2.5)	2.5	$LiOH \cdot H_2O$ (1.5)	0.1	80[a]
9	No light				n.r
10	No.base				n.r
11	No light 40 °C				n.r



$[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$
Ir1



fac-$[Ir(ppy)_3]$
Ir2



MesAcr1

[a] Average yields over 3 runs. n.r = No Reactivity.

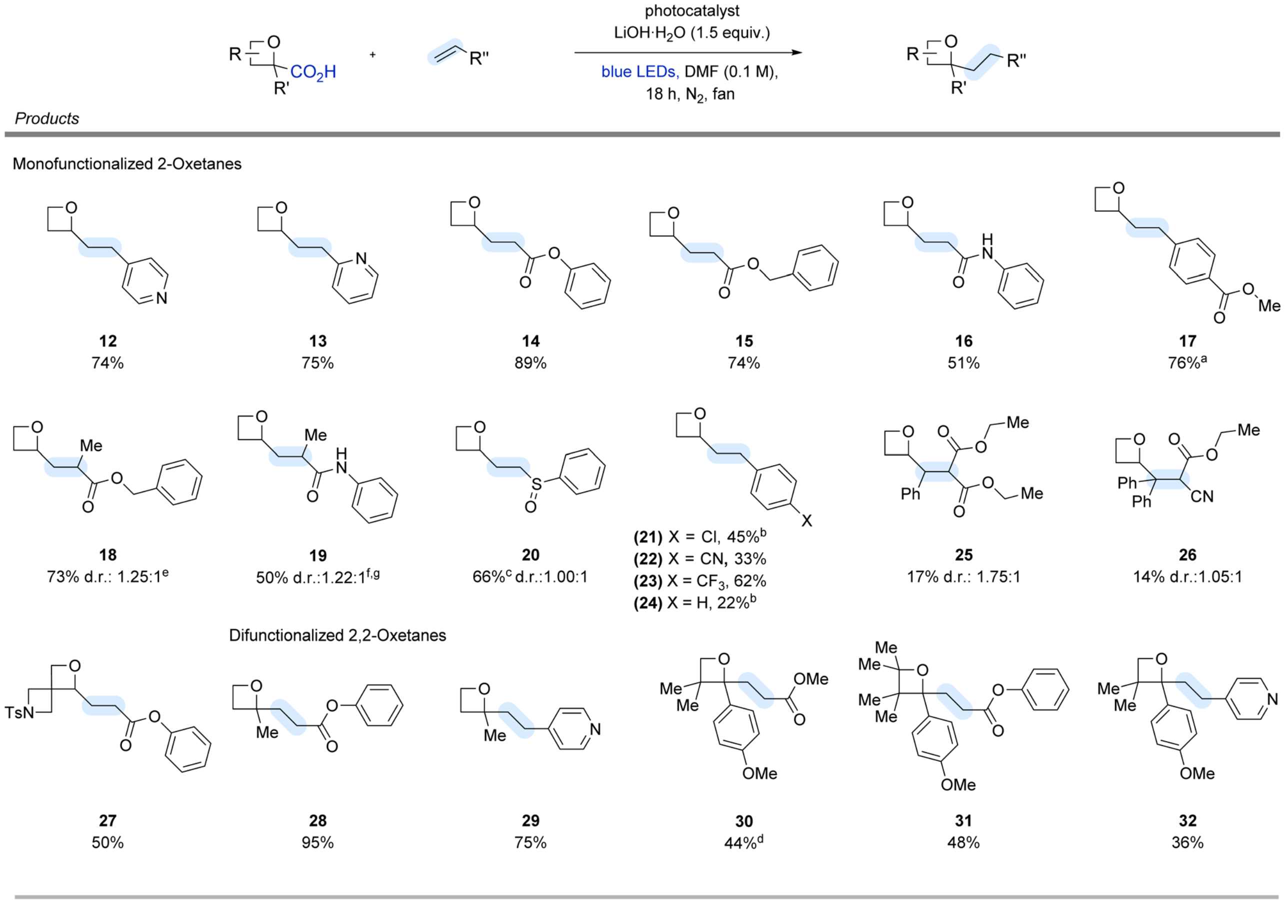


Fig. 2 Substrate scope. Conditions: unless otherwise stated, reactions were performed using 2.5 equiv. of alkene, **Ir1** (2.5 mol%), 456 nm, in DMF [0.1 M]. [a]Alkene (5.0 equiv.), **Ir1** (2.5 mol%), 456 nm, in DMF [0.1 M]. [b]Alkene (5.0 equiv.), 4CzIPN (2.5 mol%), LiOH·H_2O (1.5 equiv.), 390 nm, in DMF [0.1 M]. [c]Alkene (2.5 equiv.), 4CzIPN (2.5 mol%), Cs_2CO_3 (1.5 equiv.), 390 nm in DMF [0.2 M].[d]Alkene (2.0 equiv.), **Ir1** (2.5 mol%), Cs_2CO_3 (1.3 equiv.), 456 nm in DMF [0.2 M]. [e]d.r. Determined based on isolated product. [f]Crude d.r. Reported. [g]Product isolated as a single diastereomer.

bearing a tri- or tetra-substituted (**25** and **26**, respectively) pattern were also amenable to reactivity. Oxetanes bearing an azetidinyl substituents (**27**) also furnished the desired product in 50% yield, demonstrating the implementation of this protocol even in spirocyclic scaffolds. To further highlight the generality of our method, a range of difunctionalized 2,2-oxetane carboxylic acids were subjected to reactivity. Using 2-methyloxetane-2-carboxylic acid in conjunction with either phenyl acrylate or 4-vinylpyridine, the desired 2,2-difunctionalized oxetanes (**28** and **29**) can be obtained in 95% and 75% yield, respectively. Furthermore, leveraging recent results from our lab on the hydrodecarboxylation of 2-aryl oxetanes *via* the generation of an α-oxy radical,[19] we envisioned an extension of this work in applying substrates towards this process, thereby accessing the corresponding Giese adducts (**30–32**). Di- and tetra-substituted 2-aryl oxetanes such as 2-(4-methoxyphenyl)-3,3,4,4-tetramethyloxetane-2-carboxylic acid and 2-(4-methoxyphenyl)-3,3-dimethyloxetane-2-carboxylic acid were observed to undergo productive reactivity with either 4-vinylpyridine (**32**, 36%), methyl acrylate (**30**, 44%), or phenyl acrylate (**31**, 48%).

Finally, the utility of our process was further exemplified with a 1.0 mmol scale up reaction (Fig. 3), which is shown to effectively produce the corresponding product **14** in 82% yield.

Given that photoredox decarboxylative Giese reactions typically proceed *via* a reductive quenching pathway, the following mechanism is proposed (**A**, Fig. 4).[28–30] Following photocatalyst excitation of the ground state photocatalyst *via* visible-light, the corresponding photoexcited species (***Ir1**) engages in an oxidative single electron transfer (SET) process with **31**, made accessible by a base-mediated deprotonation of **30**. Facile decarboxylation followed by the conjugate addition to a Michael-acceptor generates the carbon-centered radical intermediate **33**. The reduced photocatalyst species ($\mathbf{Ir1_{red}}$)

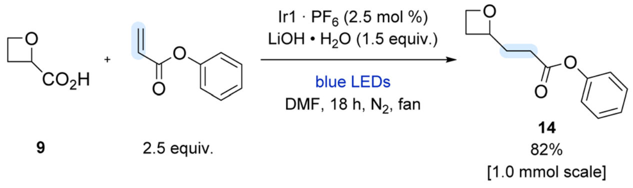


Fig. 3 1.0 mmol Scale–up reaction of **14**.

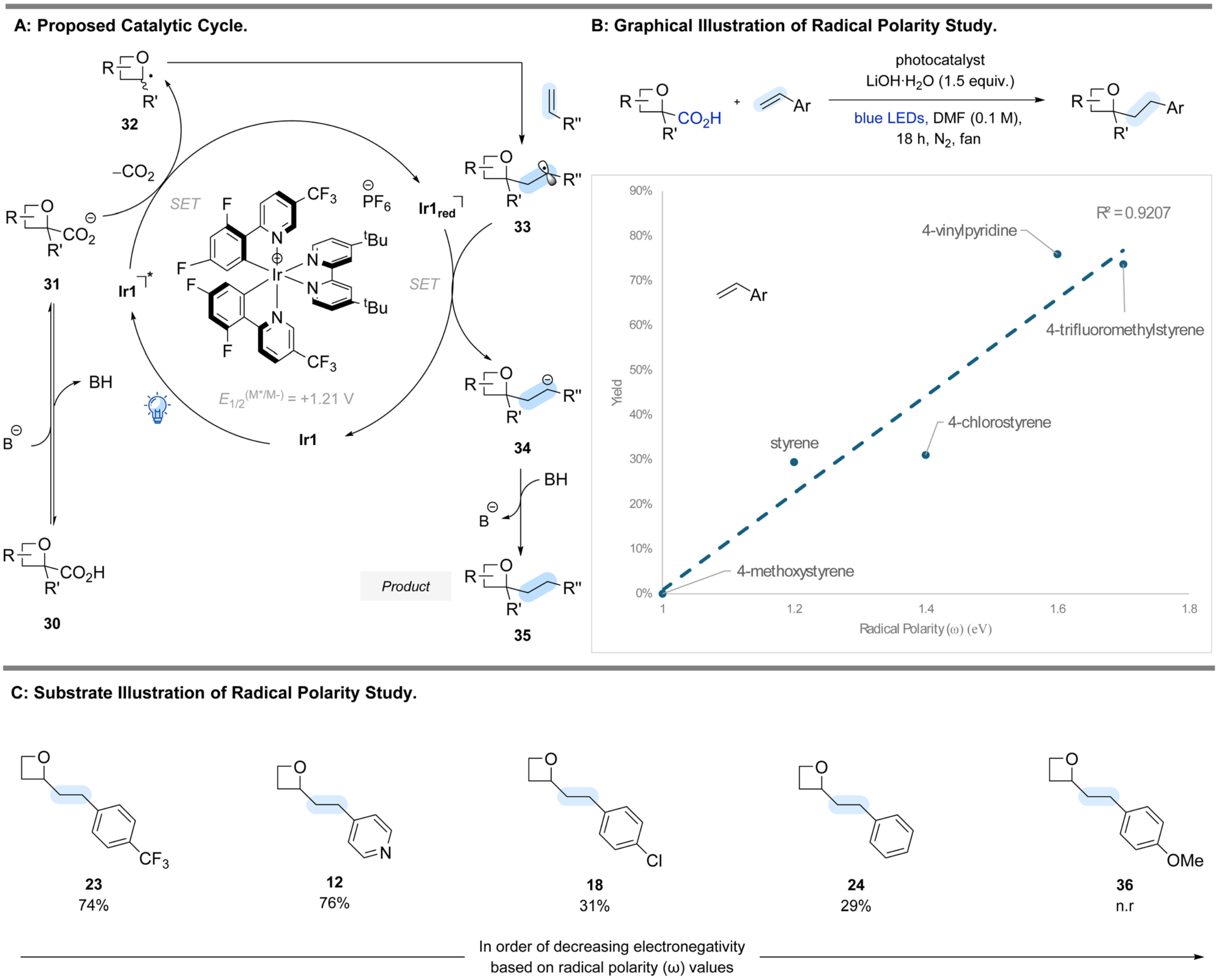


Fig. 4 Mechanistic studies. Conditions: reactions were performed using 2.5 equiv. of alkene, **Ir1** (2.5 mol%), 456 nm, in DMF [0.1 M]. Yields determined using quantitative NMR experiments. 1,3,5-trimethoxybenzene used as an internal standard. Radical polarity values (ω) taken from literature precedence.

participates in a second single electron transfer with intermediate **33**, reducing it to the corresponding carbanion **34**, in addition to the regeneration of **Ir1**, completing the catalytic cycle.[29] The carbanion intermediate **34** is subsequently protonated, resulting in the desired 2-functionalized oxetane product **35**. We next sought out to investigate the impact of the α-oxy radical on radical philicity (**B** and **C**, Fig. 4). Recently, Nagib and coworkers present an experimentally validated database of radical polarities[31],† Using this, alkenes with varying radical polarities values (*ω*) were investigated and the corresponding oxetane product yields show a correlation between product yields and increasing electrophilicity in the alkene (**B** and **C**, Fig. 4), suggesting that the α-oxy radical formed may be inherently nucleophilic.

Conclusions

We herein developed a novel method for the synthesis of various alkyl and aryl 2-oxetanes through a visible-light-mediated decarboxylation and subsequent Giese addition of the resulting α-oxy radicals. Our protocol provides a framework that is complementary to existing strategies for functionalization of 3-oxetanes.[8–18] This method contributes to the synthetic toolbox for medicinal and organic chemists interested in incorporating oxetanes as bioisosteres[1,4,32–38] for modulating the physicochemical activity of drugs or for generating building blocks for drug discovery.

Author contributions

M. L and E. C. M designed and conducted experiments. All authors have given approval to the final version of the manuscript.

Conflicts of interest

The authors declare no competing financial interest.

Data availability

All data supporting the findings of this study are available within the article and its supplementary information (SI) file. Supplementary information: general information, experimental procedures, characterization data, and spectroscopic data. See DOI: https://doi.org/10.1039/d5sc07764h.

Acknowledgements

This work was supported by the Natural Sciences and Engineering Research Council of Canada (NSERC). This research was performed, in part, with funding from the Canada Research Chairs Program. M. L thanks S. A. Chamness for helpful discussions. The authors thank J. Zhu for performing mass spectrometry and P. Xu for aid in setting up NMR spectroscopic parameters. The authors thank D. A. Nagib and K. Mikhaeel for their support with radical polarity calculations.

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† Radical polarity values for 4-vinylpyridine were provided by D. A. Nagib and K. Mikhaeel by personal communication.

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