PAPER

Heterogeneous palladium-catalysed Catellani reaction in biomass-derived γ-valerolactone†

Dace Rasina,[a] Arianna Kahler-Quesada,[a] Simone Ziarelli,[a] Svenja Warratz,[b] Hui Cao,[b] Stefano Santoro,[a] Lutz Ackermann*[b] and Luigi Vaccaro*[a]

Herein, we report the unprecedented use of a heterogeneous palladium catalyst for the step-economical Catellani reaction. The substrate scope with encapsulated Pd(OAc)$_2$ (Pd EnCat™ 30) or Pd/Al$_2$O$_3$ proved to be broad, while the renewable biomass-derived γ-valerolactone (GVL) was identified as an effective reaction medium. Mechanistic studies highlighted the possible heterogeneous nature of the Pd/Al$_2$O$_3$ catalyst, while showing that the reaction performed in the presence of Pd EnCat™ 30 is most likely catalysed by leached homogeneous palladium species. The heterogeneous Pd/Al$_2$O$_3$ catalyst can be easily recovered at the end of the reaction and efficiently reused in consecutive reaction runs.

Introduction

In recent years, the direct C–H functionalization of arenes has emerged as a particularly attractive alternative to classical cross-coupling approaches, allowing for late-stage diversifications without the need of prefunctionalization steps.[1] Typically, directing groups are required for achieving site-selectivity in intermolecular transformations, mostly occurring at the *ortho*-position. The Catellani reaction represents an alternative strategy in which the palladium-catalysed C–H *ortho*-functionalization of aryl iodides is mediated by norbornene, which allows for subsequent *ipso*-substitution. In the original report by Catellani and coworkers the dialkylation of the aryl iodide in the two *ortho*-positions was followed by an *ipso*-vinylation through a Mizoroki–Heck-type process.[2] Several modifications to this reaction have subsequently been devised, allowing for different functionalizations to occur both on the *ortho*- as well as on the *ipso*-position. The most synthetically useful approaches towards the *ipso*-functionalization, apart from the Mizoroki–Heck-type alkenylation, include arylations through a Suzuki–Miyaura-type reaction, the alkynylation

through a Sonogashira-type process and the hydrogenolysis of the aryl-palladium intermediate.[3]

Thus far, the vast majority of C–H functionalization reactions have relied on homogeneous transition metal catalysis. Only recently the attention has shifted to the use of versatile heterogeneous catalysts for C–H activation chemistry.[4] However, to the best of our knowledge, examples of heterogeneous metal-catalysed Catellani reactions have as of yet proven elusive. It is particularly noteworthy that the use of heterogeneous catalysts offers great advantages as compared to homogeneous catalysts, especially in terms of recoverability of the catalysts, ease of purification and minimization of metal contamination.

Thus far, the Catellani reaction has largely been conducted in polar aprotic solvents, such as DMF, DMA or acetonitrile. These solvents, particularly DMF and DMA, present major issues related to their toxicity, and their substitution is highly desirable, especially for large-scale applications.[5] Acetonitrile is typically considered the "greenest" option among polar aprotic solvents.[6] However, this actually represents a rather poor alternative due to its volatility and toxicity.[7]

γ-Valerolactone (GVL), is a renewable biomass-derived chemical featuring high polarity, high boiling point, and good stability towards bases and acids. Only few applications employing GVL as reaction media have been disclosed.[8] Recently, we have reported for the first time that GVL can be used as an environmentally-benign alternative to common toxic polar aprotic solvents.[8i–k] In some cases we have also observed that the use of GVL in combination with a heterogeneous catalyst lead to lower product contamination by the metal, compared to the same reaction performed in common polar aprotic solvents.[8i–k] This is particularly relevant since

[a]*Laboratory of Green Synthetic Organic Chemistry, CEMIN – Dipartimento di Chimica, Biologia e Biotecnologie, Università di Perugia Via Elce di Sotto, 8, 06123 Perugia, Italy. E-mail: luigi.vaccaro@unipg.it*
[b]*Institut für Organische und Biomolekulare Chemie, Georg-August-Universität Göttingen, Tammannstrasse 2, 37077 Göttingen, Germany. E-mail: lutz.ackermann@chemie.uni-goettingen.de*

metal contamination represent a major issue in the synthesis of pharmaceutical compounds.[9,10]

In this article we report the first example of a Catellani reaction catalysed by a heterogeneous palladium species. The reaction is performed in a sustainable reaction media (GVL) and the optimal catalyst can be easily recovered and reused for consecutive reaction runs. Experimental mechanistic investigations were also conducted in order to clarify the nature of the catalytically active species.

Results and discussion

At the outset of our studies, we tested representative heterogeneous palladium catalysts in the Catellani reaction with methyl 2-iodobenzoate (1a) and methyl acrylate (2a), using K_2CO_3 as the base and GVL as the medium (Table 1).[11] Commercially available encapsulated $Pd(OAc)_2$,[12] either with or without PPh_3 (Pd EnCat™ 30 and Pd EnCat™ TPP30, respectively) performed with high efficacy, affording the expected product 3a in more than 90% yield (Table 1, entries 1 and 2). The simple Pd/C catalyst gave comparable results, with an isolated yield of 94% (Table 1, entry 3). The addition of 2.5 equivalents of PPh_3, either soluble or immobilized on a polystyrene support, led to a slight decrease in catalytic activity, with the product being obtained in 82–87% yield (Table 1, entries 4 and 5). Also commercially available Pd/Al_2O_3 gave excellent results, providing the expected product in 95% yield (Table 1, entry 6). DMF, NMP, and MeCN were also tested as representative aprotic reaction media (Table 1, entries 7–9). While in the case of DMF satisfactory results were obtained, the use of NMP and MeCN led to poor conversion of the substrate 1a.

The effect of different bases – both organic and inorganic – on the reaction was also investigated, with K_2CO_3 giving the best results (see ESI†).

Next, we explored the scope of the reaction between methyl 2-iodobenzoate (1a) and several olefins 2. We chose to conduct all reactions with Pd EnCat™ 30 as well as Pd/Al_2O_3, in order to investigate possible differences in reactivity between these two rather diverse heterogeneous catalysts. Generally, both catalysts performed well, providing the expected products in moderate to very good yields. In several cases Pd EnCat™ 30 gave slightly better results in terms of yields than Pd/Al_2O_3. α,β-Unsaturated esters and ketones (2a–c) were efficiently converted to the product by either of the two catalytic systems in yields ranging from 60% to 95% (Tables 2 and 3, entries 1–3). Acrylonitrile (2d) furnished good results in the reaction catalysed by Pd EnCat™ 30 (Table 2, entry 4), while much lower yield was obtained using Pd/Al_2O_3, which also needed longer reaction times (Table 3, entry 4).

Vinyl alkyl ethers (2e–f) proved to be more challenging, and the efficacy was strongly dependent on the nature of the catalyst (Tables 2 and 3, entries 5 and 6).

Moreover, the reaction conducted on vinyl ethyl ether (2f) with Pd EnCat™ 30 delivered the formyl-substituted product through a Domino Catellani reaction along with hydrolysis and keto/enol tautomerization. Styrene (2g) and para-substituted styrenes (2h–i) reacted efficiently with both catalysts (Tables 2 and 3, entries 7–9).

Interestingly, in both the reactions performed with the two catalysts, the chlorine functionality was well tolerated (Tables 2 and 3, entry 9), which should prove instrumental for further late-stage diversifications.

1,1-Disubstituted olefins were also subjected to the optimized reaction conditions with either Pd EnCat™ 30 or

Table 1 Heterogeneous catalysts and reaction media optimization[a]

Entry	Palladium catalyst	Reaction medium	Yield[b] (%)
1	Pd EnCat™ 30	GVL	93
2	Pd EnCat™ TPP30	GVL	92
3	Pd/C	GVL	94
4	Pd/C, TPP[c]	GVL	82
5	Pd/C, PS-TPP[c]	GVL	87
6	Pd/Al_2O_3	GVL	95
7	Pd/Al_2O_3	DMF	82
8	Pd/Al_2O_3	NMP	58
9	Pd/Al_2O_3	MeCN	20

[a] Reaction conditions: 1a (0.330 mmol), 2a (0.195 mmol), norbornene (0.127 mmol), K_2CO_3 (0.340 mmol), [Pd] (5 mol%), reaction medium (3.75 mL). [b] Isolated yields. [c] PPh_3 (15 mol%).

Table 2 Scope of the Catellani reaction using Pd EnCat™ 30 as catalyst[a]

Entry	2	R^1	R^2	Time	Yield[b] (%)
1	2a	CO_2Me	H	24 h	93 (3a)
2	2b	CO_2nBu	H	24 h	73 (3b)
3	2c	COMe	H	24 h	77 (3c)
4	2d	CN	H	24 h	68 (3d)
5	2e	OnBu	H	—	—
6	2f	OEt	H	24 h	48[c] (3f)
7	2g	Ph	H	24 h	63 (3g)
8	2h	p-AcO-C_6H_4	H	24 h	79[d] (3h + 3'h)
9	2i	p-Cl-C_6H_4	H	24 h	68 (3i)
10	2j	CO_2Me	Me	2 d	50 (3j : 4j 1 : 1.9)
11	2k	CHO	Me	24 h	68 (3k : 4k 1 : 1.6)

[a] Reaction conditions: 1a (0.330 mmol), 2a (0.195 mmol), norbornene (0.127 mmol), K_2CO_3 (0.340 mmol), [Pd] (5 mol%,), GVL (3.75 mL). [b] Isolated yields. [c] Product deriving from the ether hydrolysis and subsequent keto/enol tautomerization. [d] 1.6 : 1 mixture of the acetylated product and the phenol from ester hydrolysis, see ESI for details.

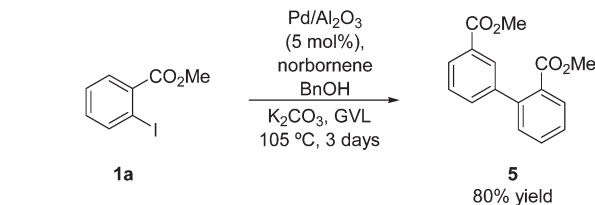**Table 3** Scope of the Catellani reaction using Pd/Al$_2$O$_3$ as catalyst[a]

Entry	2	R^1	R^2	Time	Yield[b] (%)
1	2a	CO$_2$Me	H	24 h	95 (3a)
2	2b	CO$_2$nBu	H	3 d	60 (3b)
3	2c	COMe	H	24 h	68 (3c)
4	2d	CN	H	3 d	32 (3d)
5	2e	OnBu	H	2 d	40 (3e)
6	2f	OEt	H	—	—
7	2g	Ph	H	24 h	74 (3g)
8	2h	p-AcO-C$_6$H$_4$	H	24 h	54[c] (3h + 3'h)
9	2i	p-Cl-C$_6$H$_4$	H	24 h	86 (3i)
10	2j	CO$_2$Me	Me	7 d	41 (3j : 4j 1 : 3.2)
11	2k	CHO	Me	3 d	57 (3k : 4k 1 : 1.5)

[a] Reaction conditions: 1a (0.330 mmol), 2a (0.195 mmol), norbornene (0.127 mmol), K$_2$CO$_3$ (0.340 mmol), [Pd] (5 mol%,), GVL (3.75 mL). [b] Isolated yields. [c] As a 1 : 4 mixture of the expected product and the phenol deriving from the ester hydrolysis.

Pd/Al$_2$O$_3$ as the catalysts (Tables 2 and 3, entries 10 and 11). Their reactivity was in line with that observed for the mono-substituted olefins, with yields ranging from 41% to 68%. However, due to the presence of the methyl group on the substrate, the β-elimination step of the final Mizoroki–Heck-type reaction could occur in two positions, thus generating two isomeric products (3 and 4). As to the substitution pattern on the aryl iodides 1, the optimized palladium catalyst also enabled the synthesis of products 3l–3o (Scheme 1).

The coupling of the Catellani reaction with a terminal hydrogenolysis step provides step-economical access to *meta*-difunctionalized aromatic species.[3,13] We tested the applicability of this strategy under the optimized reaction conditions with Pd/Al$_2$O$_3$ as the catalyst and benzyl alcohol as hydride donor (Scheme 2). The reaction proceeded efficiently, affording the expected coupling product 5 in high yield.

A major issue associated with transition metal catalysis, and in particular with palladium chemistry, is the nature of the catalytic active species. Indeed, it frequently was noted that
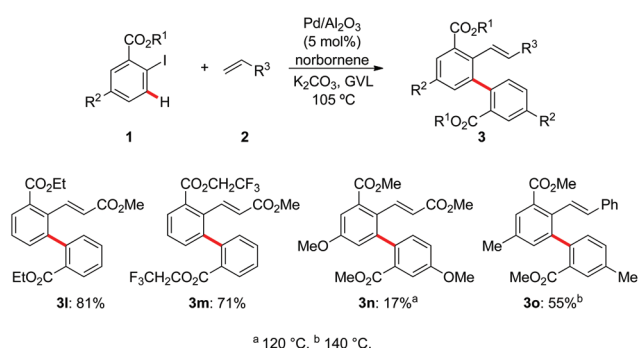

Scheme 2 Catellani reaction with terminal hydrogenolysis.

operationally heterogeneous reactions actually occur through the catalysis of soluble leached metal species or, *vice versa*, that operationally homogeneous reactions were catalysed by *in situ* formed insoluble metal particles.[14] This problem is also of key relevance for C–H functionalization reactions.[4] It is worth considering that the actual nature of the catalyst is not only important for mechanistic reasons, but also has practical implications, since it finally controls the possibility to reuse the recovered catalyst and the metal contamination of the products. Unfortunately, assessing the nature of the catalytic active species (homogeneous *vs.* heterogeneous) is not a simple task. Several experiments have been proposed but none of them is able to give conclusive evidence about the mechanism. Instead, it is necessary to rely on multiple experiments in order to possibly obtain sufficient support to one of the mechanistic scenarios.[14]

For these reasons, we decided to investigate the nature of the catalytically active species through various approaches, for both the reactions catalysed by Pd EnCat™ 30 and by Pd/Al$_2$O$_3$. First, we performed a hot-filtration test by removing the solid catalyst one hour after the beginning of the representative reaction between 1a and 2a, and allowing the filtrate to stir for 3 days at 105 °C. Interestingly, the two catalysts led to quite different results. Thus, while Pd/Al$_2$O$_3$ gave a very low conversion (7%), Pd EnCat™ 30 furnished 3a in 37% conversion. Second, for the same reaction we performed a mercury-poisoning test for both catalysts. Again, the two catalysts behaved differently. In fact, while the addition of Hg(0) completely hampered the catalytic activity of Pd/Al$_2$O$_3$ with only 4% conversion after 20 hours, the reaction with Pd EnCat™ 30 gave 46% conversion under otherwise identical reaction conditions (see ESI†). These results suggest that leached palladium species might play a key role in the reaction catalysed by Pd EnCat™ 30, but not in the reaction with Pd/Al$_2$O$_3$.[15]
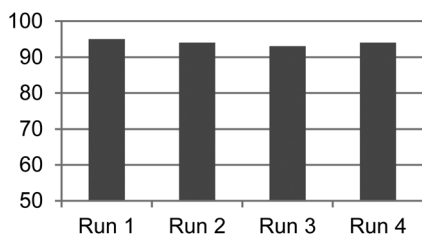
Third, we measured the amount of palladium leached into the crude product by inductively coupled plasma optical emission spectrometry (ICP-OES), for both catalysts, before and after aqueous work-up (Table 4). The amount of palladium leached from Pd/Al$_2$O$_3$ was very low, even before aqueous work-up (∼2 ppm). However, the extent of metal leaching from Pd EnCat™ 30 is relatively high (52.4 and 10.5 ppm before and after aqueous work-up, respectively), and in line with previous findings[15] and with our hot-filtration and Hg-poisoning tests.

Overall, these results suggest that the two tested catalysts exert their catalytic activity in different ways. While Pd EnCat™ 30 is proposed to catalyse the reaction by releasing homo-

Scheme 1 Further examples of Pd/Al$_2$O$_3$ catalysed Catellani reactions.

Table 4 Palladium leaching measured by ICP-OES analysis at the end of the reaction between **1a** and **2a** in GVL

Catalyst	Palladium leaching (ppm)	
Pd EnCat™ 30	no work-up	52.4
	aq. work-up	10.5
Pd/Al$_2$O$_3$	no work-up	2.2
	aq. work-up	0.5

Fig. 1 Reuse of Pd/Al$_2$O$_3$ in the reaction of **1a** and **2a**.

geneous soluble palladium species, the C–H activation catalysed by Pd/Al$_2$O$_3$ is either genuinely heterogeneous or may proceed through a "release and catch" mechanism.[16]

From sustainability and chemical efficiency point of views, it is mostly important that the amount of palladium leached into the product is very low and that the solid catalyst can be efficiently reused. Therefore we tested the recyclability of Pd/Al$_2$O$_3$ in the reaction between **1a** and **2a** in GVL, by recovering the catalyst by simple filtration. The catalyst fully retained its activity for at least three reaction runs, constantly giving full conversion to the products. Thus, the reaction of substrates **1a** and **2a** was repeated for four consecutive runs giving the desired product **3a** constantly in 93–95% yield (Fig. 1).

Conclusions

In conclusion, we have developed the first Catellani reaction catalysed by a solid palladium catalyst. The reaction proceeded efficiently on a variety of alkenes in the renewable biomass-derived medium GVL. The process could also be merged with a terminal hydrogenolysis, which gave step-economical access to valuable *meta*-difunctionalized[17] arenes. The nature of the catalytically active species was investigated and provided support for the versatile Pd/Al$_2$O$_3$ catalyst to operate in a heterogeneous fashion. Importantly, the catalyst could be efficiently recovered and reused, featuring a very low metal leaching. Studies on the use of other economically attractive organic electrophiles are currently ongoing in our laboratories and will be reported in due course.

Experimental

Typical procedure for the Catellani reaction

To a 4 mL vial containing the palladium catalyst (0.00825 mmol, 5 mol%), the base (0.340 mmol), and 2-norbornene

(12 mg, 0.127 mmol) was added a GVL solution (3.75 mL) of the aryl iodide **1** (0.33 mmol) and the terminal olefin **2** (0.195 mmol). The resulting mixture was stirred at 105 °C.

The solids were then separated from the solution by vacuum filtration and rinsed with cyclopentyl methyl ether. The organic layer was washed with water and dried over anhydrous Na$_2$SO$_4$. The products were isolated by flash column chromatography using a 4 : 1 mixture of petroleum ether and ethyl acetate as the eluent.

Procedure for catalyst recovery and recycling

After stirring at 105 °C for 24 h, the reaction mixture was centrifuged and the solvent was decanted. The catalyst was washed, first with water (0.2 mL) and GVL (3.0 mL), then with GVL (3.8 mL). New substrates (**1a** and **2a**), reagents and solvent were added and left for 24 h at 105 °C for the next run. In four consecutive reaction runs Pd/Al$_2$O$_3$ consistently led to full conversion to the expected product in 24 h.

References

1 Representative recent reviews on C–H activation: (*a*) B. Ye and N. Cramer, *Acc. Chem. Res.*, 2015, **48**, 1308–1318; (*b*) K. Shin, H. Kim and S. Chang, *Acc. Chem. Res.*, 2015, **48**, 1040–1052; (*c*) O. Daugulis, J. Roane and L. D. Tran, *Acc. Chem. Res.*, 2015, **48**, 1053–1064; (*d*) Y. Segawa, T. Maekawa and K. Itami, *Angew. Chem., Int. Ed.*, 2015, **54**, 66–81; (*e*) L. Ackermann, *Org. Process Res. Dev.*, 2015, **18**, 260–269; (*f*) M. Zhang, Y. Zhang, X. Jie, H. Zhao, G. Li and W. Su, *Org. Chem. Front.*, 2014, **1**, 843–895; (*g*) N. Kuhl, N. Schroeder and F. Glorius, *Adv. Synth. Catal.*, 2014, **356**, 1443–1460; (*h*) T. Mesganaw and J. A. Ellman, *Org. Process Res. Dev.*, 2014, **18**, 1097–1104; (*i*) S. A. Girard, T. Knauber and C.-J. Li, *Angew. Chem., Int. Ed.*, 2014, **53**, 74–100; (*j*) G. Rouquet and N. Chatani, *Angew. Chem., Int. Ed.*, 2013, **52**, 11726–11743; (*k*) S. R. Neufeldt and M. S. Sanford, *Acc. Chem. Res.*, 2012, **45**, 936–946; (*l*) L. Ackermann, *Chem. Rev.*, 2011, **111**, 1315–1345; (*m*) J. Wencel-Delord, T. Dröge, F. Liu and F. Glorius, *Chem.*

Soc. Rev., 2011, **40**, 4740–4761; (*n*) D. J. Schipper and K. Fagnou, *Chem. Mater.*, 2011, **23**, 1594–1600; (*o*) C. S. Yeung and V. M. Dong, *Chem. Rev.*, 2011, **111**, 1215–1292; (*p*) T. Satoh and M. Miura, *Chem. – Eur. J.*, 2010, **16**, 11212–11222; (*q*) O. Daugulis, *Top. Curr. Chem.*, 2010, **292**, 57–84; (*r*) R. Giri, B.-F. Shi, K. M. Engle, N. Maugel and J.-Q. Yu, *Chem. Soc. Rev.*, 2009, **38**, 3242–3272; (*s*) L. Ackermann, R. Vicente and A. Kapdi, *Angew. Chem., Int. Ed.*, 2009, **48**, 9792–9826, and references cited therein.

2 M. Catellani, F. Frignani and A. Rangoni, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 119–122.

3 (*a*) J. Ye and M. Lautens, *Nat. Chem.*, 2015, **7**, 863–870; (*b*) A. Martins, B. Mariampillai and M. Lautens, *Top. Curr. Chem.*, 2010, **292**, 1–33; (*c*) M. Catellani, E. Motti and N. Della Ca', *Acc. Chem. Res.*, 2008, **41**, 1512–1522; (*d*) M. Catellani, *Top. Organomet. Chem.*, 2005, **14**, 21–53. For recent examples of Catellani–type reactions, see: (*e*) X.-X. Wu, Y. Shen, W.-L. Chen, S. Chen, P.-F. Xu and Y.-M. Liang, *Chem. Commun.*, 2015, **51**, 16798–16801; (*f*) Y. Huang, R. Zhu, K. Zhao and Z. Gu, *Angew. Chem., Int. Ed.*, 2015, **54**, 12669–12672; (*g*) Z. Dong, J. Wang, Z. Ren and G. Dong, *Angew. Chem., Int. Ed.*, 2015, **54**, 12664–12668; (*h*) P.-X. Shen, X.-C. Wang, P. Wang, R.-Y. Zhu and J.-Q. Yu, *J. Am. Chem. Soc.*, 2015, **137**, 11574–11577; (*i*) F. Sun and Z. Gu, *Org. Lett.*, 2015, **17**, 2222–2225; (*j*) Z. Dong, J. Wang and G. Dong, *J. Am. Chem. Soc.*, 2015, **137**, 5887–5890; (*k*) X.-C. Wang, W. Gong, L.-Z. Fang, R.-Y. Zhu, S. Li, K. M. Engle and J.-Q. Yu, *Nature*, 2015, **519**, 334–338; (*l*) P.-X. Zhou, Y.-Y. Ye, C. Liu, L.-B. Zhao, J.-Y. Hou, D.-Q. Chen, Q. Tang, A.-Q. Wang, J.-Y. Zhang, Q.-X. Huang, P.-F. Xu and Y.-M. Liang, *ACS Catal.*, 2015, **5**, 4927–4931; (*m*) Z. Dong and G. Dong, *J. Am. Chem. Soc.*, 2013, **135**, 18350–18353; (*n*) X. Sui, R. Zhu, G. Li, X. Ma and Z. Gu, *J. Am. Chem. Soc.*, 2013, **135**, 9318–9321; (*o*) H. Weinstabl, M. Suhartono, Z. Qureshi and M. Lautens, *Angew. Chem., Int. Ed.*, 2013, **52**, 5305–5308; (*p*) L. Jiao, E. Herdtweck and T. Bach, *J. Am. Chem. Soc.*, 2012, **134**, 14563–14572; (*q*) L. Jiao and T. Bach, *J. Am. Chem. Soc.*, 2011, **133**, 12990–12993; (*r*) A. Rudolph, N. Rackelmann and M. Lautens, *Angew. Chem., Int. Ed.*, 2007, **46**, 1485–1488; (*s*) T. Wilhelm and M. Lautens, *Org. Lett.*, 2005, **7**, 4053–4056; (*t*) C. Bressy, D. Alberico and M. Lautens, *J. Am. Chem. Soc.*, 2005, **127**, 13148–13149, and references cited therein.

4 For reviews, see: (*a*) S. Santoro, S. Kozhushkov, L. Ackermann and L. Vaccaro, *Green Chem.*, 2016, **18**, 3471–3493; (*b*) A. J. Reay and I. J. S. Fairlamb, *Chem. Commun.*, 2015, **51**, 16289–16307; (*c*) C. Cano, A. F. Schmidt and G. P. McGlacken, *Chem. Sci.*, 2015, **6**, 5338–5346; (*d*) L. Djakovitch and F.-X. Felpin, *ChemCatChem*, 2014, **6**, 2175–2187. For recent examples, see: (*e*) K. D. Collins, R. Honeker, S. Vásquez-Céspedes, D.-T. D. Tang and F. Glorius, *Chem. Sci.*, 2015, **6**, 1816–1824; (*f*) D.-T. D. Tang, K. D. Collins, J. B. Ernst and F. Glorius, *Angew. Chem., Int. Ed.*, 2014, **53**, 1809–1813; (*g*) D.-T. D. Tang, K. D. Collins

and F. Glorius, *J. Am. Chem. Soc.*, 2013, **135**, 7450–7453; (*h*) T.-H. Park, A. J. Hickman, K. Koh, S. Martin, A. G. Wong-Foy, M. S. Sanford and A. J. Matzger, *J. Am. Chem. Soc.*, 2011, **133**, 20138–20141; (*i*) S. Kawamorita, T. Miyazaki, H. Ohmiya, T. Iwai and M. Sawamura, *J. Am. Chem. Soc.*, 2011, **133**, 19310–19313; (*j*) K. Yamazaki, S. Kawamorita, H. Ohmiya and M. Sawamura, *Org. Lett.*, 2010, **12**, 3978–3981; see also: (*k*) L. Ackermann and R. Vicente, *Org. Lett.*, 2009, **11**, 4922–4925.

5 D. Prat, A. Wells, J. Hayler, H. Sneddon, C. R. McElroy, S. Abou-Shehada and P. J. Dunn, *Green Chem.*, 2016, **18**, 288–296.

6 M. C. Bryan, B. Dillon, L. G. Hamann, G. J. Hughes, M. E. Kopach, E. A. Peterson, M. Pourashraf, I. Raheem, P. Richardson, D. Richter and H. F. Sneddon, *J. Med. Chem.*, 2013, **56**, 6007–6021.

7 K. Alfonsi, J. Colberg, P. J. Dunn, T. Fevig, S. Jennings, T. A. Johnson, H. P. Kleine, C. Knight, M. A. Nagy, D. A. Perry and M. Stefaniak, *Green Chem.*, 2008, **10**, 31–36.

8 For some selected contributions see: (*a*) P. Pongrácz, L. Kollár and L. T. Mika, *Green Chem.*, 2016, **18**, 842–847; (*b*) Z. Zhang, *ChemSusChem*, 2016, **9**, 156–171; (*c*) L. Qi, Y. F. Mui, S. W. Lo, M. Y. Lui, G. R. Akien and I. T. Horváth, *ACS Catal.*, 2014, **4**, 1470–1477; (*d*) E. I. Gürbüz, J. M. R. Gallo, D. M. Alonso, S. G. Wettstein, W. Y. Lim and J. A. Dumesic, *Angew. Chem., Int. Ed.*, 2013, **52**, 1270–1274; (*e*) S. G. Wettstein, D. M. Alonso, Y. Chong and J. A. Dumesic, *Energy Environ. Sci.*, 2012, **5**, 81998203; (*f*) Z.-Q. Duan and F. Hu, *Green Chem.*, 2012, **14**, 1581–1583; (*g*) L. Qi and I. T. Horváth, *ACS Catal.*, 2012, **2**, 2247–2249; (*h*) I. T. Horváth, H. Mehdi, V. Fábos, L. Boda and L. T. Mika, *Green Chem.*, 2008, **10**, 238–242. For recent examples from our group, see: (*i*) G. Strappaveccia, L. Luciani, E. Bartollini, A. Marrocchi, F. Pizzo and L. Vaccaro, *Green Chem.*, 2015, **17**, 1071–1076; (*j*) G. Strappaveccia, E. Ismalaj, C. Petrucci, D. Lanari, A. Marrocchi, M. Drees, A. Facchetti and L. Vaccaro, *Green Chem.*, 2015, **17**, 365–372; (*k*) E. Ismalaj, G. Strappaveccia, E. Ballerini, F. Elisei, O. Piermatti, D. Gelman and L. Vaccaro, *ACS Sustainable Chem. Eng.*, 2014, **2**, 2461–2464.

9 C. E. Garrett and K. Prasad, *Adv. Synth. Catal.*, 2004, **346**, 889–900.

10 Note for Guidance on Specification Limits for Residues of Metal Catalysts, The European Agency for the Evaluation of Medicinal Products, Evaluation of Medicines for Human Use; London, 17 December 2002; http://www.emea.eu.int.

11 E. Motti, G. Ippomei, S. Deledda and M. Catellani, *Synthesis*, 2003, 2671–2678.

12 (*a*) S. V. Ley, C. Ramarao, R. S. Gordon, A. B. Holmes, A. J. Morrison, I. F. McConvey, I. M. Shirley, S. C. Smith and M. D. Smith, *Chem. Commun.*, 2002, 1134–1135; (*b*) C. Ramarao, D. J. Tapolczay, I. M. Shirley, S. C. Smith and S. V. Ley, Microencapsulated Catalyst Methods of Preparation and Method of Use Thereof, *U.S. Patent*, 8828902B2, September 9, 2014.

13 S. Deledda, E. Motti and M. Catellani, *Can. J. Chem.*, 2005, **83**, 741–747.

14 (*a*) R. H. Crabtree, *Chem. Rev.*, 2012, **112**, 1536–1554; (*b*) M. Pagliaro, V. Pandarus, R. Ciriminna, F. Béland and P. Demma Carà, *ChemCatChem*, 2012, **4**, 432–445; (*c*) N. T. S. Phan, M. Van Der Sluys and C. W. Jones, *Adv. Synth. Catal.*, 2006, **348**, 609–679; (*d*) J. A. Widegren and R. G. Finke, *J. Mol. Catal. A: Chem.*, 2003, **198**, 317–341.

15 (*a*) S. J. Broadwater and D. T. McQuade, *J. Org. Chem.*, 2006, **71**, 2131–2134; (*b*) J. M. Richardson and C. W. Jones, *Adv. Synth. Catal.*, 2006, **348**, 1207–1216.

16 M. Gruttadauria, F. Giacalone and R. Noto, *Green Chem.*, 2013, **15**, 2608–2618.

17 A recent review: J. Li, S. De Sarkar and L. Ackermann, *Top. Organomet. Chem.*, 2016, **55**, 217–257.