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One-Pot Reductive Amination

Efficient One-Pot Reductive Aminations of Carbonyl Compounds with Aquivion-Fe as a Recyclable Catalyst and Sodium Borohydride

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Abstract: A one-pot reductive amination of aldehydes and ketones with $NaBH_4$ was developed with a view to providing efficient, economical and greener synthetic conditions. A recyclable iron-based Lewis catalyst, Aquivion-Fe, was used to promote imine formation in cyclopentyl methyl ether, followed by the addition of a small amount of methanol to the reaction mixture to enable C=N reduction by $NaBH_4$. The protocol, applied to a wide number of amines and carbonyl compounds, resulted in ever complete conversion of these latter with excellent chemoselectivity towards the expected amination products in the most cases. Isolated yields, determined for a selection of the screened substrates, were found consistent with the previously obtained conversion and selectivity data. Cinacalcet, an important active pharmaceutical ingredient, was efficiently prepared by the title procedure.

Introduction

Many different strategies have been developed for the synthesis of amines. The vast majority of them can be summarized and classified as: (i) alkylation of ammonia and amines; (ii) reduction of nitrogen containing groups; (iii) Gabriel synthesis and (iv) reductive amination (RA) of carbonyl compounds. The latter is the most widely used method and novel protocols, reactants and catalysts are currently sought to improve it.[1–10] Its success has been determined by commercial availability of the substrates, mild reaction conditions, sustainable and economical protocol, high atom economy without toxic wastes, high tolerance to other functional groups, chemoselective conversion to secondary or tertiary amine. By this method, for instance, amine nitrogen deprotection and subsequent alkylation can be safely relegated to the ultimate step in the synthesis of polyfunctionalized amines.[11–13] Its attractiveness has been further increased by practicability in a single one-pot operation (direct reductive amination, DRA) by mixing carbonyl compound, amine and a suitable reducing agent without isolation of imine intermediates.[2,14–16]

Since the first report almost a hundred years ago,[17] RA has been declined in a multitude of different procedures, which are generally classified depending on how the reduction of the intermediate imine or iminium ion is done.[3] Two are the main options: hydrogenation with hydrogen or hydrogen donors and reduction by the use of compounds or complex systems (hydride reagents) acting as a hydride source (Figure 1). Both the approaches have been widely explored and developed in the past decades by using a large variety of reducing agents and catalysts.

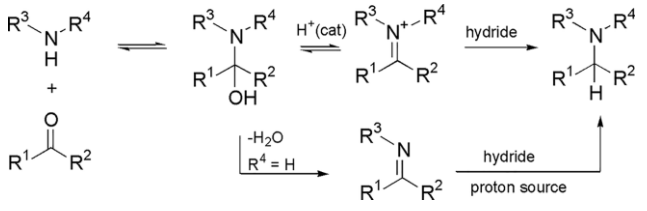

Figure 1. Proposed mechanism of reductive amination with a hydride source.

However, it was only after 2000 that search for new RA methods began to conjugate efficiency and economic viability with environmental benignity, in particular of the reducing agent. Indeed, recently drafted green criteria for RA are mainly focused on the choice and the amount of the reductants: H_2/metal catalyst is preferred over the others and, in case of hydride reagents, sodium borohydride (SB) is the best option.[18] However, though recommended, the use of hydrogen is not compatible with other reducible functional groups and requires expensive and toxic metals as catalysts. On the other hand, SB is safe, quite inexpensive and water tolerant. Ease of work-up and good atom economy (81 %)[19] characterize its use. However, SB is usually

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unsuitable for DRA due to the competitive reduction of starting carbonyls. Its addition has to be postponed after imine formation, which is often far from reaching completeness. Alternative borane-based reducing agents, such as sodium cyanoborohydride (SCB), sodium triacetoxyborohydride (STAB) and picoline-borane complex (Pic-B), selectively reduce the in situ generated imine driving conversion of carbonyl compound into imine to completeness and enabling one-pot procedures.[20] But they are not advantageous in terms of atom economy and, for a number of reasons, they do not satisfy safety and/or cost criteria. Last but not least, RA should be accomplished in more environmentally friendly solvents in replacement of less desirable solvents such as dichloromethane (DCM), THF and DMF.[20]

As is evident from the above, a number of issues has to be simultaneously addressed in designing a sustainable and efficient DRA: greener solvent, environmentally acceptable and safe reductant, such as SB, and one-pot protocol. In order to meet the above requirements, a DRA method cannot work without a suitable catalysis promoting efficient imine formation before SB exerts its unselective reduction power. Here we report our efforts in developing a DRA procedure with such features. A number of aldehydes and ketones were reductively aminated with different amines using SB in cyclopentyl methyl ether (CPME), preferably chosen among other advisable solvents, and in the presence of a recyclable Lewis acid, the iron salt of Aquivion-H (Aquivion-Fe) (Figure 2),[21] catalysing the imine formation. We report also the recycling of this catalyst and the extension of the method from model substrates to Cinacalcet, an important active pharmaceutical ingredient.[22]

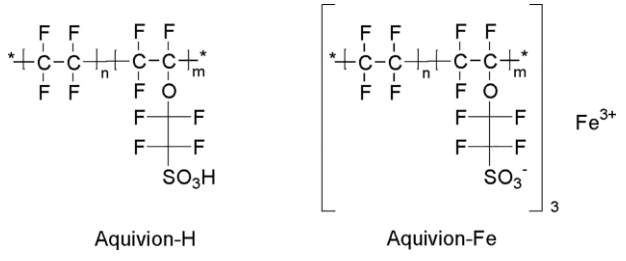


Figure 2. Chemical structure of Aquivion-H and Aquivion-Fe.

Results and Discussion

DRA with Aquivion-Fe and SB in DCM

It is known that SB alone may not afford excellent DRA yields. Poor nucleophilic amines, poor electrophilic carbonyls and sterically encumbered reactive centers result in incomplete imine formation. The use of Brønsted and Lewis acids facilitate imine formation and, according to some authors, also imine reduction coordinating carbonyl oxygen and imine nitrogen respectively.[16,23–29] In particular, special attention has been paid to catalysts based on iron, a non-toxic, environmentally acceptable and inexpensive metal.[27,28] Recently, the efficient activity and recyclability as a Lewis catalyst in Friedel-Crafts acylations of the iron salt of Aquivion-H (Figure 2) has been reported.[21] Aquivion-H is a commercially available perfluorosulfonic ionomer, used to prepare polymer electrolyte membranes.[30]

We started considering the conversion of benzaldehyde into N-benzylaniline by treatment with equimolar aniline and SB as a model reductive amination. First, the reaction was carried out in DCM and in the presence of 3.3 mol-% Aquivion-Fe. After 3 hours at 40 °C, a methanol amount equal to one fifth of DCM was added dropwise at 0 °C. After 30 minutes, the reaction mixture was washed with water and the catalyst was recovered by filtration. The aqueous phase was separated and extracted with DCM. The two organic layers were combined and concentrated. The resultant residue, analysed by ^{1}H NMR, was the desired N-benzylaniline with a minority presence of benzyl alcohol and aniline. As expected, benzaldehyde and the intermediate imine were absent. These analytical data indicated that the conversion degree (CV%) of benzaldehyde was 100 %. The selectivity towards the desired N-benzylaniline was 71 % as indicated by the integration of the singlet due to its CH_2 compared to that of the CH_2 of the other product, the undesired benzyl alcohol. The minority, but not negligible formation of benzyl alcohol could be reasonably imputed to incomplete imine formation in the DRA first step. Undoubtedly, the imine formation was minimal without catalyst. In its absence, we observed complete conversion of benzaldehyde into benzyl alcohol and N-benzylaniline but with a very low amination selectivity (5 %), thus proving the essential role played by Aquivion-Fe.

Searching for More Eco-Friendly Solvents

After ascertaining that Aquivion-Fe efficiently catalyzed the conversion of benzaldehyde and aniline into benzylideneaniline in DCM and that the successive addition of methanol enabled its reduction to benzylaniline, we moved on to replacement of DCM with solvents having acceptable EHS (Environmental, Health, Safety) properties. In 2013, dimethyl carbonate and ethyl acetate were proposed as successful green alternatives to chlorinated solvents, THF and DMF after a selection based on 360 reductive aminations accomplished between two aldehydes and six amines in ten different solvents using SCB, STAB or pic-B as reducing agents.[20] On our part, we needed a solvent stable under basic conditions, compatible with hydrides and, above all, apolar enough to avoid SB solubilisation and to exclude its reducing action during the DRA first stage. The choice, inspired by the recently reported replacement of banned solvents in L-amino acids esterification,[31–33] fell on the green ethers *tert*-amyl methyl ether (TAME), cyclopentyl methyl ether (CPME) and 2-methyl-tetrahydrofuran (Me-THF) and on *p*-cymene, which is much less toxic than toluene. By the same protocol previously used in DCM, benzaldehyde was completely converted into benzylaniline and benzyl alcohol with a selectivity of 94 % in TAME, of 91 % in CPME, of 57 % in Me-THF and of 97 % in *p*-cymene. Difficult removal of high boiling *p*-cymene, high cost of TAME and the lower efficiency of Me-THF prompted us to select CPME as a preferable solvent. In the absence of catalyst, we noted that the benzylaniline formation was modest (17 % selectivity) in CPME but not so negligible as in DCM (5 % selectivity). This would indicate that the solvent plays some role in imine formation and that the considerable amount of benzyl alcohol resulting from the DRA in DCM in

the presence of the catalyst might be imputed, as previously hypothesized, to a less efficient imine formation rather than to an anticipated SB reducing action. In fact, in DCM, which has solvent characteristics very similar to those of CPME, SB should be as unable to exert its reducing action as in CPME. Different is the case of the other ether, Me-THF, which is significantly more polar than CPME and DCM. In this solvent, where benzyl alcohol and N-benzylaniline were formed in comparable amounts in the presence of the catalyst, it is reasonable that SB partially acts reducing unreacted benzaldehyde before methanol addition. DRA of benzaldehyde with aniline without catalyst was accomplished also in Me-THF. As expected, the already modest 57 % selectivity towards N-benzylaniline registered in the presence of Lewis catalysis resulted in a negligible 7 % in its absence.

Lastly, we considered the use conditions of methanol in the DRA of benzaldehyde with aniline in CPME. Addition of methanol at room temperature without cooling caused temperature enhancement and, concomitantly, incomplete imine reduction was observed. Use of methanol amounts lower than one fifth of the CPME volume led to incomplete imine reduction as well as to less favourable final benzylaniline/benzyl alcohol ratio.

The Catalyst: Characterization, Role and Recycling

Before extending the new amination protocol to other carbonyl compounds and amines, we verified the recyclability of our iron-based catalyst and its ability to maintain the initial metal content through repeated catalytic cycles. We chose the conversion of benzaldehyde (0.5 g) into dibenzylamine by treatment with equimolar benzylamine as a model reaction. The imine was formed in CPME at 40 °C in the presence of 3.3 mol-% Aquivion-Fe and of undissolved stoichiometric SB. After 3 hours, methanol was added at 0 °C to enable reduction by SB. The reaction was prolonged to 30 minutes and then worked up as described previously for the reaction in DCM but using EtOAC to extract the aqueous phase. Benzaldehyde was converted into dibenzylamine with 91 % selectivity. The catalyst, recovered by filtration, was washed with acetonitrile, dried and reused nine times for the same reaction and under the same conditions. In the further nine reductive aminations, benzaldehyde was completely converted into amine and benzyl alcohol with selectivity towards amine ranging from 91 % to 98 %.

As recently outlined, "consistently high yields in repeated runs cannot be taken as satisfactory evidence for high catalyst stability" although "they testify to the robust nature of a catalyst system, which is a necessary requirement for long-term uses".[34] Therefore, while not seeing catalyst performance drops through the ten cycles, we monitored the iron content of the catalyst as a stability index. We used Aquivion-H ($R\text{-}SO_3H$) powder having a nominal equivalent weight of 870 g/eq to prepare Aquivion-Fe ($(R\text{-}SO_3)_3Fe$), whose theoretical iron loading was therefore 2.10 % (w/w%). The initial metal content, measured by ICP-OES, was 2.35 %; after ten cycles, the metal loading was 1.92 %. The found values indicate that the Aquivion-H salification procedure was effective in quantitatively exchanging the sulfonic acid functions and that extended recycling resulted in a limited drop of the initial metal loading. This observation raised the question whether minimal iron loss from the catalyst into the reaction mixture could contribute to the catalysis. Indeed, such an eventuality should be excluded because we did not observe any reductive amination of benzaldehyde with aniline when we applied our DRA protocol without Aquivion-Fe using CPME previously stirred in the presence of Aquivion-Fe and SB at 40 °C for 3 hours and then filtered before SB reintegration and addition of the two substrates. Titration with 0.1 M NaOH of Aquivion-H confirmed the declared 870 equivalent weight of the unsalified ionomer, while, as expected, we registered no titrant consumption by fresh Aquivion-Fe and recycled Aquivion-Fe as proof of its complete and permanent salification resulting from treatment with iron powder.

An issue to be addressed was the advantage from using Aquivion-Fe instead of its immediately available precursor Aquivion-H. This, in the same way as other carbon-based solid Brønsted acids,[24] should be able to favour imine formation. Indeed, when used in catalytic amount (3.3 mol-%), Aquivion-H showed lower efficiency than that of Aquivion-Fe. Moreover, as expected, it was recovered devoid of any acidic character and therefore not directly recyclable, unlike Aquivion-Fe, in successive DRAs.

As outlined above, the presence of Aquivion-Fe was essential in the one-pot RA of benzaldehyde with aniline and SB. In its absence, we had almost quantitative conversion into benzyl alcohol and minimal amount of benzylaniline. Furthermore, we wished to assess whether it was determinant in both the formation and the reduction of imine. Therefore, we repeated the reaction in CPME removing SB and Aquivion-Fe after 3 hours reaction at 40 °C, re-adding SB to the filtrate at room temperature and adding, after cooling to 0 °C, methanol. Under such conditions where the catalysts was excluded from the reduction step, the yield of benzylaniline was analogous to that obtained without Aquivion-Fe removal. This indicates that the main role of the catalytic system is to favour the formation of the intermediate imine.

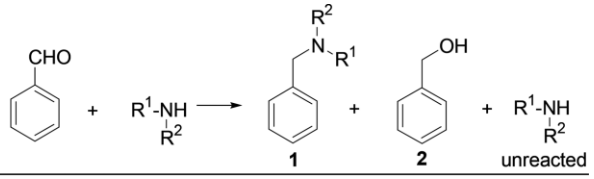
Screening of Carbonyl Compounds and Amines

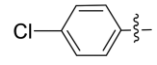
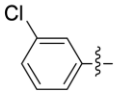
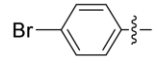
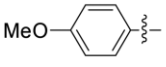
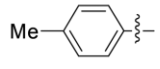
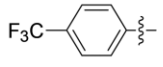
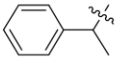
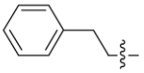
After designing the two-step/one-pot reductive amination in DCM/methanol, replacing DCM with CPME and demonstrating Aquivion-Fe catalyst recyclability, the fourth step of our investigation was the extension of the method to other carbonyl compounds and amines applying the protocol followed for the reaction benzaldehyde-benzylamine. Forty-one reactions were planned. The selectivity towards the desired amine was determined by ^1H NMR analysis of the crude resulting from the reactions work-up, by comparing the integrations of two diagnostic peaks, one unequivocally ascribable to amine product and the other to the undesired alcohol side-product. Furthermore, the same crude products were GC/MS analysed to ascertain the identity of the amine produced by the reductive amination.

First, benzaldehyde was treated with fifteen amines (Table 1). These were: seven primary aromatic amines (aniline, *p*-chloro-, *m*-chloro-, *p*-bromo-, *p*-methoxy-, *p*-methyl- and *p*-trifluoromethyl-aniline; entries 1–7), three primary arylalkylamines

(benzylamine, α-methylbenzylamine and 2-phenylethylamine; entries 8–10), two primary alkylamines (*tert*-butylamine and cyclohexylamine; entries 11 and 12) and three secondary alicyclic amines (piperidine, pyrrolidine and morpholine; entries 14–16). Benzaldehyde was aminated also with aqueous ammonia (entry 13). In this case, SB and methanol addition was postponed to imine formation.

Table 1. Reductive aminations of benzaldehyde (Aq-Fe, $NaBH_4$, CPME, 40 °C, 3 h and then MeOH, rT, 30 min).



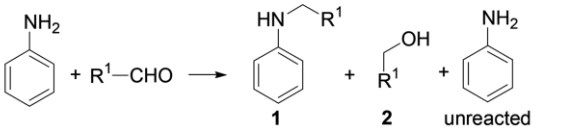
Run	R^1	R^2	Conv. %[a]	**1** Sel. %[b]	**2** Sel. %[c]
1	Ph	H	100	91	9
2		H	100	58	42
3		H	100	51	49
4		H	100	54	46
5		H	100	84	16
6		H	100	81	19
7		H	100	47	53
8	Bn	H	100	92	8
9		H	100	90	10
10		H	100	90	10
11		H	100	31	69
12	Cy	H	100	70	30
13	H	H	100	98	2
14			100[d]	91	9
15			100[d]	81	19
16			100[d]	95	5

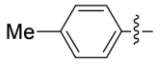
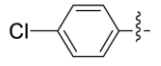
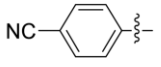
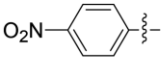
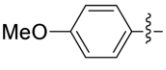
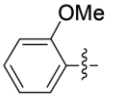
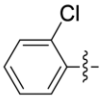
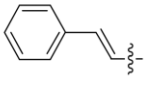
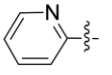
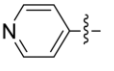
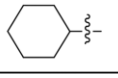
[a] Percent conversion of benzaldehyde. [b] Selectivity towards **1**. [c] Selectivity towards **2**. [d] *p*-cymene, 20 °C, 3 h.

Benzaldehyde was always completely converted with selectivity towards the sixteen different benzylamines generally ranging from good to excellent. Relatively lower or moderate selectivities were encountered only when aniline bears an electron withdrawing substituent (chloro, bromo, trifluoromethyl; Table 1, entries 2–4 and 7) and with hindered primary alkylamine (*tert*-butylamine; Table 1, entry 11). In the case of the three secondary alicyclic amines, which contribute to SB solubilisation, CPME had to be replaced with less polar *p*-cymene, to procrastinate SB reductant action to methanol addition, and the reaction temperature was lowered to 20 °C to promote iminium formation. So, the selectivities were very high (Table 1, entries 14–16).

In the second set of aminations (Table 2), aniline was treated with twelve aldehydes: seven substituted benzaldehydes (*p*-methyl, *p*-chloro, *p*-cyano, *p*-nitro, *p*-methoxy, *o*-methoxy-

Table 2. Reductive aminations of aldehydes with aniline (Aq-Fe, $NaBH_4$, CPME, 40 °C, 3 h and then MeOH, rT, 30 min).



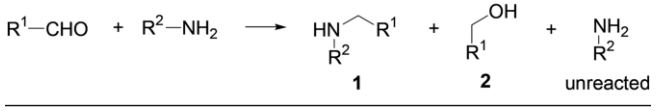
Run	R^1	Conv. %[a]	**1** Sel. %[b]	**2** Sel. %[c]
1		100	81	19
2		100	79	21
3		100	67	33
4		100	66	34
5		100	72	28
6		100	88	12
7		100	64	36
8		100	66	34
9		100	72	28
10		100	81	19
11		100	70	30
12		100	80	20

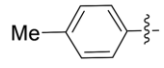
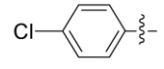
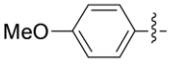
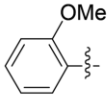
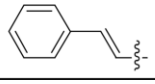
[a] Percent conversion of aldehyde. [b] Selectivity towards **1**. [c] Selectivity towards **2**.

and *o*-chloro-benzaldehyde; entries 1–7), 2-furancarbaldehyde, cinnamaldehyde, picolinaldeheyde, isonicotinaldehyde, and cyclohexanecarbaldehyde (entries 8–12). Again, the conversion of the aldehydes was complete and the selectivities towards N-alkylated aniline were all from good to very high. Here, the substitution pattern of aldehydes, possibly because of the role played by the Lewis catalyst, turned out to be less determinant than that of aniline in the previous set of benzaldehyde aminations.

In the third set of aminations, seven in all, benzylamine or cyclohexylamine were treated with aromatic aldehydes other than benzaldehyde (Table 3). The reactions of the aldehydes were complete and the selectivity towards the desired products were from high to very high.

Table 3. Reductive aminations of aldehydes with benzylamine or cyclohexylamine (Aq-Fe, $NaBH_4$, CPME, 40 °C, 3 h and then MeOH, rT, 30 min).

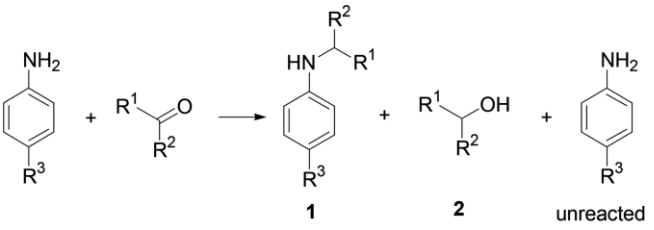


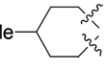
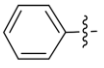
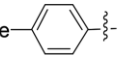
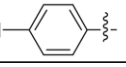
Run	R^1	R^2	Conv. %[a]	**1** Sel. %[b]	**2** Sel. %[c]
1		Bn	100	77	23
2		Bn	100	100	0
3		Bn	100	83	17
4		Bn	100	100	0
5		Cy	100	82	18
6		Cy	100	67	33
7		Cy	100	86	14

[a] Percent conversion of aldehyde. [b] Selectivity towards **1**. [c] Selectivity towards **2**.

Lastly, we considered ketones (Table 4), whose carbonyl carbon is notoriously less susceptible of electrophilic attack than that of aldehydes for both steric and electronic factors. Indeed, cyclohexanone was reductively aminated by *p*-methoxyaniline with a moderate 44 % selectivity under the same conditions adopted for aldehydes (entry 2), while amination of cyclohexanone and its 4-methyl derivative with unsubstituted aniline required a higher temperature (80 °C) to reach analogous selectivity degrees (entries 1 and 3). Aromatic ketones (acetophenone and its *p*- methyl and *p*-chloro derivatives) were even less prone to amination. Their reaction with aniline had to be prolonged to 6 hours to get modest or moderate amination selectivity (entries 4–6).

Table 4. Reductive aminations of ketones with aniline (Aq-Fe, NaBH4, CPME, 40 °C or 80 °C, 3 or 6 h and then MeOH, rT, 30 min).



Run	R^1	R^2	R^3	Conv. %[a]	**1** Sel. %[b]	**2** Sel. %[c]
1			H	100[d]	50	50
2			OMe	100[e]	44	56
3	Me 		H	100[d]	48	52
4		Me	H	100[f]	45	55
5	Me 	Me	H	100[f]	35	65
6	Cl 	Me	H	100[f]	18	82

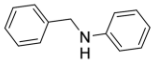
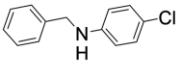
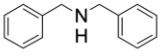
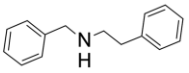
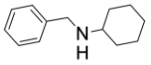
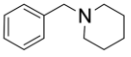
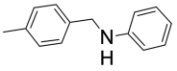
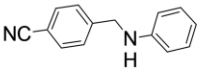
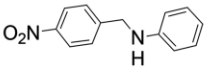
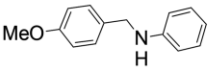
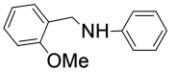
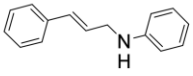
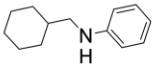
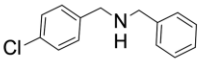
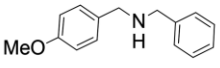
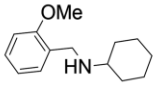
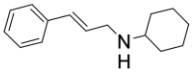
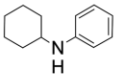
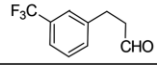
[a] Percent conversion of ketone. [b] Selectivity towards **1**. [c] Selectivity towards **2**. [d] 3 hours at 80 °C. [e] 3 hours at 40 °C. [f] 6 hours at 80 °C.

Application of the Procedure to Some Selected Substrates and to Cinacalcet

The above protocol of one-pot reductive amination was applied to a representative selection of the previously screened carbonyl compounds and amines this time isolating the amination products **1a**–**1r** (Table 5) by chromatography in order to verify the consistency, expected on the basis of the 100 % conversions, between yields and previously observed selectivities. The isolated yields of the selected eighteen aminations, reported in Table 5, confirm such an expectation. In fact, compared with the corresponding amination selectivities listed in the Table 1, Table 2, Table 3, and Table 4, they are all only a few percent points lower as expectable after a chromatographic separation.

At the end of the investigation, to showcase the synthetic utility of the developed DRA, we wished to apply this amination procedure to the preparation of an active pharmaceutical ingredient. We chose the calcimimetic Cinacalcet, a secondary amine obtainable by different synthetic approaches,[35] among which reductive amination of 3-(3-trifluoromethylphenyl)propionaldehyde with (*R*)-1-(α-naphthyl)ethylamine ((*R*)-1-NEA) is one of the most industrially applied methods (Figure 3).[36] Based on our long-acquired familiarity with chlorinated isocyanurates,[37–41] mild, green oxidants and halogenating agents,[42,43] we decided to prepare the aldehyde by oxidation of the corresponding alcohol with trichloroisocyanuric acid (TCCA) instead of applying procedures previously reported in papers and patents.[44–48] The conversion was quantitative and the crude aldehyde, isolated by simple extraction, could be directly aminated without chro-

Table 5. Isolated yields of reductive aminations (Aq-Fe, NaBH4, CPME, 40 °C, 3 h and then MeOH, rT, 30 min).

Run	Carbonyl compound	Amine	Product	Yield %
1	Benzaldehyde	Aniline		**1a** 86
2	Benzaldehyde	*p*-Cl-aniline		**1b** 55
3	Benzaldehyde	$BnNH_2$		**1c** 90
4	Benzaldehyde	2-PEA		**1d** 85
5	Benzaldehyde	CHA		**1e** 68
6	Benzaldehyde	Piperidine		**1f** 84[a]
7	*p*-Tolualdehyde	Aniline		**1g** 77
8	*p*-CN-Benzaldehyde	Aniline		**1h** 63
9	*p*-NO_2-Benzaldehyde	Aniline		**1i** 60
10	4-Anisaldehyde	Aniline		**1j** 70
11	*o*-Anisaldehyde	Aniline		**1k** 82
12	Cinnamaldehyde	Aniline		**1l** 69
13	Formylcyclohexane	Aniline		**1m** 73
14	*p*-Cl-benzaldehyde	$BnNH_2$		**1n** 96
15	4-Anisaldehyde	$BnNH_2$		**1o** 81
16	*o*-Anisaldehyde	CHA		**1p** 61
17	Cinnamaldehyde	CHA		**1q** 84
18	Cyclohexanone	Aniline		**1r** 47[b]
19		(*R*)-1-NEA	Cinacalcet	76

[a] *p*-Cymene, 20 °C, 3 h. [b] 3 h at 80 °C.

matographic purification or conversion into Bertagnini adduct. The reaction with (*R*)-1-NEA was carried out as described above for benzaldehyde with benzylamine. Cinacalcet was isolated in 76 % yield as hydrochloride by crystallization (Table 5, entry 19). Compared to the reported reductive aminations of 3-(3-trifluoromethylphenyl)propionaldehyde with (*R*)-1-NEA, this procedure shows analogous efficiency offering the advantage of using SB and crude aldehyde in a green solvent according to a simple one-pot protocol.

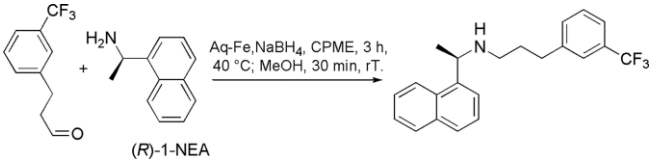


Figure 3. Preparation of Cinacalcet by reductive amination of 3-(3-trifluoromethylphenyl)propionaldehyde with (*R*)-1-(α-naphthyl)ethylamine ((*R*)-1-NEA).

Conclusions

In summary, we have developed an efficient and sustainable reductive amination protocol that meets some very desirable requirements: the use of a recoverable and recyclable catalyst, based on a non-toxic metal, in greener solvents with an inexpensive and eco-friendly reductant realising a one-pot procedure. Aquivion-Fe has been proved to catalyse the amination of a number of aldehydes and ketones with primary and secondary amines and to be reusable several times. The use of the green ether CPME (and, where necessary, of cymene) and the delayed addition of methanol have allowed sodium borohydride, a largely available, but unselective reductant, to be used in a one-pot procedure with high chemoselectivity for reductive amination vs. C=O reduction. The model reaction has been successfully applied to the preparation of nineteen amines, among which the active pharmaceutical ingredient Cinacalcet.

Experimental Section

^{1}H-NMR and ^{13}C-NMR spectra were recorded in $CDCl_3$ at 300 MHz and 75 MHz respectively, with Varian Mercury 300 Spectrometer and elaborated with Mnova software. Chemical shifts are reported in ppm relative to residual solvent as internal standard. The percent of conversion was evaluated by NMR analysis. The percent of selectivity was determined by comparing the integration value of a peak of the desired product (for instance the CH_2N signal of benzylamines resulting from benzaldehydes) with that of a peak ascribable to the alcohol resulting from the carbonyl compound reduction.

GC/MS analyses were performed on a Dani Master GCs with Mass Selective Detector Dani Master TOF and autosampler Dani Master AS. Samples were diluted in toluene at final concentration of 1 mg/mL. 0.5 mL of sample solution were added to 0.5 mL of IS solution (Diphenylamine 0.6 mg/mL in toluene). Data were handled with a Master Lab software (Dani); chromatographic separation was carried out on a HP-5MSUI inert capillary column (20 m × 0.18 mm i.d., film thickness 0.18 μm, J.& W. Scientific). The GC/MS system was operated under the following conditions: injection temperature 250 °C (split mode 50:1); interface transfer line 260 °C; ion source 200 °C; initial column temperature 50 °C. Temperature was subsequently increased to 300 °C at a rate of 15 °C/min. Helium was used as the carrier gas at a flow rate of 0.5 mL/min. MS analysis was performed in SCAN (50/550 *m/z*) operated in electron ionization mode, the beam energy being 70 eV with a solvent delay of 180 s and an acquisition rate of 5 spectra/s. Injection volume was 1 μL.

High Resolution Electrospray Mass Spectra were acquired with Q-TOF Synapt G2 Si (WATERS).

The determination of iron loading in fresh Aquivion-Fe was performed using ICP-OES (inductively coupled plasma optical emission spectrometry) by Solvay Specialty Polymers S.p.A.

Titrations of Aquivion®-H and Aquivion®-Fe were carried out as already reported (W. Fang et al., Catal. Sci. Technol., 2015, 5, 3980).

For further details, see the Supporting Information.

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Keywords: Amination · Aquivion · Chemoselectivity · Cinacalcet · Sodium borohydride

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