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Reaction of Grignard reagents with carbonyl compounds under continuous flow conditions

E. Riva [a], S. Gagliardi [b], M. Martinelli [b], D. Passarella [a], D. Vigo [b], A. Rencurosi [b,*]

[a] Dipartimento di Chimica Organica e Industriale, Università degli Studi di Milano, Via Venezian 21, 20133 Milano, Italy
[b] NiKem Research S.r.l., via Zambeletti 25, 20021 Baranzate, Milano, Italy

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ABSTRACT

This contribution details how a continuous flow reactor was used to react carbonyl compounds with Grignard reagents at room temperature in an efficient and safe manner. Flow rate, residence time and temperature were optimized for the preparation of a small collection of secondary and tertiary alcohols. Excellent yields and general applicability were observed using the set-up protocol. The procedure was also applied for the preparation of Tramadol, an analgesic drug belonging to the opioid group. The developed conditions allowed the selective addition of Grignard reagents to aldehydes and ketones in the presence of a nitrile function.

1. Introduction

Flow technologies have recently received a great deal of attention and a fair number of scientific publications have demonstrated their potential for improving productivity in organic synthesis.[1] Established advantages of continuous flow chemistry processes include: precise control of variables such as temperature, pressure, residence time and heat transfer. All these aspects significantly affect the reaction outcome improving yield and selectivity.[2] As part of a discovery program, we became interested in performing Grignard addition to carbonyl compounds in a *meso*-scale flow reactor. Organomagnesium reagents were firstly prepared over a hundred years ago by Grignard and still occupy a central place in organic chemistry.[3] They show excellent reactivity towards a wide range of electrophiles and, for this reason, the reactions involving Grignard reagents often need to be controlled by operating at low temperature. The flow technique represents an innovative way to control such a reactivity since its homogeneous mixing and heat transfer narrows the temperature distribution and restricts the reaction output to the target product.[4] The addition of Grignard reagents to aldehydes and ketones under flow conditions was mentioned in the literature as an application of CPC-CYTOS microreactor system and its evolution SEQUOA with limited experimental details.[5] While the reaction of a Grignard reagent with thiolactones,[6] diethyl oxalate,[7] and acyl chlorides[8] were reported using specifically developed microreactors often operating at low temperatures. Some examples dealing with the generation and the addition of aryllithium compounds to electrophiles under flow conditions are present in the literature[4b,9] pointing out, once more, the advantages of the flow approach when using highly reactive species. Moreover, the use of Grignard reagents in coupling or exchange reactions under flow condition was also reported.[10] In the light of the broad application of Grignard reagents in organic synthesis we decided to set up and optimise the addition of Grignard reagents to aldehydes and ketones using the commercially available Vapourtec® flow reactor,[11] and to explore the reaction selectivity in the presence of reactive moieties such as nitriles.

2. Results and discussion

In a typical experiment two solutions of 4-isopropylbenzalehyde **1** and (2-methylallyl)magnesium chloride in THF, stored under N_2, were simultaneously pumped at room temperature into the flow apparatus equipped with a 10 ml tubing reactor (Scheme 1).[11] The reaction stream was then directly passed through a short column containing polymer-supported benzaldehyde for the scavenging of the excess of Grignard reagent. The optimization of the experimental parameters was investigated by varying the temperature of

* Corresponding author. Tel.: +39 02356947568; fax: +39 02356947606.
E-mail address: anna.rencurosi@nikemresearch.com (A. Rencurosi).

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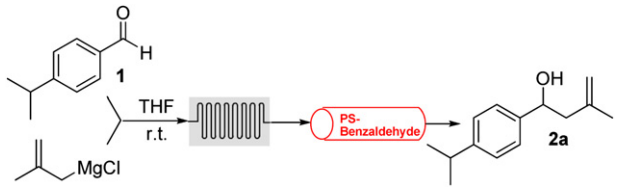


Scheme 1. Flow synthesis of secondary alcohols.

Table 1
Optimization of the experimental parameters

Entry	Grignard (equiv)	T (°C)[a]	Residence time (min)	Flow rate (ml/min)	(%)[b]
1	2	−78	66[c]	0.30	95
2	2	−78	33	0.30	96
3	2	0	33	0.30	94
4	2	rt	33	0.30	97
5	1.2	rt	33	0.30	98
6[d]	1.2	rt	120	—	29
7[d]	2	−20 °C	50	—	95

[a] Stock solution temperature.
[b] The conversion was determined by peak integration at 215 nm (UPLC/MS).
[c] Reaction performed using 20 ml tubing reactor.
[d] Reaction performed in batch.

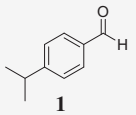
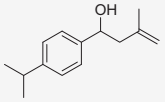
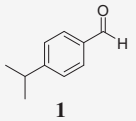
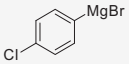
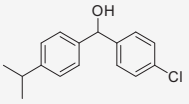
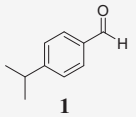
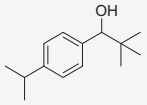
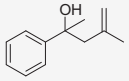
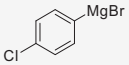
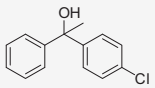
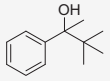
the stored solution, the residence time and the number of Grignard equivalents (Table 1).

We started our investigation by pre-cooling both the stock solutions at −78 °C and by varying the residence time (entries 1 and 2). Then, the temperature of the reagent solutions was raised up to 0 °C and finally to room temperature (entries 3 and 4) without observing any variation in terms of conversion and purity in the reaction profile. This result is a direct consequence of the efficient mixing and heat dispersion due to the high surface area-to-volume ratio in the PTFE tubing that keeps the temperature constant minimizing the occurrence of side reactions. The Grignard equivalents were then reduced from 2 to 1.2 (entry 5), without affecting the conversion. For comparative purposes the same reaction was performed in traditional batch conditions (entry 6) by adding (2-methylallyl)magnesium chloride to 4-isopropylbenzalehyde **1** at room temperature. The reaction mixture was thermostated and the temperature was kept constant in the course of the reaction. After 2 h, the desired product was detected with a conversion of 29% (UPLC/MS 215 nm) showing that, in the specified reaction conditions, the flow system is really advantageous in term of efficacy if compared to the batch one. In order to achieve complete conversion, the number of Grignard equivalents was risen (2 equiv) and the temperature was kept at −20 °C during the addition (entry 7), suggesting that the poor conversion in the previous experiment could have been determined by Grignard degradation in the reaction mixture.

In continuous flow synthesis, scale up is generally accomplished by running the microreactor for an extended time or by employing multi-channel parallel reactors (numbering-up process).[12] A demonstration of this preparative capability was readily obtained. Applying the optimized conditions (*i.e.*, stored solution at room temperature; flow rate: 0.30 ml min^{-1}; residence time: 33 min) 2 g of **2a** were straightforwardly produced with an output of 0.9 g/h. Yield and purity were similar to the smaller scale proving that the reaction conditions identified for the production of few milligrams can be directly transferred to a larger scale.

To assess the limit and the scope of this procedure, the same protocol was tested reacting different Grignard reagents (aryl, alkyl, allyl) with 4-isopropylbenzaldehyde and acetophenone (Table 2) on a 200 mg scale.

Table 2
Conversion of 4-isopropylbenzaldehyde into secondary alcohols and of acetophenone into tertiary alcohols

Entry	Carbonyl compound	Grignard reagent	Alcohol	Yield[a] (%)
1	 **1**		 **2a**	92
2	 **1**		 **2b**	93
3	 **1**		 **2c**	87
4	 **3**		 **4a**	94
5	 **3**		 **4b**	95
6	 **3**		 **4c**	90
7	 **3**		 **4d**	95

[a] Isolated yields; purity >95% (UPLC/MS).

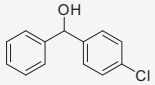
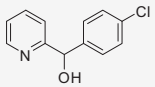
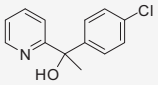
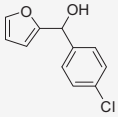
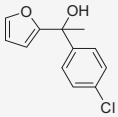
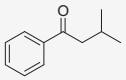
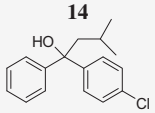
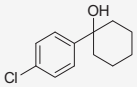
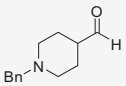
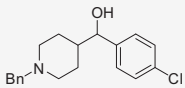
The desired alcohols were efficiently obtained using starting materials such as allyl (entries 1, 4), aryl (entries 2, 5) and alkyl (entries 3, 6, 7) magnesium derivatives. In all examples, the isolated yields were excellent: of special interest are the results obtained with the hindered *tert*-butyl magnesium bromide as a reagent (entries 3, 6).

To verify the effectiveness and reproducibility of the optimized protocol, the synthesis of a small collection of secondary and tertiary alcohols was also undertaken. (4-Chlorophenyl)magnesium bromide was chosen as reference Grignard reagent and the optimized conditions were applied to different substrates on a 200 mg scale (Table 3).

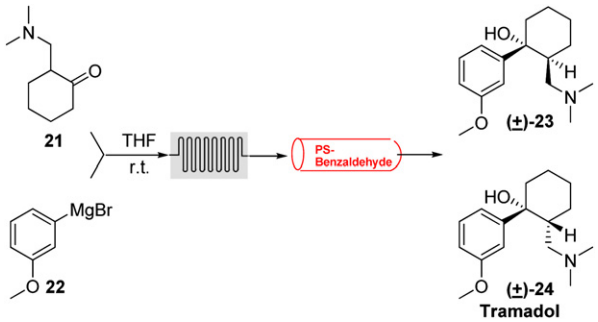
The formation of alcohols from aldehydes and ketones was general and occurred smoothly in the continuous flow system. Simple aryl carbonyl compounds, besides reference substrates, (entries 1 and 6), heteroaryl aldehydes and ketones (entries 2–5) and alkyl compounds (entries 7 and 8) were suitable substrates for the reaction. All of the desired products were obtained in yields higher than 90%, with no detection of by-products.

The protocol was finally applied to the synthesis of Tramadol[13] **24**, a well known centrally active analgesic used for treating moderate to severe pain (Scheme 2).[14] This drug is commercialized as racemic mixture and the final step of the published synthesis consists in the addition of (3-methoxyphenyl)magnesium bromide **22** to racemic 2-((dimethylamino) methyl)-cyclohexanone **21**.[14]

Table 3
Reaction of different aldehydes and ketones with (4-chlorophenyl)magnesium bromide

Entry	Carbonyl compound	Alcohol	Yield[a] (%)
1	 **5**	 **6**	90
2	 **7**	 **8**	94
3	 **9**	 **10**	92
4	 **11**	 **12**	96
5	 **13**	 **14**	96
6	 **15**	 **16**	95
7	 **17**	 **18**	98
8	 **19**	 **20**	93

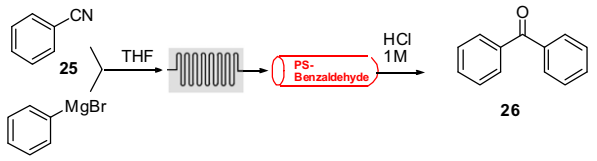
[a] Isolated yields; purity >95% (UPLC/MS).



Scheme 2. Flow synthesis of Tramadol.

The reaction affords a diastereomeric mixture with a 8/2 ratio between **24** and **23**.[15] The desired product **24** is obtained after crystallization of the corresponding hydrochloride salt.[16] The flow synthesis of Tramadol is unprecedented.[4b] In our study the suitable intermediates were reacted in the flow system using the described optimized protocol to obtain, after chromatographic purification, the diastereomeric mixture in 96% yield, with a significant improvement respect to the data reported in the literature (Scheme 2).[14b] The 8/2 ratio of the two diastereoisomers was confirmed by UPLC/MS and by NMR analyses. Tramadol **24** was converted into its hydrochloride salt and purified by crystallization as reported.[16]

The possibility to perform selective addition of Grignard reagent to bifunctional compound was then taken into account. In particular the discrimination of aldehydes and ketones respect to nitriles was investigated. At first, the reactivity of nitriles under the flow conditions was explored. The addition of phenylmagnesium bromide to benzonitrile was performed, and the obtained product was quenched in 1 M HCl in order to afford benzophenone (Scheme 3).



Entry	Grignard (eq)	T (°C)	residence time (min)	flow rate (ml/min)	yield (%)
1	1.2	r.t	33	0.30	59[a]
2	1.2	50°C	33	0.30	90
3	1.2	r.t	66[b]	0.30	91

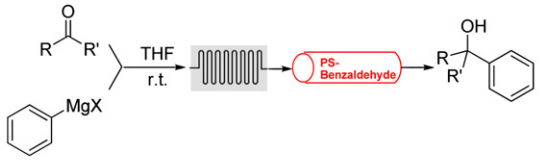
[a] Conversion determined by peak integration at 215 nm (UPLC/MS)
[b] Reaction performed using 20 ml tubing reactor.

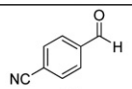
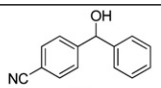
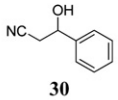
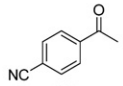
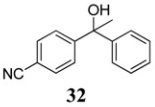
Scheme 3. Conversion of benzonitrile into benzophenone.

Using the previously optimized conditions (1.2 equiv, RT, 33 min) the conversion was not complete and around 40% of the starting material remained unreacted (entry 1). In order to drive the reaction to completion, the temperature was raised to 50 °C (entry 2), alternatively the residence time had to be doubled (entry 3).

This interesting result let us to envisage the possibility to react aldehydes or ketone in the presence of nitriles (Scheme 4).

The reaction was performed on aryl and alkyl aldehydes (entries 1 and 2) and on one aryl ketone (entry 3) flowing the starting



Entry	carbonyl compound	Alcohol	yield (%)
1	 **27**	 **28**	94
2	 **29**	 **30**	85
3	 **31**	 **32**	89

Scheme 4. Flow addition of benzyl magnesium bromide to aldehydes and ketone in the presence of nitriles.

materials for 10 min at RT in presence of 1 equiv of Grignard reagent. We observed the selective addition of Grignard reagent to the carbonyl moiety and no product of double addition or deriving from the Grignard reaction on the nitrile group was detected. After purification, all of the products were recovered in very good yields with a significant simplification in their synthesis respect to the known methods.[17]

The reaction of phenylmagnesium bromide with 3-oxopropanenitrile (entry 2) is particularly interesting. In fact this example offers an alternative approach to the synthesis of β-hydroxy nitriles, which are commonly prepared by ring opening of epoxides with sodium cyanide,[18] by reaction of cyano-methyllithium with the suitable aldehyde,[19] or by cyanomethylation of carbonyl compounds with trimethylsilyil acetonitrile.[20]

3. Conclusion

In conclusion, a protocol for performing the addition of Grignard reagents to carbonyl compounds in a continuous flow apparatus was set-up. The reaction required very mild conditions avoiding cryogenic temperatures. Other major advantages were the high yields and the easy scale up. Our results confirm the general applicability of the flow protocol and gain a specific interest if we consider the possibility of synthesizing large amounts of addition products by reacting small amounts of potentially dangerous Grignard reagents at a time. The methodology was successfully applied for the preparation of a small collection of secondary and tertiary alcohols using different carbonyl compounds and for the synthesis of the analgesic Tramadol. The possibility of discriminating the carbonyl moiety respect to cyano group was demonstrated offering a new methodology for the preparation of β-hydroxy nitriles. Further investigation to broaden the use of Grignard reagents on bifunctional compound is in progress.

4. Experimental

4.1. General

^{1}H NMR spectra were recorded at temperature of 303 K, on a spectrometer at 300.13 MHz. The instrument is equipped with multinuclear inverse probe and temperature controller. Chemical shifts are expressed in ppm, utilizing the solvent peaks as the reference and the coupling constants (*J*) in Hertz. ^{13}C NMR spectra were recorded on the same instrument at 75.47 MHz. LC/MS analyses were performed using an UPLC/MS instrument (column: Acquity BEH C18 2.1×50 mm 1.7 μm 35 °C flow 0.6 mL/min). High resolution electrospray mass spectra (HRESI-MS) were acquired with an FT-ICR (Fourier Transfer Ion Cyclotron Resonance) instrument equipped with a 4.7 Tesla cryo-magnet. Samples were dissolved in CH_3CN and injected into the instrument equipped with its own ESI source. Spectra were recorded in the HR mode with resolutions ranging from 20,000 to 30,000. Anhydrous tetrahydrofuran was purified by MB SPS Solvent Purification System (MBraun). Unless otherwise specified, solutions of common inorganic salts used in workups are aqueous solutions. Common solvents are abbreviated as follows: DCM, dichloromethane; DMSO, dimethyl sulfoxide; THF, tetrahydrofuran; AcOEt, ethyl acetate. Poly(tetrafluoroethylene) is abbreviated in PTFE. Flow reactions were performed using a combination of R-2 Pump Module and R-4 Reactor Module (Vapourtec®),[11] equipped with PTFE tubing (diameter 1 mm, reactor volume 10 mL). The mixing of the solutions was achieved through a standard T-junction piece (for THF solutions, a laminar flow post T-piece is ensured by the manufacturer for flow-rates ranging from 0.1 to 5 mL/min).

4.2. General procedure for the synthesis of secondary and tertiary alcohols

4.2.1. General optimized reaction procedure. Two solutions of starting materials were prepared and stored at room temperature under N_2 atmosphere: Reagent stock bottle A: suitable aldehyde or ketone; 200 mg (1 equiv) dissolved in dry THF in order to obtain a 0.25 M solution. Reagent stock bottle B: suitable Grignard reagent (THF or diethyl ether solution; 1.2 equiv); dissolved in dry THF obtaining a THF 0.3 M solution. The system was primed by flowing dry THF for 30 min. Using the automated injection system, the solutions were transferred at a constant flow rate (0.3 ml/min) into a PTFE tubing reactor (reactor volume 10 ml) maintained at room temperature (residence time 33 min). The reactor was connected to an Omnifit® glass column (6.6 mm id) packed with PS-Benzaldehyde (loading 1.09 mmol/g; 1 equiv or 0.5 equiv for gram scale reactions) to trap Grignard reagent in excess. After this purification step, the product was collected in an apposite product stock bottle. The solvent was evaporated under vacuum and the crude was partitioned between saturated solution of NH_4Cl and DCM. The organic phase was dried and evaporated and the product was purified by the suitable reported method. For known products analytical characterization (LC/MS, ^{1}H and ^{13}C NMR) was in agreement with what reported in the cited literature.

*4.2.2. 1-(4-Isopropylphenyl)-3-methylbut-3-en-1-ol (**2a**).* Starting material: 4-isopropylbenzaldehyde (**1**); 92% Yield; Colourless oil; Purification: flash chromatography (eluent: Petroleum ether/AcOEt 9/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.33 (2H, m) 7.23 (2H, m) 4.86–4.98 (2H, m) 4.76–4.85 (1H, m) 2.93 (1H, spt, *J* 7.0 Hz,) 2.39–2.53 (2H, m) 1.83 (3H, s) 1.27 (6H, d, *J* 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 148.2, 142.6, 141.5, 126.5 (2C), 125.8 (2C), 113.8, 71.4, 48.2, 33.8, 24.0 (2C), 22.4; HRMS (ESI): calcd for $C_{14}H_{20}O_1Na_1$ (+1): 227.14064; found: 227.14070.

*4.2.3. (4-Chlorophenyl)(4-isopropylphenyl)methanol (**2b**).* Starting material: 4-isopropylbenzaldehyde (**1**); 93% Yield; Off-white solid; Purification: flash chromatography (eluent: Petroleum ether/AcOEt 9.5/0.5). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.13–7.44 (8H, m) 5.80 (1H, s) 2.92 (1H, spt, *J* 6.9 Hz,) 2.29 (1H, br s) 1.27 (6H, d, *J* 6.9 Hz,); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 148.6, 142.4, 140.9, 133.2, 128.5 (2C), 127.8 (2C), 126.7 (2C), 126.6 (2C), 75.5, 33.8, 23.9 (2C); HRMS (ESI): calcd for $C_{16}H_{17}ClO_1Na_1$(+1): 283.08601; found: 283.08603.

*4.2.4. 1-(4-Isopropylphenyl)-2,2-dimethylpropan-1-ol (**2c**).* Starting material: 4-isopropylbenzaldehyde (**1**); 87% Yield; Colourless oil; Purification: flash chromatography (eluent: Petroleum ether/AcOEt 9.8/0.2). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.25 (2H, m) 7.19 (2H, m) 4.40 (1H, s) 2.92 (1H, spt, *J* 6.9 Hz) 1.61 (1H, br s) 1.27 (6H, d, *J* 6.9 Hz) 0.95 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 139.4, 136.3, 127.5 (2C), 125.6 (2C), 82.3, 35.6, 33.7, 25.9 (3C), 24.0 (2C); HRMS (ESI): calcd for $C_{14}H_{22}O_1Na_1$(+1): 229.15629; found: 229.15631.

4.2.5. 4-Methyl-2-phenylpent-4-en-2-ol[21] *(**4a**).* Starting material: acetophenone (**3**); 94% Yield; Colourless oil; Purification: flash chromatography (eluent: Petroleum ether/AcOEt 9.8/0.2).

4.2.6. 1-(4-Chlorophenyl)-1-phenylethanol[22] *(**4b**).* Starting material: acetophenone (**3**); 95% Yield; Colourless oil; Purification: flash chromatography (eluent: Petroleum ether/AcOEt 9.8/0.2).

4.2.7. 3,3-Dimethyl-2-phenylbutan-2-ol[23] *(**4c**).* Starting material: acetophenone (**3**); 90% Yield; Colourless oil; Purification: flash chromatography (eluent: Petroleum ether/AcOEt 9.8/0.2).

4.2.8. 2-Phenylpropan-2-ol[24] ***(4d)***. Starting material: acetophenone (**3**); 95% Yield; Colourless oil; Purification: flash chromatography (eluent: Petroleum ether/AcOEt 9.9/0.1).

4.2.9. (4-Chlorophenyl)(phenyl)methanol[25] ***(6)***. Starting material: benzaldehyde (**5**); 97% Yield; Colourless oil; Purification: flash chromatography (eluent: Petroleum ether/AcOEt 9.7/0.3).

4.2.10. (4-Chlorophenyl)(pyridin-2-yl)methanol[26] ***(8)***. Starting material: picolinaldehyde (**7**); 94% Yield; Colourless oil; Purification: silica cartridge (eluent: from 100% CH_2Cl_2 to CH_2Cl_2/MeOH 95/5).

4.2.11. 1-(4-Chlorophenyl)-1-(pyridin-2-yl)ethanol[27]***(10)***. Starting material: 1-(pyridin-2-yl)ethanone (**9**); 92% Yield; Colourless oil; Purification: flash chromatography (eluent: Petroleum ether/AcOEt 9.5/0.5).

4.2.12. (4-Chlorophenyl)(furan-2-yl)methanol ***(12)***. Starting material: furan-2-carbaldehyde (**11**); 96% Yield; Brown oil; Purification: flash chromatography (eluent: Petroleum ether/AcOEt 9.8/0.2). ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 7.56 (1H, dd, *J* 1.8, 0.8 Hz,) 7.34–7.50 (4H, m) 6.37 (1H, dd, *J* 3.2, 1.8 Hz,) 6.17 (1H, ddd, *J* 3.2, 0.8, 0.8 Hz,) 6.08 (1H, d, *J* 4.3 Hz,) 5.73 (1H, d, *J* 4.3 Hz,); ^{13}C NMR (75 MHz, DMSO-d_6) δ ppm 157.3, 142.8, 142.1, 132.2, 128.8 (2C), 128.5 (2C), 110.7, 107.0, 68.1; HRMS (ESI): calcd for $C_{11}H_9ClO_2Na_1(+1)$: 231.01833; found: 231.01837.

4.2.13. 1-(4-Chlorophenyl)-1-(furan-2-yl)ethanol[28] ***(14)***. Starting material: 1-(furan-2-yl)ethanone (**13**); 90% Yield; Yellow oil; Purification: flash chromatography (eluent: Petroleum ether/AcOEt 9.7/0.3).

4.2.14. 1-(4-Chlorophenyl)-3-methyl-1-phenylbutan-1-ol ***(16)***. Starting material: 3-methyl-1-phenylbutan-1-one (**15**); 95% Yield; Colourless oil; Purification: flash chromatography (eluent: Petroleum ether/AcOEt 9.8/0.2). ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 7.39–7.50 (4H, m), 7.28–7.35 (2H, m), 7.23–7.28 (2H, m), 7.09–7.20 (1H, m), 5.50 (1H, s), 2.17 (2H, d, *J* 5.7 Hz,), 1.63 (1H m), 0.77 (3H, d, *J* 6.7 Hz,), 0.76 (3H, d, *J* 6.7 Hz,); ^{13}C NMR (75 MHz, DMSO-d_6) δ ppm 149.0, 148.5, 131.0, 128.3 (2C), 128.2 (2C), 128.0 (2C), 126.5, 126.2 (2C), 76.9, 49.6, 24.9 (2C), 24.2; HRMS (ESI): calcd for $C_{17}H_{19}ClO_1Na_1(+1)$: 297.10166; found: 297.10168.

4.2.15. 1-(4-Chlorophenyl)cyclohexanol ***(18)***. Starting material: cyclohexanone (**17**); 98% Yield; Off-white solid; Purification: flash chromatography (eluent: Petroleum ether/AcOEt 9.5/0.5). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.45 (2H, m) 7.31 (2H, m) 1.53–1.90 (10H, m) 1.18–1.43 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 148.0, 132.4, 128.2 (2C), 126.2 (2C), 72.9, 38.8 (2C), 25.4, 22.1 (2C); HRMS (ESI): calcd for $C_{12}H_{15}ClO_1Na_1(+1)$: 233.07036; found: 233.07040.

4.2.16. (1-Benzylpiperidin-4-yl)(4-hlorophenyl)methanol ***(20)***. Starting material: 1-benzylpiperidine-4-carbaldehyde (**19**); 90% Yield; Colourless oil; Purification: flash chromatography (eluent: Petroleum ether/AcOEt 9.7/0.3). ^{1}H NMR (300 MHz, DMSO-d_6) ppm δ 7.17–7.42 (9H, m), 5.19 (1H, d, *J* 4.3 Hz,), 4.28 (1H, dd, *J* 6.5, 4.3 Hz,), 3.39 (2H, s), 2.66–2.90 (2H, m), 1.61–1.95 (3H, m), 1.33–1.52 (1H, m) 1.07–1.33 (3H, m); ^{13}C NMR (75 MHz, DMSO-d_6) δ ppm 144.2, 139.2, 131.5, 129.1 (2C), 128.8 (2C), 128.5 (2C), 128.1 (2C), 127.2, 76.2, 62.9, 53.7, 53.6, 43.6, 28.6, 28.2; HRMS (ESI): calcd for $C_{19}H_{22}ClONa(+1)$: 338.12821; found: 338.12824.

4.3. General procedure for the synthesis of Tramadol (24)

4.3.1. Reaction procedure. Two solutions of starting materials were prepared and stored at room temperature under N_2 atmosphere: Reagent stock bottle A: 2–dimethylaminomethylcyclohexanone[16] (200 mg; 1.29 mmol) dissolved in 5.2 ml of dry THF. Reagent stock bottle B: 3-methoxyphenylmagnesium bromide (THF solution 1 M; 1.55 mmol; 1.55 ml) dissolved in 3.6 ml of dry THF. The system was primed by flowing dry THF for 30 min. Using the automated injection system, the solutions were transferred at a constant flow rate (0.30 ml/min) into a PTFE tubing reactor (reactor volume 10 ml) maintained at room temperature (residence time 33 min). The reactor was connected to an Omnifit® glass column (6.6 mm id) packed with PS-Benzaldehyde (loading 1.09 mmol/g; 1.18 g) to trap Grignard reagent in excess. After this purification step, the product was collected in an apposite product stock bottle. The solvent was evaporated under vacuum and the crude was partitioned between saturated solution of NH_4Cl and DCM. The organic phase was dried and evaporated and the product was purified by flash chromatography in order to isolate the product as a diastereoisomeric mixture (96% yield; 8/2 ratio between **24** and **23**). Water was added and the product was extracted with ethyl ether. The extracts were dried over sodium sulfate, filtered and evaporated in vacuum. The residue was treated ethyl ether saturated with hydrogen chloride; the ethyl ether was evaporated in vacuo and the resulting solid was purified by crystallization from acetone. Tramadol (**24**) hydrochloride was obtained as white crystals. Analytical characterization (LC/MS, ^{1}H and ^{13}C NMR) was in agreement with that reported in the cited literature.[14,16]

4.4. Procedure for the synthesis of 4-benzoylbenzonitrile (26)

4.4.1. Reaction procedure 1. Two solutions of starting materials were prepared and stored at room temperature under N_2 atmosphere. Reagent stock bottle A: benzonitrile (**25**) (200 mg; 1.94 mmol) dissolved in 7.8 ml of dry THF. Reagent stock bottle B: phenylmagnesium bromide (diethyl ether solution 1 M; 2.33 mmol, 2.33 ml) dissolved in 5.5 ml of dry THF. The system was primed flowing dry THF for 30 min. Using the automated injection system, both solutions were transferred at a constant flow rate (0.30 ml/min) into a preheated PTFE tubing reactor (reactor volume 10 ml) maintained at 50 °C (residence time 33 min). The reactor was connected to an Omnifit® glass column (6.6 mm id) packed with PS-Benzaldehyde (loading 1.09 mmol/g; 1.78 g) to trap Grignard reagent in excess. After this purification step, the product was directly collected in an apposite product stock bottle containing 1 M aqueous HCl. The aqueous phase was extracted by AcOEt and the organic layer was dried over Na_2SO_4 and evaporated. The crude was purified by flash chromatography (eluent: Petroleum ether/AcOEt 9.5/0.5) to obtain 378.3 mg of desired compound as off-white powder. 90% Yield.

4.4.2. Reaction procedure 2. Two solutions of starting materials were prepared and stored at room temperature under N_2 atmosphere. Reagent stock bottle A: benzonitrile (**25**) (200 mg; 1.94 mmol) dissolved in 7.8 ml of dry THF. Reagent stock bottle B: phenylmagnesium bromide (diethyl ether solution 1 M; 2.33 mmol, 2.33 ml) dissolved in 5.5 ml of dry THF. The system was primed flowing dry THF for 30 min. Using the automated injection system, the solutions were transferred at a constant flow rate (0.30 ml/min) into a PTFE tubing reactor (reactor volume 20 ml) maintained at room temperature (residence time 66 min). The reactor was connected to an Omnifit® glass column (6.6 mm id) packed with PS-Benzaldehyde (loading 1.09 mmol/g; 1.78 g) to trap Grignard reagent in excess. After this purification step, the product was directly collected in an apposite product stock bottle containing 1 M aqueous HCl. The aqueous phase was extracted by AcOEt and the organic layer was dried over Na_2SO_4 and evaporated. The crude was purified by flash chromatography (eluent: Petroleum

ether/AcOEt 9.5/0.5) to obtain 382.1 mg of desired compound as off-white powder. 91% Yield.

4.5. General procedure for the flow addition of benzyl magnesium bromide to aldehydes and ketone in the presence of nitrile

Two solutions of starting materials were prepared and stored at room temperature under N_2 atmosphere. Reagent stock bottle A: suitable aldehyde or ketone (1 equiv); 200 mg dissolved in dry THF in order to obtain a 0.25 M solution. Reagent stock bottle B: phenylmagnesium bromide (THF solution; 1 equiv); dissolved in dry THF in order to obtain a 0.25 M solution. The system was primed flowing dry THF for 30 min. Using the automated injection system, both solutions were transferred at a constant flow rate (0.8 ml/min) into a PTFE tubing reactor (reactor volume 10 ml) maintained at room temperature (residence time 12.5 min). The reactor was connected to a Omnifit® glass column (6.6 mm id) packed with PS-Benzaldehyde (loading 1.09 mmol/g; 1 equiv) to trap unreacted Grignard reagent. After this purification step, the product was collected in an apposite product stock bottle. The solvent was evaporated under vacuum and the crude was partitioned between saturated solution of NH_4Cl and DCM. The organic phase was dried and evaporated and the product was purified by the product was purified by the suitable reported method.

4.5.1. 4-(Hydroxy(phenyl)methyl)benzonitrile[17f] *(**28**).* Starting material: 4-formylbenzonitrile (**27**); 94% Yield; Off-white solid; Purification: flash chromatography (Eluent: Petroleum ether/AcOEt 9.8/0.2).

4.5.2. 3-Hydroxy-3-phenylpropanenitrile[18b] *(**30**).* Starting material: 3-oxopropanenitrile (**29**); 85% Yield; Colourless oil; Purification: flash chromatography (Eluent: Petroleum ether/AcOEt 9.9/0.1).

4.5.3. 4-(1-Hydroxy-1-phenylethyl)benzonitrile[29] *(**32**).* Starting material: 4-acetylbenzonitrile (**31**); 89% Yield; Off-white solid; Purification: flash chromatography (Eluent: Petroleum ether/AcOEt 9.5/0.5).

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