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# An integrative sustainability assessment of the Tsuji–Trost reaction simulating allylic amination under non-conventional (vs. conventional) conditions†

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With allyl compounds being a valuable chemical commodity, it is important to understand the sustainability aspects of the Tsuji–Trost reaction in terms of productivity (reactivity-coupled utility), environmental impact (including health hazards), and economic burden and benefits of commercially available allylic precursors under varying conditions. However, comprehensive literature searches reveal that no such study is publicly accessible; the majority of the literature focuses only on the synthetic utility of a few allylic precursors. In this context, we undertook a study for sustainability assessment of 26 allyl precursors (with diverse ionisable partners) by simulating an allylic amination reaction in an alternative reaction medium, water (vs. an organic solvent, OS), under Earth-abundant nickel (vs. traditional palladium) catalysis. The study was accomplished through: (1) conducting reactivity-utility profiling of allylic precursors; (2) identifying the major side reactions occurring with allylic precursors (water vs. OS); and (3) determining green metrics (*E*-factor, atom economy, atom efficiency, RME, and EcoScale) of the amination process linked with allylic precursors. The key highlights of the study include the following: (a) water is as diverse as an organic solvent in facilitating the Tsuji–Trost allylic amination; (b) diverse allylic precursors could be employed in water as well as in an organic solvent to realize allylic amination; (c) nickel catalysis is a viable alternative to palladium for allylic amination with distinct superiority in the water medium while using an allyl alcohol and allyl amine (*trans*-*N*-allylation). Further advancing sustainability and catalysis, we demonstrated for the first time a fully catalytic ‘in-water’ allylic amination reaction using an allylic alcohol and a Ni(II)-catalyst with features like scale-up synthesis (up to 10 g), catalytic usage of a reductant, etc. The authors propose this work as a sustainability guide to steer further research and developments in academia and industry related to allylation chemistries.

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## Introduction

Sustainable development in chemical processes and technology is essential for tackling global issues and creating a more resilient and eco-friendly future.<sup>1–4</sup> It benefits present and future generations by reducing the environmental impact (including carbon footprints), preserving resources, promoting economic success, and increasing health and well-being. One crucial step towards achieving this goal is to advance and

embrace green (sustainable) chemistry in the ongoing chemical process, considering the negative impacts of the manufacturing of fine chemicals, agrochemicals, and pharmaceuticals on health and environmental wellness.<sup>5–15</sup>

The presence of an allylic functionality in an organic framework is very diverse owing to its direct utility (as pharmaceuticals, bioactive compounds, and fine chemicals) and indirect applications (further derivatization through vinylic C=C and/or allylic C–H bond manipulations).<sup>16–26</sup> As a consequence, the direct installation of an allyl functionality is a hot area of research, and substantial progress has been made to introduce it using diverse methods and strategies.<sup>27–33</sup> In this context, the Tsuji–Trost reaction remains the prime tool considering its process robustness, broad scope, functional group compatibility, and adaptation to asymmetric variations. Over time, promising growth has been realised in this field, including the use

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of different allylic precursors, the use of alternative reaction media, and the inclusion of Earth-abundant metal catalysis.<sup>34–52</sup>

Given the rapid expansion of the Tsuji–Trost reaction,<sup>34–52</sup> it is important to have an integrative (and holistic) sustainability assessment of the Tsuji–Trost reaction in the context of productivity (reactivity-coupled utility), environmental impact (including health hazards), and economic burden of commercially available allylic precursors under varying conditions to fulfil the sustainability goal of an important chemical transformation. It is to be noted that no such information (or study) is publicly available or accessible; the majority of the literature deals with the synthetic utility of a few allylic precursors. In this context, we looked into an integrative sustainability assessment of 26 allyl precursors (with diverse ionisable partners) by simulating an allylic amination reaction in the most preferred

green solvent water (vs. a traditional organic solvent) under nickel (vs. traditional palladium) catalysis. The key findings indicate: (a) the suitability and compatibility of water in facilitating the allylic amination reaction with diverse allylic partners; (b) the superior catalysis of nickel over palladium in water, particularly using an allylic alcohol; (c) the possibility of *trans*-*N*-allylation in water under nickel catalysis; and (d) elucidating the role of H-bond networking in activating allylic precursors. In a further sustainable development, we demonstrated for the first time a fully catalytic ‘in-water’ allylic amination using an allylic alcohol and a Ni(II) catalyst, featuring properties such as scale-up synthesis (up to 10 g), catalytic usage of a reductant, *etc.*, representing further advancement in catalysis and sustainability of the allylic amination reaction.

| Allylic precursors under examination and model reaction conditions |  |   |  | Method A   | Method B  | Method C  |  |  |
|--|--|---|--|--|---|---|--|--|
|  |  |   |  | Ni(cod) <sub>2</sub> (2 mol%),<br>dppf (4 mol%)  | Ni(cod) <sub>2</sub> (2 mol%),<br>dppf (4 mol%)         | Pd(PPh <sub>3</sub> ) <sub>4</sub> (2 mol%),<br>dppf (4 mol%) |  |  |
|  |  |   |  | Aq. TPGS-750-M<br>(2% w/w, 0.5 mL),<br>rt, 24 h  | 1,4-Dioxane (0.5 mL),<br>rt, 24 h                       | Aq. TPGS-750-M<br>(2% w/w, 0.5 mL),<br>rt, 24 h               |  |  |
| Ionisation via Allylic C-X bond cleavage (X = Cl, Br, I)           |  |   |  | <br>1,1'-Bis(diphenylphosphino)ferrocene (dppf)      DL-α-Tocopherol methoxypolyethylene glycol succinate (TPGS-750-M) |   |   |  |  |
| <br>2a<br>Allyl chloride<br>CAS No.: 107-05-1                      | <br>2b<br>Allyl bromide<br>CAS No.: 106-95-6           | <br>2c<br>Allyl iodide<br>CAS No.: 556-56-9             |  |  |   |   |  |  |
| Ionisation via Allylic C-O bond cleavage                           |  |   |  |  |   |   |  |  |
| <br>2d<br>Allyl alcohol<br>CAS No.: 107-18-6                       | <br>2e<br>Allyl acetate<br>CAS No.: 591-87-7           | <br>2f<br>Allyl trifluoroacetate<br>CAS No.: 383-67-5   | <br>2g<br>Allyl cinnamate<br>CAS No.: 1866-31-5    | <br>2h<br>Allyl methyl carbonate<br>CAS No.: 35466-83-2  | <br>2i<br>Allyl phenyl carbonate<br>CAS No.: 16308-68-2 | <br>2j<br>Allyl carbamate<br>CAS No.: 2114-11-6               |  |  |
| <br>2k<br>Diethyl allyl phosphate<br>CAS No.: 3066-75-9            | <br>2l<br>Allyl oxalyl chloride<br>CAS No.: 74503-07-4 | <br>2m<br>Allyl imidate<br>CAS No.: 51479-73-3          | <br>2n<br>Allyl methyl ether<br>CAS No.: 627-40-7  | <br>2o<br>Allyl phenyl ether<br>CAS No.: 1746-13-0   | <br>2p<br>Allyl glycidyl ether<br>CAS No.: 106-92-3     |   |  |  |
| Ionisation via Allylic C-N bond cleavage                           |  |   |  | Ionisation via Allylic C-S bond cleavage   |   | Ionisation via Allylic C-P bond cleavage                      |  |  |
| <br>2q<br>N-Allylmethylamine<br>CAS No.: 627-37-2                  | <br>2r<br>Allyl urea<br>CAS No.: 557-11-9              | <br>2s<br>Allyl isocyanate<br>CAS No.: 1476-23-9        | <br>2t<br>Allyl isothiocyanate<br>CAS No.: 57-06-7 | <br>2u<br>Allyl methyl sulfide<br>CAS No.: 0152-76-8   | <br>2v<br>Allyl phenyl sulfone<br>CAS No.: 16212-05-8   | <br>2w<br>Diethyl allylphosphonate<br>CAS No.: 1067-87-4      |  |  |
| Ionisation via Allylic C-Si bond cleavage                          |  | Ionisation via Allylic C-B bond cleavage                |  | Ionisation via Allylic C-C bond cleavage   |   |   |  |  |
| <br>2x<br>Allyl(chloro)dimethylsilane<br>CAS No.: 4028-23-3        |  | <br>2y<br>Allyl pinacol boronate<br>CAS No.: 72824-04-5 |  | <br>2z<br>Allylbenzene<br>CAS No.: 300-57-2  |   |   |  |  |

Fig. 1 List of allylic precursors (2a–2z) under examination and adopted methodology (model reaction conditions).

## Results and discussion

### Background information and methodology employed

The Tsuji–Trost reaction is a palladium-catalysed substitution reaction involving the reaction of a nucleophile with a substrate having a leaving group at an allylic position. Originally discovered as an allylic alkylation reaction, the scope of the reaction has been expanded significantly to different carbon, nitrogen, and oxygen-based nucleophiles.<sup>53–55</sup> Among the adopted nucleophiles, nitrogen-based nucleophiles are very well adapted owing to the diverse applications of allylamines ranging from materials to medicines.<sup>17,56–59</sup> Logically, it was decided to adhere to an amine as a model nucleophile for the target study as described in the Fig. 1.

Our lab is actively engaged in the development of sustainable organic reactions for diverse applications, including clean pharmaceutical synthesis.<sup>60–66</sup> In this context, we recently described an elegant Ni(cod)<sub>2</sub>-catalyzed ‘in-water’ allylic amination protocol with a diverse substrate scope.<sup>61</sup> To the best of our knowledge, there is no existing method that demonstrates a better diversity and adaptability of the substrate scope than this protocol in an aqueous environment, and hence we adopted this protocol as a model reaction and reference method (Method A) for this study. Further variations were done relative to Method A to constitute Method B (allylic amination in organic media under nickel catalysis) and Method C (allylic amination in water under palladium catalysis), as described in Fig. 1.

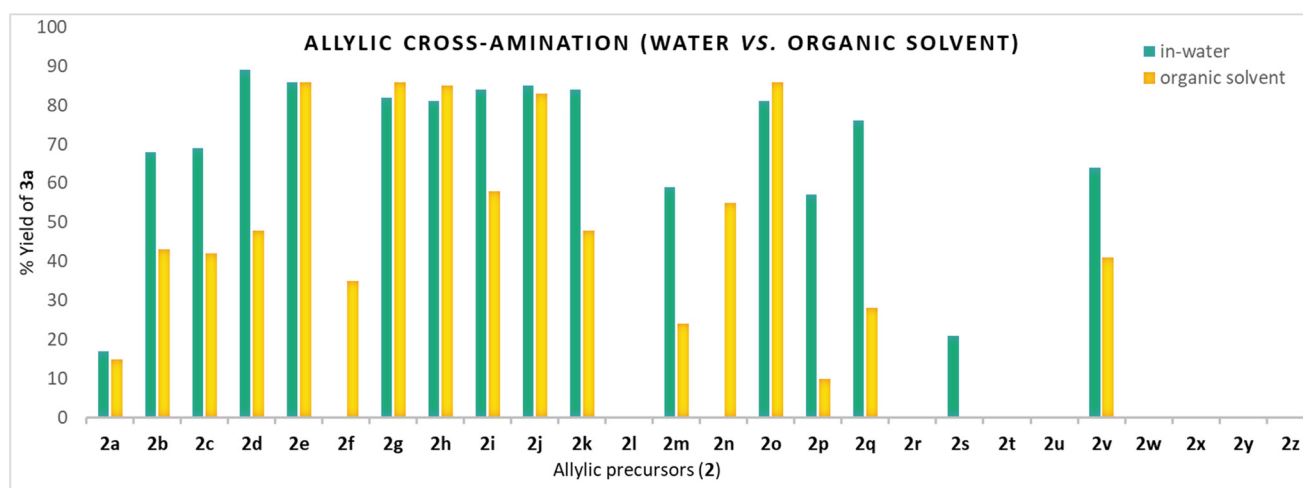


Fig. 2 Assessment of allylic precursors towards allylic amination yielding **3a** under Ni(0)-catalysis (aqueous media vs. OS).

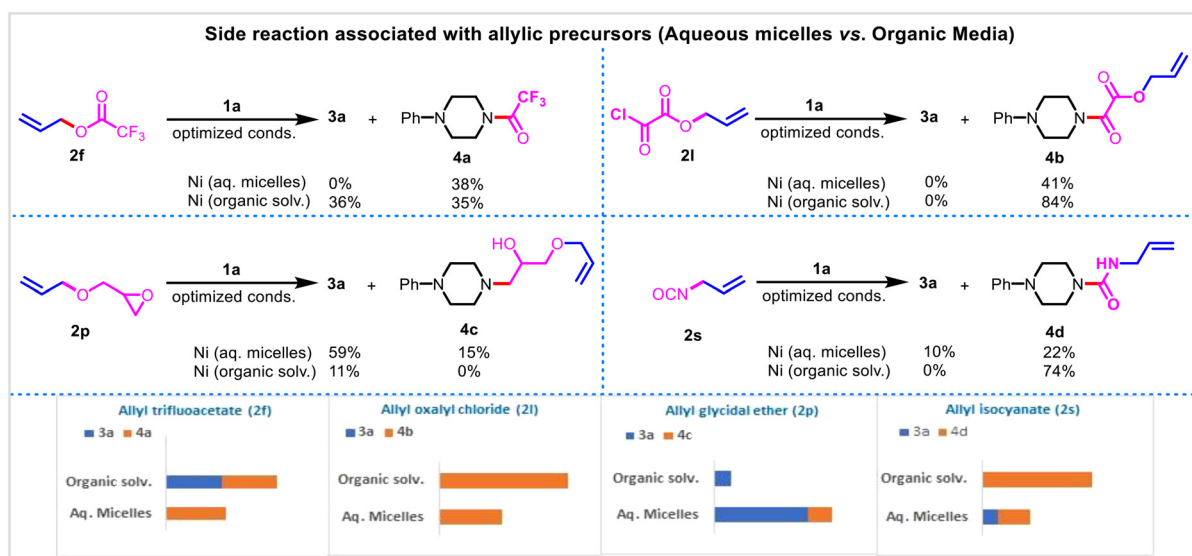


Fig. 3 Identification of major side reactions occurring with allylic precursors.

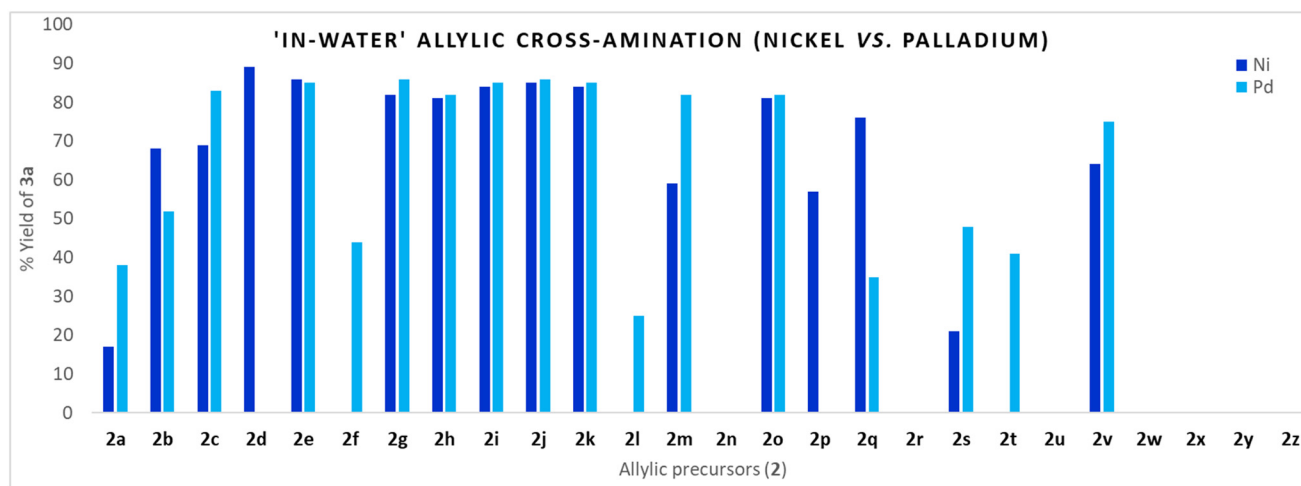


Fig. 4 Allylic cross-amination employing different allylic precursors in aqueous micelles: Ni vs. Pd.

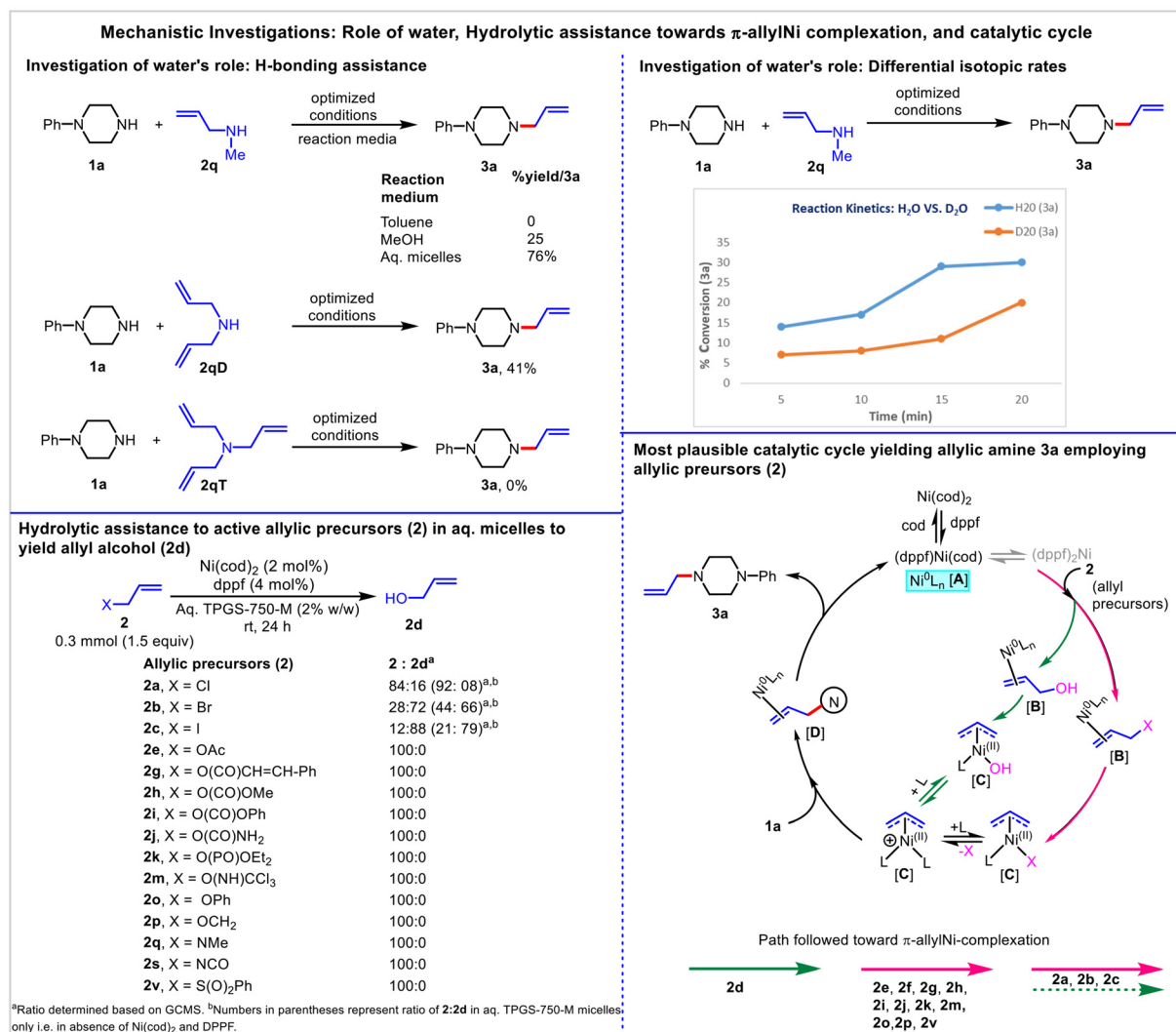


Fig. 5 Differential ionization pathways delivering  $\pi$ -allyl-Ni-complex to yield 3a employing different allylic precursors in aqueous micelles under Ni(0)-catalysis.

### Assessment of the reactivity-utility profile of allyl precursors in water under nickel catalysis (Method A)

Using the model reaction conditions, the reactivity-coupled utility of 26 different allyl precursors (**2a–2z**) featuring C–X (X = O/N/S/P/C/B/Si) bond ionisation with phenyl piperazine **1a** in aqueous TPGS media under Ni-catalysis was assessed (Method A, Fig. 1). Allyl halides (chloro **2a**, bromo **2b**, and iodo **2c**) underwent amination to yield **3a** in 15, 68, and 69%, respectively; the corresponding yields may be correlated to intrinsic halide ionisation properties. Allyl alcohol **2d** and their derivatives (**2e–2p**) were found to be effective in producing **3a**, the noted exceptions were allyl trifluoroacetate **2f**, allyl oxalyl chloride **2l**, and allyl methyl ether **2n**. Alcohol **2d** and their derivatives, acetate **2e**, cinnamate **2g**, carbonates (**2h**, **2i**), carbamate **2j**, phosphate **2k**, and phenyl ether **2o**, were superior to give **3a** with yields ranging from 81–89% owing to their ease of ionisation of the C–O bond. Allyl trifluoroacetate **2f** underwent competitive *N*-acylation (vs.  $\pi$ -allyl-Ni-complexation) to yield the corresponding amide **4a** (38%) as the exclusive product. Similarly, **2l** did not yield any desired product **3a**; the obtained product corresponds to amide **4b** (41%). Allyl glycidyl ether **2p** gave **3a** (59%) as the major product, along with the epoxide aminolysis product **4c** (15%). Allyl methyl ether **2n** was found to be non-reactive under the reaction conditions.

Allylic amination (*trans-N*-allylation) following C–N bond ionisation was insignificant (urea **2r**, isocyanate **2s**, isothiocyanate **2t**) except for **2q** (*N*-methylallylamine) wherein the formation of the desired product **3a** was observed with an excellent yield (76%). In the case of isocyanate **2s**, the major product corresponds to urea **4c** (22%).

The **3a** formation following C–S bond ionization was observed in sulfone **2v** (64%) only. No allylic amination was noticed following C–P (**2w**), C–Si (**2x**), C–B (**2y**), or C–C (**2z**) cleavage. Thus, out of 26 allylic precursors (**2a–2z**) tested, 16 were found to be reactive under the reaction conditions, yielding **3a** with variable yields, validating the wider catalytic profile of nickel in the aqueous system (Fig. 2 & 3).

### Assessment of the reactivity-utility profile of allyl precursors in an organic solvent (OS) under nickel catalysis (Method B)

Next, we examined the reactivity-coupled-utility of these 26 precursors in an organic solvent (1,4-dioxane)<sup>67</sup> under similar conditions but in the absence of aq. TPGS (Method B, Fig. 1). The reactivity-utility profile of **2e**, **2g**, **2h**, **2j**, and **2o** in dioxane nearly parallels that under aqueous conditions with comparable yields. The striking difference was in the yields of **3a** employing allyl alcohol **2d** (48% in OS vs. 89% in aq. TPGS) and *N*-allylmethylamine **2q** (28% in OS vs. 76% in aq. TPGS). Such significant yield variations (OS vs. H<sub>2</sub>O) in turn provide insights into the distinct role of water (H-bond networking) in the activation of **2d** (and **2q**) towards the  $\pi$ -allyl-Ni-complexation. Similarly, the yields of **3a** employing **2k** and **2m** could be explained on the basis of the H-bond-assisted activation of allyl precursors (Fig. 2 & 3). The other noted differences were in the case of allyl trifluoroacetate **2f**, which formed 35% of **3a**

(vs. 0% in aq. TPGS). The halide precursors (**2a**, **2b**, **2c**) also resulted in an inferior **3a** yield (vs. aq. TPGS) (Fig. 2).

### Assessment of the reactivity-utility profile of allyl precursors in water under palladium catalysis (Method C)

The analogous Pd(0)-catalysed reactions were performed to measure the relative scope, reactivity, and utility of allyl precursors in water under palladium catalysis (Method C, Fig. 1). As indicated, in many cases, palladium offers a similar reactivity-utility profile to allyl precursors as nickel; however, surprisingly, allylic amination was distinctly inferior using allyl alcohol **2d** under the optimized conditions (Ni vs. Pd: 89 and 0). Such contrasting yields of **3a** could be due to the smaller size of Ni, resulting in a higher nucleophilic nature, and variable oxidation states (0, +2 as well as +1, +3) making them more effective to harness C–O bond manipulations compared to Pd.<sup>68</sup> The other noted difference with respect to the formation of **3a** was observed in the cases of allyl trifluoroacetate **2f** (Ni vs. Pd: 0 and 44), allyl oxalyl chloride **2l** (Ni vs. Pd: 0 and 25), allyl isocyanate **2s** (Ni vs. Pd: 21 and 48), and allyl isothiocyanate **2t** (Ni vs. Pd: 0 and 41). The comparative yields corresponding to each allylic precursor (Ni vs. Pd) are depicted in Fig. 4.

**Table 1** Estimation of the green metrics of the allylic amination process linked with active allylic precursors under 'in-water' nickel catalysis

| Allylic pre<br>.<br>(2) | <i>E</i> -Factor | % atom<br>economy | %Atom<br>efficiency | %<br>RME | Rel.<br>EcoScale <sup>a</sup> |
|-------------------------|------------------|-------------------|---------------------|----------|-------------------------------|
| <b>2a</b>               | 8.15             | 84.66             | 12.69               | 10.92    | 42.5                          |
| <b>2b</b>               | 1.50             | 71.37             | 48.53               | 39.93    | 69                            |
| <b>2c</b>               | 2.80             | 61.21             | 33.05               | 26.30    | 62                            |
| <b>2d</b>               | 0.38             | 91.75             | 81.65               | 72.04    | 79.5                          |
| <b>2e</b>               | 0.79             | 77.04             | 66.25               | 55.56    | 78                            |
| <b>2f</b>               | N/A              | N/A               | N/A                 | N/A      | N/A                           |
| <b>2g</b>               | 1.68             | 57.68             | 47.29               | 37.23    | 81                            |
| <b>2h</b>               | 1.05             | 72.62             | 58.82               | 48.59    | 75.5                          |
| <b>2i</b>               | 1.53             | 59.38             | 49.87               | 39.48    | 82                            |
| <b>2j</b>               | 0.82             | 76.76             | 65.24               | 54.69    | 82.5                          |
| <b>2k</b>               | 1.6              | 56.71             | 47.63               | 37.40    | 82                            |
| <b>2l</b>               | N/A              | N/A               | N/A                 | N/A      | N/A                           |
| <b>2m</b>               | 2.9              | 55.42             | 32.69               | 30.93    | 59.5                          |
| <b>2n</b>               | N/A              | N/A               | N/A                 | N/A      | N/A                           |
| <b>2o</b>               | 1.2              | 68.19             | 55.23               | 44.99    | 70.5                          |
| <b>2p</b>               | 1.8              | 73.14             | 41.68               | 34.52    | 63.5                          |
| <b>2q</b>               | 0.7              | 86.60             | 65.81               | 57.10    | 86.5                          |
| <b>2r</b>               | N/A              | N/A               | N/A                 | N/A      | N/A                           |
| <b>2s</b>               | 5.7              | 82.39             | 17.30               | 14.77    | 45.5                          |
| <b>2t</b>               | N/A              | N/A               | N/A                 | N/A      | N/A                           |
| <b>2u</b>               | N/A              | N/A               | N/A                 | N/A      | N/A                           |
| <b>2v</b>               | 2.3              | 58.68             | 37.55               | 29.66    | 72                            |
| <b>2w</b>               | N/A              | N/A               | N/A                 | N/A      | N/A                           |
| <b>2x</b>               | N/A              | N/A               | N/A                 | N/A      | N/A                           |
| <b>2y</b>               | N/A              | N/A               | N/A                 | N/A      | N/A                           |
| <b>2z</b>               | N/A              | N/A               | N/A                 | N/A      | N/A                           |

<sup>a</sup> The EcoScale has been represented as relative EcoScale wherein the common parameters (technical setup, temperature/time, workup and purification) have been excluded while calculating the penalty points as they will be the essentially same in all the cases.



### Role of water

Two substantial issues were brought to light by the results of the current investigation. First, how important is water, especially considering that some allyl precursors, such as *N*-methylallylamine **2q**, show excellent reactivity and yield (**3a**) when dissolved in aqueous micelles (vs. organic solvent)? Second, in the case of allyl precursors (where  $X \neq \text{OH}$ ), whether the 'in-water' allylic amination follows the direct ionization of allylic C–X or it is combined, including the ionization of allyl alcohol **2d** resulting from the hydration of allylic precursors.

To access the specific role of water, analogous reactions employing **2q** were performed in toluene and MeOH under optimized conditions. The reaction was non-productive in toluene (**3a**, 0%), while MeOH was found to be conducive to yield **3a**, albeit in poor yield (25%). Furthermore, the **3a** (41%) formation was observed in the case of diallylamine **2qD** (having free NH) while no such amination was noticed using triallylamine **2qT** (lacking free NH). These results suggested the definitive role of H-bond networking and insights into the water-enabled hydrogen bond-assisted activation of allyl amine **2q** towards the  $\pi$ -allyl-Ni complexation.<sup>46,69</sup> To investigate the role of the HB effect in the activation of allyl amine **2q** further, a kinetic (yield vs. time) study of the model reaction was planned ( $\text{D}_2\text{O}$  vs.  $\text{H}_2\text{O}$ -derived micelles).<sup>70,71</sup> Treatment of **1a** with **2q** separately in  $\text{H}_2\text{O}$ -micelles and  $\text{D}_2\text{O}$ -micelles under the optimized conditions, and the formation of **3a** were monitored for 20 minutes at a 5-minute interval. On each occasion,

a better yield of **3a** was obtained for the reactions performed in  $\text{H}_2\text{O}$  compared to the  $\text{D}_2\text{O}$  system. This decrease in **3a** yield is indicative of the lesser HB affinity of  $\text{N-D}_2\text{O}$  vs.  $\text{N-H}_2\text{O}$ . This agrees with the reported results of weaker hydrogen bonding by deuterium with oxygen and nitrogen acceptors.<sup>72,73</sup>

Thus, water not only provides sustainability by eliminating the need for VOS as reaction media, but it also activates otherwise poorly reactive (or non-reactive) allyl amine **2q** via H-bond networking and stabilization of the resulting amine anion by a strong solvation effect (Fig. 5).

Subsequently, to determine whether the 'in-water' allylic amination follows the direct ionization of allyl precursors (where  $X \neq \text{OH}$ ) or it is combined, including the ionization of **2d** resulting from the hydration of allyl precursors (where  $X \neq \text{OH}$ ), the different allyl precursors (where  $X \neq \text{OH}$ ) were subjected to the optimized conditions but in the absence of **1a**. A variable amount of **2d** (GCMS) was observed in **2a** (16%), **2b** (72%), and **2c** (88%) indicating the possible hydrolytic assistance towards the formation of **3a** in the case of allylic halides. In other cases,  $\pi$ -allyl complexation resulted directly via ionization of allyl precursors, as no formation of **2d** was observed (Fig. 5). The above study also justifies the higher **3a** yield in aq. micelles (vs. organic solvent) employing an allylic halide. In many cases, in addition to the C–X bond dissociation energy ( $\text{ESI}^\dagger$ ),<sup>74</sup> the effects of water's atypical chemical and physical properties cannot be ruled out as contributing factors to the observed reactivity or selectivity of allylic precursors.

Based on these studies, the proposed Ni(0)/Ni(II) catalytic cycle that accounts for product formation is shown in Fig. 5.

**Table 2** Environmental, health, and safety (EHS) hazards assessment of employed allylic precursors (**2a–2z**)

| Allylic precursors          | Code      | Flammability       | Mutagenicity        | Carcinogenicity     | Aquatic hazard   | Biodegradability | LD <sub>50</sub> oral (rat) |
|-----------------------------|-----------|--------------------|---------------------|---------------------|------------------|------------------|-----------------------------|
| Allyl chloride              | <b>2a</b> | Flammable (Cat. 2) | Suspected (Cat. 2)  | Suspected (Cat. 2)  | Very toxic       | Readily          | 419 mg kg <sup>−1</sup>     |
| Allyl bromide               | <b>2b</b> | Flammable (Cat. 2) | Suspected (Cat. 1B) | Suspected (Cat. 1B) | Very toxic       | Readily          | 200 mg kg <sup>−1</sup>     |
| Allyl iodide                | <b>2c</b> | Flammable (Cat. 2) | Suspected (Cat. 1B) | Suspected (Cat. 1B) | Very toxic       | Readily          | 200 mg kg <sup>−1</sup>     |
| Allyl alcohol               | <b>2d</b> | Flammable (Cat. 2) | —                   | NO <sup>b</sup>     | Very toxic       | Readily          | 105 mg kg <sup>−1</sup>     |
| Allyl acetate               | <b>2e</b> | Flammable (Cat. 2) | NDA <sup>a</sup>    | NO <sup>b</sup>     | NDA <sup>a</sup> | NDA <sup>a</sup> | 130 mg kg <sup>−1</sup>     |
| Allyl trifluoroacetate      | <b>2f</b> | Flammable (Cat. 2) | NDA <sup>a</sup>    | NDA <sup>a</sup>    | NDA <sup>a</sup> | NDA <sup>a</sup> | NDA <sup>a</sup>            |
| Allyl cinnamate             | <b>2g</b> | NDA <sup>a</sup>   | NDA <sup>a</sup>    | NO <sup>b</sup>     | NDA <sup>a</sup> | NDA <sup>a</sup> | 1.52 mg kg <sup>−1</sup>    |
| Allyl methyl carbonate      | <b>2h</b> | Flammable (Cat. 3) | NDA <sup>a</sup>    | NO <sup>b</sup>     | NDA <sup>a</sup> | NDA <sup>a</sup> | NDA <sup>a</sup>            |
| Allyl phenyl carbonate      | <b>2i</b> | NDA <sup>a</sup>   | NDA <sup>a</sup>    | NO <sup>b</sup>     | NDA <sup>a</sup> | NDA <sup>a</sup> | NDA <sup>a</sup>            |
| Allyl carbamate             | <b>2j</b> | NDA <sup>a</sup>   | NDA <sup>a</sup>    | NO <sup>b</sup>     | Very toxic       | NDA <sup>a</sup> | NDA <sup>a</sup>            |
| Allyl diethyl phosphate     | <b>2k</b> | NDA <sup>a</sup>   | NDA <sup>a</sup>    | NDA <sup>a</sup>    | NDA <sup>a</sup> | NDA <sup>a</sup> | NDA <sup>a</sup>            |
| Allyl oxalyl chloride       | <b>2l</b> | Flammable (Cat. 3) | NDA <sup>a</sup>    | NDA <sup>a</sup>    | Toxic            | NDA <sup>a</sup> | NDA <sup>a</sup>            |
| Allyl imidate               | <b>2m</b> | NDA <sup>a</sup>   | NDA <sup>a</sup>    | NDA <sup>a</sup>    | NDA <sup>a</sup> | NDA <sup>a</sup> | NDA <sup>a</sup>            |
| Allyl methyl ether          | <b>2n</b> | Flammable (Cat. 2) | NDA <sup>a</sup>    | NO <sup>b</sup>     | NDA <sup>a</sup> | NDA <sup>a</sup> | NDA <sup>a</sup>            |
| Allyl phenyl ether          | <b>2o</b> | NDA <sup>a</sup>   | NDA <sup>a</sup>    | NDA <sup>a</sup>    | NDA <sup>a</sup> | NDA <sup>a</sup> | NDA <sup>a</sup>            |
| Allyl glycidyl ether        | <b>2p</b> | Flammable (Cat. 3) | Suspected (Cat. 2)  | Suspected (Cat. 2)  | Harmful          | Not readily      | 1.60 mg kg <sup>−1</sup>    |
| <i>N</i> -Allylmethylamine  | <b>2q</b> | Flammable (Cat. 2) | NDA <sup>a</sup>    | NDA <sup>a</sup>    | NDA <sup>a</sup> | NDA <sup>a</sup> | 100 mg kg <sup>−1</sup>     |
| Allyl urea                  | <b>2r</b> | NDA <sup>a</sup>   | NDA <sup>a</sup>    | NO <sup>b</sup>     | NDA <sup>a</sup> | NDA <sup>a</sup> | NDA <sup>a</sup>            |
| Allyl isocyanate            | <b>2s</b> | Flammable (Cat. 3) | NDA <sup>a</sup>    | NDA <sup>a</sup>    | NDA <sup>a</sup> | NDA <sup>a</sup> | 168 mg kg <sup>−1</sup>     |
| Allyl isothiocyanate        | <b>2t</b> | Flammable (Cat. 3) | NDA <sup>a</sup>    | NO <sup>b</sup>     | Very toxic       | Not readily      | 425.4 mg kg <sup>−1</sup>   |
| Allyl methyl sulfide        | <b>2u</b> | Flammable (Cat. 2) | NDA <sup>a</sup>    | NO <sup>b</sup>     | NDA <sup>a</sup> | NDA <sup>a</sup> | NDA <sup>a</sup>            |
| Allyl phenyl sulfone        | <b>2v</b> | NDA <sup>a</sup>   | NDA <sup>a</sup>    | NDA <sup>a</sup>    | NDA <sup>a</sup> | NDA <sup>a</sup> | NDA <sup>a</sup>            |
| Diethyl allyl phosphonate   | <b>2w</b> | NDA <sup>a</sup>   | NDA <sup>a</sup>    | NDA <sup>a</sup>    | NDA <sup>a</sup> | NDA <sup>a</sup> | NDA <sup>a</sup>            |
| Allyl(chloro)dimethylsilane | <b>2x</b> | Flammable (Cat. 2) | NDA <sup>a</sup>    | NDA <sup>a</sup>    | NDA <sup>a</sup> | NDA <sup>a</sup> | NDA <sup>a</sup>            |
| Allyl pinacol boronate      | <b>2y</b> | Flammable (Cat. 3) | NDA <sup>a</sup>    | NO <sup>b</sup>     | NDA <sup>a</sup> | NDA <sup>a</sup> | NDA <sup>a</sup>            |
| Allyl benzene               | <b>2z</b> | Flammable (Cat. 3) | NDA <sup>a</sup>    | NO <sup>b</sup>     | NDA <sup>a</sup> | NDA <sup>a</sup> | 5.54 mg kg <sup>−1</sup>    |

<sup>a</sup> No data available. <sup>b</sup> Carcinogenicity, no ingredient of this product present at levels greater than or equal to 0.1% is identified as probable, possible, or confirmed human carcinogen by IARC.

First, ligand exchange between  $\text{Ni}(\text{cod})_2$  and dppf generates the catalytically active Ni-complex  $[(\text{dppf})\text{Ni}(\text{cod})]$  **A**.<sup>75–77</sup> Because of the greater steric demand of dppf, the favored state involves a single dppf ligand in the Ni sphere with additional stabilization by the relatively small cod ligand. The formed Ni-complex **A** coordinates with the vinylic C=C double bond of **2** to generate the complex **B**. Subsequent oxidative addition (facilitated by water-assisted H-bond networking) results in the formation of the electrophilic  $\eta^3$   $\pi$ -allyl-Ni<sup>II</sup> complex **C**. This was followed by the nucleophilic attack to generate the penultimate intermediate **D**, which ultimately led to product formation following the detachment of nickel from alkene. The formation of a  $\pi$ -allyl-Ni-complex employing different allylic precursors in aqueous micelles is presented in Fig. 5. It is to be noted that the formation of  $(\text{dppf})_2\text{Ni}$  cannot be ruled out; however, it suffers from an initial high-energy dissociation of one ligand prior to oxidative addition, rendering the system poorly active. Whereas in the case of  $[(\text{dppf})\text{Ni}(\text{cod})]$ , a weaker-binding cod ligand displaced easily to enable a facile oxidative addition.<sup>75</sup> Furthermore, the role of water in the stabilization of cationic nickel allylic complexes with a hydroxyl group cannot be ruled out.

### Estimation of green metrics and environmental, health, and safety (EHS) hazards assessment of allyl precursors (2a–2z)

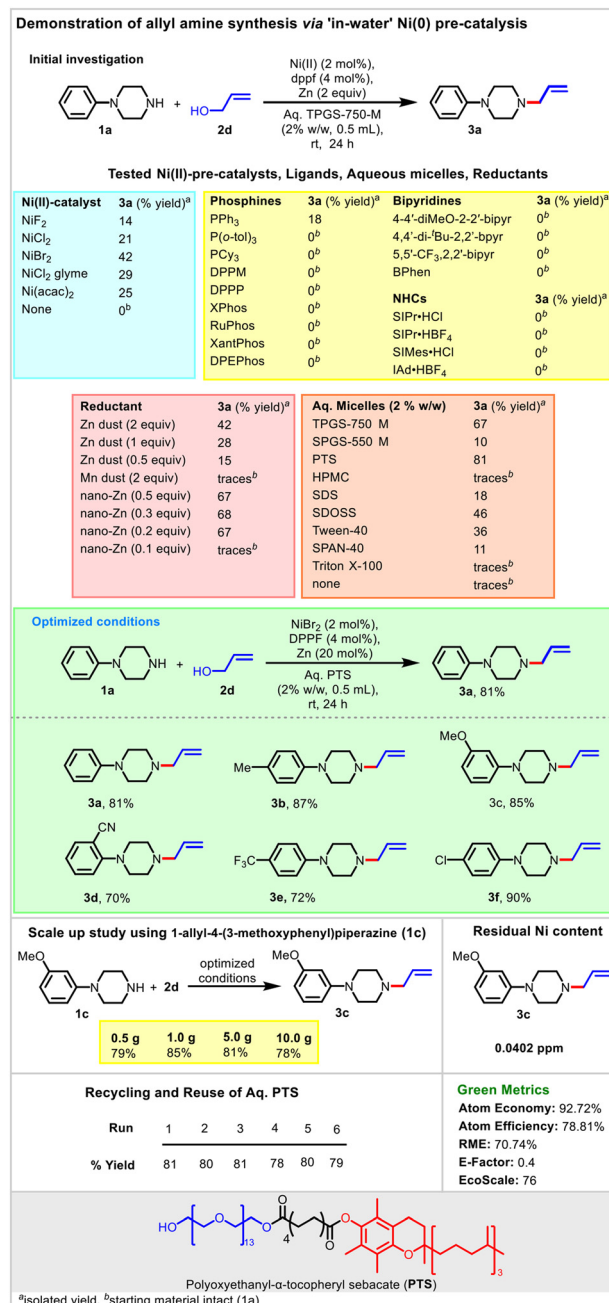
The environmental and eco-toxicological impact of allyl precursors, as well as the relative green metrics of the associated process, were subsequently established.<sup>78–81</sup> To calculate green metrics (*E*-factor, atom economy, atom efficiency, RME, and EcoScale), we chose allyl precursors (**2a**, **2b**, **2c**, **2d**, **2e**, **2g**, **2h**, **2i**, **2j**, **2k**, **2m**, **2o**, **2p**, **2q**, **2s**, **2v**) that were found to be active in aqueous micelles under nickel catalysis, as shown in Table 1. It should be emphasised that the EcoScale has been presented as a relative EcoScale due to shared factors such as technical setup, temperature/time, workup, and purification. The EHS risks of the allyl precursors (**2a–2z**), specifically in terms of flammability, mutagenicity, carcinogenicity, aquatic hazard, biodegradability, and the LD<sub>50</sub> (oral) value, were analysed based on the information retrieved from the MSDS data of the allyl precursors (**2a–2z**) (Table 2).

### Practical demonstration of true catalytic 'in-water' allylic amination using a Ni(0) pre-catalyst

In the context of allylic amination reactions,  $\text{Ni}(\text{cod})_2$ -catalyzed allylic amination reactions were found to be highly promising with diverse substrate scope, selectivity, and sustainability.<sup>46,47,52</sup> However, the air-sensitive nature of  $\text{Ni}(\text{cod})_2$  poses a handling issue and limits their catalytic applications.<sup>82</sup> This implies looking out for an alternative Ni(0) pre-catalytic system aiming to address the challenges of using reductants in an aqueous environment. The intense interest in this area led to the development of an elegant Ni(0) pre-catalyst system with a wide substrate scope.<sup>50,51</sup> Despite notable development, these protocols require organic solvents as reaction media, including the use of dimethylacetamide (DMA), a solvent classified as a Substance of Very High Concern (SVHC) for its reproductive

toxicity and teratogenicity.<sup>83,84</sup> Therefore, we planned to investigate a genuine catalytic 'in-water' allylic amination employing alcohol directly using a Ni(0)-pre-catalyst.

The study began with a systematic evaluation of different Ni(0) pre-catalysts in the presence of the dppf ligand and stoichiometric Zn powder (reductant) for the model reaction involving treatment of **1a** with **2a** at room temperature in aq. TPGS-750-M micelles. Promising results were obtained in the case of  $\text{NiBr}_2$  (**3a**, 42%) followed by  $\text{NiCl}_2$  glyme (**3a**, 29%). We next explored the opportunity to improve the **3a** yield with a



**Fig. 6** Demonstration of the Ni(0)-precatalyst for the 'in-water' allylic amination.

catalytic nano-Zn reductant. It was delightful to note that the stoichiometric replacement of Zn powder (2 equiv.) with catalytic nano-Zn (20 mol%) not only minimizes the waste footprint of the process but also improves the product yield significantly (**3a**, 42 → 67%). Replacement of aq. TPGS-750 M with aq. PTS significantly improved the product yield further (**3a**, 67 → 81%). Keeping these parameters intact, a detailed optimization study revealed that the use of 2 mol% of NiBr<sub>2</sub>, 4 mol% of dppf, and nano-Zn (20 mol%) at rt is optimal with an excellent yield of **3a** (81%). The use of other ligands (phosphines, bisphosphines, bipyridines, and NHCs) was not found to be superior to that of dppf under the optimized conditions (Fig. 6). The key highlight of this protocol is its adaptability to scale up reactions. Reactions at the scale of 0.5 g, 1.0 g, 5.0 g, and 10.0 g were found to be promising, with yields ≥78% in each case. Another important aspect of this process concerns the amount of Ni that is carried through and into the product. ICP-MS analysis of **3c**, prepared and isolated using standard chromatography, afforded product **3c** with 0.0402 ppm nickel (ESI†). The recyclability of the spent micelles was studied. Aq. PTS micelles were found to be recyclable up to five times without compromising the **3a** yield. The comparative analysis of the micellar composition (1<sup>st</sup> vs. 6<sup>th</sup> run) indicated that although there is a significant change in the average particle size and particle distribution index (PDI) of the micelles, these ranges are conducive to performing micellar catalysis, justifying the multiple recycling and reuse of aq. PTS (ESI†). Towards the end, the calculation of commonly exercised green metrics (atom economy, atom efficiency, RME, *E*-factor, and EcoScale) indicated promising values (well within the acceptable range) considering the making of fine chemicals.

## Conclusions

The study provides for the first time an integrated sustainability assessment of the widely used Tsuji–Trost reaction modelling allylic amination reaction, taking into account the reactivity-coupled utility, environmental impact (including health hazards), and economic burden (and benefits) of various allylic precursors in alternative solvents (water) under alternative Earth-abundant metal catalysis. The finding suggested the remarkable adaptability of water as a reaction medium for the Tsuji–Trost allylic aminations with a variety of allylic precursors and the superiority of nickel catalysis (over palladium) in a water medium, particularly using an allyl alcohol and non-reactive allyl amine (*trans*-*N*-allylation). We believe this study will work as a guide to stimulate further research and developments in academia and industry related to allylation chemistries in an environmentally friendly fashion.

## Conflicts of interest

There is no conflict of interest.

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## References

- 1 P. T. Anastas and J. C. Warner, *Green chemistry: theory and practice*, Oxford University Press, 2000.
- 2 F. Gallou, *Chimia*, 2020, **74**, 538–548.
- 3 I. T. Horváth, *Chem. Rev.*, 2018, **118**, 369–371.
- 4 S. Lems, H. J. Van der Kooi and J. d. Swaan Arons, *Green Chem.*, 2002, **4**, 308–313.
- 5 V. G. Zuin, I. Eilks, M. Elschami and K. Kümmerer, *Green Chem.*, 2021, **23**, 1594–1608.
- 6 R. A. Sheldon, *Green Chem.*, 2017, **19**, 18–43.
- 7 F. Ferlin, G. Brufani, G. Rossini and L. Vaccaro, *Green Chem.*, 2023, **25**, 7916–7933.
- 8 W. J. W. Watson, *Green Chem.*, 2012, **14**, 251–259.
- 9 P. T. Anastas, *Green Chem.*, 2003, **5**, G29–G34.
- 10 M. Poliakov and P. Licence, *Nature*, 2007, **450**, 810–812.
- 11 G. T. Whiteker, *Org. Process Res. Dev.*, 2019, **23**, 2109–2121.
- 12 S. Kar, H. Sanderson, K. Roy, E. Benfenati and J. Leszczynski, *Chem. Rev.*, 2022, **122**, 3637–3710.
- 13 D. E. Fitzpatrick, C. Battilocchio and S. V. Ley, *ACS Cent. Sci.*, 2016, **2**, 131–138.
- 14 C. M. Friend and B. Xu, *Acc. Chem. Res.*, 2017, **50**, 517–521.
- 15 D. J. C. Constable, C. Jimenez-Gonzalez and R. K. Henderson, *Org. Process Res. Dev.*, 2007, **11**, 133–137.
- 16 L. E. Overman, *Acc. Chem. Res.*, 1980, **13**, 218–224.
- 17 E. M. Skoda, G. C. Davis and P. Wipf, *Org. Process Res. Dev.*, 2012, **16**, 26–34.
- 18 T. Itoh, K. Jitsukawa, K. Kaneda and S. Teranishi, *J. Am. Chem. Soc.*, 1979, **101**, 159–169.
- 19 I. Strambeanu and M. C. White, *J. Am. Chem. Soc.*, 2013, **135**, 12032–12037.
- 20 N. Astrain-Redin, C. Sanmartin, A. K. Sharma and D. Plano, *J. Med. Chem.*, 2023, **66**, 3703–3731.
- 21 J. Fong, M. Yuan, T. H. Jakobsen, K. T. Mortensen, M. M. S. Delos Santos, S. L. Chua, L. Yang, C. H. Tan, T. E. Nielsen and M. Givskov, *J. Med. Chem.*, 2017, **60**, 215–227.
- 22 H. Zhao, J. Brånalt, M. Perry and C. Tyrchan, *J. Med. Chem.*, 2023, **66**, 7730–7755.
- 23 I. V. Overmeire, S. A. Boldin, K. Venkataraman, R. Zisling, S. D. Jonghe, S. V. Calenbergh, D. D. Keukeleire, A. H. Futerman and P. Herdewijn, *J. Med. Chem.*, 2000, **43**, 4189–4199.
- 24 H. Kuramochi, *J. Med. Chem.*, 1996, **39**, 2877–2886.



- 25 W. K. Anderson, R. H. Dewey and B. Mulumba, *J. Med. Chem.*, 1979, **22**, 1270–1272.
- 26 M. Rahman, A. Ali, E. Sjöholm, S. Soindinsalo, C.-E. Wilén, K. K. Bansal and J. M. Rosenholm, *Pharmaceutics*, 2022, **14**, 798.
- 27 B. M. Trost, *Tetrahedron*, 2015, **71**, 5708–5733.
- 28 N. K. Mishra, S. Sharma, J. Park, S. Han and I. S. Kim, *ACS Catal.*, 2017, **7**, 2821–2847.
- 29 R. Blicek, M. Taillefer and F. Monnier, *Chem. Rev.*, 2020, **120**, 13545–13598.
- 30 C. J. Lu, D. K. Chen, H. Chen, H. Wang, H. Jin, X. Huang and J. Gao, *Org. Biomol. Chem.*, 2017, **15**, 5756–5763.
- 31 M. Albert-Soriano, L. Hernández-Martínez and I. M. Pastor, *ACS Sustainable Chem. Eng.*, 2018, **6**, 14063–14070.
- 32 W. P. Teh, D. C. Obenschain, B. M. Black and F. E. Michael, *J. Am. Chem. Soc.*, 2020, **142**, 16716–16722.
- 33 H. Huang and J. Y. Kang, *J. Org. Chem.*, 2017, **82**, 6604–6614.
- 34 S.-C. Sha, J. Zhang, P. J. Carroll and P. J. Walsh, *J. Am. Chem. Soc.*, 2013, **135**, 17602–17609.
- 35 W.-B. Xu, M. Sun, M. Shu and C. Li, *J. Am. Chem. Soc.*, 2021, **143**, 8255–8260.
- 36 P. Fang, M. R. Chaulagain and Z. D. Aron, *Org. Lett.*, 2012, **14**, 2130–2133.
- 37 F. Ozawa, H. Okamoto, S. Kawagishi, S. Yamamoto, T. Minami and M. Yoshifuji, *J. Am. Chem. Soc.*, 2002, **124**, 10968–10969.
- 38 T. Ohshima, Y. Miyamoto, J. Ipposhi, Y. Nakahara, M. Utsunomiya and K. Mashima, *J. Am. Chem. Soc.*, 2009, **131**, 14317–14328.
- 39 D. Banerjee, R. V. Jagadeesh, K. Junge, H. Junge and M. Beller, *Angew. Chem., Int. Ed.*, 2012, **51**, 11556–11560.
- 40 D. Kumar, S. R. Vemula and G. R. Cook, *Green Chem.*, 2015, **17**, 4300–4306.
- 41 J. Jing, X. Huo, J. Shen, J. Fu, Q. Meng and W. Zhang, *Chem. Commun.*, 2017, **53**, 5151–5154.
- 42 G. Hirata, H. Satomura, H. Kumagae, A. Shimizu, G. Onodera and M. Kimura, *Org. Lett.*, 2017, **19**, 6148–6151.
- 43 C. Qiao, M. M. Belmonte, E. C. Escudero-Adán and A. W. Kleij, *ChemSusChem*, 2019, **12**, 3152–3158.
- 44 H. Kinoshita, H. Shinokubo and K. Oshima, *Org. Lett.*, 2004, **6**, 4085–4088.
- 45 T. Nishikata and B. H. Lipshutz, *Org. Lett.*, 2009, **11**, 2377–2379.
- 46 Y. Kita, H. Sakaguchi, Y. Hoshimoto, D. Nakauchi, Y. Nakahara, J.-F. Carpentier, S. Ogoshi and K. Mashima, *Chem. – Eur. J.*, 2015, **21**, 14571–14578.
- 47 M. S. Azizi, Y. Edder, A. Karim and M. Sauthier, *Eur. J. Org. Chem.*, 2016, **2016**, 3796–3803.
- 48 M. Lamblin, L. Nassar-Hardy, J.-C. Hierro, E. Fouquet and F.-X. Felpin, *Adv. Synth. Catal.*, 2010, **352**, 33–79.
- 49 N. R. Lee, F. A. Moghadam, F. C. Braga, D. J. Lippincott, B. Zhu, F. Gallou and B. H. Lipshutz, *Org. Lett.*, 2020, **22**, 4949–4954.
- 50 J. B. Sweeney, A. K. Ball, P. A. Lawrence, M. C. Sinclair and L. J. Smith, *Angew. Chem., Int. Ed.*, 2018, **57**, 10202–10206.
- 51 G. N. Vaidya, M. Nagpure and D. Kumar, *ACS Sustainable Chem. Eng.*, 2021, **9**, 1846–1855.
- 52 G. N. Vaidya, R. H. Choudhary, M. Nagpure, S. K. Lokhande, P. Rana and D. Kumar, *Green Chem.*, 2022, **24**, 3977–3984.
- 53 J. Tsuji, H. Takahashi and M. Morikawa, *Tetrahedron Lett.*, 1965, **6**, 4387–4388.
- 54 B. M. Trost and T. J. Fullerton, *J. Am. Chem. Soc.*, 1973, **95**, 292–294.
- 55 O. Pàmies, J. Margalef, S. Cañellas, J. James, E. Judge, P. J. Guiry, C. Moberg, J. E. Bäckvall, A. Pfaltz, M. A. Pericàs and M. Diéguez, *Chem. Rev.*, 2021, **121**, 4373–4505.
- 56 A. Stütz, *Angew. Chem., Int. Ed.*, 1987, **26**, 320–328.
- 57 D. H. Halat, S. Younes, N. Mourad and M. Rahal, *Membrane*, 2022, **12**, 1171.
- 58 W. G. Xiao, B. Xuan, L. J. Xiao and Q. L. Zhou, *Chem. Sci.*, 2023, **14**, 8644–8650.
- 59 J. Al Ameri, A. Alsuraifi, A. Curtis and C. Hoskins, *J. Pharm. Sci.*, 2020, **109**, 3125–3133.
- 60 G. N. Vaidya, M. Nagpure and D. Kumar, *ACS Sustainable Chem. Eng.*, 2021, **9**, 1846–1855.
- 61 G. N. Vaidya, R. H. Choudhary, M. Nagpure, S. K. Lokhande, P. Rana and D. Kumar, *Green Chem.*, 2022, **24**, 3977–3984.
- 62 G. N. Vaidya, S. K. Lokhande, S. D. Shinde, D. P. Satpute, G. Narang and D. Kumar, *Green Chem.*, 2022, **24**, 4921–4927.
- 63 G. N. Vaidya, S. Fiske, H. Verma, S. K. Lokhande and D. Kumar, *Green Chem.*, 2019, **21**, 1448–1454.
- 64 S. Kumar, D. P. Satpute, G. N. Vaidya, M. Nagpure, S. K. Lokhande, D. Meena and D. Kumar, *Tetrahedron Lett.*, 2020, **61**, 152017.
- 65 S. K. Lokhande, G. N. Vaidya, D. P. Satpute, A. Venkatesh, S. Kumar and D. Kumar, *Adv. Synth. Catal.*, 2020, **362**, 2857–2863.
- 66 D. P. Satpute, G. N. Vaidya, S. K. Lokhande, S. D. Shinde, S. M. Bhujbal, D. R. Chatterjee, P. Rana, A. Venkatesh, M. Nagpure and D. Kumar, *Green Chem.*, 2021, **23**, 6273–6300.
- 67 Evaluation of organic solvents (toluene, 1,4-dioxane, THF, DMF, acetonitrile) concluded 1,4-dioxane is optimal.
- 68 B. M. Rosen, K. W. Quasdorf, D. A. Wilson, N. Zhang, A.-M. Resmerita, N. K. Garg and V. Percec, *Chem. Rev.*, 2011, **111**, 1346–1416.
- 69 Y.-N. Wang, B.-C. Wang, M.-M. Zhang, X.-W. Gao, T.-R. Li, L.-Q. Lu and W.-J. Xiao, *Org. Lett.*, 2017, **19**, 4094–4097.
- 70 M. Calvin, J. Hermans and H. A. Scheraga, *J. Am. Chem. Soc.*, 1959, **81**, 5048–5050.
- 71 D. N. Kommi, P. S. Jadhavar, D. Kumar and A. K. Chakraborti, *Green Chem.*, 2013, **15**, 798.
- 72 G. Dahlgren and F. A. Long, *J. Am. Chem. Soc.*, 1960, **82**, 1303–1308.
- 73 A. Grimison, *J. Phys. Chem.*, 1963, **67**, 962–964.
- 74 P. C. St John, Y. Guan, Y. Kim, S. Kim and R. S. Paton, *Nat. Commun.*, 2020, **11**, 1–12.
- 75 G. Yin, I. Kalvet, U. Englert and F. Schoenebeck, *J. Am. Chem. Soc.*, 2015, **137**, 4164–4172.

- 76 A. B. Dürr, G. Yin, I. Kalvet, F. Napoly and F. Schoenebeck, *Chem. Sci.*, 2016, **7**, 1076–1081.
- 77 M. E. Greaves, T. O. Ronson, F. Maseras and D. J. Nelson, *Organometallics*, 2021, **40**, 1997–2007.
- 78 J. Dewulf, H. Van Langenhove, J. Mulder, M. M. D. Van Den Berg, H. J. Van Der Kooi and J. De Swaan Arons, *Green Chem.*, 2000, **2**, 108–114.
- 79 T. Collins, *Green Chem.*, 2003, **5**, G51–G52.
- 80 I. Yasui, *Green Chem.*, 2003, **5**, G70–G73.
- 81 S. M. Mercer, J. Andraos and P. G. Jessop, *J. Chem. Educ.*, 2012, **89**, 215–220.
- 82 S. Li and J. Gong, *Chem. Soc. Rev.*, 2014, **43**, 7245–7256.
- 83 Agreement of the Member State Committee on the Identification of *N,N*-Dimethylacetamide (DMAC) as a Substance of Very High Concern – Adopted on 24 November 2011 <https://echa.europa.eu/documents/10162/8b76202f-f4e0-5909-ee10-0ceb4861f3f2>.
- 84 Committee for Risk Assessment RAC Opinion on *N,N*-Dimethylacetamide (DMAC), European Chemicals Agency, 12 September 2014 <https://www.echa.europa.eu/documents/10162/a435d3fca05f-b558-3f51-9aff166f2de0>.