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Double dehydrogenative coupling of amino alcohols with primary alcohols under Mn(I) catalysis†

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Herein, we unveil a method for synthesizing substituted pyrrole and pyrazine compounds *via* a double dehydrogenative coupling of amino alcohols with primary alcohols, facilitated by Mn(I)-PNP catalysis, which uniquely enables the simultaneous formation of C–C and C–N bonds.

The essence of sustainable chemical synthesis lies in its commitment to reducing environmental impact and preserving resources. This approach involves devising synthetic pathways that leverage renewable resources, decrease energy demands, minimize waste, and avoid hazardous by-products.¹ The sustainable synthesis of N-heterocyclic compounds is particularly noteworthy in contemporary science due to their extensive chemical and biological properties, essential in areas such as materials science, pharmaceuticals, and agrochemicals.² Consequently, a plethora of methods for synthesizing N-heterocyclic compounds have been established.³ Of particular interest is the recent rise of acceptorless dehydrogenative coupling for producing aromatic N-heterocycles, a method that notably employs environmentally benign alcohols as starting materials. Extensive research has been conducted on various catalytic systems utilizing 3d and 4d-transition metals.^{4,5}

In the realm of acceptorless dehydrogenative coupling (ADC), the spotlight has traditionally been on secondary alcohols, such as diols and activated benzylic alcohols, for crafting N-heterocyclic compounds, with both noble and base-metal catalysts playing a pivotal role.⁶ However, the synthesis techniques for N-heteroaromatics that employ unactivated primary alcohols, such as phenylethyl alcohol, remain underdeveloped despite the use of precious metal catalysts. Recently, we have demonstrated the synthesis of quinolines and pyridines by

employing a variety of primary alcohols in a double dehydrogenative coupling process with amino alcohols facilitated by manganese-based catalysis.^{5k} Following our research work, the research group of Banerjee also achieved a similar synthesis employing a nickel-catalysis system.^{7a} This reflects an increased focus on primary alcohols in ADC, especially for the synthesis of the pyrrole derivatives. Expanding on this, we have honed our synthetic strategy to produce pyrrole *via* tandem double dehydrogenative coupling with primary and amino alcohols and to generate the pyrazine structure through dehydrogenative self-coupling of amino alcohols. The importance of pyrroles is underscored by their widespread presence in various natural products, pharmaceuticals, catalysts, and materials science.

Polypyrroles, known for their conductive properties, are utilized in the fabrication of batteries and solar cells.^{7b,c} The conventional synthesis of pyrrole has been traditionally accomplished *via* well-known methodologies, including the Paal-Knorr, Knorr, and Hantzsch techniques.⁸ Recent advancements in research have introduced a variety of dehydrogenative coupling methods for the formation of pyrroles (see ESI†).^{4c,i,o,9} These methods predominantly utilize a variety of substituted secondary alcohols, ketones, and diols. However, the literature has not yet reported on the synthesis of pyrrole through dehydrogenative coupling involving primary alcohols. Our present work deals with the unprecedented synthesis of pyrrole directly from primary alcohols, employing a double dehydrogenative coupling with amino alcohol in a solvent-free environment (Scheme 1).

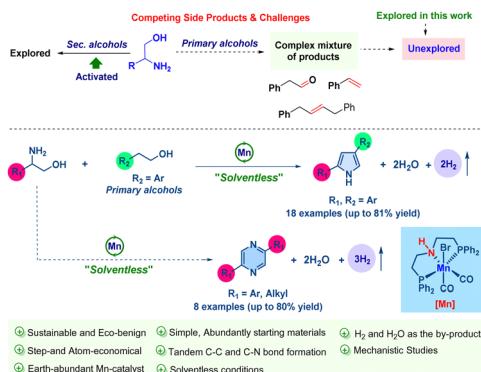
Initially, we selected 2-phenylglycinol and 2-phenylethanol as representative substrates. A systematic investigation was conducted to assess diverse Mn-based catalysts, bases, and temperatures, aiming to determine the optimal reaction conditions for the selective synthesis of pyrrole derivatives (Table 1 and ESI†). Consequently, the reaction of 2-phenylglycinol (1a) with 2-phenylethanol (2a) in the presence of [Mn]-1 (2 mol%) and Cs₂CO₃ (10 mol%) under solvent-free conditions at 130 °C, emerged as the optimal protocol. The present catalytic system

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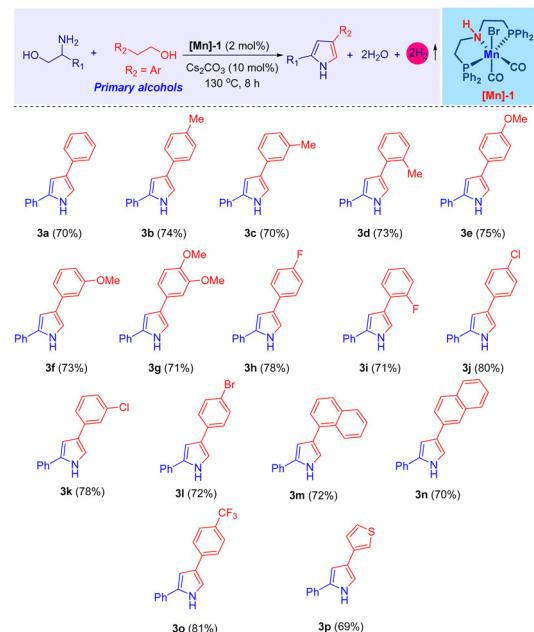




Scheme 1 Direct synthesis of pyrrole and pyrazine via the ADDC strategy.

yielded product **3a** with an isolated yield of 70%, while the self-dehydrogenated product **4a** was produced in negligible quantities (Table 1, entry 1). A series of [Mn]-complexes were evaluated for their efficacy in synthesizing 2,4-disubstituted pyrrole (Table 1, entries 2–4, and ESI†). The [Mn]-1 complex emerged as particularly potent, significantly advancing the catalytic tandem transformation. Notably, in the absence of the **Mn**[I]-catalyst and base, the formation of product **3a** was minimal (Table 1, entries 5 and 6). Exploring solvent influence with *n*-octane, 1,4-dioxane, *m*-xylene, THF, mesitylene, and toluene, we achieved a moderate yield of **3a** under standard conditions (Table 1, entry 7). Notably, substituting Cs_2CO_3 with other bases such as $\text{NaO}^\circ\text{Bu}$, KO°Bu , KOH , and KH led to a lower yield of **3a** (Table 1, entry 8), indeed, with stronger bases favoring the by-product **4a**. Additionally, lowering the reaction temperature was found to adversely affect the yield of **3a**.

Upon establishing the optimal conditions for the tandem catalytic synthesis of pyrrole derivatives, we expanded our investigation to encompass the generality of the present [Mn]-catalysis, as detailed in Table 2. The compound 2-phenylglycinol (**1a**) was selected as a standard substrate. Thus, under optimal reaction conditions, **1a** dehydrogenatively coupled with various phenethyl alcohols (**2**) and effectively led to the formation of the desired 2,4-disubstituted pyrroles (**3**), achieving high yields, as shown in Table 2. Indeed, the use of

Table 2 ADC of primary alcohols with amino alcohols: direct synthesis of pyrrole derivatives^a

^a Reaction conditions: substrate **1** (0.5 mmol), **2a** (0.75 mmol), [Mn]-1 (2 mol%), and Cs_2CO_3 (10 mol%) were heated at 130 °C (silicone oil-bath temperature) for 8 h under an argon atmosphere. ^b Isolated yields.

2-phenylethanol bearing electron-donating methyl and methoxy groups on the aromatic ring led to the synthesis of 2,4-disubstituted pyrroles, achieving very good isolated yields (up to 75%; Table 2, products **3b**–**3g**).

Notably, employing phenyl ethylalcohols with halogen substituents (–Br, –Cl, –F), such as compounds **2h**–**2l**, resulted in the corresponding pyrroles with excellent yields, ranging from 72% to 80% (Table 2, products **3h**–**3l**). The significance of these halogenated derivatives lies in their potential to facilitate further functionalization reactions, thereby unlocking avenues for the synthesis of diverse molecular forms. Furthermore, the incorporation of extended π -conjugated systems, as seen with 2-(1-naphthyl)ethanol (**2m**) and 2-(2-naphthyl)ethanol (**2n**),

Table 1 Optimization studies^a

Entry	Deviation from above	3a Yield ^b (%)	4a Yield ^b (%)
1	No variation	70	<5
2	[Mn]-2 as a catalyst	63	<10
3	[Mn]-3 as a catalyst	60	<10
4	$\text{Mn}(\text{CO})_5\text{Br}/\text{PhPNP-ligand}$ (1 : 1)	<58	<15
5	No [Mn]-catalyst	—	Trace
6	No Cs_2CO_3	—	Trace
7	<i>n</i> -Octane, 1,4-dioxane, <i>m</i> -xylene, THF, mesitylene, toluene as a solvent	<50	<10
8	$\text{NaO}^\circ\text{Bu}$, KO°Bu , KOH , KH as a base	<52	<25

^a Reaction conditions: substrate **1a** (0.5 mmol), **2a** (0.6 mmol), [Mn]-1 (2 mol%), and Cs_2CO_3 (10 mol%) were heated at 130 °C (silicone oil-bath temperature) for 8 h under an argon atmosphere. ^b Isolated yield.

culminated in the high yield of the expected compounds **3m–3n** (up to 80% isolated yield). Under the optimal reaction conditions, 2-phenyl ethanol derivatives with electron-withdrawing functionalities, specifically 2-(4-(trifluoromethyl)phenyl)ethanol (**2o**), and heteroaromatic alcohols such as 2-(thiophene-2-yl)ethanol (**2p**), demonstrated excellent reactivity. This led to the successful synthesis of compounds **3o** and **3p**, achieving yields of 81% and 69%, respectively. However, it was found that aliphatic primary alcohols, modified 2-phenylglycinol derivatives, and aliphatic amino alcohols did not undergo the Mn-catalyzed reaction under the same conditions.

Furthermore, we have expanded the present **Mn[II]**-catalysis for the dehydrogenative self-coupling of β -amino alcohols, enabling the synthesis of pyrazine derivatives. The current methodology for self-coupling amino alcohols to produce pyrazines has been explored in the literature.^{4o,6d,10a} Pioneering work by Milstein's group illustrated this process utilizing PNP-Ru and an acridine-derived PNP-Mn complex.^{6d,10a} In continuation of our work on base metal catalysis, we have demonstrated a transformation akin to that of Milstein's group, utilizing a cobalt-based complex.^{6d} In the current study, we have used a molecularly defined PNP-Mn catalyst, *i.e.*, **[Mn]-1**, for the self-coupling of β -amino alcohols under acceptorless conditions, further expanding the utility of this catalytic system. After establishing the optimized conditions for the dehydrogenative self-coupling method in the synthesis of pyrazine derivatives (see ESI†), the reaction involving 2-phenylglycinol (**1a**), a catalytic amount of **[Mn]-1** (2 mol%), and 20 mol% KOH under solvent-free conditions at 130 °C was identified as the optimal condition, affording the desired product **4a** with an isolated yield of 80% (Table 3, product **4a**). A variety of 2-phenylglycinol derivatives, including those with methyl (**1b**), dimethyl (**1c**), *tert*-butyl (**1d**) and halogen ($-F$, $-Cl$, and $-Br$) substituents (**1e–1g**), as well as aliphatic β -amino alcohols like

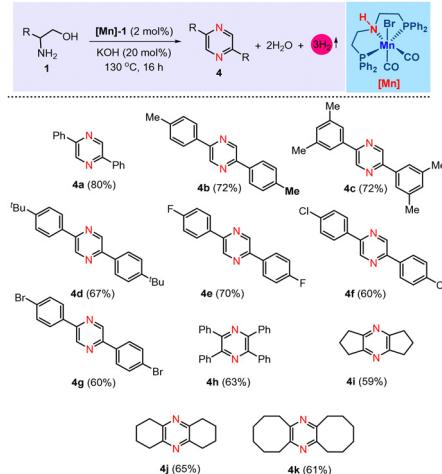
2-amino-1,2-diphenylethan-1-ol (**1h**), 2-aminocyclopentan-1-ol (**1i**), 2-aminocyclohexan-1-ol (**1j**) and 2-aminocyclooctan-1-ol (**1k**) were employed. These substrates successfully produced an array of substituted pyrazines, achieving yields as high as 80% (Table 3).

Control experiments were conducted to elucidate the underlying mechanism (Scheme 2). Initially, the generation of H₂ gas was qualitatively analyzed under optimal conditions (Scheme 2a). Further experiments showed that independent reactions of 2-phenylglycinol (**1a**) and 2-phenyl ethanol (**2a**) under the standard conditions led to the formation of 2-amino-2-phenylacetaldehyde (**5**) and phenylacetaldehyde (**6**), respectively. This was accompanied by the release of H₂ gas, as outlined in Scheme 2b. These results suggest that the reaction follows the acceptorless dehydrogenative pathway. Moreover, the intermolecular coupling for C–N and C–C bond formation was substantiated by reacting *in situ* formed intermediate, such as aldehyde **6** with alcohol **1a**, under standard conditions. This reaction yielded the anticipated 2,4-disubstituted pyrrole product in good yield (Scheme 2c). Notably, the presence of radical scavengers, such as TEMPO and BHT, led to a slight decrease in product yield. This observation suggests that a single electron transfer (SET) pathway cannot be entirely ruled out (Scheme 2d).

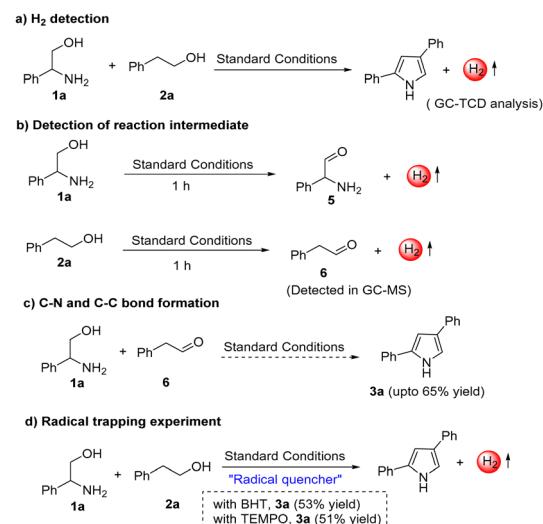
Based on the insights gained from control experiments and previous literature reports,^{5k,10b} we propose a plausible reaction mechanism for the synthesis of pyrrole and pyrazine compounds *via* a double dehydrogenative coupling of amino alcohols with primary alcohols, facilitated by Mn(i)-PNP catalysis (Scheme 3).

Initially, the active Mn-catalyst **Mn(i)-B** is generated from the precatalyst **Mn(i)-A** in the presence of Cs₂CO₃. Subsequently, the intermediate complex **Mn(i)-C** is formed from the active catalyst **Mn(i)-B** by activating the O–H bond of 2-phenylglycinol through metal–ligand cooperation (MLC). Following this, the intermediate **Mn(i)-C** undergoes β -hydride elimination, resulting in the production of 2-amino-2-phenylacetaldehyde (**5**) and intermediate **Mn(i)-E**. Concurrently, 2-phenylacetaldehyde (**6**) is

Table 3 ADC of amino alcohols: direct synthesis of pyrazine derivatives^{a,b}

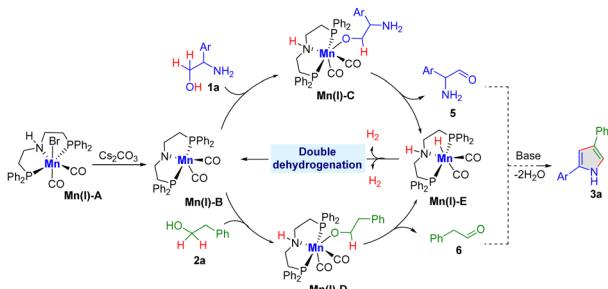


^a Reaction conditions: substrate 1 (0.5 mmol), **[Mn]-1** (2 mol%), and KOH (20 mol%) were heated at 130 °C (silicone oil-bath temperature) for 16 h under an argon atmosphere. ^b Isolated yields.



Scheme 2 Control experiments.





Scheme 3 A plausible mechanism.

generated *via* intermediate **Mn(I)-D**, where 2-phenylethanol coordinates with the active Mn-catalyst **Mn(I)-B**, followed by β -hydride elimination to form intermediate **Mn(I)-E**. Subsequently, a base-mediated coupling takes place, bringing together 2-amino-2-phenylacetaldehyde (5) and 2-phenylacetaldehyde (6) to yield 2,4-disubstituted pyrrole **3a** while eliminating two molecules of water. Finally, the active Mn catalyst **Mn(I)-B** is regenerated from intermediate **Mn(I)-E**, with the liberation of H_2 gas through the MLC process.

In summary, we have successfully demonstrated the direct synthesis of substituted pyrrole and pyrazine compounds through the double acceptorless dehydrogenative coupling of amino alcohols with primary alcohols under solvent-free conditions. This process results in the release of molecular hydrogen and water as by-products. The utilization of an earth-abundant manganese catalyst in combination with readily available starting materials enhances the atom efficiency of this approach, making it more environmentally friendly and sustainable for the synthesis of N-heterocycles.

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Data availability

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

Conflicts of interest

The authors declare no competing financial interest.

Notes and references

- (a) T. Keijer, V. Bakker and J. C. Slootweg, *Nat. Chem.*, 2019, **11**, 190–195; (b) S. A. Matlin, S. E. Cornell, A. Krief, H. Hopf and G. Mehta, *Chem. Sci.*, 2022, **13**, 11710–11720.
- 2 A. Gomtsyan, *Chem. Heterocycl. Compd.*, 2012, **48**, 7–10.
- 3 (a) P. A. Keller, A. R. Katritzky, C. A. Ramsden, E. F. V. Scriven and R. J. K. Taylor, *Comprehensive Heterocyclic Chemistry III*, Elsevier, Oxford, U.K., 2008, vol. 7; (b) I. Nakamura and Y. Yamamoto, *Chem. Rev.*, 2004, **104**, 2127–2198.
- 4 (a) R. Yamaguchi, K.-I. Fujita and M. Zhu, *Heterocycles*, 2010, **81**, 1093; (b) D. Srimani, Y. Ben-David and D. Milstein,

Chem. Commun., 2013, **49**, 6632; (c) S. Michlik and R. Kempe, *Nat. Chem.*, 2013, **5**, 140–144; (d) D. Forberg, J. Obenauf, M. Friedrich, S.-M. Hühne, W. Mader, G. Motz and R. Kempe, *Catal. Sci. Technol.*, 2014, **4**, 4188–4192; (e) A. Nandakumar, S. P. Midya, V. G. Landge and E. Balaraman, *Angew. Chem. Int. Ed.*, 2015, **54**, 11022–11034; (f) N. Deibl, K. Ament and R. Kempe, *J. Am. Chem. Soc.*, 2015, **137**, 12804–12807; (g) I. Bauer and H.-J. Knölker, *Chem. Rev.*, 2015, **115**, 3170–3387; (h) F. Li, L. Lu and P. Liu, *Org. Lett.*, 2016, **18**, 2580–2583; (i) P. Daw, S. Chakraborty, J. A. Garg, Y. Ben-David and D. Milstein, *Angew. Chem. Int. Ed.*, 2016, **55**, 14373–14377; (j) R. H. Crabtree, *Chem. Rev.*, 2017, **117**, 9228–9246; (k) B. Paul, M. Maji, K. Chakrabarti and S. Kundu, *Org. Biomol. Chem.*, 2020, **18**, 2193–2214; (l) M. Garbe, K. Junge and M. Beller, *Eur. J. Org. Chem.*, 2017, 4344–4362; (m) B. Maji and M. Barman, *Synthesis*, 2017, 3377–3393; (n) G. A. Filonenko, R. van Putten, E. J. M. Hensen and E. A. Pidko, *Chem. Soc. Rev.*, 2018, **47**, 1459–1483; (o) S. P. Midya, V. G. Landge, M. K. Sahoo, J. Rana and E. Balaraman, *Chem. Commun.*, 2018, **54**, 90–93; (p) A. Mukherjee and D. Milstein, *ACS Catal.*, 2018, **8**, 11435–11469; (q) S. Shee, K. Ganguli, K. Jana and S. Kundu, *Chem. Commun.*, 2018, **54**, 6883–6886.

- 5 (a) F. Kallmeier and R. Kempe, *Angew. Chem. Int. Ed.*, 2018, **57**, 46–60; (b) S. Parua, R. Sikari, S. Sinha, G. Chakraborty, R. Mondal and N. D. Paul, *J. Org. Chem.*, 2018, **83**, 11154–11166; (c) B. G. Reed-Berendt, K. Polidano and L. C. Morrill, *Org. Biomol. Chem.*, 2019, **17**, 1595–1607; (d) K. Das, A. Mondal, D. Pal and D. Srimani, *Org. Lett.*, 2019, **21**, 3223–3227; (e) S. Waiba and B. Maji, *ChemCatChem*, 2020, **12**, 1891–1902; (f) N. Hofmann and K. C. Hultzsch, *Eur. J. Org. Chem.*, 2021, 6206–6223; (g) S. Shee, D. Panja and S. Kundu, *J. Org. Chem.*, 2020, **85**, 2775–2784; (h) K. Bera and A. Mukherjee, *Tetrahedron Lett.*, 2021, **81**, 153326; (i) M. Maji, D. Panja, I. Borthakur and S. Kundu, *Org. Chem. Front.*, 2021, **8**, 2673–2709; (j) I. Borthakur, A. Sau and S. Kundu, *Coord. Chem. Rev.*, 2022, **451**, 214257; (k) G. Sivakumar, M. Subaramanian and E. Balaraman, *ACS Sustainable Chem. Eng.*, 2022, **10**, 7362–7373.

- 6 (a) M. Mastalir, M. Glatz, E. Pittenauer, G. Allmaier and K. Kirchner, *J. Am. Chem. Soc.*, 2016, **138**, 15543–15546; (b) F. Kallmeier, B. Dudzic, T. Irrgang and R. Kempe, *Angew. Chem. Int. Ed.*, 2017, **56**, 7261–7265; (c) N. Deibl and R. Kempe, *Angew. Chem. Int. Ed.*, 2017, **56**, 1663–1666; (d) P. Daw, A. Kumar, N. A. Espinosa-Jalapa, Y. Diskin-Posner, Y. Ben-David and D. Milstein, *ACS Catal.*, 2018, **8**, 7734–7741; (e) M. K. Barman, A. Jana and B. Maji, *Adv. Synth. Catal.*, 2018, **360**, 3233–3238; (f) K. Das, A. Mondal and D. Srimani, *J. Org. Chem.*, 2018, **83**, 9553–9560; (g) K. Das, A. Mondal and D. Srimani, *Chem. Commun.*, 2018, **54**, 10582–10585; (h) A. Mondal, M. K. Sahoo, M. Subaramanian and E. Balaraman, *J. Org. Chem.*, 2020, **85**, 7181–7191.

- 7 (a) M. Sk, A. Bera and D. Banerjee, *ChemCatChem*, 2023, **15**(11), e202300412; (b) H. Nishide and K. Oyaizu, *Science*, 2008, **319**, 737–738; (c) A. Hagfeldt, G. Boschloo, L. Sun, L. Kloo and H. Pettersson, *Chem. Rev.*, 2010, **110**, 6595–6663.

- 8 (a) T. A. Moss and T. Nowak, *Tetrahedron Lett.*, 2012, **53**, 3056–3060; (b) Z. Wang, Knorr Pyrrole Synthesis, in *Comprehensive Organic Name Reactions and Reagents*, 2010, pp. 1634–1637.

- 9 (a) S.-I. Murahashi, T. Shimamura and I. Moritani, *J. Chem. Soc., Chem. Commun.*, 1974, 931; (b) Y. Tsuji, Y. Yokoyama, K.-T. Huh and Y. Watanabe, *Bull. Chem. Soc. Jpn.*, 1987, **60**, 3456–3458; (c) S. J. Pridmore, P. A. Slatford, A. Daniel, M. K. Whittlesey and J. M. J. Williams, *Tetrahedron Lett.*, 2007, **48**, 5115–5120; (d) N. D. Schley, G. E. Dobereiner and R. H. Crabtree, *Organometallics*, 2011, **30**, 4174–4179; (e) K. Iida, T. Miura, J. Ando and S. Saito, *Org. Lett.*, 2013, **15**, 1436–1439; (f) T. Yan and K. Barta, *ChemSusChem*, 2016, **9**, 2321–2325; (g) B. Emayavaramban, M. Sen and B. Sundararaju, *Org. Lett.*, 2017, **19**, 6–9; (h) K. Singh, L. M. Kabadwal, S. Bera, A. Alanthadka and D. Banerjee, *J. Org. Chem.*, 2018, **83**, 15406–15414; (i) D. Srimani, Y. Ben-David and D. Milstein, *Angew. Chem. Int. Ed.*, 2013, **52**, 4012–4015; (j) M. Zhang, X. Fang, H. Neumann and M. Beller, *J. Am. Chem. Soc.*, 2013, **135**, 11384–11388.

- 10 (a) B. Gnanaprakasam, E. Balaraman, Y. Ben-David and D. Milstein, *Angew. Chem. Int. Ed.*, 2011, **50**, 12240–12244; (b) M. Peña-López, P. Piehl, S. Elangovan, H. Neumann and M. Beller, *Angew. Chem. Int. Ed.*, 2016, **55**, 14967–14971.

