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Catalytic photochemical enantioselective α -alkylation with pyridinium salts†

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We have developed a chiral amine catalyzed enantioselective α -alkylation of aldehydes with amino acid derived pyridinium salts as alkylating reagents. The reaction proceeds in the presence of visible light and in the absence of a photocatalyst *via* a light activated charge-transfer complex. We apply this photochemical stereoconvergent process to the total synthesis of the lignan natural products (–)-enterolactone and (–)-enterodiol. Mechanistic studies support the ground-state complexation of the reactive components followed by divergent charge-transfer processes involving catalyst-controlled radical chain and in-cage radical combination steps.

Introduction

Carbonyl compounds with α -stereocenters are key components of many biologically active molecules, including pharmaceutical drugs and secondary metabolites.¹ To access this important class of compounds, chemists have developed numerous transformative concepts in asymmetric catalysis for the enantioselective α -alkylation of enolates.² While these reactions are often categorized by the mode of catalysis and the enolate precursor, an underappreciated component of these processes is the identity of the alkylating reagents that are coupled with enolates. Commonly employed alkylating reagents include alkyl halides and sulfonates (2, Scheme 1A).

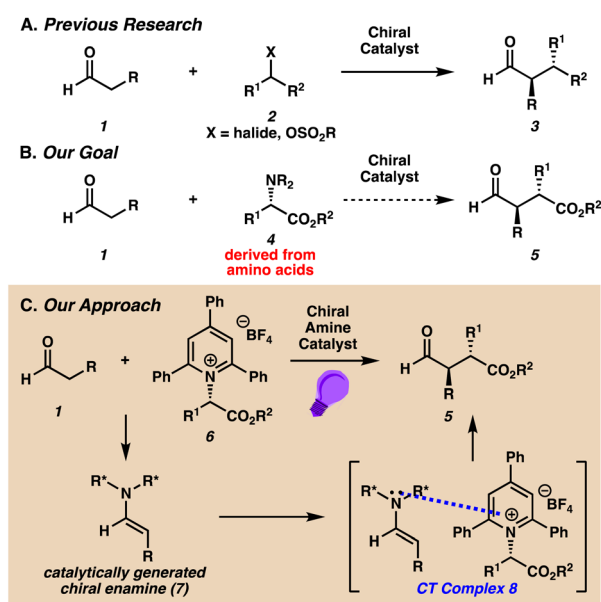
Recent elegant examples of photochemical enantioselective α -functionalizations of carbonyl compounds have been developed with alkyl halides.^{3–6} Notably, Melchiorre and co-workers pioneered the use of α -bromoketones and benzylic bromides as alkylating agents *via* light activated charge-transfer complexes.⁵ We were interested in developing a complementary approach for the catalytic enantioselective α -alkylation of aldehydes 1 based on renewable and sustainable sources of alkylating reagents. We identified amino acid derived substrates 4 as ideal reagents for enantioselective alkylations (Scheme 1B), as they possess several inherent advantages over traditionally used alkyl halides with respect to abundance, stability, versatility, and ease of preparation.⁷ In light of the poor electrophilicity of amino acid derivatives in enolate alkylations, we were motivated to devise a strategy for the activation of this class of substrates.

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We report a catalytic photochemical enantioselective α -alkylation of aldehydes with amino acid derived pyridinium salts as alkylating reagents (Scheme 1C). These compounds are air and moisture stable crystalline solids that can be easily purified and stored for extended periods of time. Moreover, pyridinium salts can be generated on preparative scale from the facile condensation of amino acid derivatives and pyrylium salts.⁸

We hypothesized that pyridinium salts could form ground-state encounter complexes with catalytically generated electron rich chiral enolate equivalents.^{9,10} Our approach was supported by an early report from Katritzky on the α -benzylation of



Scheme 1 Strategy for catalytic enantioselective α -alkylation with amino acid derivatives.



diethylmalonate with pyridinium salts of benzylamine, which he postulated proceeds through the formation of light activated charge-transfer (CT) complexes.¹¹ More recently, Melchiorre has demonstrated the formation of CT complexes between enamines and alkyl halides.⁵ In our case, the generation of chiral enamine **7** from the condensation of aldehyde substrate **1** and a chiral amine catalyst could form CT complex **8** with pyridinium salt **6**, which would then undergo stereoselective C–C bond formation in the presence of visible light.

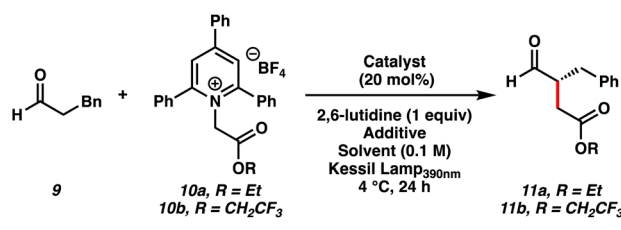
Our proposal to utilize pyridinium salts in enantioselective α -alkylations is motivated by their storied history as radical precursors.^{12–16} More recently, pyridinium salts have been utilized in deaminative transformations through activation by photoredox catalysis¹⁷ or the formation of CT complexes with electron rich molecules.¹⁸ Despite the widespread application of pyridinium salts as radical precursors, the use of these substrates in catalytic enantioselective transformations is rare,¹⁹ and enantioselective reactions with prochiral enolate equivalents is unprecedented.

Results

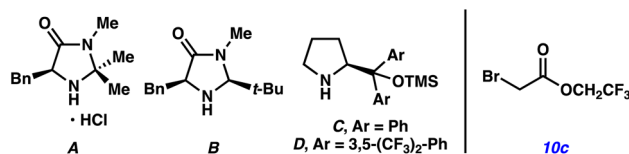
We initiated our studies by coupling hydrocinnamaldehyde **9** with Katritzky salt **10a** derived from the ethyl ester of glycine as the alkylating agent (Table 1). In the presence of MacMillan's amine catalyst **A**, 2,6-lutidine, and purple light (390 nm) in CH₂Cl₂, we observed trace amounts of product **11a** in 58% ee (entry 1). Interestingly, the deaminated byproduct of Katritzky salt **10a** and the corresponding 2,4,6-triphenylpyridine were formed, suggesting the formation of a light activated CT complex. We reasoned that the radical philicity of intermediates generated upon charge transfer between the enamine of aldehyde **9** and pyridinium **10a** may not be matched for the desired C–C bond forming event.²⁰ To test this hypothesis, we subjected electron-deficient Katritzky salt **10b** derived from the 2,2,2-trifluoroethyl ester of glycine to the reaction conditions (entry 2). Gratifyingly, we obtained α -alkylation product **11b** in 36% yield and 60% ee, presumably *via* a more electron-deficient α -carboxy radical. In a Lewis basic medium such as DMA, the desired product was formed in 40% yield and 92% ee (entry 3). Although other amine catalysts **B–D** also furnished product **11b** (entries 4–6), catalyst **A** was still best for enantioselectivity.

With enantioselectivity optimized, we focused on improving the yield of the reaction by employing additives that could enhance the ground-state complexation of the reaction components. Ultimately, the addition of stoichiometric NaI resulted in an increase in yield to 65% (entry 7), presumably through the formation of a multicomponent CT complex.²¹ Inclusion of water to help solubilize NaI further improved the yield to 75% while maintaining the enantioselectivity at 92% ee, which represented the optimal conditions for the reaction (entry 8). Interestingly, while α -bromoketones have been demonstrated to be competent acceptors in CT complexes with catalytically generated enamines,⁵ the corresponding 2,2,2-trifluoroethyl ester of α -bromoacetic acid (**10c**) was not a suitable alkylating agent under our optimized conditions (entry 9). This result highlights a unique advantage of pyridinium derived

Table 1 Optimization studies^a



Entry	Alkylating agent	Catalyst	Solvent	Additive	Yield ^b (%)	ee ^c (%)
1	10a	A	CH ₂ Cl ₂	—	5	58
2	10b	A	CH ₂ Cl ₂	—	36	60
3	10b	A	DMA	—	40	92
4	10b	B	DMA	—	22	5
5	10b	C	DMA	—	55	15
6	10b	D	DMA	—	52	23
7	10b	A	DMA	NaI	65	92
8	10b	A	DMA	NaI, H ₂ O	75	92
9	10c	A	DMA	NaI, H ₂ O	<5	—
10 ^d	10b	A	DMA	NaI, H ₂ O	80	46
11 ^e	10b	A	DMA	NaI, H ₂ O	62	92
12 ^f	10b	A	DMA	NaI, H ₂ O	18	92
13 ^g	10b	A	DMA	NaI, H ₂ O	<5	—



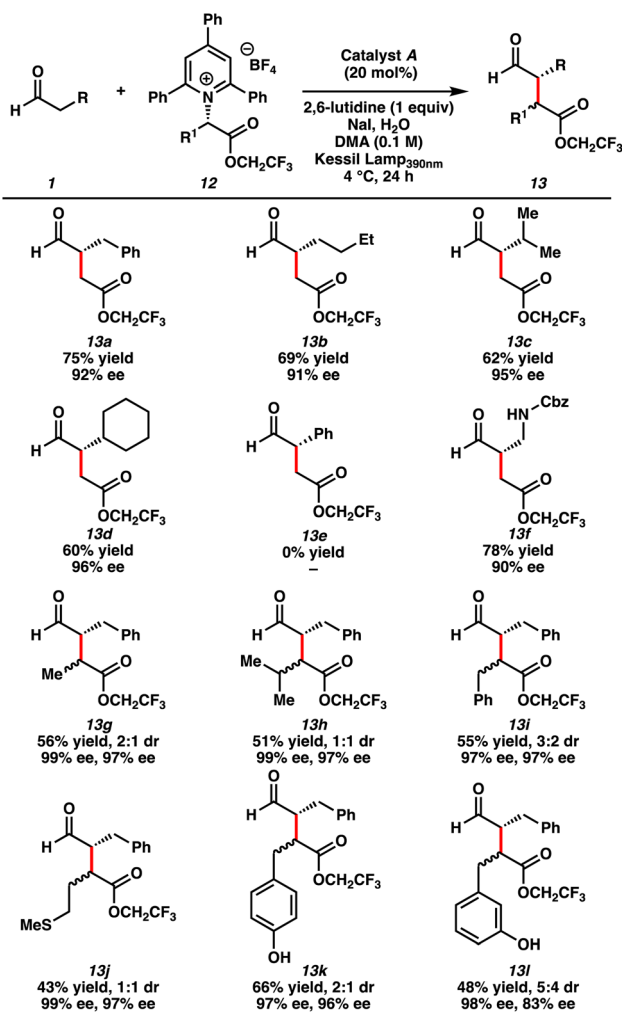
^a Reaction conditions: **9** (0.30 mmol), **10** (0.1 mmol), catalyst (20 mol%), 2,6-lutidine (0.1 mmol) NaI (0.1 mmol), H₂O (1.0 mmol), 4 °C, 24 h. ^b Isolated yield. ^c Enantiomeric excess determined by chiral HPLC analysis of a lactone derivative (see ESI). ^d Reaction conducted at 23 °C. ^e Irradiation with 370 nm Kessil lamp. ^f Irradiation with 427 nm Kessil lamp. ^g No light.

alkylating agents over the more traditionally used alkyl bromides in enantioselective α -alkylations.

We performed a series of control experiments to gain insight into the reaction (entries 10–13). Conducting the reaction at room temperature instead of 4 °C resulted in a loss of enantioselectivity (entry 10). Irradiation with various wavelengths of light resulted in diminished yields (entries 11–12), which confirmed the importance of activating the ground-state encounter complex at the appropriate wavelength. Furthermore, no product was observed in the absence of light (entry 13).

With optimal reaction conditions identified, we examined the substrate scope of the transformation (Table 2). The Katritzky salt of the trifluoroethyl ester of glycine was coupled with various aldehydes to furnish the desired products in

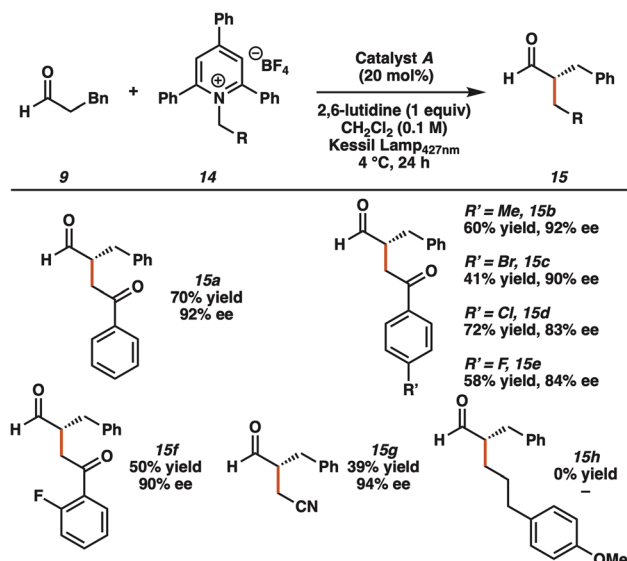


Table 2 Enantioselective α -alkylation with amino acid derived pyridinium salts^a

^a Reaction conditions: aldehyde (0.30 mmol), pyridinium salt (0.1 mmol), catalyst A (20 mol%), 2,6-lutidine (0.1 mmol), NaI (0.1 mmol), H₂O (1.0 mmol), DMA (0.1 M), Kessil lamp 390 nm, 4 °C, 24 h.

synthetically useful yields and greater than 90% ee (**13a–d**). We obtained products from linear aldehydes (**13a–b**) and branched aldehydes (**13c–d**). Although we did not observe any product with phenylacetaldehyde (**13e**), a carbamate functionalized aldehyde yielded the desired alkylation product (**13f**). Enantioenriched alkylation products were also formed from the coupling of hydrocinnamaldehyde and Katritzky salts derived from various natural amino acids, such as alanine (**13g**), valine (**13h**), phenylalanine (**13i**), methionine (**13j**), and tyrosine (**13k**). In addition, we generated the alkylated product derived from an unnatural amino acid (**13l**). The products were generated with high enantioselectivity but poor diastereoselectivity, presumably because of the formation of open-shell intermediates (*vide infra*).

To demonstrate the utility of this new mode of activation with other classes of substrates, we reacted hydrocinnamaldehyde **9** with Katritzky salts derived from various

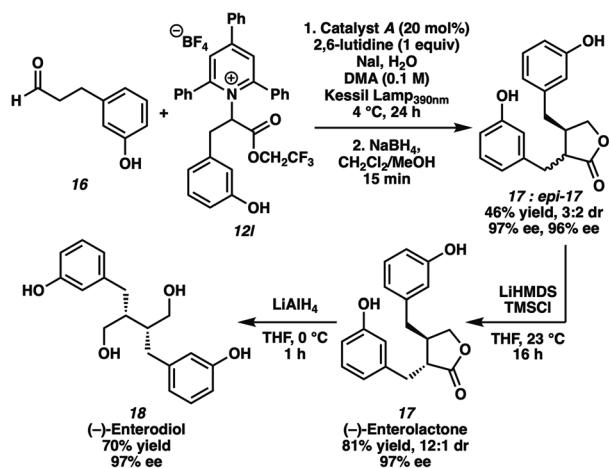
Table 3 Enantioselective α -alkylation with other amine derived pyridinium salts^a

^a Reaction conditions: aldehyde (0.30 mmol), pyridinium salt (0.1 mmol), catalyst A (20 mol%), 2,6-lutidine (0.1 mmol), CH₂Cl₂ (0.1 M), Kessil lamp 427 nm, 4 °C, 24 h.

amines (Table 3). Notably, these reactions were performed in CH₂Cl₂ in the absence of NaI and water. An electron-withdrawing group adjacent to the amine functionality was necessary for reactivity. For example, several 2-aminoacetophenone pyridinium salts were compatible substrates for the enantioselective transformation (**15a–f**). Through optimization, 427 nm irradiation performed as well as 390 nm for the aminoketone derived pyridinium salts, presumably because of different photophysical properties of the charge transfer complexes. With 427 nm being lower in energy, we chose to move forward with this wavelength. We also observed the desired product derived from aminoacetonitrile (**15g**). However, the Katritzky salt derived from 3-phenyl-1-propylamine did not yield alkylation product **15h** under the reaction conditions. The requirement for an electron-withdrawing group in the pyridinium salt further demonstrates the importance of matching the radical philicities of intermediates generated upon light activated charge transfer.

The synthetic utility of our new catalytic method is highlighted by the enantioselective total synthesis of the lignan natural products (–)-enterolactone **17** and (–)-enterodiol **18** (Scheme 2).²² Under optimal conditions, 3-(3-hydroxyphenyl) propanal **16** and the pyridinium salt of racemic *m*-tyrosine (**12l**) reacted in a stereoconvergent process to form the α -alkylated product, which was subjected to reductive conditions without purification to furnish (–)-enterolactone **17** and its epimer (*epi*-**17**) in 46% yield over 2 steps. Although the diastereomeric lactones were obtained in high ee but poor dr, we recognized the opportunity to epimerize the mixture for the synthesis of more complex structures with high diastereoselectivity.





Scheme 2 Synthesis of lignan natural products *via* enantioselective α -alkylation with pyridinium salts.

Therefore, the diastereomers were subjected to LHMDS and TMSCl to yield (–)-enterolactone **17** in 81% yield, 12 : 1 dr, and 97% ee upon diastereoselective protonation of the enolate intermediate. Reduction with LiAlH₄ resulted in the formation of (–)-enterodiol **18** in 70% yield and 97% ee as a single diastereomer. Optical rotations of the synthetic samples of the two natural products also confirmed the absolute stereochemistry of the alkylation products obtained in our enantioselective reaction.

Based on our initial proposal of a light activated CT complex between the pyridinium substrate and a catalytically generated enamine (Scheme 1C), we performed a series of experiments to gain insight into the mechanism of the photochemical process. The subjecting of either enantiomer of Katritzky salt **12g** to the optimized reaction conditions with aldehyde **9** resulted in the stereoconvergent formation of the same major enantiomer of both diastereomers of product **13g** (Fig. 1A). These experiments with both enantiomers of Katritzky salt **12g**, in combination with the absence of product formation in the presence of 1 equivalent of TEMPO,²³ are consistent with the formation of α -carboxy radical **19** as a common intermediate, which also accounts for the low diastereoselectivity in the transformation.

We were also interested in gaining insight into the role of NaI in the catalytic process. The use of 50 mol% NaI led to 58% isolated yield of the coupled product **11b**. In addition, the pyridinium substrate **10b** was not converted to the α -iodoester in the presence of NaI and absence of aldehyde.²³ However, NaI caused a bathochromatic shift into the purple region of the absorption spectrum (Fig. 1B). Moreover, the inclusion of NaI had a profound impact on the equilibrium of enamine formation, presumably by affecting the equilibrium of CT complex **21** (Fig. 1B). Therefore, we believe NaI may affect the identity of the CT complex by forming a ternary complex with the catalytically generated enamine and pyridinium substrate.²⁴

Next, we used the *trans* and *cis* isomers of the radical probe **22** as the aldehyde component to determine whether the enantioselective reaction proceeds through a radical chain or

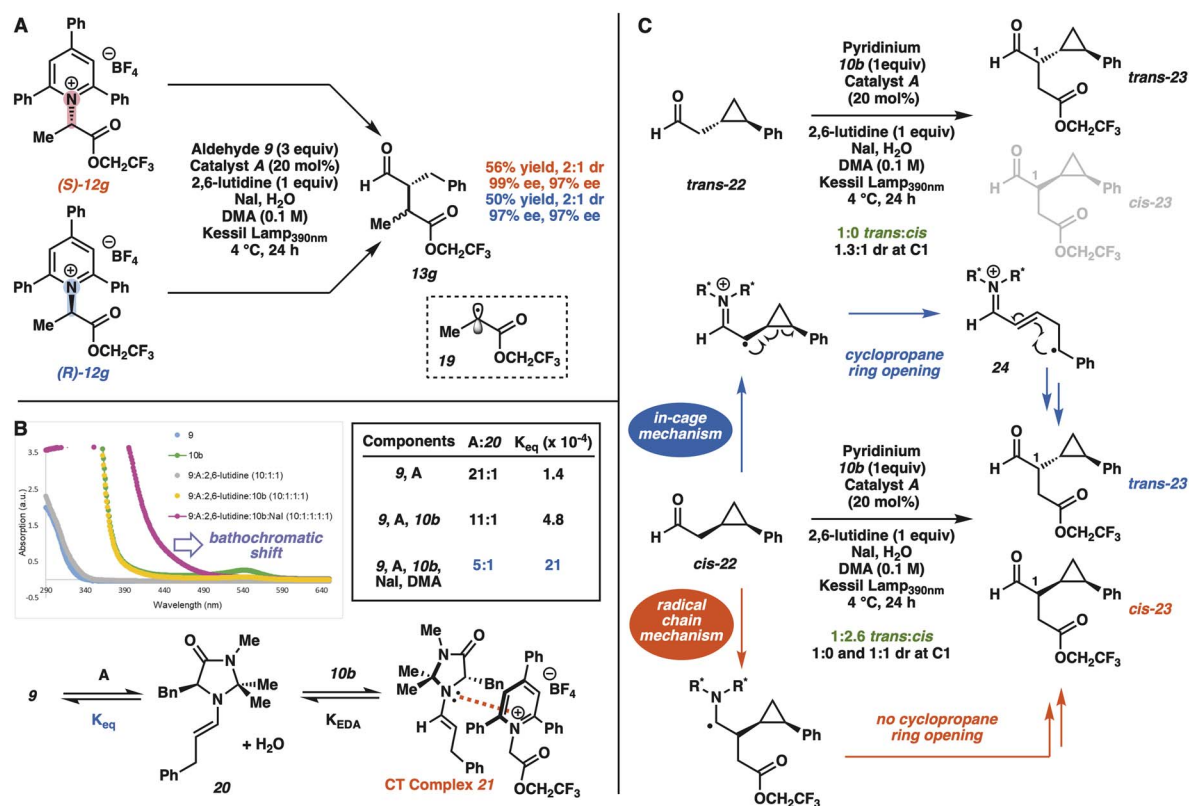
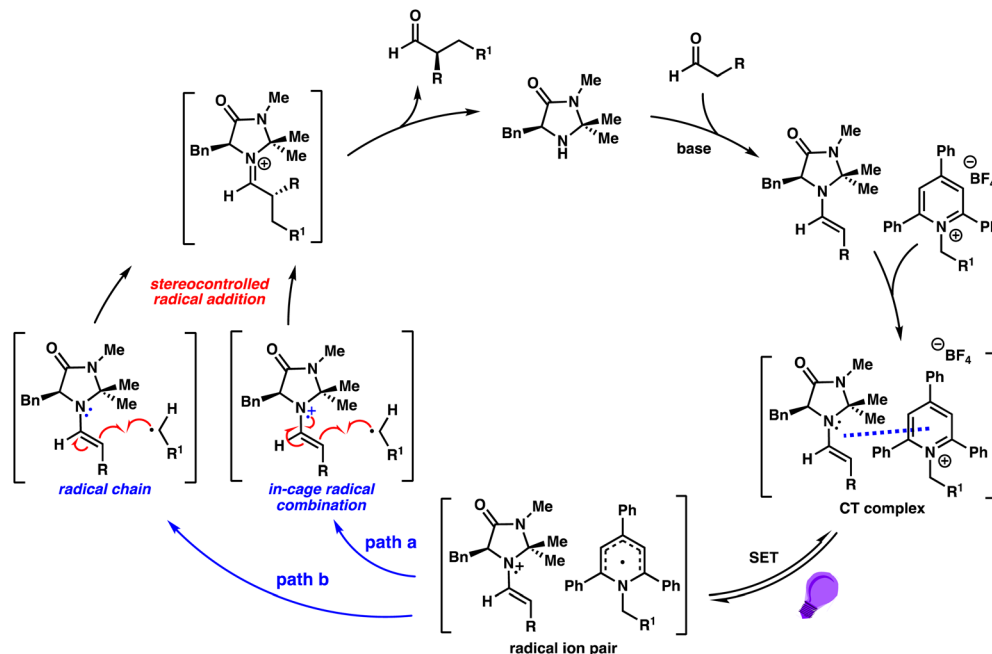


Fig. 1 Mechanistic experiments.





Scheme 3 Proposed mechanism.

in-cage radical combination process (Fig. 1C and S7[†]).^{4g,5a} Radical probe *trans*-22 exclusively formed the alkylation product *trans*-23 as a mixture of diastereomers at C1, which is consistent with either a radical chain or in-cage radical combination. With radical probe *cis*-22, the expectation was that an in-cage radical process would exclusively furnish the thermodynamically stable alkylation product *trans*-23 via acyclic intermediate 24.^{5a} Alternatively, the alkylation product *cis*-23 would form exclusively if the reaction proceeded through a radical chain.^{4g} Surprisingly, starting from radical probe *cis*-22, we isolated both *trans* and *cis* isomers of alkylation product 23 in a 1 : 2.6 ratio.

These observations suggest that the catalytic enantioselective reaction may proceed simultaneously through two highly enantioselective processes (Scheme 3 and Fig. S7[†]): an in-cage radical combination mechanism (path a) and a radical chain mechanism (path b). Although we cannot rule out the possibility of a radical chain mechanism with cyclopropane ring opening as an off-cycle process, we believe the measured quantum yield of 4 may be more consistent with the co-existence of two distinct mechanisms.²³

Conclusions

In summary, we have developed a catalytic enantioselective alkylation of aldehydes with pyridinium salts derived from amino acids and other α -stabilized amines. The reaction is enabled by a visible light activated CT complex between electron-deficient pyridinium salts and electron-rich components of the reaction. The mild conditions are compatible with several functional groups, enabling the enantioselective synthesis of lignan natural products. Future studies will

examine the mechanism of this process in more detail. We anticipate this approach may be extended to the photochemical catalytic enantioselective alkylation of several classes of carbonyl compounds with pyridinium salts based on other modes of catalysis.

Data availability

The datasets supporting this article have been uploaded as part of the ESI.[†]

Author contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

- 1 (a) V. Farina, J. T. Reeves, C. H. Senanayake and J. J. Song, *Chem. Rev.*, 2006, **106**, 2734; (b) N. A. McGrath, M. Brichacek and J. T. Njardarson, *J. Chem. Educ.*, 2010, **87**, 1348; (c) R. M. Wilson and S. J. Danishefsky, *Angew. Chem., Int. Ed.*, 2010, **49**, 6032; (d) W. H. Brooks, W. C. Guida and K. G. Daniel, *Curr. Top. Med. Chem.*, 2011, **11**, 760; (e) D. J. Newman and G. M. Cragg, *J. Nat. Prod.*, 2020, **83**, 770.
- 2 (a) D. L. Hughes, in *Alkylation of enolates*, Springer-Verlag, 1999, pp. 1273–1294; (b) T. Wirth, *New strategies to α -alkylated α -amino acids*, Wiley-VCH Verlag GmbH, 2000, pp. 26–33; (c) K. Koga, *Organomet. News*, 2003, **3**, 100; (d) K. Maruoka and T. Ooi, *Chem. Rev.*, 2003, **103**, 3013; (e) J. Eames and M. J. Suggate, *Angew. Chem., Int. Ed.*, 2005, **44**, 186; (f) M. Braun and T. Meier, *Synlett*, 2006, **5**, 661; (g) M. Ikunaka and K. Maruoka, in *Asymmetric phase-transfer catalysis for the production of non-proteinogenic α -amino acids*, Wiley-VCH Verlag GmbH & Co. KGaA, 2010, pp. 151–169; (h) C. M. Reeves and B. M. Stoltz, in *Catalytic enantioselective alkylation of prochiral ketone enolates*, Wiley-VCH Verlag GmbH & Co. KGaA, 2012, pp. 1–10; (i) S. Shirakawa and K. Maruoka, in *Asymmetric α -functionalization of carbonyl compounds and alkylation of enolates*, Georg Thieme Verlag, 2012, pp. 601–615; (j) M. Remes and J. Vesely, in *α -Alkylation of carbonyl compounds*, John Wiley & Sons, Inc., 2013, pp. 267–312; (k) J. C. Hethcox, S. E. Shockley and B. M. Stoltz, *ACS Catal.*, 2016, **6**, 6207; (l) U. Kazmaier, *Org. Chem. Front.*, 2016, **3**, 1541; (m) S. G. Davies, A. M. Fletcher, P. M. Roberts and J. E. Thomson, *Tetrahedron: Asymmetry*, 2017, **28**, 1842; (n) A. Cruz, I. I. Padilla-Martinez and M. E. Bautista-Ramirez, *Curr. Org. Synth.*, 2018, **15**, 38; (o) S. E. Denmark and G. L. Beutner, *Angew. Chem., Int. Ed.*, 2008, **47**, 1560; (p) S. Mondal, F. Dumur, D. Gignes, M. P. Sibi, M. P. Bertrand and M. Nechab, *Chem. Rev.*, 2022, **122**, 5842; (q) J. Guo, X. Liu, C. He, F. Tan, S. Dong and X. Feng, *Chem. Commun.*, 2018, **54**, 12254; (r) H. Hu, J. Xu, W. Liu, S. Dong, L. Lin and X. Feng, *Org. Lett.*, 2018, **20**, 5601; (s) Y. Luo, Q. Wei, L. Yang, Y. Zhou, W. Cao, Z. Su, X. Liu and X. Feng, *ACS Catal.*, 2022, **12**, 12984; (t) J. Xu, Z. Zhong, M. Jiang, Y. Zhou, X. Liu and X. Feng, *CCS Chem.*, 2020, **3**, 1894.
- 3 (a) D. A. Nicewicz and D. W. C. MacMillan, *Science*, 2008, **322**, 77; (b) D. A. Nagib, M. E. Scott and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2009, **131**, 10875; (c) H.-W. Shih, M. N. Vander Wal, R. L. Grange and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2010, **132**, 13600; (d) E. R. Welin, A. A. Warkentin, J. C. Conrad and D. W. C. MacMillan, *Angew. Chem., Int. Ed.*, 2015, **54**, 9668.
- 4 (a) M. Neumann, S. Földner, B. König and K. Zeitler, *Angew. Chem., Int. Ed.*, 2011, **50**, 951; (b) M. Cherevatskaya, M. Neumann, S. Földner, H. Christoph, K. Susanne, D. Stephan, P. Arno, Z. Kirsten and K. Burkhard, *Angew. Chem., Int. Ed.*, 2012, **51**, 4062; (c) K. Fidaly, C. Ceballos, A. Falguières, M. S.-I. Veitia, A. Guy and C. Ferroud, *Green Chem.*, 2012, **14**, 1293; (d) P. Wu, P. C. He, J. Wang, X. Peng, X. Li, Y. An and C. Duan, *J. Am. Chem. Soc.*, 2012, **134**, 14991; (e) P. Riente, A. M. Adams, J. Albero, E. Palomares and M. A. Pericàs, *Angew. Chem., Int. Ed.*, 2014, **53**, 9613; (f) Y. Zhu, L. Zhang and S. Luo, *J. Am. Chem. Soc.*, 2014, **136**, 14642; (g) A. Gualandi, M. Marchini, L. Mengozzi, M. Natali, M. Lucarini, P. Ceroni and P. G. Cozzi, *ACS Catal.*, 2015, **5**, 5927; (h) X. Li, J. Wang, D. Xu, Z. Sun, Q. Zhao, W. Peng, Y. Li, G. Zhang, F. Zhang and X. Fan, *ACS Sustainable Chem. Eng.*, 2015, **3**, 1017; (i) T. Rigotti, A. Casado-Sánchez, S. Cabrera, R. Pérez-Ruiz, M. Liras, V. A. de la Peña O'Shea and J. A. Alemán, *ACS Catal.*, 2018, **8**, 5928; (j) A. Gualandi, M. Marchini, L. Mengozzi, H. T. Kidanu, A. Franc, P. Ceroni and P. G. Cozzi, *Eur. J. Org. Chem.*, 2020, 1486.
- 5 (a) E. Arceo, I. D. Jurberg, A. Álvarez-Fernández and P. Melchiorre, *Nat. Chem.*, 2013, **5**, 750; (b) M. Silvi, E. Arceo, I. D. Jurberg, C. Cassani and P. Melchiorre, *J. Am. Chem. Soc.*, 2015, **137**, 6120; (c) A. Bahamonde and P. Melchiorre, *J. Am. Chem. Soc.*, 2016, **138**, 8019; (d) G. Filippini, M. Silvi and P. Melchiorre, *Angew. Chem., Int. Ed.*, 2017, **56**, 4447.
- 6 (a) Y.-Q. Zou, F. M. Hörmann and T. Bach, *Chem. Soc. Rev.*, 2018, **47**, 278; (b) M. Silvi and P. Melchiorre, *Nature*, 2018, **554**, 41; (c) S. Roy, H. Paul and I. Chatterjee, *Eur. J. Org. Chem.*, 2022, **25**, e202200446.
- 7 (a) C. O. Tuck, E. Pérez, I. T. Horváth, R. A. Sheldon and M. Poliakov, *Science*, 2012, **337**, 695; (b) T. M. Lammens, M. C. R. Franssen, E. L. Scott and J. P. M. Sanders, *Biomass Bioenergy*, 2012, **44**, 168; (c) T. Yan, B. L. Feringa and K. Barta, *Sci. Adv.*, 2017, **3**, eaao6494.
- 8 (a) A. R. Katritzky, R. H. Manzo, J. M. Lloyd and R. C. Patel, *Angew. Chem., Int. Ed.*, 1980, **19**, 306; (b) S. Sowmiah, J. M. S. S. Esperança, L. P. N. Rebelo and C. A. M. Afonso, *Org. Chem. Front.*, 2018, **5**, 453.
- 9 (a) R. S. Mulliken, *J. Am. Chem. Soc.*, 1950, **72**, 600; (b) R. S. Mulliken, *J. Phys. Chem.*, 1952, **56**, 801; (c) J. K. Kochi, *Angew. Chem., Int. Ed.*, 1988, **27**, 1227; (d) R. A. Marcus, *Angew. Chem., Int. Ed.*, 1993, **32**, 1111; (e) S. V. Rosokha and J. K. Kochi, *Acc. Chem. Res.*, 2008, **41**, 641.
- 10 (a) C. G. S. Lima, T. M. Lima, M. Duarte, I. D. Jurberg and M. W. Paixão, *ACS Catal.*, 2016, **6**, 1389; (b) G. E. M. Crisenza, D. Mazzarella and P. Melchiorre, *J. Am. Chem. Soc.*, 2020, **142**, 5461; (c) Y.-Q. Yuan, S. Majumder, M.-H. Yang and S.-R. Guo, *Tetrahedron Lett.*, 2020, **61**, 151506; (d) X. Cheng, A. Lei, T.-S. Mei, H.-C. Xu, K. Xu and C. Zeng, *CCS Chem.*, 2022, **4**, 1120.
- 11 A. R. Katritzky, G. Z. de Ville and R. C. Patel, *Tetrahedron Lett.*, 1980, **21**, 1723.
- 12 (a) N. F. Eweiss, A. R. Katritzky, P.-L. Nie and C. A. Ramsden, *Synthesis*, 1977, **1977**, 634; (b) A. R. Katritzky, *Tetrahedron*, 1980, **36**, 679; (c) A. R. Katritzky and C. M. Marson, *Angew. Chem., Int. Ed.*, 1984, **23**, 420.
- 13 (a) F.-S. He, S. Ye and J. Wu, *ACS Catal.*, 2019, **9**, 8943; (b) Y. Pang, D. Moser and J. Cornella, *Synthesis*, 2020, **52**, 489; (c) S. L. Rössler, B. J. Jelier, E. Magnier, G. Dagousset,



- E. M. Carreira and A. Togni, *Angew. Chem., Int. Ed.*, 2020, **59**, 9264.
- 14 (a) C. H. Basch, J. Liao, J. Xu, J. J. Piane and M. P. Watson, *J. Am. Chem. Soc.*, 2017, **139**, 5313; (b) W. Guan, J. Liao and M. P. Watson, *Synthesis*, 2018, **50**, 3231; (c) J. Liao, W. Guan, B. P. Boscoe, J. W. Tucker, J. W. Tomlin, M. R. Garnsey and M. P. Watson, *Org. Lett.*, 2018, **20**, 3030; (d) M. E. Hoerrner, K. M. Baker, C. H. Basch, E. M. Bampo and M. P. Watson, *Org. Lett.*, 2019, **21**, 7356.
- 15 (a) J. Liao, C. H. Basch, M. E. Hoerrner, M. R. Talley, B. P. Boscoe, J. W. Tucker, M. R. Garnsey and M. P. Watson, *Org. Lett.*, 2019, **21**, 2941; (b) R. Martin-Montero, V. R. Yatham, H. Yin, J. Davies and R. Martin, *Org. Lett.*, 2019, **21**, 2947; (c) S. Ni, C.-X. Li, Y. Mao, J. Han, Y. Wang, H. Yan and Y. Pan, *Sci. Adv.*, 2019, **5**, eaaw9516; (d) H. Yue, C. Zhu, L. Shen, Q. Geng, K. J. Hock, T. Yuan, L. Cavallo and M. Rueping, *Chem. Sci.*, 2019, **10**, 4430–4435.
- 16 S.-Z. Sun, C. Romano and R. Martin, *J. Am. Chem. Soc.*, 2019, **141**, 16197.
- 17 (a) F. J. R. Klauck, M. J. James and F. Glorius, *Angew. Chem., Int. Ed.*, 2017, **56**, 12336; (b) M. Ociepa, J. Turkowska and D. Gryko, *ACS Catal.*, 2018, **8**, 11362; (c) M.-M. Zhang and F. Liu, *Org. Chem. Front.*, 2018, **5**(23), 3443; (d) F. J. R. Klauck, H. Yoon, M. J. James, M. Lautens and F. Glorius, *ACS Catal.*, 2019, **9**, 236; (e) J. Yi, S. O. Badir, L. M. Kammer, M. Ribagorda and G. A. Molander, *Org. Lett.*, 2019, **21**, 3346; (f) Z.-F. Zhu, M.-M. Zhang and F. Liu, *Org. Biomol. Chem.*, 2019, **17**, 1531; (g) G. R. Mathi, Y. Jeong, Y. Moon and S. Hong, *Angew. Chem., Int. Ed.*, 2020, **59**, 2049.
- 18 (a) J. Hu, G. Wang, S. Li and Z. Shi, *Angew. Chem., Int. Ed.*, 2018, **57**, 15227; (b) F. Sandfort, F. Strieth-Kalthoff, F. J. R. Klauck, M. J. James and F. Glorius, *Chem.–Eur. J.*, 2018, **24**, 17210; (c) J. Wu, L. He, A. Noble and V. K. Aggarwal, *J. Am. Chem. Soc.*, 2018, **140**, 10700; (d) J. Hu, B. Cheng, X. Yang and T.-P. Loh, *Adv. Synth. Catal.*, 2019, **361**, 4902; (e) M. J. James, F. Strieth-Kalthoff, F. Sandfort, F. J. R. Klauck, F. Wagener and F. Glorius, *Chem.–Eur. J.*, 2019, **25**, 8240; (f) J. Wu, P. S. Grant, X. Li, A. Noble and V. K. Aggarwal, *Angew. Chem., Int. Ed.*, 2019, **58**, 5697; (g) M. Lübbesmeyer, E. G. Mackay, M. A. R. Raycroft, J. Elfert, D. A. Pratt and A. Studer, *J. Am. Chem. Soc.*, 2020, **142**, 2609.
- 19 A conceptually distinct study was recently reported for the Ni-catalyzed enantioselective hydroamination of amino alkenes with pyridinium salts: S.-Z. Sun, Y.-M. Cai, D.-L. Zhang, J.-B. Wang, H.-Q. Yao, X.-Y. Rui, R. Martin and M. Shang, *J. Am. Chem. Soc.*, 2022, **144**, 1130.
- 20 F. Parsaee, M. C. Senarathna, P. B. Kannangara, S. N. Alexander, P. D. E. Arche and E. R. Welin, *Nat. Rev. Chem.*, 2021, **5**, 486.
- 21 (a) C.-S. Zhang, L. Bao, K.-Q. Chen, Z.-X. Wang and X.-Y. Chen, *Org. Lett.*, 2021, **23**, 1577; (b) M.-C. Fu, R. Shang, B. Zhao, B. Wang and Y. Fu, *Science*, 2019, **363**, 1429.
- 22 For a recent review of photocatalysis in natural product synthesis, see: M. S. Galliher, B. J. Roldan and C. R. J. Stephenson, *Chem. Soc. Rev.*, 2021, **50**, 10044.
- 23 See ESI† for details.
- 24 We cannot rule out the possibility that DMA and other reaction components, such as 2,6-lutidine, also impact the nature of the CT complex.

