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by

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Advanced Synthesis and Catalysis, 2018, 360(5), 893-900.

Catalytic Enantioselective Povarov Reactions of Ferrocenecarbaldehyde-Derived Imines – Brønsted Acid Catalysis at Parts-Per-Million Level Loading

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Abstract. Despite the broad interest in ferrocene containing compounds, ferrocenyl substrates have been employed in catalytic asymmetric settings only sporadically. Herein, catalytic asymmetric Povarov reactions with ferrocenecarbaldehyde-derived *N*-aryl imines are presented. This study demonstrates that the stereoelectronic properties of ferrocenyl imines do not preclude their engagement in enantioselective phosphoric acid catalysis: cycloadducts derived from benzyl *N*-vinylcarbamate were obtained in good yields and nearly enantiopure form using 0.1 mol% of a standard Brønsted acid catalyst. Furthermore, it is shown that specific optimisation with some substrates allowed to lower the catalyst loading up to 10-20 parts-per-million, an unprecedented value for phosphoric acid catalysts. Such low loading protocol could be applied to a preparative scale reaction, and to imines derived from arylaldehydes.

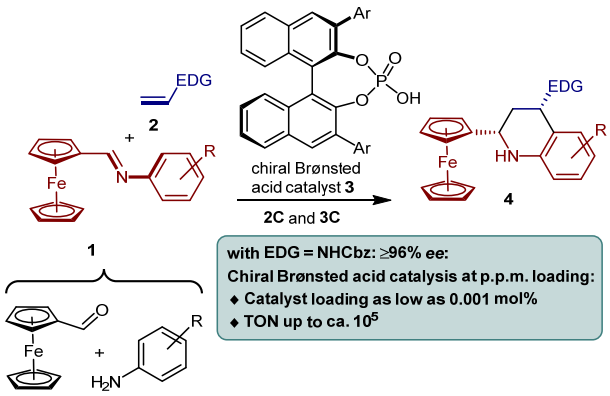
Keywords: Asymmetric Catalysis; Ferrocene; Organocatalysis; Phosphoric Acid Catalysis; Povarov Cycloaddition; Schiff Bases

The electronic and structural features of the ferrocene moiety endow its derivatives with peculiar physico-chemical properties. Ferrocene-containing compounds are increasingly important structures, instrumental to different fields, ranging from medicinal chemistry and material science to synthetic organic chemistry.[1,2]

Combining our experitises in ferrocene chemistry[3] and in asymmetric catalysis mediated by chiral Brønsted acids,[4] we set up to study asymmetric reactions with ferrocenecarbaldehyde-derived *N*-aryl imines **1**. Our choice fell on the inverse-electron-demand aza-Diels-Alder cycloaddition (Povarov reaction)[5,6] with dienophiles **2**, catalysed by phosphoric acids **3**,[7] which delivers 2-ferrocenyl-1,2,3,4-tetrahydroquinolines **4** (Scheme 1). This work was motivated by the combination of two elements:

i) the potential interesting features of products **4**: while the 1,2,3,4-tetrahydroquinoline scaffold is itself a very common unit in biologically active compounds,[8] the insertion of a ferrocene unit in a molecular structure has sometimes resulted in dramatic improvements of its biological properties;[2,3]

ii) the curiosity to explore the behaviour of imines **1** in catalytic asymmetric settings: to our knowledge, ferrocenecarbaldehyde and its imine derivatives **1** have not been so far investigated in chiral Brønsted acid catalysed reactions.[9] We were thus wondering how these substrates, which possess some unusual stereoelectronic properties, would have responded to common catalytic systems.



Scheme 1. Chiral Brønsted acid **3** catalyzed Povarov reactions of ferrocenecarbaldehyde-derived imines **1**.

An unexpected yet remarkable result that has emerged from this study is a new and exceedingly efficient protocol for two and three component (2C and 3C) Povarov reactions with benzyl *N*-vinylcarbamate **2a**.[10] Products **4** were obtained with very high enantioenrichment (≥96% *ee*) in all cases. More importantly, by slightly forcing the reaction conditions the catalyst loading in the 2C version could be lowered to 10-20 p.p.m. values, with only a small erosion in enantioselectivity. This is a relevant result considering the notoriously low turnover numbers of organocatalytic reactions.[11] Only a small number of works demonstrated high enantioselectivities and yields at catalyst loadings lower than 100 p.p.m.[12]

None of these has involved a phosphoric acid as catalyst. In fact, the turnover numbers of up to *ca.* 10^5 achieved in this reaction are not only unprecedented for phosphoric acid catalysts, but also approach the lower limits of the current literature describing organocatalytic asymmetric reactions.[12b] It is worth stressing that a relatively simple and commercially available structure is used as catalyst, and that the reaction at such low loadings is not limited to ferrocene substrates, but could be applied to imines derived from different arylaldehydes.

We started this study by reacting imine **1a** with benzyl *N*-vinylcarbamate **2a**, in the presence of BINOL-derived chiral phosphoric acid catalysts **3** at 10 mol% loading (Table 1). Although the first attempts using dichloromethane as solvent and 2 hours reaction time[10a,b] gave only poor conversion to the desired tetrahydroquinoline **4a**, enantioselectivities were good with most catalysts tested (entries 1-4). In these as well as in the following experiments, the 2,4-*cis*-diastereoisomeric product **4a** was exclusively obtained, as expected.[10] From this preliminary catalyst screening, the 4-nitrophenyl and the 2,4,6-tri-*iso*propylphenyl derivatives **3a** and **3c** ((*R*)-TRIP) were identified as the most promising structures, and were selected for further studies. A simple solvent switch from dichloromethane to toluene (entries 5,6) allowed to increase considerably the conversion of the reaction, providing better results also compared to other reaction media such as THF (entries 7,8). At this point, we tried to lower the catalyst loading. As shown in entries 9 and 10, even a loading of 0.1 mol% allowed to produce the product **4a** with optimal results, when the reaction time was increased to 6 h. Under these conditions, catalyst **3c** gave slightly better results, furnishing **4a** in nearly enantiopure form.

Despite these optimal results achieved with imine **1a**, when we moved to study reactions with imines derived from electron poor anilines we found these were not giving clean reaction profiles. As exemplified in Scheme 2 for the 4-bromo and 4-fluoroaniline derived substrates **1b,c**, considerable (>25%) amounts of co-products **4'b** and **4'c** formed. These adducts **4'**, observed as diastereomeric mixtures, were the result of the interruption[4e,13] of the Povarov reactions by the aniline, acting as an external nucleophile on the intermediate **A** (see pathway (*b*) *vs* pathway (*a*) in Scheme 2).[14] As the only source of aniline could be the hydrolysis of the imines **1**, we reasoned that drying agents could avoid this process. Indeed, performing the reaction in the

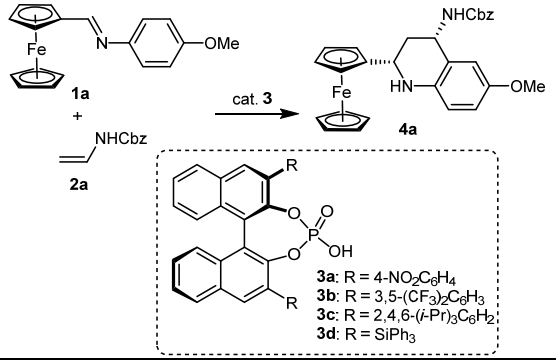
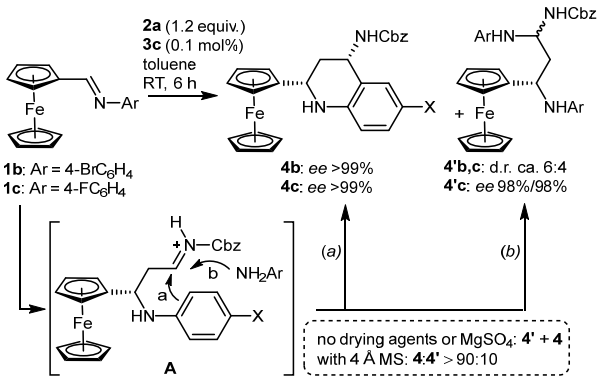


Table 1. Optimization of catalysts and reaction conditions in the Povarov reaction between imine **1a** and *N*-vinyl carbamate **2a**. Representative results.[a)]

Entry	Cat. **3** (mol%)	Solvent	Conv. (%)[b)]	*ee* (%)[c)]
1	**3a** (10)	CH_2Cl_2	21	93
2	**3b** (10)	CH_2Cl_2	18	87
3	**3c** (10)	CH_2Cl_2	10	98
4	**3d** (10)	CH_2Cl_2	<10	89
5	**3a** (10)	toluene	>95	96
6	**3c** (10)	toluene	>95	96
7	**3a** (10)	THF	94	93
8	**3c** (10)	THF	92	90
9[d)]	**3a** (0.1)	toluene	90	97
10[d)]	**3c** (0.1)	toluene	>95	>99

[a)] Conditions: imine **1a** (0.05 mmol), *N*-vinylcarbamate **2a** (0.06 mmol), catalyst **3**, solvent (200 μL), RT, 2 h. [b)] Determined by ^{1}H NMR on the crude mixture. A single *cis*-**4a** stereoisomer was observed in all cases. [c)] Determined by chiral stationary phase HPLC. [d)] 6 h reaction time.

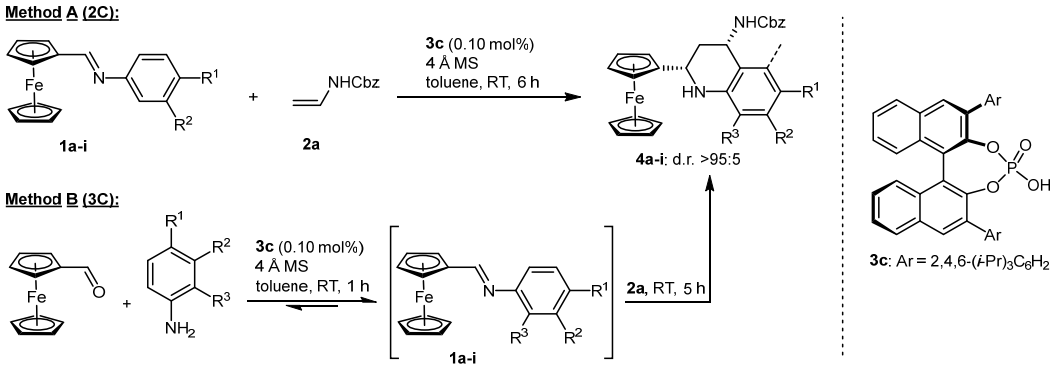


Scheme 2. Povarov cycloaddition reaction of imines **1b,c** (pathway (*a*)) giving **4b** and **4c** *vs* interrupted Povarov reaction (pathway (*b*)) leading to **4'b** and **4'c**.

presence of activated 4 Å molecular sieves allowed the nearly exclusive obtainment of the desired cycloadducts **4** (Scheme 2). $MgSO_4$ as drying agent was instead less effective.

We thus applied these newly developed conditions to few ferrocenecarbaldehyde imines **1a-i** derived from anilines featuring different electronic properties

Table 2. Catalytic asymmetric two component (method A) and three component (method B) Povarov reactions between benzyl *N*-vinylcarbamate **2a** and ferrocenecarbaldehyde imines **1a-i** catalysed by **3c**.



Entry	**1**	R^1	R^2	R^3	**4**[c)]	Method A (2C)[a)]		Method B (3C)[b)]	
						Yield (%)[d)]	*ee* (%)[e)]	Yield (%)[d)]	*ee* (%)[e)]
1	**1a**	OMe	H	H	**4a**	99	>99	99	>99
2	**1b**	Br	H	H	**4b**	96	>99	80	>99
3	**1c**	F	H	H	**4c**	86	>99	95	>99
4	**1d**	Me	H	H	**4d**	92	>99	92	>99
5	**1e**	H	H	H	**4e**	83	>99	80	>99
6	**1f**	OMe	OMe	H	**4f**[f)]	98	99	88	99
7	**1g**	H	Cl	H	**4g**[g)]	90[h)]	99[i)]/99[j)]	90[h)]	99[i)]/>99[j)]
8	**1h**	H	H	Me	**4h**	75[k)]	98	52[k,l)]	97
9	**1i**	H	-(CH)$_4$-		**4i**	50[k)]	98	60[k,l)]	96

[a)] Conditions (method A, 2C): imine **1a-f** (0.20 mmol), *N*-vinylcarbamate **2a** (0.24 mmol), catalyst **3c** (0.1 mol%), activated 4 Å MS (60 mg), toluene (800 µL), RT, 6 h. [b)] Conditions (method B, 3C): ferrocenecarbaldehyde (0.20 mmol), aniline (0.20 mmol), catalyst **3c** (0.10 mol%), activated 4 Å MS (60 mg), toluene (800 µL), RT, 1 h, then *N*-vinylcarbamate **2a** (0.24 mmol), RT, 5 h. [c)] A single *cis*-diastereoisomer **4** was observed in the crude mixtures by ^{1}H NMR. [d)] Isolated yield after chromatography on silica gel. [e)] Determined by chiral stationary phase HPLC. [f)] The 6,7-dimethoxy regioisomer of **4f** was selectively obtained. [g)] Mixture of 7-chloro and 5-chloro **4g** regioisomers (56:44 favouring 5-Cl regioisomer). [h)] Combined yield of the two **4g** regioisomers. [i)] 7-Cl **4g** isomer. [j)] 5-Cl **4g** isomer. [k)] 18 h reaction time. [l)] 2.0 mol% catalyst **3c** was used.

(Table 2, method A). Products **4a-e** derived from *para*-substituted/unsubstituted anilines were produced as single *cis*-diastereoisomers and in nearly enantiopure form in all cases, demonstrating the outstanding efficiency of catalyst **3c** in imparting enantioselectivity to this reaction (entries 1-5). The absolute and relative configuration of cycloadduct **4b** was determined as *S*,*S* by single crystal X-ray diffraction (Figure 1),[15] and is fully consistent with previous chiral phosphoric acid catalysed Povarov reactions.[4b,d-f,10] The configuration of all products **4** (and **5-8**, vide infra) was assigned by analogy. Reactions with *meta* substituted anilines were then explored. While the 3,4-dimethoxyaniline derived substrate **1f** afforded exclusively the 6,7-dimethoxy regioisomer **4f**, the 3-chloro substituted substrate **1g** gave a nearly equimolar mixture of the 5-chloro and 7-chloro **4g** regioisomers, in line with previous studies.[10b] Yields and enantioselectivites were very good in both cases (entries 6,7). Two *ortho*-substituted aniline derived substrates **1h** and **1i** derived from 2-methylaniline and 1-naphthylamine, respectively, were then tested in the reaction. Although requiring longer reaction times, also these more challenging imines reacted well in the reaction. The corresponding products **4h** and **4i** were afforded in moderate yields and very good enantioselectivities (entries 8,9).

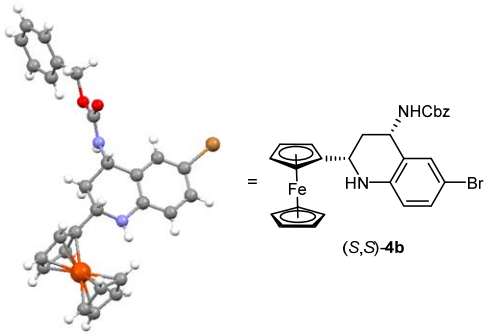


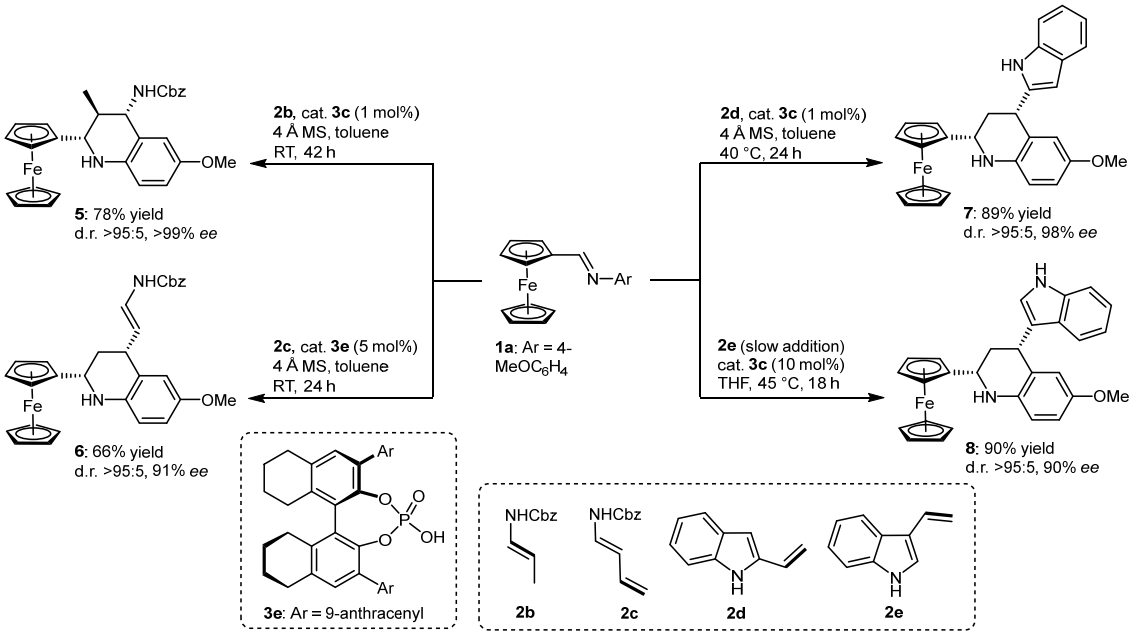
Figure 1. X-Ray structure of compound **4b**.

Moving to develop the 3C version of the reaction, we had to face again the issue of co-product **4'** formation when electron poor anilines were employed (see Scheme 2), which occurred even in the presence of molecular sieves. In more detail, if the imine was not quantitively formed before the addition of *N*-vinylcarbamate **2a** to the reaction mixture, residual

aniline interfered with the cycloaddition reaction resulting in substantial amounts of co-product **4'**. Ultimately, we found that leaving the aniline and ferrocenecarbaldehyde condensing in the presence of the catalyst **3c** and 4 Å molecular sieves for 1 hour before the addition of the dienophile **2a**, was sufficient to avoid the formation of undesired adducts **4'**. Accordingly, this optimised protocol for the 3C reaction (method B, Table 2) was applied to the same substrates previously employed in the 2C version. Most substrates reacted very well, giving results comparable to the 2C version of the reaction (entries 1-7). A higher catalyst loading (2 mol%) and longer reaction times were instead necessary to achieve satisfactory results in the reactions of *ortho*-substituted aniline derived substrates **1h** and **1i** (entries 8,9).

We then verified the applicability of imine **1a** in other asymmetric Povarov reactions, by reacting it with four different dienophiles **2b-e**, known to be competent in chiral phosphoric acid catalysed Povarov reactions.[4b,e,f,10b] As shown in Scheme 3, product **5** derived from benzyl (*E*)-prop-1-en-1-ylcarbamate **2b** was obtained with good results, using conditions similar to the ones employed for **2a**. A higher catalyst loading (1 mol% instead of 0.1 mol%) and longer reaction times were necessary, presumably due to the higher steric hindrance of enecarbamate **2b** compared to unsubstituted **2a**. As expected, dienophile **2c** (a dienecarbamate reacting at the vinylogous double bond)[4b,f] required instead a different catalyst (**3e**) to afford the cycloadduct **6** with good enantioselectivity. Moving to heteroarene activated dienophiles, 2-vinylindole **2d** reacted very well under conditions related to the ones used for **2a** and **2b**, using just 1 mol% of catalyst **3c** at 40 °C. In contrast, 3-vinylindole **2e** gave initially disappointing results. This very electron rich dienophile is not only prone to acid promoted degradation, but also feature a tendency towards the formation of piperidines resulting from interrupted Povarov reaction. In line with our previous work with this dienophile,[4e] good results were ultimately achieved by using more diluted conditions in a coordinating solvent (THF), and adding slowly a solution of **2e** in THF to the reaction mixture (by syringe pump).

Prompted by the outstanding performance displayed by catalyst **3c** in the 2C reaction between imine **1a** and *N*-vinyl carbamate **2a** (≥99% *ee* and quantitative yield in 6 h using 0.10 mol% **3c**, Table 1, entry 10), we decided to challenge the system to ascertain the lowest catalyst loading reachable in this reaction (Table 3). A decrease in the amount of catalyst **3c** from 0.1 mol% to 0.01 mol% gave still fully satisfactory results, even if the reaction time had to be increased from 6 to 24 h (entries 1 and 2). A further decrease to 0.001 mol% (10 p.p.m.) worsened the conversion, even at prolonged reaction times (entry 3). Rising the reaction temperature to 40 °C restored a moderate conversion value, accompanied by a slightly lower but still very high enantiomeric excess (entry 4). Under these conditions, we tested some drying agents, standard additives in phosphoric acid catalysed reactions.[16] As shown in entry 5, the presence of 4 Å molecular sieves was surprisingly detrimental to catalyst activity with this little amount of catalyst.[17] In contrast, dry $MgSO_4$ gave a small yet important improvement (entry 6), compared to the reaction performed in its absence (entry 4).



Scheme 3. Catalytic enantioselective Povarov reactions between imine **1a** and dienophiles **2b-e**.

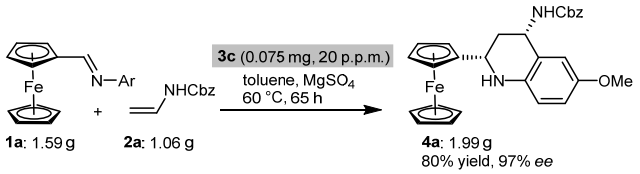
Table 3. Representative results on the catalytic asymmetric Povarov reactions between benzyl *N*-vinylcarbamate **2a** and ferrocenecarbaldehyde imine **1a** catalysed by **3c** at low catalyst loading.[a)]

Entry	**3c** mol%	**3c** p.p.m.	Additive	T (°C)	t (h)	Conversion (%)[b)]	*ee* (%)[c)]
1[d)]	0.1	1'000	-	RT	6	>95	>99
2	0.01	100	-	RT	24	91	>99
3	0.001	10	-	RT	120	29	95
4	0.001	10	-	40	48	56	96
5	0.001	10	4 Å MS	40	48	21	n.d.
6	0.001	10	$MgSO_4$	40	48	70	96
7	0.001	10	$MgSO_4$	60	60	85	94
8	0.001	10	4 Å MS	60	96	39	n.d.
9	0.002	20	$MgSO_4$	60	60	93	96
10	0.0001	1	$MgSO_4$	60	60	22	82

[a)] Conditions: imine **1a** (0.20 mmol), *N*-vinylcarbamate **2a** (0.24 mmol), catalyst **3c**, (additive (60 mg)), solvent (800 µL). [b)] Determined by ^{1}H NMR on the crude mixture. A single *cis*-**4a** stereoisomer was observed in all cases. [c)] Determined by chiral stationary phase HPLC. [d)] Reaction performed on 0.05 mmol scale (Table 1, entry 10).

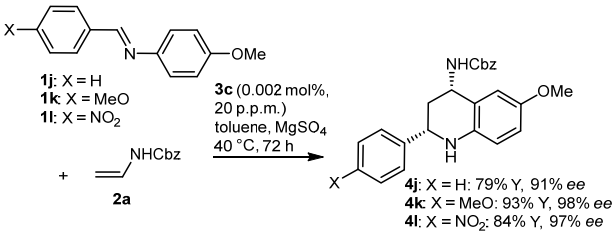
Ultimately, satisfactory conversion accompanied by very good enantioselectivity could be achieved at this 10 p.p.m. loading by increasing the reaction temperature to 60 °C, and the reaction time to 60 h (entry 7). Under these conditions, the negative effect displayed by molecular sieves was confirmed (entry 8). Conversely, slightly higher conversion and enantioselectivity was achieved using 20 p.p.m. loading with $MgSO_4$ (entry 9). It is worth stressing that these reactions were performed using reagent grade toluene, as drying or degassing the solvent did not give any beneficial effect on the reaction outcome. A further decrease in the loading to 0.0001 mol% (1 p.p.m.) was unfortunately not practical (entry 10).

The conditions of Table 3, entry 9 were enough robust to be successfully applied on a preparative scale (5 mmol) reaction (Scheme 4). In fact, the reaction proved to be very tolerant to this 25 × scale up, providing product **4a** in very good yield and enantioselectivity. Remarkably, as low as 0.075 mg of catalyst **3c** (added from a mother solution) were sufficient to produce 1.99 g of product **4a** in 97% *ee*.



Scheme 4. Preparative scale Povarov reaction of ferrocenecarbaldehyde imine **1a** with *N*-vinyl carbamate **2a** catalysed by **3c** at 20 p.p.m. loading.

At this stage, we wondered if the efficiency of this reaction in terms of catalyst loading, unprecedented in the frame of phosphoric acid catalysis, had to be ascribed to the peculiar stereoelectronic properties of the ferrocene moiety of substrate **1a**. We thus engaged in the reaction other *N*-4-methoxyphenyl aldimines **1j-l** derived from arylaldehydes bearing electron releasing or electron withdrawing aromatic rings. Such type of imines has been reported to react very well with dienophile **2a** under the action of phosphoric acid catalysts related to **3c**. These reactions were performed in dichloromethane as solvent, and the imines were prepared *in situ* via a 3C protocol.[10] The lowest catalyst loading attainable has been 0.5 mol% (5'000 p.p.m.). Our experiments, performed under the conditions we optimised for **1a**, gave instead good results even at 20 p.p.m. loading (Scheme 5).[18] Cycloadducts **4j-l** were in fact obtained with very good yields and enantioselectivities in all three cases. Thus, the efficacy of this low loading protocol is not restricted to ferrocenecarbaldehyde imine **1a**. It can also be concluded that the high catalyst efficiency displayed by catalyst **3c** in these Povarov reactions is not due to the ferrocenyl moiety of **1a**, but rather to the specific conditions we have used in the reaction.



Scheme 5. Povarov reaction of arylaldehyde imines **1j-l** with *N*-vinyl carbamate **2a** catalysed by **3c** at 20 p.p.m. loading. Cycloadducts **4j-l** were obtained as single *cis*-diastereoisomers.

In conclusion, we have developed catalytic enantioselective Povarov reactions of *N*-aryl ferrocenecarbaldehyde imines **1**. The reactions furnished highly enantioenriched 2-ferrocenyl-1,2,3,4-tetrahydroquinoline compounds **4-8**, of potential interest due to the combination of the properties of the tetrahydroquinoline and the ferrocenyl groups. This study demonstrates that the stereoelectronic properties of ferrocenyl imines **1** do not preclude their

engagement in enantioselective Brønsted acid catalysis. An efficient protocol for the Povarov reaction with benzyl *N*-vinyl carbamate **2a** was developed, enabling the obtainment of the products with ≥96% *ee* in all cases. With some specific substrates, it was possible to further optimise the reaction reaching a record low catalyst loading of 10-20 p.p.m. in the reactions.

Experimental Section

Preparative catalytic asymmetric Povarov reaction of 1-ferrocenyl-*N*-(4-methoxyphenyl)methanimine 1a with benzyl *N*-vinylcarbamate 2a at 20 p.p.m. catalyst loading.

To a Schlenk tube equipped with a magnetic stirring bar, dry $MgSO_4$ (1.50 g) was added and thermally activated (heat gun) under vacuum for *ca.* 10 minutes and then allowed to cool to room temperature. After cooling, the Schlenk tube was filled with nitrogen. Ferrocenyl-*N*-(4-methoxyphenyl)methanimine **1a** (1.59 g, 5.0 mmol) and toluene (20 mL) were added under nitrogen atmosphere, followed by 20 µL of a 5 mM mother solution of (*R*)-TRIP **3c** in toluene (corresponding to 0.075 mg, 1.0×10^{-4} mmol, 20 p.p.m.: this solution was prepared dissolving 3.8 mg of **3c** in 1.0 mL of toluene). Benzyl *N*-vinylcarbamate **2a** (1.06 g, 6.0 mmol) was then added, the reaction mixture was heated to 60 °C and stirred at this temperature under nitrogen atmosphere. After 65 h, the mixture was filtered through a plug of silica gel and the plug washed with Et_2O (4×). After the evaporation of the solvents, the residue was analyzed by ^{1}H NMR spectroscopy to determine the diastereomeric ratio of the product (a single *cis*-diastereoisomer was detected). Finally, the crude product was purified by column chromatography (SiO_2; *n*-hexane-EtOAc 9:1). 1.99 g (4.0 mmol, 80% yield) Of benzyl ((2*S*,4*S*)-2-ferrocenyl-6-methoxy-1,2,3,4-tetrahydroquinolin-4-yl)carbamate **4a** were thus obtained as a yellow solid. The *ee* of the product was determined by HPLC using a Chiralpak AD-H column (*n*-hexane/*i*-PrOH 80:20, flow-rate 0.75 mL/min, t_{maj}= 32.5 min, t_{min}= 36.6 min, *ee* 97%).

Acknowledgements

We acknowledge financial support by the University of Bologna (RFO program). Donation of chemicals from Dr. Reddy's Chirotech Technology Centre (Cambridge, U.K.) is gratefully acknowledged. We thank Prof. Carmen Nájera for a gift of (R)-BINOL. D.S. is grateful for a postdoctoral fellowship from the Ministry of Education, Science and Technological Development of the Republic of Serbia (Grant No. 451-03-1026/2016-14).

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[15] See the Supporting Information. CCDC no 1559241 contains the crystallographic data of **4b**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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catalyst to metal phosphate species. Calcium phosphates derived from catalysts **3** are known to be inefficient in the promotion of Povarov reactions.[10b] Prompted by another reviewer, we have also verified that the magnesium salt of catalyst **3c** is not efficient in the promotion of these reactions, although we could not reach a decisive conclusion (see Supporting Information). We thank two anonymous reviewers for these useful suggestions.

[18] Compared to the reaction with **1a**, with imines **1j-l** it proved advantageous to perform the reactions at 40 °C, in terms of enantiomeric excess.