Full paper

Applied Organometallic Chemistry

Received: 26 February 2015 Revised: 4 April 2015 Accepted: 8 April 2015 Published online in Wiley Online Library: 22 May 2015

(wileyonlinelibrary.com) DOI 10.1002/aoc.3327

D-Glucosamine in iron-catalysed cross-coupling reactions of Grignards with allylic and vinylic bromides: application to the synthesis of a key sitagliptin precursor

Matej Sova[a], Rok Frlan[a], Stanislav Gobec[a], Gaj Stavber[b] and Zdenko Časar[a,b,c]*

A sustainable D-glucosamine ligand is successfully introduced into iron-catalysed C–C cross-coupling reactions for the first time. The $Fe(acac)_2$/D-glucosamine·HCl/Et_3N catalytic system was effective at 5 mol% loading in coupling reactions of Grignard reagents with organic bromides. Moderate to high efficiency was achieved with preserved stereochemistry when allyl (Csp^3) or alkenyl (Csp^2) bromides were coupled with phenylmagnesium (Csp^2) or benzylmagnesium (Csp^3) bromides. The catalytic system developed was also successfully applied for the novel and economic preparation of a Michael-acceptor-like starting material used in an alternative synthesis of the drug sitagliptin, a known blockbuster for the treatment of type II diabetes mellitus. Copyright © 2015 John Wiley & Sons, Ltd.

Additional supporting information may be found in the online version of this article at the publisher's web-site

Keywords: cross-coupling; iron; glucosamine; Grignard reagent; catalysis

Introduction

Over the past decade, carbon–carbon bond-forming cross-coupling reactions have become powerful and indispensable tools in modern and advanced organic synthesis.[1] One of the useful and common ways for single C–C bond formation is the coupling of an organometallic nucleophile and an organic halide, generally in the presence of a transition metal and/or a specific ligand system.[2] Several transition metal catalysts have been applied for this purpose.[1,2] However, the use of iron (Fe) has gained impetus over the past decade as the cheapest, most environmentally friendly and least toxic transition metal alternative.[3] Furthermore, Fe-catalysed reactions have several advantages, such as high reaction rates, wide scope of tolerated substrates and broad functional group compatibility under mild reaction conditions.[3] A large number of Fe-catalysed cross-coupling reactions between an organic halide and Grignard reagents have been reported, which started with Kochi and co-workers in 1971[4] and was later followed by other groups.[5–12] Among the various Fe precatalysts or catalysts, Fe(II) and Fe(III) salts most commonly catalyse the reactions with the highest levels of conversion.[3] Recently, Fe 1,3-diketonates (especially $Fe(acac)_3$) have been used as the most convenient precatalysts, due to their low cost, commercial availability, stability and relatively non-hygroscopic and non-toxic nature.[6a,6b,13] Isolated Fe complexes with a variety of synthetically prepared ligands,[14] including those with 'artificial *N*,*O*-ligands' (e.g. Fe amine-bis(phenolate) complexes),[14c] have also been applied to C–C cross-coupling reactions. However, additional synthetic efforts are needed for their preparation, which makes them a second-choice option in comparison with directly *in situ* formed Fe catalytic systems. To avoid the formation of possible side products, several ligands, additives[7a] and co-solvents (e.g. *N*-methyl-2-pyrrolidone (NMP)[5b,5c]) have been used in combination with Fe (pre)catalysts. *N*,*N*,*N*′,*N*′-Tetramethylethane-1,2-diamine (TMEDA), hexamethylenetetramine (HMTA) and 1,4-diazabicyclo[2.2.2]octane (DABCO) were shown to be the most promising ligands, as they show great selectivity.[5f,5g,7a,9b,13] Although the mechanisms of Fe-catalysed C–C cross-coupling reactions are still being investigated,[3c,15] the exact mechanisms of action of the above-mentioned ligands and additives remain elusive and under debate. For example, the initial proposal of an Fe/TMEDA-based catalytic cycle by Nagashima and co-workers[16] was recently revisited by Bedford *et al.*[17] Knowledge of the actions of HMTA and NMP in these reactions is even more slender. The positive effects of NMP have been assumed to be associated with a reduction in the decomposition pathways (i.e. β-hydride elimination) via stabilization of intermediate Fe species.[5c] Moreover, only a few new original ligands have been proposed for Fe-catalysed C–C cross-couplings in the past few

* *Correspondence to: Zdenko Časar, Lek Pharmaceuticals d.d., Sandoz Development Center Slovenia, API Development, Organic Synthesis Department, Kolodvorska 27, 1234 Mengeš, Slovenia. E-mail: zdenko.casar@sandoz.com*

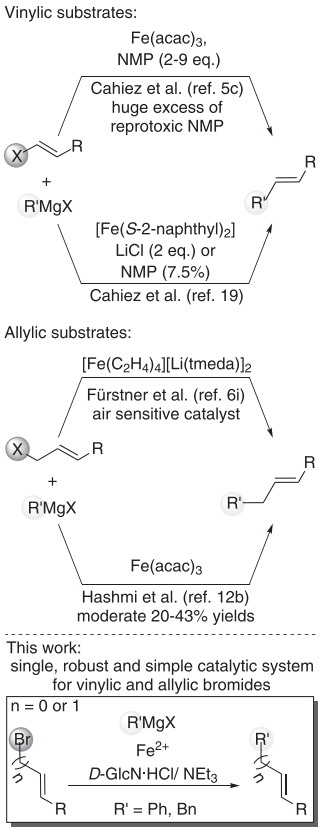
a *Faculty of Pharmacy, University of Ljubljana, Aškerčeva cesta 7, 1000, Ljubljana, Slovenia*

b *Lek Pharmaceuticals d.d., Sandoz Development Center Slovenia, API Development, Organic Synthesis Department, Kolodvorska 27, 1234, Mengeš, Slovenia*

c *Sandoz GmbH, Global Portfolio Management API, Biochemiestrasse 10, 6250, Kundl, Austria*

years.[18] In one of the latest studies by Cahiez *et al*., it was noted that the discovery of specific new ligands is a forthcoming challenge for Fe-catalysed organic synthesis.[19]

Substituted olefins represent an important structural motif in organic chemistry. Their importance as principal building blocks in organic synthesis, which enables many important functional group interconversions, is widely recognized. Approaches to substituted olefins from vinylic and allylic halides via cross-coupling reactions using efficient, cheap and benign transition metal catalysts are limited.[3o] In the context of iron catalysis, vinylic bromides were cross coupled with Grignards using a very large excess of reprotoxic NMP[5b,5c] or with iron catalyst based on the tedious-to-prepare (on industrial scale) thiolate ligands,[19] while allylic halides were efficiently coupled with Grignards only with highly air-sensitive lithium ferrate complex[6i] or in moderate yields with $Fe(acac)_3$ (Scheme 1).[12b] In addition to vinyl halides, vinyl triflates[6c,6g,6h,6j,12f,12g] and dienol phosphates[5h] have also been used as substrates in cross-coupling reactions with Grignard reagents for the construction of substituted olefins. In contrast to vinyl halides, the coupling usually proceeds well in the presence of $Fe(acac)_3$ in pure THF or THF–NMP without the necessity of additional ligand utilization. However, the use of expensive trifluoromethanesulfonic anhydride or toxic diethoxyphosphoryl chloride for the preparation of these substrates and lower atom economy render these approaches less attractive for industrial application. Therefore, a need exists to discover an efficient, robust and benign catalytic system, which could be easily used in the industrial setting in order to minimize waste streams.



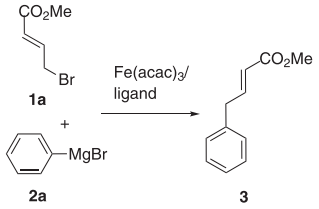
Scheme 1. Previously reported iron-catalysed cross-couplings of vinylic and allylic halides with Grignards[3o] and the method developed herein.

Results and discussion

As a response to the challenge mentioned above, and in view of our interest in the development of simple and especially more sustainable catalytic methodologies for C–C coupling reactions, our initial study started with the screening of several different transition metal catalysts in the presence of selected well-known ligands or ligand systems (TMEDA[7a] and HMTA–TMEDA at 2/1[5f,5g]) in a model non-optimized C–C coupling reaction. For this purpose, we used methyl 4-bromocrotonate (**1a**) and phenylmagnesium bromide (**2a**) to identify the catalytic systems with broad functional group compatibility. Based on the data obtained (supporting information, Table S1), $Fe(acac)_3$ was selected as the catalyst, due to the high efficiency potential and the appropriate industrial applicability associated with it being environmentally friendlier due to its low toxicity. In the continuation of our study, we focused on the search for new specific ligands for Fe-catalysed organic reactions, to define a cheap, simple and bio-inspired catalytic system that would be efficient for our model reaction between **1a** and **2a**. Initially, we performed screening of several natural molecules, including carbohydrates, ascorbic and citric acids, amino acids, nicotinamide, reduced forms of alaninol and 3-picolylamine, and catechol as a well-known Fe chelator,[20] and we compared their efficiencies with those of some of the more well-known additives/ligands, such as triethylamine (Et_3N), DABCO, HMTA and TMEDA, and combinations thereof.[9b] The data obtained are summarized in Table 1. It is worth mentioning that carbohydrates and some basic amino acids are the most bio-abundant groups of molecules that have environmentally benign natures and can provide promising cost benefits for industrial processes, and this is why they have high potential for use in various synthetic applications. Chemists are using these very often as the main precursors in the synthesis of natural compounds and pharmaceutically important drugs, while significant progress has been made in the field of selective catalytic reactions, where they have important roles as efficient bio-based ligands.[21–25]

Most of the sugars and amino acids used as ligands give similar yields in comparison to the well-known ligands like TMEDA and HMTA–TMEDA. To compare the efficiencies of ligands, the same unoptimized reaction conditions were used for all entries in Table 1. The substrate and Grignard reagent were used in 1:1 ratio to avoid the possible influence of excess amounts of organomagnesium reagent on the yield of the reaction and the formation of side products. However, it is worth mentioning that part of the organomagnesium reagent is probably consumed for the reduction of the iron catalyst and/or deprotonation of the chosen protic additive. This is taken into consideration when we compare the efficiencies of selected ligands. Surprisingly, the highest yield among the natural ligands is obtained when D-glucosamine hydrochloride (D-GlcN·HCl; Table 1, entry 3) and *N*,*N*-dimethylglycine (Table 1, entry 7) are used as ligands in the catalytic system. It is well known that both of these molecules work as efficient bidentate chelators towards many metal ions in organometallic complexes, including Fe.[26,27] On the other hand, D-glucosamine has also been reported to be an efficient and green ligand for some metal-catalysed reactions with palladium, in the well-known Heck reactions,[28] in copper-catalysed synthesis of anilines from aryl halides[29] and in *N*-arylation of imidazoles with aryl and heteroaryl bromides.[30] However, to the best of our knowledge, D-glucosamine has never been used in Fe-catalysed C–C coupling reactions. In our efforts towards potential uses in industrial applications, D-glucosamine might offer lower costs compared to *N*,*N*-dimethylglycine. In addition, D-glucosamine has already been used for the synthesis

Table 1. Ligands screened in the $Fe(acac)_3$-catalysed $C(sp^2)$–$C(sp^3)$ C–C coupling model system



Entry	Additive/ligand	Yield (%)[a,b]
1	Glucose	30
2	Ribose	24
3	D-Glucosamine·HCl	39 (43[c])
4	Phenylalanine	26
5	Proline	20
6	Sarcosine (*N*-methylglycine)	38 (35[c])
7	*N*,*N*-Dimethylglycine	39 (38[c])
8	D,L-Pyroglutamic acid	34 (27[c])
10	Ascorbic acid	10
11	Citric acid	5
12	Nicotinamide	8
13	Alaninol	26
14	Picolylamine	5
15	Catechol	5
16	DABCO	23
17	TMEDA	42
18	HMTA	28
19	HMTA–TMEDA (2/1)	39

[a]Determined using HPLC analysis. 2,6-Dichlorobenzaldehyde and phthalimide were used as internal standards.

[b]Standard reaction conditions: methyl 4-bromocrotonate **1a** (3.0 mmol), $Fe(acac)_3$ (0.15 mmol), ligand (0.15 mmol), PhMgBr **2a** (3.0 mmol), anhydrous THF (20 ml), −20°C for 1 h, then room temperature overnight. Although some of the used bio-based ligands contain different numbers (2–5) of acidic protons which can consume part of the used Grignard reagent, stoichiometric amount of Grignard reagent **2** was used compared to substrate **1** for screening purposes. This result in the apparently lower observed yields for catalytic systems based on bio-based ligands, due to the partial consumption of Grignard in deprotonation of acidic protons within the ligand.

[c]$Fe(acac)_2$ was used as the catalyst.

of several antibiotics and anticarcinogens.[30] Due to its apparent advantages, we decided to use D-glucosamine as the potential ligand in our bio-inspired Fe-based catalytic system for C–C coupling reactions.

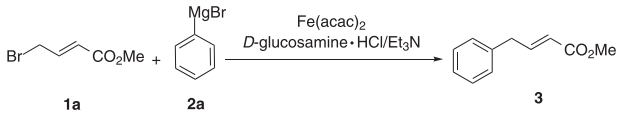
The poor solubility of D-GlcN·HCl in organic solvents is probably one of the main reasons for the lower efficiency in the first experiment. To circumvent the potential solubility problems, structurally different bases were added to the $Fe(acac)_3$/D-GlcN·HCl couple and the yields were determined using HPLC (supporting information, Table S2). As expected, the addition of a base such as Et_3N to the reaction mixture deprotonates the D-GlcN·HCl salt to its neutral free base analogue (the pK_a of D-glucosammonium ions is *ca* 7.9–8.1[31] and the pK_a of triethylammonium ions is *ca* 10.7[32]), and increases its solubility as well as its possibility for iron chelation, and consequently improves the yield from 39 to 50%. According to the literature, Et_3N can also act as a ligand in Fe-catalysed C–C coupling reactions of alkyl halides bearing β-hydrogens with Grignard reagents, albeit at 10 mol% loading of Et_3N.[9b] This might explain the slightly higher efficiency of the reactions when Et_3N is used. However, when compared to other bases used (supporting information, Table S2), only a slightly higher yield is obtained with Et_3N, which indicates clearly that the main contributing effect in our catalytic system does not originate from the presence of Et_3N. Lower cost and better solubility of Et_3N in THF compared to Cs_2CO_3 are the main reasons for the selection of Et_3N as a base in all of the further reactions. In our first set of experiments (supporting information, Table S1), both Fe(II) and Fe(III) stabilized with 1,3-diketonates are effective in our model reaction. Additional screening of four best ranked ligands with $Fe(acac)_2$ shows the highest yield for D-GlcN·HCl (Table 1, entries 3 and 6–8). This observation can be explained by the recent study of Lefévre *et al.*,[15b] where it was shown that additional equivalent of Grignard reagent (e.g. PhMgBr) is consumed from $Fe(acac)_3$ compared to $Fe(acac)_2$ in successive reductions to generate the active Fe(I) complex that couples with electrophiles ($Fe(acac)_2$ is an intermediate in successive reductions of $Fe(acac)_3$ by Grignards towards Fe(I) species). This could suggest that in the case of $Fe(acac)_3$ part of the excess Grignard is consumed for the reduction of $Fe(acac)_3$ to $Fe(acac)_2$ and generation of Ph–Ph by-product (which was also detected in our case using NMR spectroscopy) instead for the desired reaction, which results in lower observed yields. Accordingly, we performed the reaction between **1a** and **2a** in the presence of the $Fe(acac)_2$/D-GlcN·HCl/Et_3N catalytic system, and we obtain a higher yield than with the comparable Fe(III) analogue. Thus, we decided to use $Fe(acac)_2$ as the metal catalyst for all of our further experiments.

In the following optimization of $Fe(acac)_2$/D-GlcN·HCl/Et_3N as the selected catalytic system, the effects of catalyst and ligand loading, reaction temperature and amount of Grignard reagent were examined for the cross-coupling reaction of a model system based on **1a** and **2a** (Table 2). To demonstrate the efficiency of the assembled catalytic system, we performed the reaction in the absence and presence of a ligand and a base (Table 2, entries 1–3). We started the optimization with 5 mol% metal catalyst and ligand at a temperature of −20°C, which are standard conditions in similar metal-based catalytic systems for C–C coupling reactions.[6b] Under these conditions, a promising 60% conversion is achieved with $Fe(acac)_2$/D-GlcN·HCl, and (*E*)-methyl-4-phenylbut-2-enoate (**3**) is isolated at a 43% yield (Table 2, entry 1). When Et_3N is used in the absence of D-GlcN·HCl, 79% conversion is reached, and **3** is isolated at a 52% yield (Table 2, entry 2). Moreover, as expected, the yield of **3** is low when only $Fe(acac)_2$ is used as the catalyst (Table 2, entry 3).

To explore potential synergistic effects of all of the tested species, and to address the poor solubility of D-GlcN·HCl in THF, our initial reaction was run in the presence of 5 mol% of all of the 'catalytic' components. This combination enables excellent conversion (92%), and **3** is obtained with a 60% isolated yield (Table 2, entry 4). These experiments also show that the addition rate of the Grignard reagent has an important role as a critical factor in the efficiency of the cross-coupling reaction with the catalytic system developed (Table 2, entries 4 and 5).[7a] The best data are obtained with the slow addition of the Grignard reagent (4 ml h^{-1}), although, on the other hand, slower rates (<4 ml h^{-1}) provide significantly lower efficiency. Slow addition rates are generally preferred, to avoid possible over-reduction of Fe species.[33]

To make the methodology even more economical, 1 mol% $Fe(acac)_2$ is used, where 87% conversion is detected and **3** is obtained with a moderate 50% isolated yield (Table 2, entry 6). Higher catalyst

Table 2. Effects of reaction conditions on $Fe(acac)_2$/D-glucosamine·HCl/Et_3N-catalysed cross-coupling between **1a** and **2a**



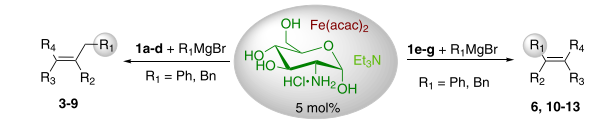
1a **2a** **3**

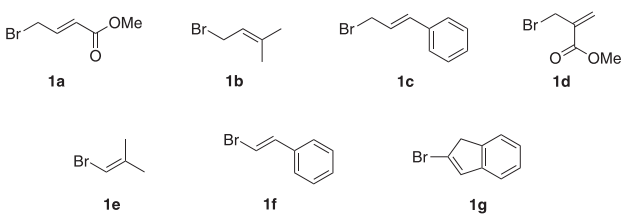
Entry	Fe $(acac)_2$ (mol%)	D-Glucosamine·HCl (mol%)	Et_3N (mol%)	PhMgBr, **2a** (equiv.)	*T* (°C)	Conversion (%)	Yield (%)[a]
1	5	5	—	1	−20	60	43
2	5	—	5	1	−20	79	52
3	5	—	—	1	−20	50	20
4	5	5	5	1	−20	92	60
5	5	5	5	1	−20	88	39[b]
6	1	1	1	1	−20	87	50
7	5	10	10	1	−20	88	46
8	5	15	15	1	−20	93	40
9	10	10	10	1	−20	79	43
10	5	5	5	1	0	95	31
11	5	5	5	1	25	49	24
12	5	5	5	1.5	−20	99	74
13	2.5	2.5	2.5	1.5	−20	97	60
14	5	5	5	2.0	−20	98	36

[a]Determined using HPLC analysis. 2,6-Dichlorobenzaldehyde was used as internal standard. Standard reaction conditions: methyl 4-bromocrotonate **1a** (3.0 mmol), $Fe(acac)_2$ (1–10 mol%), D-glucosamine hydrochloride (1–15 mol%), Et_3N (1–15 mol%), PhMgBr **2a** (3.0–6.0 mmol, addition rate 4 ml h^{-1}, anhydrous THF (20 ml), −20°C, 1 h.

[b]Addition rate was 2 ml h^{-1}.

Table 3. $Fe(acac)_2$/D-glucosamine·HCl/Et_3N-catalysed C–C cross-coupling of allyl and alkenyl bromides with Grignard reagents





Entry	Substrate (**1**)	R_1MgBr (**2**)	Product	Yield (%)[a,b]
1	**1a**	PhMgBr (**2a**)	**3**	67
2	**1b**	PhMgBr (**2a**)	**4**	65
3	**1b**	BnMgBr (**2b**)	**5**	63
4	**1c**	PhMgBr (**2a**)	**6**	70
5	**1c**	PhMgBr (**2a**)	**6**	37[c]
6	**1c**	BnMgBr (**2b**)	**7**	84
7	**1d**	PhMgBr (**2a**)	**8**	79
8	**1d**	BnMgBr (**2b**)	**9**	40
9	**1e**	PhMgBr (**2a**)	**10**	80
10	**1f**	PhMgBr (**2a**)	**11**	72
11	**1f**	BnMgBr (**2b**)	**6**	92
12	**1g**	PhMgBr (**2a**)	**12**	83
13	**1g**	PhMgBr (**2a**)	**12**	70[c]
14	**1g**	BnMgBr (**2b**)	**13**	89

[a]Yields were obtained after column chromatography (SiO_2; diethyl ether–petroleum ether = 1/10).

[b]Standard reaction conditions: substrate **1** (3.0 mmol), $Fe(acac)_2$ (0.15 mmol), D-glucosamine hydrochloride (0.15 mmol), Et_3N (0.15 mmol), R_1MgBr **2** (4.5 mmol; 1.5 equiv.), anhydrous THF (20 ml), −20°C for 1 h, then slowly to room temperature for 1 h.

[c]$Fe(acac)_3$ was used as the catalyst.

and/or ligand loading (>5 mol%) does not improve the yield further (Table 2, entries 7–9). Therefore, we decided to use the initial amounts of 5 mol% $Fe(acac)_2$ and D-GlcN·HCl in the presence of Et_3N for all of the further experiments.

Next, we checked the effects of temperature on the reaction system. It is known that a significant number of reported Fe-catalysed reactions have been performed at temperatures below 0°C;[5–12] however, it would be preferable to perform these reactions at ambient temperature. Unfortunately, the reaction temperatures between 0 and 25°C are not well tolerated, and result in decreased reaction yields of 31 and 24%, respectively (Table 2, entries 10 and 11).

Last but not least, the amount of the Grignard reagent (**2a**) was also studied. In many Fe-catalysed cross-coupling reactions reported, up to 2 equiv. of Grignard reagents were often used.[5–12] Accordingly, our reaction was performed in the presence of 1 to 2 equiv. of **2a**. The data demonstrate that **3** is obtained with a higher isolated yield of 74% when 1.5 equiv. of the Grignard reagent is used (Table 2, entry 12). When lower catalyst loadings are used in the presence of higher amounts of the Grignard reagents, lower efficiencies are again obtained (Table 2, entry 13). When 2 equiv. of **2a** is used, the yield does not exceed 36% (Table 2, entry 14).

Having defined this set of appropriate reaction conditions, we explored the efficiency and applicability of the developed catalytic system for organic bromides. Several allyl and alkenyl bromides and two different Grignard reagents (**2a** and benzylmagnesium bromide, **2b**) were used to examine the efficiencies of our catalytic system in diverse Csp^2/Csp^3 C–C cross-coupling reactions (Table 3). It is important to note here that, in most cases, the levels of conversion are quantitative and the isolated yields are up to 92%. Thus, the Fe(II)/D-GlcN·HCl/Et_3N bio-inspired catalytic system proves to be relatively general with respect to different allyl or alkenyl bromides, and provides a diverse set of useful products with high yields (Table 3). Additionally, to test the selection of $Fe(acac)_2$ as a catalyst, we selected two substrates and performed the reaction in the presence of $Fe(acac)_3$ instead of $Fe(acac)_2$ (Table 3; entries 5 and 13). As can be seen from the data obtained, the isolated yield is lower in the case of $Fe(acac)_3$, which confirms our initial findings in the reaction between **1a** and **2a**.

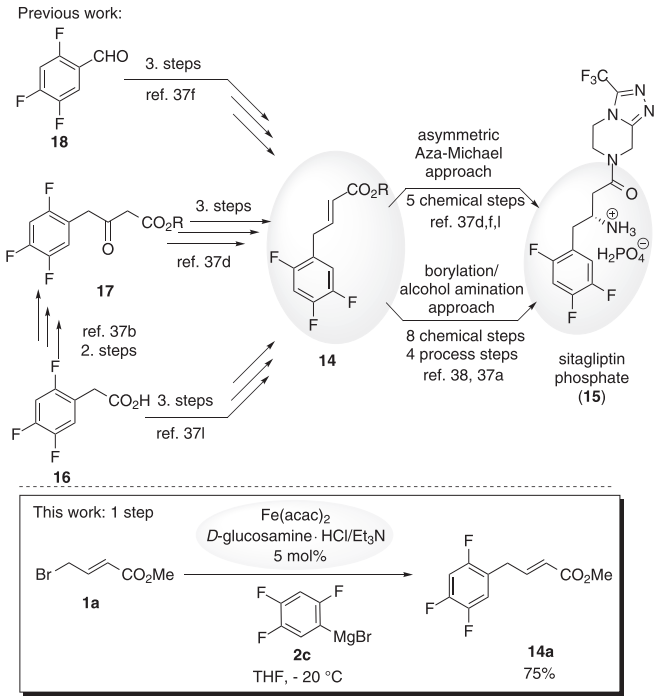
The catalytic system developed proves to be efficient across the structurally different allyl bromides **1a–d**, and the target products are obtained with 40 to 84% isolated yields (Table 3, entries 1–8). The example shown in Table 3, entry 7, is of particular interest, where high regioselectivity and efficiency are obtained when the bromide **1d** with an exocyclic double bond and an ester moiety is reacted with **2a** to product **8**, which has not been achieved with some previously developed catalytic methodologies. On the other hand, the reaction with **2b** (Table 3, entry 8) produces only 40% pure isolated product **9**. Among the selected allyl bromides **1a–d**,

the highest efficiency is obtained when cinnamyl bromide (**1c**) is used as the substrate in the C–C coupling reaction with **2a** or **2b**, where exclusively (*E*)-1,3-diphenylprop-1-ene (**6**) and (*E*)-1,4-diphenylbut-1-ene (**7**) are obtained, with 70 and 84% isolated yields, respectively (Table 3, entries 4 and 6). It is important to note that these derivatives have been rarely studied within the frame of iron catalysis.[3,6i,12b]

When alkenyl bromides **1e–g** are used in the Fe(II)/D-GlcN·HCl/Et_3N-catalysed cross-couplings, even higher efficiencies in comparison to the allyl bromides **1a–d** are obtained, and the conversions are mostly quantitative (Table 3, entries 9–14). It is worth mentioning here that, in these cases, the methodology developed provides very simple, economic, one-step synthesis to phenyl-substituted alkenes, where the desired products of 2-methyl-1-propylbenzene (**10**), (*E*)-1,2-diphenylethene (**11**), (*E*)-1,3-diphenylprop-1-ene (**6**), 3-phenyl-1*H*-indene (**12**) and 3-benzyl-1*H*-indene (**13**) are prepared at 72 to 92% isolated yields. Classical approaches to stilbene derivatives also include bioactive compounds like resveratrol, pinosylvin and pterostilbene, and these are usually more complicated chemically, and require more chemical steps and/or operations, while also showing variable stereoselectivities.[34] Various synthetic strategies and methodologies to stilbenes have been developed to date, which started with aldol-type condensations,[34a] Perkin reactions,[34b,34c] the Wittig approach,[34d] Horner–Emmons reactions[34c,34e] and, very recently, some modern Pd- and Cu-catalysed Heck-type or Suzuki-type cross-couplings.[34f–34i] Furthermore, it should be noted that the reactions catalysed with our bio-inspired catalytic system are also fully stereoselective, as we do not observe any changes in the *E*/*Z* ratio of the starting alkyl or the alkenyl bromides **1e–g** during the reactions. In all cases, (*E*)-isomers are detected and confirmed with NMR spectroscopy. We have also performed control experiments (in the absence of Et_3N) involving cross-coupling of alkenyl bromides **1e–g** with Grignards **2a** and **2b** (see supporting information for full details) to verify the utility of D-GlcN·HCl in the catalytic system. The obtained results additionally affirm the beneficial role of D-GlcN·HCl. Indeed, when **1e–g** react with **2a** in the presence of $Fe(acac)_2$, only traces (0–11%) of products **10–12** are detected in the reaction mixture, while the catalytic system based on $Fe(acac)_2$/D-GlcN·HCl provides 30–68% of **10–12**. When **1f** and **1 g** react with **2b** in the presence of $Fe(acac)_2$ alone, **6** and **13** are formed in 54 and 48% yields, respectively, while $Fe(acac)_2$/D-GlcN·HCl gives 10–19% higher yields (73% for **6** and 58% for **13**), which is also a notable difference from an industrial application perspective.

According to these data, our catalytic system complements the Cahiez benchmark methods based on $Fe(acac)_3$/THF/NMP (2–9 equiv.)[5c] or iron(II) arylthiolate complexes/NMP (7.5%) or LiCl (2 equiv.)[19] for the coupling of Grignard reagents with alkenyl halides. Namely, our approach eliminates the necessity for the use of 2–9 equiv. (200–900%) of the NMP co-solvent in exchange for the application of 5 mol% of D-GlcN·HCl/Et_3N, while 5 mol% of the lower molecular weight $Fe(acac)_2$ replaces 1 mol% of $Fe(acac)_3$. This is of great relevance when large-scale industrial processes are considered, as enormous amounts of reprotoxic and hazardous NMP solvent[5c,35] waste are eliminated in our method, while an overall marginally higher amount of benign metallic catalyst waste is generated. Namely, NMP is now known to cause reproductive toxicity. According to Regulation (EC) No. 1272/2008 and amendment by Regulation (EC) No. 790/2009, as of 1 December 2010, NMP is listed and classified in Annex VI, Part 3, Table 3.1 as toxic for reproduction category 1B (H360D: 'May damage the unborn child'). The European Chemicals Agency (ECHA) put NMP on the REACH Substance of Very High Concern (SVHC) list on 20 June 2011.[35a] The pharmaceutical industry has classified NMP as overall hazardous[35b] and alternative amide-type solvents are already being investigated.[35c] Similarly, the operational simplicity advantage of our method can also be noticed in comparison to Fe(II) arylthiolate complexes,[19] where an additional Grignard-involving step is needed for the preparation of Fe(II) arylthiolate precatalyst from the iron source (e.g. $FeCl_2$) and a foul-smelling mercaptan such as 2-naphthalenethiol. In addition, these precatalysts work best at 5 mol% load in the presence of reprotoxic and hazardous NMP[35] (7.5 mol%) or expensive LiCl (200 mol%). Furthermore, in our case, the same catalytic system also encompasses the ability to perform previously less frequently studied Fe-catalysed coupling of Grignard reagents with allyl halides in high efficiency.[3o] The present highly efficient method described by Fürstner *et al.* for this type of reaction uses the highly air-sensitive $[Fe(C_2H_4)_4][Li(tmeda)]_2$ lithium ferrate complex at 5 mol% loading,[6i] while the Hashmi method based on $Fe(acac)_3$ operates with moderate efficiency.[12b] Therefore, our method compares favourably with the existing methods, due to its operational simplicity, albeit at slightly lower attained yields compared to Fürstner *et al.*,[6i] but notably higher efficiencies compared to the Hashmi method.[12b]

In the past few years, iron catalysis has often been used for large-scale applications and/or in the synthesis of industrially relevant compounds.[36] Examples are 5-substituted 3-isoxazolol fibrinolysis inhibitor AZD6564,[36a] a calcimimetic agent and calcium-sensing receptor antagonist cinacalcet hydrochloride,[36b] highly selective adenosine A_{2A} receptor ligand antagonist ST1535,[36c] immunosuppressive agent FTY720[36d] and a new heterocyclic dual NK1/serotonin receptor antagonist.[36e] Encouraged by our results, we wanted to determine whether the presented catalytic methodology based on Fe(II)/D-GlcN·HCl/Et_3N could be used for the preparation of a target intermediate, namely 4-(2,4,5-trifluorophenyl) but-2-enoate (**14**), in an alternative process for the synthesis of the oral antihyperglycemic drug sitagliptin phosphate (**15**).[37] Compound **14** is a well-known precursor of sitagliptin chiral side chain (Scheme 2). Sitagliptin phosphate can be assembled efficiently in a concise manner from **14** either via asymmetric aza-Michael addition strategy[37d,37f,37l] in five steps (including the salt formation step) or via a lengthier borylation/alcohol amination sequence comprising eight steps (Scheme 2).[37a,38] Previous synthetic approaches to **14** are lengthy and consist of from three to five synthetic steps (Scheme 2),[37b,37d,37f,37l] which makes the abovementioned asymmetric aza-Michael addition strategy towards sitagliptin rather long and less attractive from the industrial point of view. Thus, a concise one-step synthesis of **14** from a commodity starting material such as **1a** and the corresponding fluorinated aryl Grignard could mean the aza-Michael addition strategy towards sitagliptin as a cost-effective six-step route. Namely, the current benchmark routes to sitagliptin phosphate are four to five steps long; however, they originate from more advanced starting material **16**, which already contains two atoms of the 'side chain'. Moreover, these routes use either costly Rh transition metal catalyst[37c] or an expensive custom-made enzyme.[37e] The former is prepared in several synthetic steps, while the enzyme preparation requires specialized preparation and purification steps. All these catalyst preparation steps in benchmark routes should be considered as complexity- and cost-generating factors in comparison to the aza-Michael approach. Therefore, the starting material **1a** was reacted in the Fe(II)/D-GlcN·HCl/Et_3N-catalysed reaction with freshly obtained 2,4,5-trifluoromagnesium bromide (**2c**) prepared via a Grignard exchange reaction, and the target product **14a** was



Scheme 2. Straightforward synthesis of (*E*)-methyl-4-(2,4,5-trifluorophenyl)but-2-enoate using the $Fe(acac)_2$/D-GlcN·HCl/Et_3N catalytic system, and its use in an alternative synthesis of sitagliptin phosphate.

successfully obtained with 75% isolated yield and exclusively in the (*E*)-geometrical form (Scheme 2). It is worth mentioning that fluoro-substituted Grignard reagents are very problematic for cross-coupling reactions, due to very specific electronic effects of fluorine atoms, as well as to their stability. This very encouraging result was thus obtained by implementation of a simple and environmentally friendlier catalytic system based on Fe and D-glucosamine in an important industrial application related to the improved economical synthesis of sitagliptin phosphate,[38] where usually longer syntheses with more complicated chemical steps are used for its preparation.[37a,37d,37g,37j]

Conclusions

We have shown here that D-glucosamine is an efficient, sustainable and cost-beneficial ligand alternative for Fe-catalysed cross-coupling reactions of vinylic and allylic bromides. The $Fe(acac)_2$/D-GlcN·HCl/Et_3N catalytic system showed moderate to high efficiency with preserved stereochemistry when allyl (Csp^3) or alkenyl (Csp^2) bromides were coupled with phenylmagnesium (Csp^2) or benzylmagnesium (Csp^3) bromides. To the best of our knowledge, this is the first Fe-catalysed C–C coupling using an organometallic nucleophile and a natural ligand such as D-glucosamine. Furthermore, the methodology presented was successfully applied to the stereoselective synthesis of a key intermediate in the preparation of the antidiabetic agent sitagliptin. This enables a facile and benign six-step formal synthesis of sitagliptin phosphate from commodity starting materials 1-bromo-2,4,5-trifluorobenzene and methyl 4-bromocrotonate. The use of Fe as a non-toxic metal catalyst and D-GlcN·HCl as a simple and biocompatible sugar-type ligand in the presence of catalytic amounts of Et_3N at 5 mol% loading for C–C coupling reactions with various allyl and alkenyl bromides makes this methodology industrially attractive from both economic and environmental points of view.

Experimental

General remarks

Unless otherwise noted, all of the reactions were performed in dry, round-bottomed flasks under an argon atmosphere. The chemicals were from Sigma-Aldrich, TCI and Apollo Scientific, and they were used without further purification. The reactions were conducted in anhydrous THF, which was dried and purified by distillation over Na before use. Analytical thin-layer chromatography (TLC) was performed on Merck silica gel ($60F_{254}$) plates (0.25 mm). Column chromatography was performed on silica gel 60 (particle size, 240–400 mesh; Merck). ^1H NMR spectra were recorded at 400 MHz, and ^{13}C NMR spectra at 100 MHz, with a Bruker AVANCE III 400 MHz spectrometer in $CDCl_3$. ^1H NMR chemical shifts are reported in parts per million (δ) relative to the solvent resonance used as the internal standard ($CDCl_3$, $\delta = 7.24$ ppm). Data are reported as follows: chemical shift, multiplicity (s, singlet; br s, broad singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constants (Hz) and integration. ^{13}C NMR chemical shifts are reported in ppm from the solvent resonance as the internal standard ($CDCl_3$, $\delta = 77.23$ ppm). HPLC analysis was performed using an Agilent EclipsePlus C18, 150 × 4.6 mm, 1.0 ml min^{-1}, injection volume 5 µl, 25°C, with absorbance measurement at 220 and 254 nm. Method: CH_3CN–H_2O at 4/6 to CH_3CN–H_2O at 9/1 in 15 min, then 2.5 min at CH_3CN–H_2O at 9/1, then back to CH_3CN–H_2O at 4/6 at 18 min; post-time 6 min.

General experimental procedure for $Fe(acac)_2$/D-GlcN·HCl/Et_3N-Catalysed reaction of Grignard reagents with organic bromides

A flame-dried and nitrogen-flushed flask equipped with a magnetic stirrer and a rubber septum was charged with anhydrous $Fe(acac)_2$ (0.15 mmol, 38 mg, dried 16 h under vacuum at 50°C), D-(+)-glucosamine hydrochloride (0.15 mmol, 32 mg, dried 16 h under vacuum at 50°C) and dry THF (20 ml). Then, anhydrous Et_3N (0.15 mmol, 0.021 ml) in THF (1 ml) was added, and the reaction system was stirred at room temperature for 1 h. This was then cooled to −20°C, at which point the starting material of substrate **1a–g** (3.0 mmol) was added, with vigorous stirring for 10 min. Grignard reagent **2** (1.5 equiv., 4.5 mmol, 4.5 ml) was added drop-wise (addition rate of 4 ml h^{-1}) and, after 1 h, the reaction system was slowly warmed to room temperature, when it was quenched with methanol. Then 1 M HCl solution (30 ml) was added to the reaction mixture, which was then extracted with ethyl acetate (3 × 50 ml). The combined organic phases were washed with brine (1 × 30 ml), dried over Na_2SO_4 and filtered, and the solvent was evaporated. The residue was purified by flash column chromatography using gradient elution (petroleum ether to diethyl ether–petroleum ether, 1/10), to obtain the pure products **3–13**.

Protocol for preparation of methyl (*E*)-4-(2,4,5-trifluorophenyl)but-2-enoate (14a)

A dry and nitrogen-flushed 250 ml flask equipped with a magnetic stirrer and a rubber septum was charged with anhydrous THF (7.0 ml) and cooled to −20°C. Then, 1-bromo-2,4,5-trifluorobenzene

(22.82 mmol, 2.66 ml) was introduced through a septum, followed by slow addition of *i*PrMgCl (22.82 mmol, 11.41 ml; 2 M in THF). The reaction temperature was maintained near −20°C and the reaction mixture was stirred for 1 h, until the Br/Mg exchange reaction was complete. The THF solution of 2,4,5-trifluorophenylmagnesium bromide (**2c**) obtained was immediately used for further synthesis.

A flame-dried and nitrogen-flushed flask equipped with a magnetic stirrer and a rubber septum was charged with anhydrous $Fe(acac)_2$ (0.15 mmol, 38 mg, dried 16 h under vacuum at 50°C), D-(+)-glucosamine hydrochloride (0.15 mmol, 32 mg, dried 16 h under vacuum at 50°C) and dry THF (20 ml). Then, anhydrous Et_3N (0.15 mmol, 0.021 ml) in THF (1 ml) was added and the reaction system was stirred at room temperature for 1 h. This was cooled to −20°C, where starting material of methyl 4-bromocrotonate (**1a**; 3.0 mmol, 0.353 ml) was added, with vigorous stirring for 10 min. Then, **2c** in THF (4.5 mmol, 4.5 ml) was added drop-wise (addition rate of 4 ml h^{-1}), and, after 1 h, the reaction system was slowly warmed to room temperature, and quenched with methanol. Then 1 M HCl solution (30 ml) was added to the reaction mixture, which was extracted with ethyl acetate (3 × 50 ml). The combined organic phases were washed with brine (1 × 30 ml), dried over Na_2SO_4 and filtered, and the solvent was evaporated. The residue was purified by flash column chromatography using gradient elution (petroleum ether to diethyl ether–petroleum ether, 1/10), to obtain 0.52 g (75% yield) pure product **14a**.

All of the synthesized compounds **3–14a** are known and have been previously characterized in the literature.[38–49] The ^1H NMR and ^{13}C NMR spectra of our compounds are consistent with those previously reported and are included in the supporting information.

Acknowledgements

This study was supported by the Slovenian Research Agency (grant P1-0208). In addition, the authors thank Lek Pharmaceuticals d.d. for support of the SDCCROS/2011-351 project.

References

[1] a) A. C. Frisch, M. Beller, *Angew. Chem. Int. Ed.* **2005**, *44*, 674; b) A. Rudolph, M. Lautens, *Angew. Chem. Int. Ed.* **2009**, *48*, 2656; c) L. Ackermann, R. Vicente, A. R. Kapdi, *Angew. Chem. Int. Ed.* **2009**, *48*, 9792; d) R. Jana, T. P. Pathak, M. S. Sigman, *Chem. Rev.* **2011**, *111*, 1417.

[2] a) H. M. Walborsky, R. B. Banks, *J. Org. Chem.* **1981**, *46*, 5074; b) A. de Meijere, F. Diederich, *Metal-Catalyzed Cross-Coupling Reactions*, 2nd edn, Wiley-VCH, Weinheim, **2008**.

[3] a) C. Bolm, J. Legros, J. Le Paih, L. Zani, *Chem. Rev.* **2004**, *104*, 6217; b) A. Leitner in *Iron Catalysis in Organic Chemistry: Reactions and Applications* (Ed.: B. Plietker), Wiley-VCH, Weinheim, **2008**; c) B. D. Sherry, A. Fürstner, *Acc. Chem. Res.* **2008**, *41*, 1500; d) G. Cahiez, C. Duplais, *Iron-Catalyzed Reactions of Grignard Reagents. Patai's Chemistry of Functional Groups*, John Wiley, Hoboken, NJ, **2009**; e) W. M. Czaplik, M. Mayer, J. Cvengroš, A. Jacobi von Wangelin, *ChemSusChem* **2009**, *2*, 396; f) A. A. Kulkarni, O. Daugulis, *Synthesis* **2009**, 4087; g) W. M. Czaplik, M. Mayer, S. Grupe, A. Jacobi von Wangelin, *Pure Appl. Chem.* **2010**, *82*, 1545; h) P. Knochel, T. Thaler, C. Diene, *Isr. J. Chem.* **2010**, *50*, 547; i) C.-L. Sun, B.-J. Li, Z.-J. Shi, *Chem. Rev.* **2011**, *111*, 1293; j) H. Nakazawa, M. Itazaki, *Top. Organometal. Chem.* **2011**, *33*, 27; k) L. Ilies, E. Nakamura, *Iron-Catalyzed Cross-Coupling Reactions. Patai's Chemistry of Functional Groups*, John Wiley, Hoboken, NJ, **2012**; l) D. Bézier, J.-B. Sortais, C. Darcel, *Adv. Synth. Catal.* **2013**, *355*, 19; m) K. Riener, S. Haslinger, A. Raba, M. P. Högerl, M. Cokoja, W. A. Herrmann, F. E. Kühn, *Chem. Rev.* **2014**, *114*, 5215; n) C. E. I. Knappke, S. Grupe, D. Gärtner, M. Corpet, C. Gosmini, A. Jacobi von Wangelin, *Chem. Eur. J.* **2014**, *20*, 6828; o) G. Manolikakes in *Reference Module in Chemistry, Molecular Sciences and Chemical Engineering Comprehensive Organic Synthesis II*, 2nd edition (Eds.: P. Knochel, G. A. Molander), Elsevier, Amsterdam, **2014**.

[4] M. Tamura, J. Kochi, *J. Am. Chem. Soc.* **1971**, *93*, 1483.

[5] a) G. Cahiez, S. Marquais, *Pure Appl. Chem.* **1996**, *68*, 53; b) G. Cahiez, S. Marquais, *Tetrahedron Lett.* **1996**, *37*, 1773; c) G. Cahiez, H. Avedissian, *Synthesis* **1998**, 1199; d) C. Duplais, F. Bures, I. Sapountzis, T. J. Korn, G. Cahiez, P. Knochel, *Angew. Chem. Int. Ed.* **2004**, *43*, 2968; e) G. Cahiez, C. Chaboche, F. Mahuteau-Betzer, M. Ahr, *Org. Lett.* **2005**, *7*, 1943; f) G. Cahiez, C. Duplais, A. Moyeux, *Org. Lett.* **2007**, *9*, 3253; g) G. Cahiez, V. Habiak, C. Duplais, A. Moyeux, *Angew. Chem. Int. Ed.* **2007**, *46*, 4364; h) G. Cahiez, V. Habiak, O. Gager, *Org. Lett.* **2008**, *10*, 2389.

[6] a) A. Fürstner, A. Leitner, *Angew. Chem. Int. Ed.* **2002**, *41*, 606; b) A. Fürstner, A. Leitner, M. Mendez, H. Krause, *J. Am. Chem. Soc.* **2002**, *124*, 13856; c) A. Fürstner, D. De Souza, L. Parra-Rapado, J. T. Jensen, *Angew. Chem. Int. Ed.* **2003**, *42*, 5358; d) B. Scheiper, M. Bonnekessel, H. Krause, A. Fürstner, *J. Org. Chem.* **2004**, *69*, 3943; e) R. Martin, A. Fürstner, *Angew. Chem. Int. Ed.* **2004**, *43*, 3955; f) A. Fürstner, R. Martin, *Chem. Lett.* **2005**, *34*, 624; g) A. Fürstner, H. Krause, C. W. Lehmann, *Angew. Chem. Int. Ed.* **2006**, *45*, 440; h) A. Fürstner, P. Hannen, *Chem. Eur. J.* **2006**, *12*, 3006; i) A. Fürstner, R. Martin, H. Krause, G. Seidel, R. Goddard, C. W. Lehmann, *J. Am. Chem. Soc.* **2008**, *130*, 8773; j) A. Fürstner, A. Schlecker, *Chem. Eur. J.* **2008**, *14*, 9181; k) C.-L. Sun, H. Krause, A. Fürstner, *Adv. Synth. Catal.* **2014**, *356*, 1281.

[7] a) M. Nakamura, K. Matsuo, S. Ito, B. Nakamura, *J. Am. Chem. Soc.* **2004**, *126*, 3686; b) M. Nakamura, S. Ito, K. Matsuo, E. Nakamura, *Synlett* **2005**, 1794; c) T. Hatakeyama, M. Nakamura, *J. Am. Chem. Soc.* **2007**, *129*, 9844; d) T. Hatakeyama, Y. Yoshimoto, T. Gabriel, M. Nakamura, *Org. Lett.* **2008**, *10*, 5341; e) S. Ito, Y.-I. Fujiwara, E. Nakamura, M. Nakamura, *Org. Lett.* **2009**, *11*, 4306; f) T. Hatakeyama, S. Hashimoto, K. Ishizuka, M. Nakamura, *J. Am. Chem. Soc.* **2009**, *131*, 11949; g) S. Kawamura, M. Nakamura, *Chem. Lett.* **2013**, *42*, 183.

[8] K. G. Dongol, H. Koh, M. Sau, C. L. L. Chai, *Adv. Synth. Catal.* **2007**, *349*, 1015.

[9] a) R. B. Bedford, D. W. Bruce, R. M. Frost, J. W. Goodby, M. Hird, *Chem. Commun.* **2004**, 2822; b) R. B. Bedford, D. W. Bruce, R. M. Frost, M. Hird, *Chem. Commun.* **2005**, 4161; c) R. B. Bedford, M. Betham, D. W. Bruce, S. A. Davis, R. M. Frost, M. Hird, *Chem. Commun.* **2006**, 1398; d) R. B. Bedford, P. B. Brenner, E. Carter, T. W. Carvell, P. M. Cogswell, T. Gallagher, J. N. Harvey, D. M. Murphy, E. C. Neeve, J. Nunn, D. R. Pye, *Chem. Eur. J.* **2014**, *20*, 7935.

[10] a) M. Mayer, W. M. Czaplik, A. Jacobi von Wangelin, *Adv. Synth. Catal.* **2010**, *352*, 2147; b) W. M. Czaplik, S. Grupe, M. Mayer, A. Jacobi von Wangelin, *Chem. Commun.* **2010**, *46*, 6350; c) W. M. Czaplik, M. Mayer, A. Jacobi von Wangelin, *ChemCatChem* **2011**, *3*, 135; d) S. Gülak, A. Jacobi von Wangelin, *Angew. Chem. Int. Ed.* **2012**, *51*, 1357; e) S. Gülak, T. N. Gieshoff, A. Jacobi von Wangelin, *Adv. Synth. Catal.* **2013**, *355*, 2197.

[11] a) C. K. Reddy, P. Knochel, *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1700; b) W. Dohle, F. Kopp, G. Cahiez, P. Knochel, *Synlett* **2001**, 1901; c) G. Dunet, P. Knochel, *Synlett* **2006**, 407; d) O. M. Kuzmina, A. K. Steib, D. Flubacher, P. Knochel, *Org. Lett.* **2012**, *14*, 4818.

[12] a) G. A. Molander, B. J. Rahn, D. C. Shubert, *Tetrahedron Lett.* **1983**, *24*, 5449; b) A. S. K. Hashmi, G. Szeimies, *Chem. Ber.* **1994**, *127*, 1075; c) T. Nagano, T. Hayashi, *Org. Lett.* **2004**, *6*, 1297; d) K. Itami, S. Higashi, M. Mineno, J.-I. Yoshida, *Org. Lett.* **2005**, *7*, 1219; e) K. Bica, P. Gaertner, *Org. Lett.* **2006**, *8*, 733; f) A. Hamajima, M. Isobe, *Org. Lett.* **2006**, *8*, 1205; g) G. Berthon-Gelloz, T. Hayashi, *J. Org. Chem.* **2006**, *71*, 8957; h) A. Guerinot, S. Reymond, J. Cossy, *Angew. Chem. Int. Ed.* **2007**, *46*, 6521; i) M. Carril, A. Correa, C. Bolm, *Angew. Chem. Int. Ed.* **2008**, *47*, 4862; j) C. M. R. Volla, P. Vogel, *Angew. Chem. Int. Ed.* **2008**, *47*, 1305; k) B.-J. Li, L. Xu, Z.-H. Wu, B.-T. Guan, C.-L. Sun, B.-Q. Wang, Z.-J. Shi, *J. Am. Chem. Soc.* **2009**, *131*, 14656; l) K. Weber, E.-M. Schnöckelborg, R. Wolf, *ChemCatChem* **2011**, *3*, 1572; m) S. K. Ghorai, M. Jin, T. Hatakeyama, M. Nakamura, *Org. Lett.* **2012**, *14*, 1066; n) T. Agrawal, S. P. Cook, *Org. Lett.* **2013**, *15*, 96; o) C. Bensoussan, N. Rival, G. Hanquet, F. Colobert, S. Reymond, J. Cossy, *Tetrahedron* **2013**, *69*, 7759; p) C. W. Cheung, P. Ren, X. Hu, *Org. Lett.* **2014**, *16*, 2566.

[13] P. J. Rushworth, D. G. Hulcoop, D. J. Fox, *J. Org. Chem.* **2013**, *78*, 9517.

[14] a) F. Xue, J. Zhao, T. S. A. Hor, *Dalton Trans.* **2011**, *40*, 8935; b) H.-N. Deng, Y.-L. Xing, C.-L. Xia, H.-M. Sun, Q. Shen, Y. Zhang, *Dalton Trans.* **2012**, *41*, 11597; c) E. F. Chard, L. N. Dawea, C. M. Kozak, *J. Organometal. Chem.* **2013**, *737*, 32, and references therein;

d)C.-L. Xia, C.-F. Xie, Y.-F. Wu, H.-M. Sun, Q. Shen, Y. Zhang, *Org. Biomol. Chem.* **2013**, *11*, 8135.
[15] a) J. Kleimark, A. Hedström, P.-F. Larsson, C. Johansson, P.-O. Norrby, *ChemCatChem* **2009**, *1*, 152; b) G. Lefévre, A. Jutand, *Chem. Eur. J.* **2014**, *20*, 4796; c) S. L. Daifuku, M. H. Al-Afyouni, B. E. R. Snyder, J. L. Kneebone, M. L. Neidig, *J. Am. Chem. Soc.* **2014**, *136*, 9132.
[16] D. Noda, Y. Sunada, T. Hatakeyama, M. Nakamura, H. Nagashima, *J. Am. Chem. Soc.* **2009**, *131*, 6078.
[17] R. B. Bedford, P. B. Brenner, E. Carter, P. M. Cogswell, M. F. Haddow, J. N. Harvey, D. M. Murphy, J. Nunn, C. H. Woodall, *Angew. Chem. Int. Ed.* **2014**, *53*, 1804.
[18] O. M. Kuzmina, A. K. Steib, J. T. Markiewicz, D. Flubacher, P. Knochel, *Angew. Chem. Int. Ed.* **2013**, *52*, 4945.
[19] G. Cahiez, O. Gager, J. Buendia, C. Patinote, *Chem. Eur. J.* **2012**, *18*, 5860.
[20] S. Woodward, M. Dieguez, O. Pamies, *Coord. Chem. Rev.* **2010**, *254*, 2007.
[21] F. Monnier, M. Taillefer, *Angew. Chem. Int. Ed.* **2009**, *48*, 6954.
[22] S. Katoh, J. Toyama, I. Kodama, K. Kamiya, T. Akita, T. Abe, *Eur. Surg. Res.* **1992**, *24*, 349.
[23] A. Monopoli, V. Calò, F. Ciminale, P. Cotugno, C. Angelici, N. Cioffi, A. Nacci, *J. Org. Chem.* **2010**, *75*, 3908.
[24] M. Diéguez, C. Claver, O. Pàmies, *Eur. J. Org. Chem.* **2007**, 4621.
[25] S. Lemaire, I. N. Houpis, T. Xiao, J. Li, E. Digard, C. Gozlan, R. Liu, A. Gavryushin, C. Diène, Y. Wang, V. Farina, P. Knochel, *Org. Lett.* **2012**, *14*, 1480.
[26] M. Jezowska-Bojczuk, E. Chruscińska, T. Trnka, G. Giovanni Micera, *J. Inorg. Biochem.* **1996**, *63*, 231.
[27] H.-Y. Shen, S.-Y. Lian, Z.-F. Luo, X.-C. Zhang, X.-D. Zhu, *Synth. React. Inorg. Met.-Org. Chem.* **2001**, *31*, 167.
[28] a) M. Amini, H. Etemadi, *Chem. Pap.* **2013**, *67*, 759; b) A. K. Jha, R. K. Shahni, N. Jain, *Synlett* **2015**, *26*, 259.
[29] K. Thakur Gopal, K. Srinivas Surya, K. Chiranjeevi, G. Sekar, *Green Chem.* **2011**, *13*, 2326.
[30] D. Cheng, F. Gan, W. Qian, W. Bao, *Green Chem.* **2008**, *10*, 171 and references therein.
[31] a) A. Blaskó, C. A. Bunton, S. Bunel, C. Ibarra, E. Moraga, *Carbohydr. Res.* **1997**, *298*, 163; b) A. M. Skelley, R. A. Mathies, *J. Chromatogr. A* **2006**, *1132*, 304.
[32] M. R. Crampton, I. A. Robotham, *J. Chem. Res. (S)* **1997**, 22.
[33] A. Hedström, U. Bollmann, J. Bravidor, P.-O. Norrby, *Chem. Eur. J.* **2011**, *17*, 11991.
[34] a) R. Ketcham, D. Jambotkar, L. Martinelli, *J. Org. Chem.* **1962**, *27*, 4666; b) A. K. Sinha, A. Sharma, A. Swaroop, V. Kumar, *Tetrahedron* **2007**, *63*, 1000; c) K. Gaukroger, J. A. Hadfield, L. A. Hepworth, N. J. Lawrence, A. T. McGown, *J. Org. Chem.* **2001**, *66*, 8135; d) A. Ianni, S. R. Waldvogel, *Synthesis* **2006**, 2103; e) G. Hilt, C. Hengst, *J. Org. Chem.* **2007**, *72*, 7337; f) X. Zhu, J. Liu, T. Chen, W. Su, *Appl. Organometal. Chem.* **2012**, *26*, 145; g) S. M. Nobre, M. N. Muniz, M. Seferin, W. M. da Silva, A. L. Monteiro, *Appl. Organometal. Chem.* **2011**, *25*, 289; h) M.-A. Bazzin, L. El Kihel, J.-C. Lancelot, S. Rault, *Tetrahedron Lett.* **2007**, *48*, 4347; i) C. M. Kormos, N. E. Leadbeater, *J. Org. Chem.* **2008**, *73*, 3854; j) Y. Peng, J. Chen, J. Ding, M. Liu, W. Gao, H. Wu, *Synthesis* **2011**, 213.
[35] a) European Chemicals Agency website. http://echa.europa.eu/candidate-list-table/-/substance/78/search/+/del/75/col/INCLUSIONDATECL/type/desc/pre/2/view [17 December 2014]; b) D. Prat, J. Hayler, A. Wells, *Green Chem.* **2014**, *16*, 4546; c) K. Moonen, P. Roose, B. Vandeputte, WO Pat. Appl. 2013107822, **2013**; *Chem. Abstr.* **2013**, *159*, 262122.
[36] a) S. M. Andersen, M. Bollmark, R. Berg, C. Fredriksson, S. Karlsson, C. Liljeholm, H. Sörensen, *Org. Process Res. Dev.* **2014**, *18*, 952; b) N. Tewari, N. Maheshwari, R. Medhane, H. Nizar, M. Prasad, *Org. Process Res. Dev.* **2012**, *16*, 1566; c) F. Bartoccini, G. Piersanti, S. Armaroli, A. Cerri, W. Cabri, *Tetrahedron Lett.* **2014**, *55*, 1376; d) G. Seidel, D. Laurich, A. Fürstner, *J. Org. Chem.* **2004**, *69*, 3950; e) C. Risatti, K. J. Natalie Jr., Z. Shi, D. A. Conlon, *Org. Process Res. Dev.* **2013**, *17*, 257.
[37] a) K. B. Hansen, J. Balsells, S. Dreher, Y. Hsiao, M. Kubryk, M. Palucki, N. Rivera, D. Steinhuebel, J. D. Armstrong III, D. Askin, E. J. J. Grabowski, *Org. Process Res. Dev.* **2005**, *9*, 634; b) M. Kubryk, K. B. Hansen, *Tetrahedron Asymmetry* **2006**, *17*, 205; c) K. B. Hansen, Y. Hsiao, F. Xu, N. Rivera, A. Clausen, M. Kubryk, S. Krska, T. Rosner, B. Simmons, J. Balsells, N. Ikemoto, Y. Sun, F. Spindler, C. Malan, E. J. J. Grabowski, J. D. Armstrong III, *J. Am. Chem. Soc.* **2009**, *131*, 8798; d) F. Liu, W. Yu, W. Ou, X. Wang, L. Ruan, Y. Li, X. Peng, X. Tao, X. Pan, *J. Chem. Res.* **2010**, *34*, 230; e) C. K. Savile, J. M. Janey, E. C. Mundorff, J. C. Moore, S. Tam, W. R. Jarvis, J. C. Colbeck, A. Krebber, F. J. Fleitz, J. Brands, P. N. Devine, G. W. Huisman, G. J. Hughes, *Science* **2010**, *329*, 305; f) S. G. Davies, A. M. Fletcher, L. Lv, P. M. Roberts, J. E. Thomson, *Tetrahedron Lett.* **2012**, *53*, 3052; g) M. Fisticki, O. Gundogdu, D. Aktas, H. Secen, M. F. Sahin, R. Altundas, Y. Kara, *Tetrahedron* **2012**, *68*, 2607; h) H. Bao, L. Bayeh, U. K. Tambar, *Synlett* **2013**, *24*, 2459; i) G. Stavber, Z. Časar, WO Pat. Appl. 2012163815, **2013**; *Chem. Abstr.* **2013**, *158*, 37817; j) X. Pan, X. Li, Q. Lu, W. Yu, W. Li, Q. Zhang, F. Deng, F. Liu, *Tetrahedron Lett.* **2013**, *54*, 6807; k) J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok, H. Liu, *Chem. Rev.* **2014**, *114*, 2432; l) Z. Yuhong, Y. Jinzhong, Q. Hongsheng, L. Cong, L. Guobin, T. Jiaxing, S. Chuang, CN Pat. Appl. 103819475, **2014**; *Chem. Abstr.* **2014**, *161*, 70535.
[38] a) G. Stavber, Z. Časar, *Appl. Organometal. Chem.* **2013**, *27*, 159; b) Z. Časar, G. Stavber, M. Sova, WO Pat. Appl. 2012136383, **2012**; *Chem. Abstr.* **2012**, *157*, 606235; c)G. Stavber, Z. Časar, WO Pat. Appl. 2013150125, **2013**; *Chem. Abstr.* **2013**, *159*, 608746.
[39] A. A. Poeylaut-Palena, S. A. Testero, E. G. Mata, *J. Org. Chem.* **2008**, *73*, 2024.
[40] P. Fristrup, G. Holm Jensen, M. L. Nygaard Andersen, D. Tanner, P.-O. Norrby, *J. Organometal. Chem.* **2006**, *691*, 2182.
[41] D. A. Everson, R. Shrestha, D. J. Weix, *J. Am. Chem. Soc.* **2010**, *132*, 920.
[42] L. Baker, T. Minehan, *J. Org. Chem.* **2004**, *69*, 3957.
[43] Z. Wang, J.-P. Pitteloud, L. Montes, M. Rapp, D. Derane, S. F. Wnuk, *Tetrahedron* **2008**, *64*, 5322.
[44] D. Basavaiah, K. R. Reddy, N. Kumaragurubaran, *Nat. Protoc.* **2007**, *2*, 2665.
[45] T. Yajima, C. Saito, H. Nagano, *Tetrahedron* **2005**, *61*, 10203.
[46] C. Ebner, C. A. Mueller, C. Markert, A. Pfaltz, *J. Am. Chem. Soc.* **2011**, *133*, 4710.
[47] R. Bandari, T. Hoeche, A. Prager, K. Dirnberger, M. R. Buchmeiser, *Chem. Eur. J.* **2010**, *16*, 4650.
[48] L. G. Greifenstein, J. B. Lambert, R. J. Nienhuis, H. E. Fried, G. A. Pagani, *J. Org. Chem.* **1981**, *46*, 5125.
[49] A. Martinez, M. Fernandez, J. C. Estevez, R. J. Estevez, L. Castedo, *Tetrahedron* **2005**, *61*, 485.

Supporting information

Additional supporting information may be found in the online version of this article at the publisher's web site. This includes characterization data and ^{1}H NMR and ^{13}C NMR spectra of compounds **3–14a** as well as the experimental procedures leading to the present synthetic method.