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# Sterically controlled isodesmic late-stage C–H iodination of arenes†

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Aryl iodides are key motifs in organic chemistry due to their versatility as linchpins in metal-mediated cross-coupling reactions for synthesis and drug discovery. These scaffolds are typically prepared indirectly from prefunctionalized starting materials or *via* electrophilic aromatic iodination protocols. These methods are limited to specific regioisomers by their inherent selectivities and/or the availability of the required starting materials. Herein, we describe the sterically controlled iodination of arenes through an isodesmic C–H/C–I bond metathesis approach enabled by our dual ligand-based catalysts for arene-limited nondirected C–H activation. The protocol gives direct access to a complementary product spectrum with respect to traditional methods. Its synthetic utility is demonstrated by a broad scope and the suitability for late-stage modification.

## Introduction

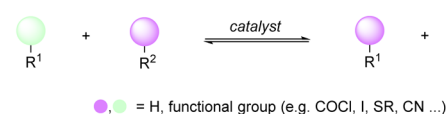
Aryl halides are synthetically versatile intermediates with an important role in the preparation of many organic molecules such as pharmaceuticals and agrochemicals.<sup>1</sup> Aryl iodides prove to be particularly advantageous as they constitute attractive coupling partners and precursors to organometallic species in cross-coupling reactions with higher reactivity than their chlorinated and brominated counterparts.<sup>2</sup> Thus, the direct conversion of C–H into C–I bonds is highly attractive, in order to access linchpins for further diversification. Electrophilic aromatic substitution (SEAr) reactions, widely used to synthesize aryl iodides, rely on the substrates' electronic properties to control the regioselectivity (Fig. 1A(I)).<sup>3</sup> However, the iodination of structurally complex arenes remains more challenging than the analogous chlorination and bromination, due to the limited availability of suitable electrophilic iodinating reagents, the typically required harsh reaction conditions leading to poor functional group tolerance.<sup>4</sup> Recent research has aimed for milder and more efficient electrophilic C–H iodination enabling the functionalization of challenging and complex molecules.<sup>5</sup> Despite these advances, many aryl iodides are prepared indirectly from prefunctionalized arenes, such as amines (Sandmeyer reaction),<sup>6</sup> carboxylic acids (*via* photochemistry),<sup>7</sup> aryl bromides (aromatic Finkelstein reaction),<sup>8</sup> or iododeborylation (Fig. 1A(II)).<sup>9</sup>

While delivering the desired compounds, these approaches require additional steps and remain limited by the availability of the required prefunctionalized starting materials. Intense efforts have been directed towards the transition metal catalyzed synthesis of aryl iodides.<sup>10</sup> Various transition metals have

### A. (Established) Routes to Aryl Iodides

<b>I. Electrophilic aromatic substitution</b> · regioselectivity governed by electronics · harsh reaction conditions · limited substrate scope	<b>II. Functional group interconversion</b> · Starting FG e.g. = Br, BR <sub>2</sub> , CO <sub>2</sub> H, N <sub>2</sub> <sup>+</sup> · selectivity determined by prefunctionalization · additional steps required
<b>III. Directed C–H iodination</b> · additional steps for DG introduction/removal · directing group controls selectivity · problem of diiodination	<b>IV. Nondirected C–H activation (this work)</b> · no DG required · sterically controlled selectivity · late-stage functionalization

### B. Concept of Isodesmic Functional Group Metathesis



### C. Reaction Design for the Sterically Controlled Iodination of Arenes

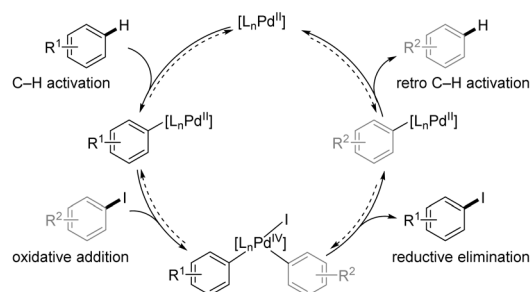


Fig. 1 Approaches towards the iodination of arenes.

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been used in conjunction with coordinating directing groups (DGs) on the substrate to enable efficient and broadly applicable C–H iodination protocols (Fig. 1A(III)).<sup>11</sup> Most of these protocols lead to *ortho* iodination, but specialized DGs have been reported that enable *meta* selectivity.<sup>12</sup> Li, Li and coworkers recently described directed *ortho* and *meta* C–H iodination reactions using a C–H/C–I metathesis approach with 2-nitro iodobenzene (**2**) as iodine source.<sup>13</sup> The authors proposed a Pd(II)/Pd(IV) cycle where the reductive elimination giving aryl iodide is favored over a competing biaryl formation. The report by Li, Li and coworkers uses the general strategy of isodesmic functional group metathesis, in which hydrogen substituents and/or functional groups are exchanged between two compounds without a change in the overall number and type of bonds (Fig. 1B).<sup>14</sup> Prominent examples for this approach are the contemporaneous reports by Morandi and Arndtsen on the interconversion of aryl chlorides and aryl iodides and related studies.<sup>15</sup>

Despite these advances in transition metal catalyzed C–H iodination, a direct iodination without DGs has not been reported to date. Recently, Pd-catalysts were developed that enable the nondirected activation/functionalization of unbiased arene C–H bonds resulting in valuable methods for late-stage modification.<sup>16</sup> Our group introduced a series of dual ligand-based Pd-catalysts for the nondirected C–H activation of complex (hetero)arenes enabling challenging functionalizations with predominantly sterically controlled regioselectivity.<sup>17</sup>

## Results and discussion

### Reaction development

We envisioned that the combination of our dual ligand catalysts and a C–H/C–I metathesis approach (Fig. 1C) could enable a sterically controlled direct iodination of complex arenes through a Pd(II)/Pd(IV) catalytic cycle.<sup>18</sup> We decided to investigate the iodination of *m*-cresol methyl ether (**1a**) as model substrate since here sterically and electronically preferred positions are orthogonal to one another, enabling us to directly monitor the factor(s) governing the regioselectivity (Table 1). Extensive optimization of the reaction conditions resulted in the use of *N*-acetylglycine and quinoxaline as suitable ligands, along with catalytic amounts of Ag<sub>2</sub>O that presumably works as Lewis acid activator and/or halide scavenger. Under these conditions even the strong electronic effect exerted by a methoxy group can be overcome, giving functionalization mainly in the  $\beta$ -position.<sup>19</sup> Control experiments confirm that both ligands are required for activity and steric control. The omission of Ag<sub>2</sub>O likewise leads to a decrease of yield and selectivity (for a discussion regarding the role of silver, see the section “Expanded mechanistic discussion” in the ESI†).

### Synthetic scope

We proceeded to investigate the substrate scope (Scheme 1). Naphthalene (**1b**) underwent iodination with excellent selectivity and synthetically useful yield. A wide range of mono-substituted arenes could be applied (**1c–h**). The iodination is

Table 1 Optimized reaction conditions and control experiments<sup>a,b</sup>

Entry	Deviation from standard conditions	Yield (%)	$\alpha : \beta : \gamma$
1	None	54	11 : 86 : 3
2	No Pd(TFA) <sub>2</sub>	2	—
3	No <i>N</i> -Ac-Gly-OH	12	59 : 0 : 41
4	No quinoxaline	39	46 : 6 : 48
5	No Ag <sub>2</sub> O	18	62 : 25 : 13

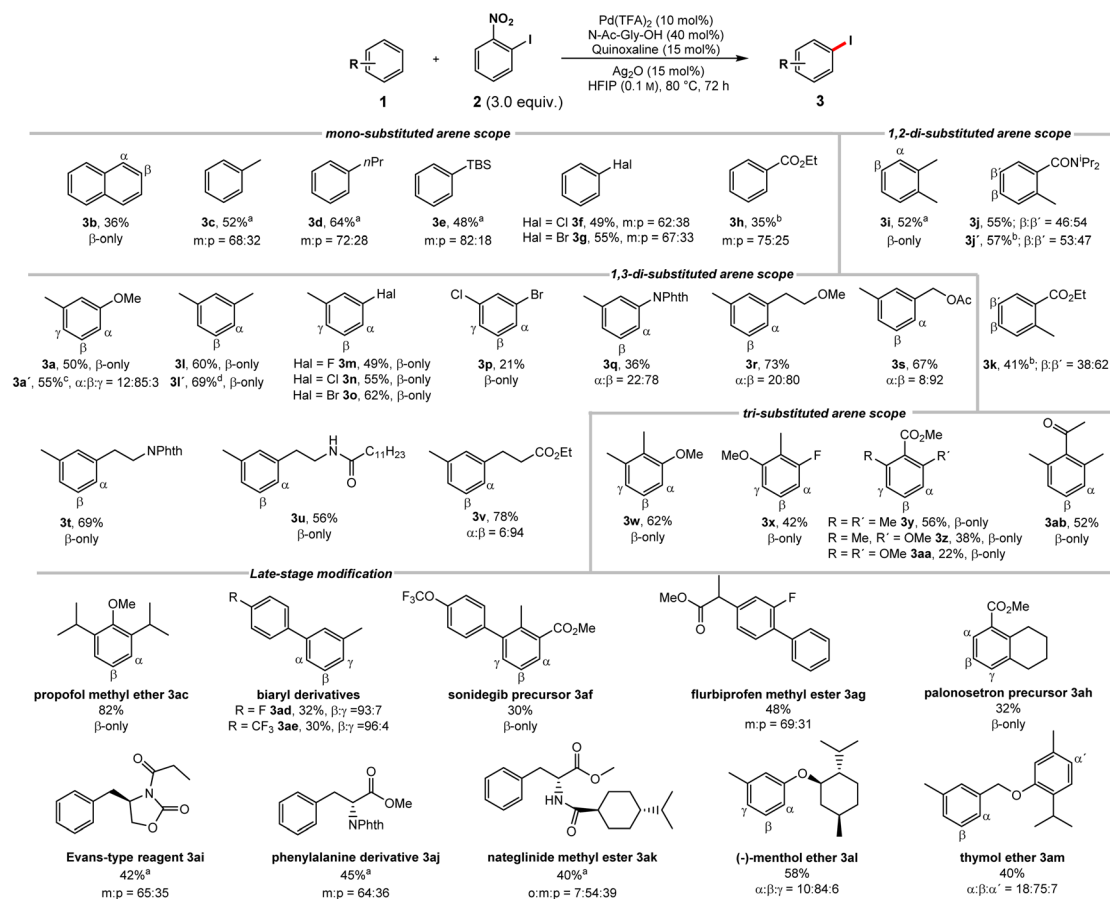
<sup>a</sup> Reactions performed on a 0.1 mmol scale. <sup>b</sup> Yields and regioselectivities determined by GC-FID using mesitylene as internal standard.

highly sensitive to steric effects, a methyl group being sufficient to completely suppress *ortho* product formation. In contrast, electronic effects have little to no influence on the regioselectivity.

Using a silylated benzene delivered the iodinated product **3e** in good yields. Notably, the C–H iodination of silyl arenes usually requires indirect approaches.<sup>20</sup> Aryl halides **1f** and **1g** show no *ortho* functionalization, despite being known to exhibit an *ortho* directing effect in related reports.<sup>16d</sup>

Importantly, the observed selectivity profile is complementary to electrophilic functionalizations of haloarenes.<sup>21</sup> Electron-poor ethyl benzoate (**1h**) gave *meta* and *para* iodination of the arene.<sup>22</sup> Despite being a potential DG, no functionalization occurred in *ortho* position. *o*-Xylene delivered **3i** as single isomer. Nonsymmetric 1,2-disubstituted arenes **1j–k** deliver nearly equal mixtures in the sterically accessible yet electronically very different  $\beta$  and  $\beta'$  positions, showcasing the low sensitivity to directing and electronic effects. 1,3-Disubstituted substrates, where electronically and sterically preferred positions are orthogonal gave preferential iodination in the sterically favored position (**3a**, **3l–v**). *m*-Xylene underwent iodination exclusively in the less congested  $\beta$ -position complementing electrophilic approaches (**3l**).<sup>20b</sup> This transformation could be performed on an increased scale without a detrimental effect. 3-Halide substituted toluene derivatives **1m–o** gave the sterically favored products in good yields. These structures are commonly synthesized using indirect approaches,<sup>23</sup> while direct approaches, deliver the electronically favored products.<sup>24</sup> 1,3-Dihalogenated **1p** was iodinated exclusively in the  $\beta$ -position. Despite the moderate yield, it should be noted that this molecule was previously only accessible through an indirect approach.<sup>9</sup> Phthaloyl protected aniline was likewise iodinated in the sterically favored position (**3q**). Substrates **1r–u** were subjected to the iodination protocol. Despite the presence of coordinating functionalities the reaction proceeded predominantly in the sterically favored position. Hydrocinnamate **1v**,





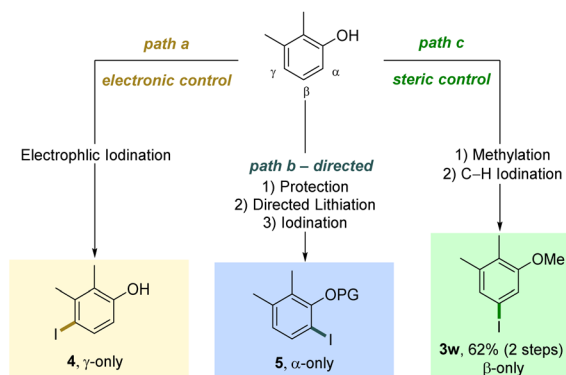
**Scheme 1** Reaction scope (for unsuccessful substrates, see Scheme S43 in the ESI†). Structures of the respective starting materials shown for simplicity. Reactions conducted on a 0.2 mmol scale; isolated yields; regioselectivities determined by NMR. <sup>a</sup> 2 = 2.0 equiv., 70 °C, 48 h. <sup>b</sup> 2 = 4.0 equiv., AgNO<sub>3</sub> (30 mol%), 100 °C. <sup>c</sup> Contains 6% di-iodinated arene. <sup>d</sup> 3.0 mmol scale.

gave a high selectivity for the *meta* position. The functionalization in this position was previously achieved indirectly, by installing a designed *meta*-directing template on the carboxylate moiety, while the analogous acid gave exclusive *ortho*-functionalization.<sup>13a</sup> Finally, we studied 1,2,3-trisubstituted arenes with a strong electronic bias towards the *ortho* positions (**3w-ab**). Despite the presence of a methoxy group our protocol addressed the electronically disfavored position (**3w**).<sup>25</sup> The fluorinated derivative **3x** gave the β-product in good yield. Substrates **1y-aa** highlight the steric control of our catalyst system as only the sterically favored yet electronically disfavored position is iodinated.<sup>26</sup> A stronger electronic bias towards the sterically disfavored positions reduces the activity of our system. Nevertheless, an arene bearing a deactivating keto group (**1ab**) could be iodinated. Next, we probed the late-stage modification of structurally more complex substrates. Propofol methyl ether (**3ac**) was efficiently iodinated. Biaryls constitute key motifs in organic chemistry,<sup>27</sup> rendering their late-stage selective iodination in unprecedented positions an attractive linchpin for further diversification. The iodination of biaryls **1ad** and **1ae** delivered products in synthetically useful yields and excellent selectivities for the sterically favored C–H bond. Analogously, sonidegib precursor **1af** and the flurbiprofen methyl ester **1ag**

containing a biaryl scaffold were iodinated with remarkable selectivities. Palonosetron precursor **1ah** was exclusively iodinated in the β-position. The Evans-type reagent **1ai** and the phenylalanine derivative **1aj** likewise delivered *meta* iodinated products as major isomer, which is inaccessible through direct electrophilic approaches.<sup>28</sup> The iodination of nateglinide ester **1ak** and the (–)-menthol ether of *m*-cresol **1al** likewise gave regioisomers, which would otherwise be challenging to obtain. The thymol ether of *m*-cresol **1am** was mainly iodinated in the sterically most accessible β-position of the *m*-cresol moiety. Remarkably, the more electron-rich thymol motif barely underwent iodination.

As evidenced by these scope studies, we have developed a broadly applicable protocol for the nondirected late-stage iodination of arenes with predominant steric control of the regioselectivity. To highlight the complementarity of our transformation with traditional approaches, we compared different iodination procedures using substrate **1w** (Scheme 2). Subjecting this arene to an electrophilic iodination was reported to deliver the electronically favored γ-product **4**.<sup>29</sup> The synthesis of the corresponding α-isomer **5** was achieved by an *ortho*-lithiation step.<sup>30</sup> Our approach complements these methods by forming the sterically controlled product **3w**.





Scheme 2 Complementarity with traditional approaches.

## Mechanistic studies

We proceeded to interrogate the mechanism of our protocol (Scheme 3). Based on the general pathway shown in Fig. 1C, all steps of the reaction could in principle be reversible. We thus investigated if the process is thermodynamically or kinetically controlled. Scrambling experiments were performed, in which

isomerically pure (disfavored isomer) aryl iodides were added to a reaction forming a different product (Scheme 3A). While the formation of the expected products shows that catalysis took place under these conditions, the absence of scrambling in the additives clearly demonstrates that the overall reaction occurs irreversibly (*i.e.* kinetically controlled).<sup>31</sup> Parallel ( $k_H/k_D = 1.9$ ) and competition ( $k_H/k_D = 1.7-1.8$ ) KIE-experiments indicated that the C-H activation step is turnover-limiting and thus responsible for the kinetically controlled regioselectivity (Scheme 3B). The kinetic orders with respect to arene **1** (0.5) and iodine reagent **2** (0.2) were determined (Scheme 3C). These broken kinetic orders indicate that besides the C-H activation the subsequent oxidative addition also contributes to the overall rate of the reaction, which implies that the C-H activation may be partially reversible. Reversibility was probed using **1h-d5** (Scheme 3D). In the absence of reagent **2a** substantial H/D exchange occurred showing that the C-H activation is reversible when no reaction partner is available (some H/D exchange was observed in the *ortho* position, which is not iodinated in the overall process). In the presence of reagent **2** H/D exchange in the remaining substrate was strongly reduced. This demonstrates that when product formation is possible, it can outcompete the retro-C-H activation. These results show that the observed regioselectivity is predominantly defined by the kinetically controlled C-H activation step. The selectivity is further increased, since in case of sterically hindered positions retro-C-H activation can efficiently outcompete product formation.

## Conclusions

In summary, we have developed a sterically controlled C-H iodination of arenes. Our protocol is widely applicable tolerating a broad range of functional groups and substitution patterns. The sensitivity towards steric factors, renders our approach complementary to established iodination strategies. We have demonstrated the utility of this reaction for late-stage functionalization, providing valuable linchpins for further diversification with otherwise challenging substitution patterns.

## Data availability

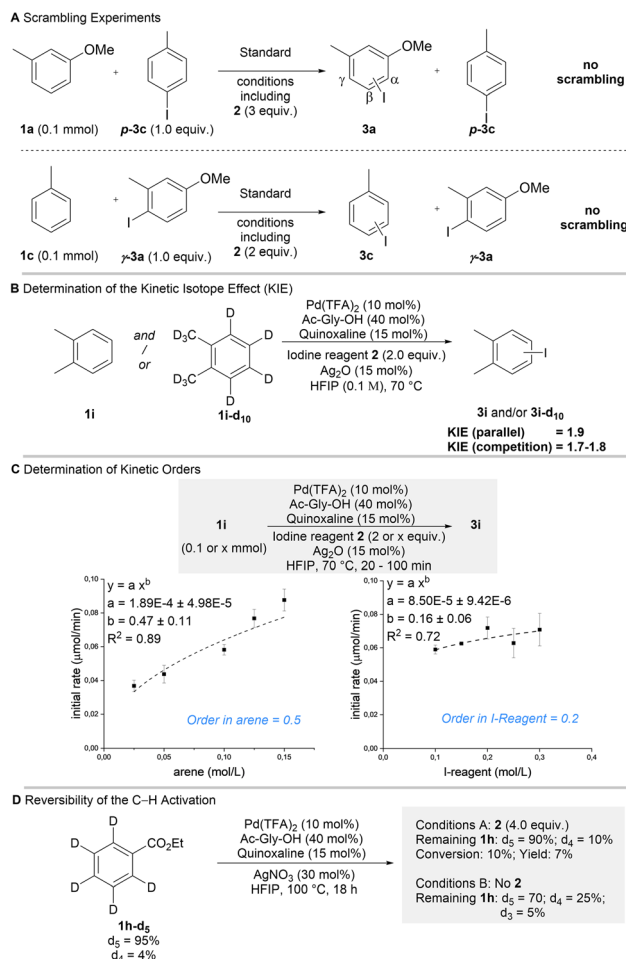
Full experimental results are available in the ESI.†

## Author contributions

M. v. G. and M. F. conceived the project; M. F., R. d. J. and J. D. performed the experiments and analyzed the data. M. F. and M. v. G. wrote the manuscript with contributions from all authors; M. v. G. supervised the project.

## Conflicts of interest

There are no conflicts to declare.



Scheme 3 Preliminary Mechanistic Studies. <sup>a</sup> All Reactions performed on a 0.1 mmol scale.





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## Notes and references

- (a) K. C. Nicolaou, P. G. Bulger and D. Sarlah, *Angew. Chem., Int. Ed.*, 2005, **44**, 4442; (b) J. Magano and J. R. Dunetz, *Chem. Rev.*, 2011, **111**, 2177; (c) D. J. Weix, *Acc. Chem. Res.*, 2015, **48**, 1767.
- (a) N. Miyaura and A. Suzuki, *Chem. Rev.*, 1995, **95**, 2457; (b) P. Knochel, W. Dohle, N. Gommermann, F. F. Kneisel, F. Kopp, T. Korn, I. Sapountzis and V. A. Vu, *Angew. Chem., Int. Ed.*, 2003, **42**, 4302; (c) T. D. Sheppard, *Org. Biomol. Chem.*, 2009, **7**, 1043.
- (a) R. Taylor, *Electrophilic aromatic substitution*; Wiley, 1990; (b) J. R. Hanson, *J. Chem. Res.*, 2006, 277; (c) S. Stavber, M. Jereb and M. Zupan, *Synthesis*, 2008, 1487; (d) M. Bergström, G. Suresh, V. R. Naidu and C. R. Unelius, *Eur. J. Org. Chem.*, 2017, 3234; (e) N. L. Sloan and A. Sutherland, *Synthesis*, 2016, **48**, 2969–2980.
- (a) J. Barluenga, J. M. Gonzalez, M. A. Garcia-Martin, P. J. Campos and G. Asensio, *J. Org. Chem.*, 1993, **58**, 2058; (b) L. Kraszkiewicz, M. Sosnowski and L. Skulski, *Tetrahedron*, 2004, **60**, 9113; (c) L. Kraszkiewicz, M. Sosnowski and L. Skulski, *Synthesis*, 2006, 1195.
- (a) L. Tanwar, J. Börgel, J. Lehmann and T. Ritter, *Org. Lett.*, 2021, **23**, 5024; (b) W. Wang, X. Yang, R. Dai, Z. Yan, J. Wei, X. Dou, X. Qiu, H. Zhang, C. Wang, Y. Liu, S. Song and N. Jiao, *J. Am. Chem. Soc.*, 2022, **144**, 13415; (c) R.-J. Tang, T. Milcent and B. Crousse, *J. Org. Chem.*, 2018, **83**, 930–938; (d) R. C. Samanta and H. Yamamoto, *Eur. J. Chem.*, 2015, **21**, 11976–11979; (e) K. Iida, S. Ishida, T. Watanabe and T. Arai, *J. Org. Chem.*, 2019, **84**, 7411–7417; (f) D. T. Racys, C. E. Warrilow, S. L. Pimlott and A. Sutherland, *Org. Lett.*, 2015, **17**, 4782–4785.
- H. H. Hodgson, *Chem. Rev.*, 1947, **40**, 251.
- T. Q. Chen, P. S. Pedersen, N. W. Dow, R. Fayad, C. E. Hauke, M. C. Rosko, E. O. Danilov, D. C. Blakemore, A.-M. Dechert-Schmitt, T. Knauber, F. N. Castellano and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2022, **144**, 8296.
- A. Klapars and S. L. Buchwald, *J. Am. Chem. Soc.*, 2002, **124**, 14844.
- B. M. Partridge and J. F. Hartwig, *Org. Lett.*, 2013, **15**, 140.
- D. A. Petrone, J. Ye and M. Lautens, *Chem. Rev.*, 2016, **116**, 8003.
- (a) D. Kalyani, A. R. Dick, W. Q. Anani and M. S. Sanford, *Org. Lett.*, 2006, **8**, 2523; (b) J.-J. Li, T.-S. Mei and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2008, **47**, 6452; (c) T.-S. Mei, R. Giri, N. Mangel and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2008, **47**, 5215; (d) T.-S. Mei, D.-H. Wang and J.-Q. Yu, *Org. Lett.*, 2010, **12**, 3140; (e) N. Schröder, J. Wencel-Delord and F. Glorius, *J. Am. Chem. Soc.*, 2012, **134**, 8298; (f) X.-C. Wang, Y. Hu, S. Bonacorsi, Y. Hong, R. Burrell and J.-Q. Yu, *J. Am. Chem. Soc.*, 2013, **135**, 10326; (g) L. Wang and L. Ackermann, *Chem. Commun.*, 2014, **50**, 1083.
- (a) L. Chu, M. Shang, K. Tanaka, Q. Chen, N. Pissarnitski, E. Streckfuss and J.-Q. Yu, *ACS Cent. Sci.*, 2015, **1**, 394; (b) G. M. Reddy, N. S. Rao and H. Maheswaran, *Org. Chem. Front.*, 2018, **5**, 1118; (c) Z. Jin, L. Chu, Y.-Q. Chen and J.-Q. Yu, *Org. Lett.*, 2018, **20**, 425; (d) M. Liu, L.-J. Li, J. Zhang, H. Xu and H.-X. Dai, *Chin. Chem. Lett.*, 2020, **31**, 1301.
- (a) S. Li, C. Zhang, L. Fu, H. Wang, L. Cai, X. Chen, X. Wang and G. Li, *CCS Chem.*, 2022, **4**, 1889; (b) N. Wang, Z. Chi, X. Wang, Z. Gao, S. Li and G. Li, *Org. Lett.*, 2022, **24**, 3657; (c) Z. Gao, H. Wang, C. Zhou, N. Wang, S. Li and G. Li, *Org. Lett.*, 2022, **24**, 3926.
- (a) B. N. Bhawal and B. Morandi, *Isr. J. Chem.*, 2018, **58**, 94; (b) B. N. Bhawal and B. Morandi, *Angew. Chem., Int. Ed.*, 2019, **58**, 10074.
- (a) Y. H. Lee and B. Morandi, *Nat. Chem.*, 2018, **10**, 1016; (b) M. de La Higuera Macias and B. A. Arndtsen, *J. Am. Chem. Soc.*, 2018, **140**, 10140; (c) R. G. Kinney, J. Zgheib, P.-L. Lagueux-Tremblay, H. Yang, D. Gauthier Jr and B. Arndtsen, *Res. Sq.*, 2022, DOI: [10.21203/rs.3.rs-1709579/v1](https://doi.org/10.21203/rs.3.rs-1709579/v1); (d) P. Boehm, P. Müller, P. Finkelstein, M. A. Rivero-Crespo, M. Ebert, N. Trapp and B. Morandi, *J. Am. Chem. Soc.*, 2022, **144**, 13096.
- (a) P. Wang, P. Verma, G. Xia, J. Shi, J. X. Qiao, S. Tao, P. T. W. Cheng, M. A. Poss, M. E. Farmer, K.-S. Yeung and J.-Q. Yu, *Nature*, 2017, **551**, 489; (b) P. Wedi and M. van Gemmeren, *Angew. Chem., Int. Ed.*, 2018, **57**, 13016; (c) D. Zhao, P. Xu and T. Ritter, *Chem*, 2019, **5**, 97; (d) A. Mondal, H. Chen, L. Flämig, P. Wedi and M. van Gemmeren, *J. Am. Chem. Soc.*, 2019, **141**, 18662; (e) M. Farizyan, A. Mondal, S. Mal, F. Deufel and M. van Gemmeren, *J. Am. Chem. Soc.*, 2021, **143**, 16370; (f) C. Santiago, H. Chen, A. Mondal and M. van Gemmeren, *Synlett*, 2022, **33**, 357.
- (a) H. Chen, P. Wedi, T. Meyer, G. Tavakoli and M. van Gemmeren, *Angew. Chem., Int. Ed.*, 2018, **57**, 2497; (b) H. Chen, M. Farizyan, F. Ghiringhelli and M. van Gemmeren, *Angew. Chem., Int. Ed.*, 2020, **59**, 12213; (c) A. Mondal and M. van Gemmeren, *Angew. Chem., Int. Ed.*, 2021, **60**, 742; (d) P. Wedi, M. Farizyan, K. Bergander, C. Mück-Lichtenfeld and M. van Gemmeren, *Angew. Chem., Int. Ed.*, 2021, **60**, 15641.
- (a) M. Catellani, E. Motti, N. Della cá and R. Ferraccioli, *Eur. J. Org. Chem.*, 2007, 4153; (b) O. Daugulis, H.-Q. Do and D. Shabashov, *Acc. Chem. Res.*, 2009, **42**, 1074; (c) K. Muniz, *Angew. Chem., Int. Ed.*, 2009, **48**, 9412; (d) L.-M. Xu, B.-J. Li, Z. Yang and Z.-J. Shi, *Chem. Soc. Rev.*, 2010, **39**, 712; (e) A. J. Hickman and M. S. Sanford, *Nature*, 2012, **484**, 177.
- R. C. Samanta and H. Yamamoto, *Eur. J. Chem.*, 2015, **21**, 11976.



- 20 (a) J. B. G. Gluyas, C. Burschka, S. Dörrich, J. Vallet, H. Gronemeyer and R. Tacke, *Org. Biomol. Chem.*, 2012, **10**, 6914; (b) E. J. Emmett, B. R. Hayter and M. C. Willis, *Angew. Chem., Int. Ed.*, 2014, **53**, 10204.
- 21 T. Sugita, M. Idei, Y. Ishibashi and Y. Takegami, *Chem. Lett.*, 1982, **11**, 1481.
- 22 P. Lulinski and L. Skulski, *Bull. Chem. Soc. Jpn.*, 1999, **72**, 115.
- 23 J. Lv, Q. Liu, J. Tang, F. Perdih and K. Kranjc, *Tetrahedron Lett.*, 2012, **53**, 5248.
- 24 S. N. Joshi, S. M. Vyas, H. Wu, M. W. Duffel, S. Parkin and H.-J. Lehmler, *Tetrahedron*, 2011, **67**, 7461.
- 25 C. A. Panetta, Z. Fang and D. L. Mattern, *J. Org. Chem.*, 1995, **60**, 7953.
- 26 (a) M. L. dos Santos, G. C. de Magalhães and R. Braz Filho, *J. Organomet. Chem.*, 1996, **526**, 15; (b) H.-G. Cheng, Z. Yang, R. Chen, L. Cao, W.-Y. Tong, Q. Wei, Q. Wang, C. Wu, S. Qu and Q. Zhou, *Angew. Chem., Int. Ed.*, 2021, **60**, 5141.
- 27 L. Yet, *Privileged Structures in Drug Discovery*; John Wiley & Sons, Inc, 2018.
- 28 J. Barluenga, J. M. Alvarez-Gutiérrez, A. Ballesteros and J. M. González, *Angew. Chem., Int. Ed.*, 2007, **46**, 1281.
- 29 (a) N. Tsuji, *Tetrahedron*, 1968, **24**, 1765; (b) A. R. Hajipour and H. Adibi, *J. Chem. Res.*, 2004, **2004**, 294.
- 30 C. Morice, M. Domostoj, K. Briner, A. Mann, J. Suffert and C.-G. Wermuth, *Tetrahedron Lett.*, 2001, **42**, 6499.
- 31 Further scrambling experiments and an expanded discussion of all mechanistic experiments are provided in the ESI.†.

