



Cite this: *Org. Biomol. Chem.*, 2024, **22**, 6684

Received 26th June 2024,  
Accepted 31st July 2024

DOI: 10.1039/d4ob01063a

rsc.li/obc

## Enantioselective Lewis base catalysed allylation of picoline- and quinaldine-based latent pronucleophiles†

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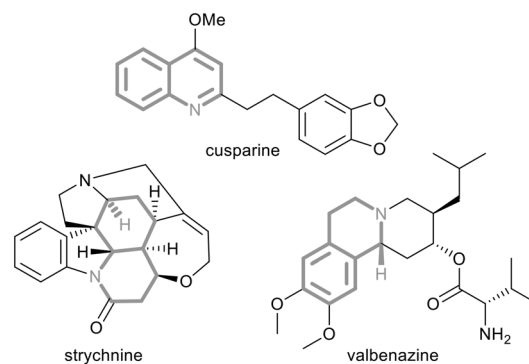
Picolines and quinaldines are valuable building blocks and intermediates in the synthesis of natural products and pharmaceuticals. Functionalization of the methyl group in picolines and quinaldines under mild conditions is challenging. We report that the concept of latent pronucleophiles enables Lewis base catalysed allylation of picolines and quinaldines with allylic fluorides starting from silylated picolines and quinaldines. Reactions afford enantioenriched allylation products when chiral Lewis base catalysts are used. The allylation products can be rapidly transformed to quinolizine-4-ones.

### Introduction

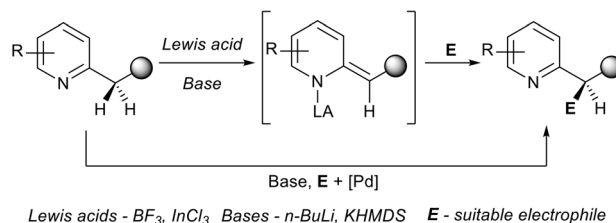
Nitrogen containing mono-, bi-, and polycyclic ring systems are omnipresent in biologically active compounds (Scheme 1a).<sup>1</sup> Among them, quinolines and pyridines that feature alkyl substituents in position 2, often referred to as picolines and quinaldines, are frequently found as key structural motifs in natural products and pharmaceuticals.<sup>2</sup> C–H functionalization of pyridines and their higher homologues to access picoline type structures is challenging due to their low intrinsic reactivity and often requires two-step processes.<sup>3</sup> Another strategy toward these structures, functionalization of the methylene carbon in picolines, usually involves deprotonation followed by reaction with an electrophile. However, the formation of picoline and quinaldine anions requires strong bases<sup>4</sup> or combinations of a strong Lewis acid and a base which greatly reduces the reaction scope.<sup>5</sup> The reported enantioselective alkylations or allylations of methyl pyridines or quinolines require equimolar chiral auxiliaries,<sup>4</sup> harsh Lewis acids<sup>6</sup> or an intervention by a palladium catalyst<sup>7</sup> (Scheme 2b).

Functionalization of alkyl pyridines and quinolines in the presence of Lewis base catalysts is hard to achieve and has not been demonstrated universally.<sup>8</sup> A possible reason for this is

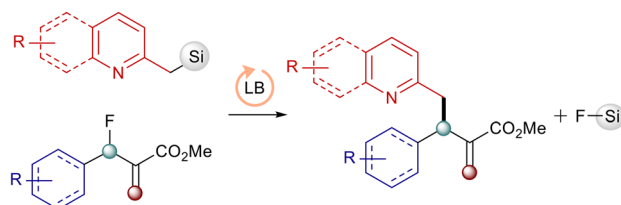
#### a) Representative quinoline alkaloids



#### b) Enantioselective alkylation and allylations of methyl pyridines and quinolines



#### c) This work - enantioselective C-allylation using latent alkyl azine pronucleophiles

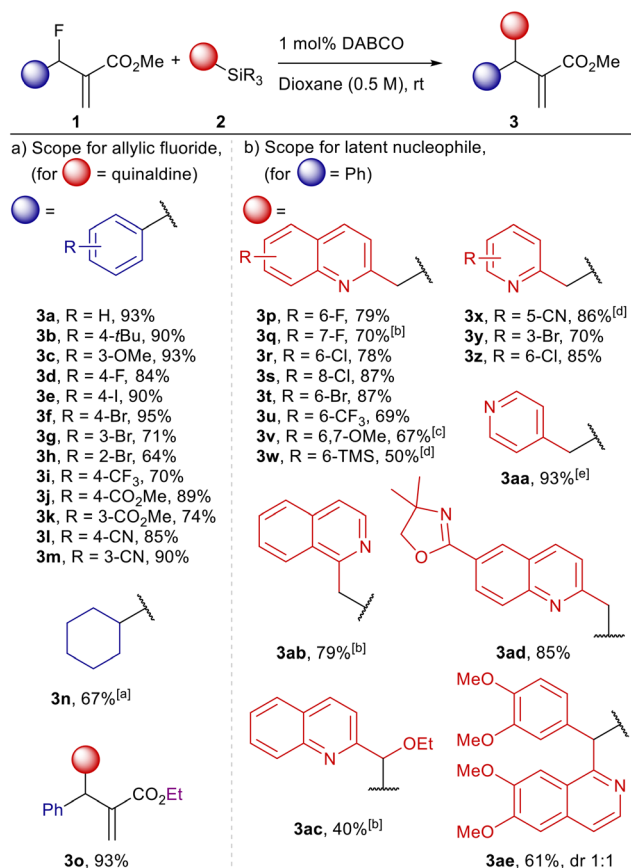


**Scheme 1** (a) Representative examples of quinoline and tetrahydroquinoline alkaloids; (b) established enantioselective alkylation and allylation procedures for 2-alkyl azines.<sup>4,6,7</sup> (c) The enantioselective allylation of alkyl pyridines and quinolines using latent pronucleophiles reported here.

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† Electronic supplementary information (ESI) available. See DOI: <https://doi.org/10.1039/d4ob01063a>





**Scheme 2** Reaction scope for (a) allylic fluorides and (b) latent pronucleophiles. For evaluation of the allylic fluorides trimethyl silyl quinaldine was used. Reaction scope for quinaldines and picolines was evaluated using fluoride **1a** and triethyl silyl quinaldines or picolines unless stated otherwise. Conditions: latent pronucleophile (1.1 equiv., 0.11 mmol), DABCO (1 mol%), allylic fluoride (1 equiv., 0.1 mmol), dioxane (0.5 M), N<sub>2</sub>-atmosphere. <sup>a</sup> 5 mol% of DABCO; <sup>b</sup> trimethylsilyl derivative was used; <sup>c</sup> crude trimethylsilyl derivative was used; <sup>d</sup> 10 mol% of DABCO; <sup>e</sup> trimethylsilyl derivative was used and 10 mol% of DABCO.

the nucleophilic character of the nitrogen atom in picolines and quinaldines which may compete with the Lewis base catalyst.<sup>9</sup> In enantioselective Lewis base catalysis this can lead to insurmountable limitations as the reactions may proceed autocatalytically without the involvement of the chiral catalyst preventing the catalyst control of the stereochemical outcome of the reaction.

To address such problems in Lewis base catalysed reactions using N-centered nucleophiles, we introduced the concept of latent (pro)nucleophiles in Lewis base catalysis.<sup>10</sup> Latent pronucleophiles are species that are themselves not strongly nucleophilic. However, at an opportune point in the catalytic cycle, they can be activated to react as strong anionic nucleophiles. If this activation is dependent on and mediated by the leaving group released during activation of the electrophile by a chiral Lewis base, the reactions exhibit excellent chemo-, regio- and enantioselectivity.<sup>10,11</sup> The combination of silylated pronucleophile, where silyl group serves as a locator of the

nucleophilic position and a readily available allylic fluoride<sup>12</sup> serving as electrophilic coupling partner<sup>13</sup> has also proven effective in allylation of C-centered nucleophiles in previous studies by Shibata,<sup>14</sup> Companyó<sup>15</sup> and our group.<sup>10,11</sup> We hypothesized, and here we report, that the concept of latent pronucleophiles can be a blueprint for the enantioselective C-allylation of methyl pyridines and quinolines when such compounds are used as silylated pronucleophiles in combination with fluorinated electrophiles (Scheme 1c).

## Results and discussion

We initiated our investigations with optimization of the DABCO-catalysed reactions between allylic fluorides **1**, derived from the corresponding Morita–Baylis–Hilman (MBH) alcohols, and silyl azines **2** produced by direct silylation of quinaldines or pyridines (Scheme 2, for details of optimization studies see ESI†). Trimethylsilyl (TMS), triethylsilyl (TES) and *tert*-butyldimethylsilyl (TBS) derivatives of quinaldine were investigated as suitable pronucleophiles. TMS quinaldine reached full conversion faster compared to the TES analogue while TBS quinaldine did not show notable reactivity under comparable conditions. When TMS quinaldine **2a** was used in combination with **1a** in the absence of Lewis base catalyst no reaction occurred, yet only 0.5 mol% of DABCO was sufficient to achieve full conversion in larger scale reactions using 5 mmol of **1a**. More polar solvents enabled faster conversion and high product yields with dioxane delivering the best results. The optimized reaction conditions included a slight excess of latent pronucleophile and 1 mol% of DABCO as catalyst in dioxane at room temperature.

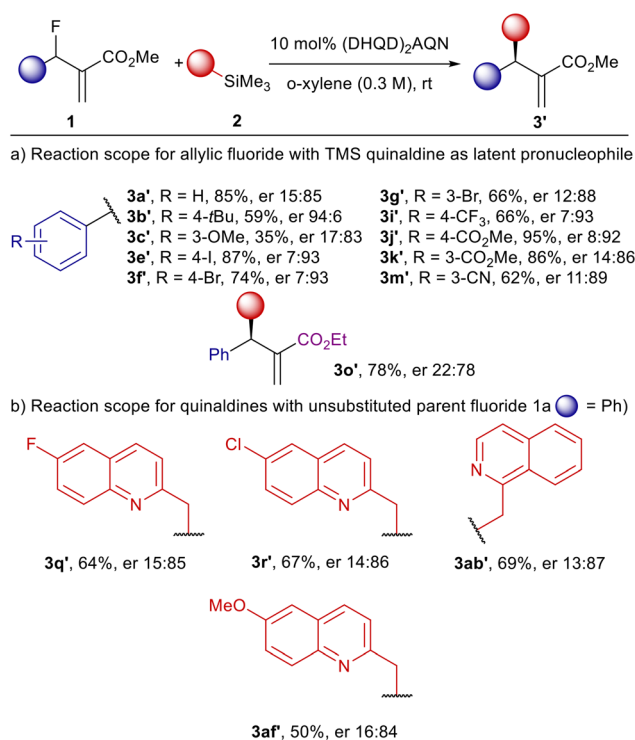
The reaction scope for allylic fluorides was evaluated first with a set of electron rich allylic fluorides (**3b–3c**) which gave the corresponding products in excellent yields of 90% and above (Scheme 2a). Allylic fluorides featuring *ortho*, *meta*, and *para* substituted aryl halides were well tolerated and furnished the allylated quinaldines (**3d–3g**) in good yields (70–95%) though slightly lower yield of 64% was observed for **3h** which features a bromo substituent in *ortho* position adjacent to the reactive centre. Reactions of allylic fluorides featuring electron withdrawing groups (**3i–3m**) were qualitatively observed to proceed with higher rates and the yields remained high as in the previous cases (70–90%). Allylic fluoride carrying a cyclohexyl group instead of an aryl substituent delivered the desired product **3n** with satisfying efficacy of 67%.

The reaction scope for the nucleophilic partner was examined with a structurally diverse set of silylated quinaldines, picolines and related compounds (Scheme 2b). The TES derivatives were preferred as they proved easier to handle than the corresponding TMS derivatives. Halogenated quinaldines with substituents in 6, 7, and 8 position, respectively, underwent the reactions with **1a** smoothly with yields for products **3p–3t** between 70 and 87%. Quinaldines with electron-withdrawing trifluoromethyl and oxazoline substituents also delivered products in high yields up to 85% (**3u** and **3ad**).



Interestingly, the presence of a trimethylaryl silane within the allylic fluoride was also well tolerated in these reactions with 6-TMS-substituted quinaldine **3w** obtained in 50% yield though increased catalyst loading was required to drive the reaction to completion. Even more complex quinaldines with additional aryl or alkoxy substituents at the methylene group performed well despite the increased steric crowding at the nucleophilic carbon. When 2-(ethoxy(trimethylsilyl)methyl)quinoline was used as the pronucleophile, the corresponding product **3ac** was obtained in 40% yield as a single diastereomer (the crude mixture contained two diastereomers but only one could be isolated in pure form). The silylated pronucleophile derived from papaverine gave the allylation product **3ae** in 61% yield as a statistical mixture of diastereomers. The use of the related silylated 1-methylisoquinoline further confirmed the generality of the process giving the product **3ab** in 79% yield. Picoline-based pronucleophiles also performed well under the optimized conditions with silylated 5-cyano-, 3-bromo and 6-chloro-2-picolines giving the desired products **3x**, **3y** and **3z** in 86%, 70% and 85% yield, respectively. Strikingly, silylated 4-picoline, which is itself nucleophilic and could compete with some Lewis base catalysts,<sup>9</sup> provided the corresponding product **3aa** in excellent yield of 93%. In this example, silylation has negligible effect on the nucleophilicity of the pyridine yet the desired reaction pathway appears to kinetically outcompete other possible pathways, *i.e.* pyridine acting as the nucleophile.

After extensively establishing the reactivity patterns in DABCO catalysed reactions, we focused on the asymmetric variant and examined the reactions in the presence of chiral Lewis base catalysts (Scheme 3). The commercially available cinchona alkaloids with a proven track record in transformations of other MBH adducts have been in focus of this study.<sup>10,14e,16</sup> In our previous work, we observed dimeric catalysts such as (DHQD)<sub>2</sub>PHAL and its pseudoenantiomer (DHQ)<sub>2</sub>PHAL to catalyse similar reactions exceptionally well. In the current study, (DHQD)<sub>2</sub>PHAL furnished products with high degrees of enantiocontrol with er up to 95 : 5 but showed poor regioselectivity for substitution of allylic electrophile. After extensive testing of reaction parameters, we arrived at the final set of conditions which involve 10 mol% (DHQD)<sub>2</sub>AQN in *o*-xylene with 1.5 equivalents of latent pronucleophile (for details of optimization studies see ESI†). In contrast to the reactions with DABCO, good conversions were observed only with TMS-quinaldines which was attributed to significantly lower reaction rates in reactions with chiral Lewis base catalysts. We employed a variety of allylic fluorides to test the reaction scope (Scheme 3a). Among electron rich (**3b'** and **3c'**), electron poor (**3i'**–**3m'**), and allylic fluorides featuring aryl halides (**3e'**–**3g'**) the enantioselectivities ranged from 14 : 86 er for **3k'** to 94 : 6 er for **3b'** while yields varied between 59% (**3b'**) to 95% (**3j'**). Yields were adversely influenced by electron donating substituents in allylic fluoride (**3c'**, 35%). Surprisingly, ethyl ester **3o'** was obtained in comparable yield but with a lower degree of stereocontrol compared to methyl ester **3a'**. While testing the scope for quinaldine and 1-methyl-



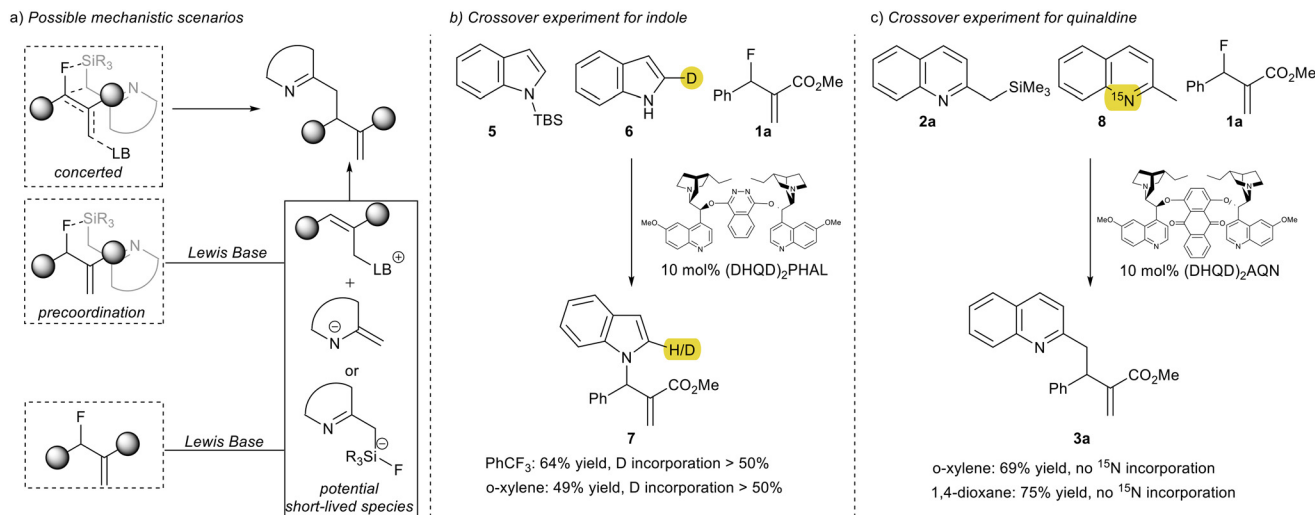
**Scheme 3** Scope of enantioselective allylation for (a) allylic fluorides and (b) latent pronucleophiles. Conditions: (DHQD)<sub>2</sub>AQN (10 mol%), latent pronucleophile (1.5 equiv., 0.15 mmol), allylic fluoride (1 equiv., 0.1 mmol), xylene (0.3 M) N<sub>2</sub>-atmosphere. The er values represent the order of elution and do not account for the stereochemical outcome being either *R* or *S*.

quinoline based pronucleophiles (Scheme 3b), the degree of enantiocontrol remained consistently around 15 : 85 (**3q'**–**3af'**) and yields ranged from 50% to 69%. The absolute configuration of the preferred product enantiomer when (DHQD)<sub>2</sub>AQN was used as the catalyst is tentatively assigned as *R* based on similar transformations using the same catalyst.<sup>16d,e</sup>

We observed the reactions to be a kinetic resolution. Both (DHQD)<sub>2</sub>PHAL and (DHQD)<sub>2</sub>AQN consume the same enantiomer of the allylic fluoride faster, however, the products are delivered as antipodes indicating that stereocontrol does not solely depend on the chiral backbone of the cinchona alkaloid but that it also depends on the linker in the dimeric catalyst (for details see ESI†).<sup>17</sup> Similar observations related to the influence of the linker in dimeric cinchona alkaloid catalysts have recently been reported in other transformations.<sup>18</sup>

Several mechanistic proposals have been put forward for the Lewis base catalysed reactions of allylic fluorides with different nucleophiles including concerted,<sup>14c,15</sup> stepwise,<sup>10</sup> and silicon-assisted pathways (Scheme 4a).<sup>15</sup> We first sought to test if the stepwise mechanism which has been reported in DABCO catalysed allylations of *N*-silylindoles with allylic fluorides holds in the presence of the less nucleophilic (DHQD)<sub>2</sub>PHAL. In a crossover experiment, allylic fluoride **1a** was reacted with silylated indole **5** and deuterium labelled indole **6** in the presence of (DHQD)<sub>2</sub>PHAL as the catalyst

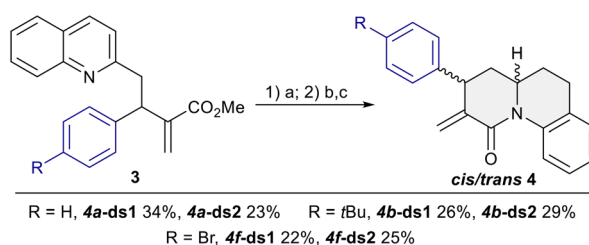




**Scheme 4** Mechanistic considerations. (a) Potential mechanistic scenarios for the allylic substitution. (b) Crossover experiment of latent nucleophile **5** and 2-D-indole **6** under enantioselective substitution conditions. (c) Crossover experiment of latent pronucleophile **2a** and <sup>15</sup>N enriched quinaldine **8** under standard enantioselective substitution conditions.

(Scheme 4b). The isolated products showed incorporation of deuterium slightly over 50% both in xylene and trifluorotoluene. We confirmed that deuterated indole does not react with **1a** in the presence of Lewis base catalyst and that there is no silyl transfer between **5** and **6** under the reaction conditions. These results indicate the transient formation of an indole anion and a crossover *via* acid–base equilibrium of indole anions derived from **5** and **6** and are consistent with a stepwise mechanism. To test if similar crossover can be observed in allylation of quinaldines, an equimolar mixture of <sup>15</sup>N enriched quinaldine **8** and trimethylsilyl quinaldine **2a** was subjected to allylation with **1a** using (DHQD)<sub>2</sub>AQN in *o*-xylene or 1,4-dioxane as solvent (Scheme 4c). The HRMS analysis of the reaction product did not show incorporation of the <sup>15</sup>N concluding that there was no acid–base equilibrium which would lead to crossover as in the case of *N*-allylation of indole. While this could speak in favour of a concerted mechanism, formation of a tight ion pair in a solvent cage<sup>19</sup> would also be consistent with this observation. The concerted mechanism proposed in allylations of silylenolethers<sup>15</sup> would either lead to *N*-allylation of picolines and quinaldines *via* a six membered transition state which was not observed or would proceed *via* a highly ordered ternary four-membered transition state that leads to C-allylation products observed in these reactions. Finally, the fact that (DHQD)<sub>2</sub>PHAL and (DHQD)<sub>2</sub>AQN consume the same enantiomer of the allylic fluoride faster but deliver the opposite antipodes of the product also speaks against the concerted mechanism.

To demonstrate the synthetic utility of the C-allylation products obtained in this study, a short synthetic sequence was developed for synthesis of functionalized quinolizine-4-ones (Scheme 5). To this end, a modified protocol for reductive alkylation<sup>20</sup> was employed to obtain reduced quinaldine. A two-step process of saponification followed by PyBop mediated



**Scheme 5** Transformation of allylated quinaldines to functionalized quinolizine-4-ones. (a) Hantzsch ester (2.5 equiv.), *m*-F<sub>3</sub>C-C<sub>6</sub>H<sub>4</sub>-B(OH)<sub>2</sub> (0.25 equiv.), C<sub>2</sub>H<sub>4</sub>Cl<sub>2</sub>, 60 °C; (b) LiOH (4.0 equiv.), THF : EtOH, 40 °C; (c) PyBOP (1.015 equiv.), DIPEA (1.1 equiv.), DCM : DMF.

lactam formation gave the desired quinolizine-4-ones. Gratifyingly, both diastereomers of each product could be isolated separately and the combined yields were 57% for **4a/4a'**, 54% for **4b/4b'**, and 47% for **4f/4f'** over two steps.

## Conclusions

We have developed a robust tool for regio- and enantioselective allylation of quinaldines and picolines in the presence of Lewis base catalysts. The reactions are enabled by the concept of latent pronucleophiles in Lewis base catalysis and the use of silyl derivatives of quinaldines and picolines in combination with allylic fluorides. They feature broad scope and deliver the products with degrees of enantiocontrol as high as 94 : 6. The products lend themselves to a rapid transformation to quinolizine-4-one frameworks. Interestingly, the stereocontrol in these reactions does not solely depend on the chiral backbone of the cinchona alkaloid but it also depends on the linker in



the dimeric catalyst. The mechanistic implications of this observation are currently under investigation.

## Data availability

The data supporting this article have been included as part of the ESI.†

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

This work was a part of a German Science Foundation (DFG) funded project number 445755502. State of Thuringia (Fellowship to M. L.) is gratefully acknowledged. We thank Dr Nico Ueberschaar for help and assistance with the MS analysis in the crossover experiment and Ms Olena Nosovska for critical proofreading of the manuscript. Support of Thüringer Aufbaubank through project NMR-ESU (2022 FGI 0015) is gratefully acknowledged.

## References

- M. M. Heravi and V. Zadsirjan, *RSC Adv.*, 2020, **10**, 44247–44311.
- (a) A. Fournet, A. A. Barrios, V. Muñoz, R. Hocquemiller, A. Cavé and J. Bruneton, *Antimicrob. Agents Chemother.*, 1993, **37**, 859–863; (b) X.-F. Shang, S. L. Morris-Natschke, Y.-Q. Liu, X. Guo, X.-S. Xu, M. Goto, J.-C. Li, G.-Z. Yang and K.-H. Lee, *Med. Res. Rev.*, 2018, **38**, 775–828.
- S. Maity, A. Bera, A. Bhattacharjya and P. Maity, *Org. Biomol. Chem.*, 2023, **21**, 5671–5690.
- J. J. Gladfelder, S. Ghosh, M. Podunavac, A. W. Cook, Y. Ma, R. A. Woltornist, I. Keresztes, T. W. Hayton, D. B. Collum and A. Zakarian, *J. Am. Chem. Soc.*, 2019, **141**, 15024–15028.
- (a) B. M. Trost and D. A. Thaisrivongs, *J. Am. Chem. Soc.*, 2008, **130**, 14092–14093; (b) B. M. Trost and D. A. Thaisrivongs, *J. Am. Chem. Soc.*, 2009, **131**, 12056–12057.
- M. Meazza, F. Tur, N. Hammer and K. A. Jørgensen, *Angew. Chem., Int. Ed.*, 2017, **56**, 1634–1638.
- (a) R. Murakami, K. Sano, T. Iwai, T. Taniguchi, K. Monde and M. Sawamura, *Angew. Chem., Int. Ed.*, 2018, **57**, 9465–9469; (b) S.-C. Sha, J. Zhang, P. J. Carroll and P. J. Walsh, *J. Am. Chem. Soc.*, 2013, **135**, 17602–17609; (c) B. M. Trost, D. A. Thaisrivongs and J. Hartwig, *J. Am. Chem. Soc.*, 2011, **133**, 12439–12441.
- (a) N. S. Kumar, L. C. Rao, N. JagadeeshBabu, V. Dileep Kumar, U. S. N. Murthy and H. M. Meshram, *Synlett*, 2015, **26**, 1808–1814; (b) J. Izquierdo, A. Landa, I. Bastida, R. López, M. Oiarbide and C. Palomo, *J. Am. Chem. Soc.*, 2016, **138**, 3282–3285.
- F. Brotzel, B. Kempf, T. Singer, H. Zipse and H. Mayr, *Chem. – Eur. J.*, 2007, **13**, 336–345.
- Y. Zi, M. Lange, C. Schultz and I. Vilotijevic, *Angew. Chem., Int. Ed.*, 2019, **58**, 10727–10731.
- (a) Y. Zi, M. Lange and I. Vilotijevic, *Chem. Commun.*, 2020, **56**, 5689–5692; (b) M. Lange, Y. Zi and I. Vilotijevic, *J. Org. Chem.*, 2020, **85**, 1259–1269; (c) M. Lange, Y. Zi and I. Vilotijevic, *Synlett*, 2020, **31**, 1237–1243; (d) S. Kumar, M. Lange, Y. Zi, H. Görls and I. Vilotijevic, *Chem. – Eur. J.*, 2023, **29**, e202300641; (e) M. Lange, F. L. Meyer, O. Nosovska and I. Vilotijevic, *Org. Lett.*, 2023, **25**, 9097–9102.
- (a) F. O. Usman, A. R. Gogoi, J. C. Mixdorf, O. Gutierrez and H. M. Nguyen, *Angew. Chem., Int. Ed.*, 2023, **62**, e202314843; (b) J. C. Mixdorf, A. M. Sorlin, Q. Zhang and H. M. Nguyen, *ACS Catal.*, 2018, **8**, 790–801.
- (a) K. Balaraman and C. Wolf, *Org. Lett.*, 2021, **23**, 8994–8999; (b) K. Balaraman and C. Wolf, *Sci. Adv.*, 2022, **8**, eabn7819.
- (a) Y. Sumii, T. Nagasaka, J. Wang, H. Uno and N. Shibata, *J. Org. Chem.*, 2020, **85**, 15699–15707; (b) T. Nishimine, H. Taira, S. Mori, O. Matsubara, E. Tokunaga, H. Akiyama, V. A. Soloshonok and N. Shibata, *Chem. Commun.*, 2017, **53**, 1128–1131; (c) S. Okusu, H. Okazaki, E. Tokunaga, V. A. Soloshonok and N. Shibata, *Angew. Chem., Int. Ed.*, 2016, **55**, 6744–6748; (d) T. Nishimine, H. Taira, E. Tokunaga, M. Shiro and N. Shibata, *Angew. Chem., Int. Ed.*, 2015, **55**, 359–363; (e) T. Nishimine, K. Fukushi, N. Shibata, H. Taira, E. Tokunaga, A. Yamano, M. Shiro and N. Shibata, *Angew. Chem., Int. Ed.*, 2013, **53**, 517–520.
- J. Duran, J. Mateos, A. Moyano and X. Companyó, *Chem. Sci.*, 2023, **14**, 7147–7153.
- (a) J.-R. Huang, H.-L. Cui, J. Lei, X.-H. Sun and Y.-C. Chen, *Chem. Commun.*, 2011, **47**, 4784–4786; (b) Z. Li, M. Frings, H. Yu, G. Raabe and C. Bolm, *Org. Lett.*, 2018, **20**, 7367–7370; (c) A. Lin, H. Mao, X. Zhu, H. Ge, R. Tan, C. Zhu and Y. Cheng, *Chem. – Eur. J.*, 2011, **17**, 13676–13679; (d) V. Dočekal, M. Šimek, M. Dračinský and J. Veselý, *Chem. – Eur. J.*, 2018, **24**, 13441–13445; (e) B. Formánek, M. Šimek, M. Kamlar, I. Cisařová and J. Veselý, *Synthesis*, 2019, **51**, 907–920; (f) O. Nosovska, P. Liebing and I. Vilotijevic, *Chem. – Eur. J.*, 2024, **30**, e202304014.
- In previous studies on the enantioselective substitution of allylic fluorides, we and other (compare ref. 10) observed that (DHQD)<sub>2</sub>AQ N and (DHQD)<sub>2</sub>PH AL produce the same product enantiomere.
- (a) P. J. Boratyński, *Mol. Diversity*, 2015, **19**, 385–422; (b) S. E. Luderer, B. Masoudi, A. Sarkar, C. Grant, A. Jaganathan, J. E. Jackson and B. Borhan, *J. Org. Chem.*, 2023, DOI: [10.1021/acs.joc.3c00084](https://doi.org/10.1021/acs.joc.3c00084); (c) K. C. Nicolaou, N. L. Simmons, Y. Ying, P. M. Heretsch and J. S. Chen, *J. Am. Chem. Soc.*, 2011, **133**, 8134–8137; (d) M. Wilking, C. G. Daniliuc and U. Hennecke, *Synlett*, 2014, **25**, 1701–1704.



- 19 (a) L. Herk, M. Feld and M. Szwarc, *J. Am. Chem. Soc.*, 1961, **83**, 2998–3005; (b) R. K. Lyon and D. H. Levy, *J. Am. Chem. Soc.*, 1961, **83**, 4290–4290; (c) C. Reichardt, *J. Org. Chem.*, 2022, **87**, 1616–1629; (d) C. G. Swain, M. S. Swain, A. L. Powell and S. Alunni, *J. Am. Chem. Soc.*, 1983, **105**, 502–513.
- 20 P. Adhikari, D. Bhattacharyya, S. Nandi, P. K. Kancharla and A. Das, *Org. Lett.*, 2021, **23**, 2437–2442.

