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A general, versatile and divergent synthesis of selectively deuterated amines†

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Deuterated organic molecules are of utmost importance in many areas of science and have been recently intensively investigated in medicinal chemistry due to their enhanced metabolic stability. The development of efficient and broadly applicable methods for the selective incorporation of deuterium atoms into organic molecules from readily available starting materials and reagents is therefore of extreme importance. Such methods however often lack generality and selectivity, notably in the nitrogen series. With nitrogen-containing molecules being indeed ubiquitous in medicinal chemistry, there is a strong need for efficient methods enabling the selective synthesis of deuterated amines. In this perspective, we report herein a general, versatile, divergent and metal-free synthesis of amines selectively deuterated at their α and/or β positions. Upon simple treatment of readily available ynamides with a mixture of triflic acid and triethylsilane, either deuterated or not, a range of amines can be smoothly obtained with high levels of deuterium incorporation by a unique sequence involving a domino keteniminium/iminium activation.

Introduction

Since its discovery in 1931 by Harold C. Urey,¹ deuterium D, or ²H, one of the three isotopes of hydrogen together with protium ¹H and tritium T, or ³H, having a natural abundance of 0.015%, has found many applications in various areas of science, notably when incorporated into organic molecules.² While a carbon–deuterium bond indeed closely resembles a carbon–hydrogen³ one, the main difference lies in the higher stability of the former compared to the latter due to a smaller vibrational frequency and hence a lower zero-point energy. This subtle difference has a dramatic effect when replacing a hydrogen atom by a deuterium in a carbon chain.² Deuterated organic molecules, in addition to their use as internal standards for mass spectrometry or NMR spectroscopy, have been indeed utilized to measure minute amounts of a specific chemical in the environment or in the body by means of the stable isotope dilution technique,^{2,4} to study reaction mechanisms as well as their kinetics – the use of deuterium as a tracer and kinetic isotope effects being especially useful in this area –^{2,5} for the elucidation of biosynthetic pathways,⁶ to alter the selectivity of some reactions^{2,7} and even to improve the properties of polymers⁸ and chemical stability of materials such as OLEDs.⁹

In addition to their use in metabolism and toxicology studies,¹⁰ the increased stability of deuterated molecules has moreover been extensively studied recently in medicinal chemistry, notably to increase the metabolic stability of some drugs and/or to avoid the formation of toxic metabolites.¹¹ Representative examples of such a strategy include deuterated Efavirenz **1_d**, an isotopologue of Bristol-Myers Squibb's Efavirenz utilized for the treatment of AIDS, in which the incorporation of a deuterium atom at the propargylic position inhibits its enzymatic oxidation, resulting in the formation of nephrotoxic metabolites (Fig. 1),¹² or deuterated Telaprevir **2_d**, a deuterated analogue of Johnson&Johnson/Vertex Pharmaceuticals' drug for the treatment of hepatitis C with improved stability due to a reduced epimerization rate.¹³ While the deuteration of drugs has been mostly studied in academia for years and was clearly recognized as a subtle, yet powerful, medicinal chemistry tool to retain potency and selectivity together with improving the overall pharmacological profile of a drug, several companies have started to focus on this area.^{11,14} It can indeed breathe new life into old drugs, with Teva's Austedo® (deutetrabenazine) **3_{d6}**, the first FDA-approved deuterated drug displaying a better safety profile than its non-deuterated analogue (tetrabenazine, readily demethylated by cytochrome CYP2D6 to less active metabolites **4** and **4'**) and commercialized since 2017 for the treatment of chorea associated with Huntington's disease, being certainly the most striking example.¹⁵ Other deuterated drugs in the pipeline include Avanir's AVP-786 (hexadeuterated dextromorphan **5_{d6}**) in phase III clinical trials for the treatment of agitation in Alzheimer's disease patients¹⁶ and phase II trials in major depressive disorder and schizophrenia,¹⁷ Vertex's VX-

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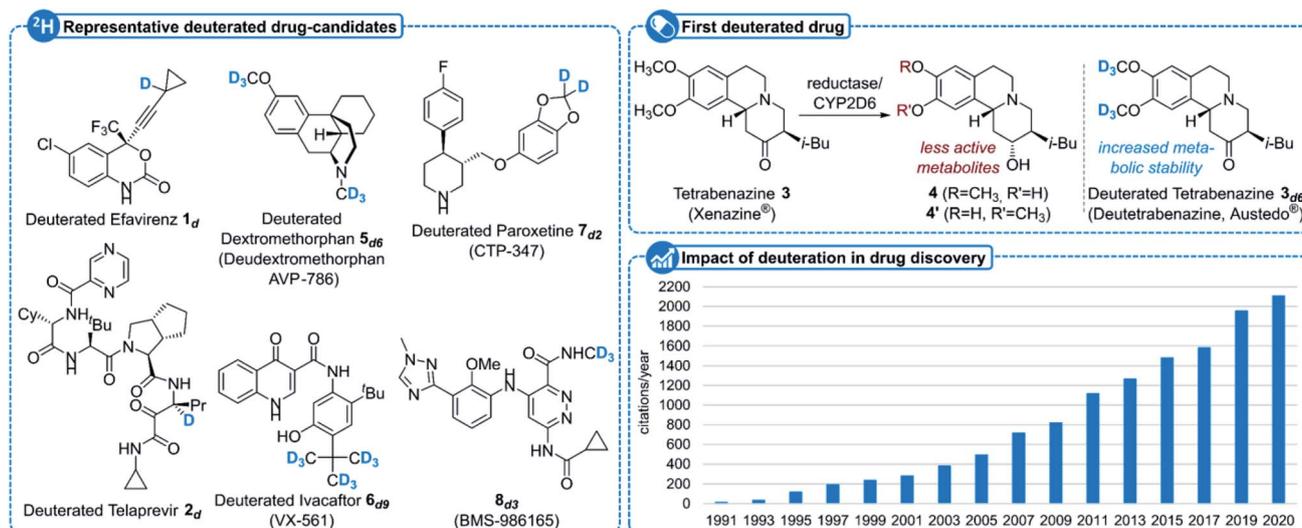


Fig. 1 Impact of deuterated molecules in drug discovery.

561 **6_{d9}**, a deuterated form of ivacaftor in phase II trials for cystic fibrosis,¹⁸ or Concert's deuterated Paroxetine CTP-347 **7_{d2}** in phase II clinical trials for non-hormonal treatment of vasomotor symptoms. In addition to bringing new life to old drugs, deuteration is now starting to be envisioned from the early stages of drug development as exemplified with Bristol-Myers Squibb's *de novo* deuterated BMS-986165 **8_{d3}** developed for the treatment of psoriasis which recently succeeded in phase II trials.¹⁹ Many more deuterated small molecule drug candidates are currently in the pipeline²⁰ and a growing number of companies are now actively pursuing the deuterated drug market which was recently estimated to represent a total value of transaction of \$5 billion.^{11k}

These recent tremendous developments obviously strongly depend on the synthesis of deuterated molecules. An analysis of the processes developed for the synthesis of all deuterated drugs/drug candidates reported to date actually reveals that they mostly rely on commercially available, simple deuterated precursors such as D₂O, CD₃I, CD₃OD, DCO₂D, CD₂O, CD₃S(O)CD₃ or CD₃NH₂ which are incorporated into organic molecules using standard and classical techniques.²¹ Further developments in this area will clearly require the use of more advanced processes either based on the use of a broader variety of deuterated reagents or for the selective introduction of deuterium atoms. A parallel can actually be drawn with fluorinated drugs: since the first approval by the FDA of such a drug, fludrocortisone, in 1955, nearly 150 fluorinated molecules have succeeded in reaching the market and a recent analysis estimates that about 30% of drugs will soon contain at least one fluorine atom,²² this dramatic increase being mainly associated with the design of novel methods for the synthesis of fluorinated organic molecules. With deuterium being considered as the potential "next fluorine" in medicinal chemistry, a strong need for new processes streamlining the synthesis of deuterated molecules is logically emerging, such methods being expected to have an important impact in drug discovery.

Among all deuterated functional groups, amines occupy a central place due to the vast majority of drugs containing at least one nitrogen atom and due to their easy metabolism. The selective introduction of deuterium atoms close to the nitrogen in amines could indeed represent a quite subtle strategy to increase the stability of nitrogen-containing drug candidates while bringing minor structural changes, a concept already validated with AVP-786 **5_{d6}**^{16,17} and BMS-986165 **8_{d3}**.¹⁹ The state-of-the-art methods available for the synthesis of deuterated amines actually reveal the limited number of possibilities as well as an important number of limitations. Incorporation of deuterium α to the nitrogen atom indeed mostly relies on the alkylation of amines or surrogates with deuterated alkyl halides or synthetic equivalents and on the reduction of nitriles, imines and amides with LiAlD₄, a reagent whose commercial availability greatly varies over time. Limitations met with these classical methods, mostly in terms of efficiency, generality and functional group tolerance, have stimulated the development of alternative processes relying on the use of readily available deuterated reducing agents such as PhSiD₃ in the presence of a nickel catalyst²³ or on the use of D₂O or EtOD under reductive conditions.²⁴ Other methods recently reported are essentially based on the use of metal catalysts²⁵ or on a cooperative acid/base catalytic system²⁶ for the direct deuteration of amines α and/or β to the nitrogen atom. While these methods are clearly attractive since they enable the synthesis of α - or α,β -deuterated amines from the corresponding non-deuterated ones using readily available sources of deuterium such as D₂O, D₂, CD₃S(O)CD₃, CD₃COCD₃ or deuterated alcohols and can be performed in a stereospecific manner with some chiral amines, they however suffer from important limitations in terms of substrate scope, regioselectivity and, more importantly, with respect to deuterium incorporation, which is far from quantitative in most cases.

Based on our long-standing interest in the chemistry of ynamides,²⁷ stable nitrogen-substituted alkynes,²⁸ and in the



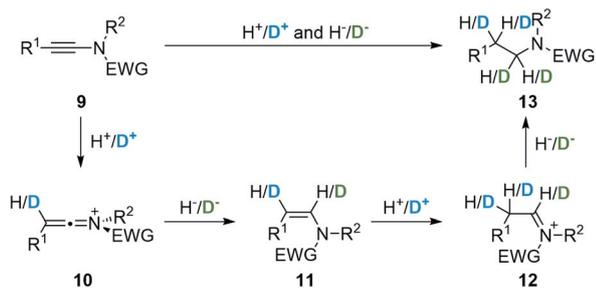


Fig. 2 Working hypothesis for the divergent and selective synthesis of deuterated amines.

unique reactivity of activated keteniminium ions²⁹ derived from these reagents, we envisioned that these building blocks – that are either commercially available or readily prepared by a range of methods³⁰ – and intermediates might provide a straightforward, versatile and divergent entry to α - and/or β -deuterated amines, which should overcome most of the limitations met with other methods. Our strategy, depicted in Fig. 2, is based on a simple, yet unexplored, and unique keteniminium/iminium activation sequence: upon reaction with an acid (deuterated or not), the starting ynamide **9** would afford a transient activated keteniminium ion **10** whose trapping with a hydride or a deuteride would yield an intermediate enamide **11**. Further reaction of this enamide with an acid would then enable the generation of an iminium ion **12** whose final reduction should provide the desired amine **13**.^{31,32} Depending on the nature of the acid and the hydride (either deuterated or not), this reaction should enable an easy and divergent access to a range of amines with selective deuteration at the α - and/or β -positions. We report in this manuscript the development of a broadly applicable versatile, and divergent synthesis of selectively deuterated amines based on this working hypothesis.

Results and discussion

Optimization of the reduction of ynamides to amines

We initiated our studies by assessing the feasibility of our working hypothesis and the identification of the optimal conditions for the reduction of ynamides to amines first using non-deuterated reagents. The main problems associated with our strategy lie in the fact that the acid and the hydride should both react faster with all intermediates than together and that the conjugated base of the acid should not competitively trap the activated keteniminium **10** and iminium **12** ions.

With this goal in mind, a series of acids and hydrides, known to be compatible and typically used in ionic reductions and deoxygenations, was first evaluated using at this stage an excess of these reagents, with ynamide **9a** as a model substrate in dichloromethane at 0 °C for 15 minutes. Results from these studies, shown in Fig. 3, reveal the feasibility of our approach as well as the superiority of triflic acid for the activation of both the starting ynamide **9a** and the transient enamide **11a**. Among the hydrides evaluated,³³ triethylsilane was found to be the most efficient one: indeed, a combination of triflic acid and

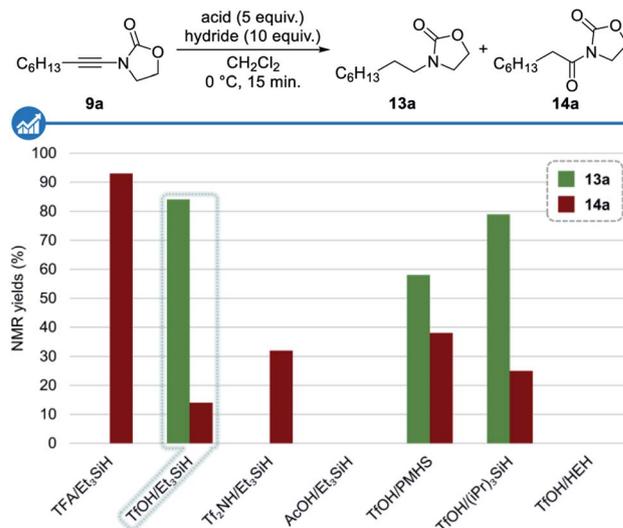


Fig. 3 Screening of acids and hydrides for the reduction of ynamides to amines. ¹H NMR yields determined with 1,1,2,2-tetrachloroethane as the internal standard; HEH: Hantzsh ester, 4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate.

triethylsilane resulted in the formation of the desired amine **13a** (84% ¹H NMR yield) together with amide **14a** (14% ¹H NMR yield) resulting from the trapping of the intermediate keteniminium ion **10a** by the triflate anion followed by further hydrolysis upon workup.^{28c} Having demonstrated the feasibility of our approach and identified the best combination of the acid and reducing agent, we next focused our attention on reducing the amount of both these reagents, a critical point in the deuterated series. A brief screening of different stoichiometries, temperatures and reaction times (not shown) revealed that the use of 2.5 equivalents of triflic acid in combination with 5 equivalents of triethylsilane at room temperature for 18 hours was optimal, resulting in the formation of the reduced product **13a** in 84% ¹H NMR yield and 72% isolated yield.

With these optimized conditions in hand, we then evaluated their extension to the deuterated series: as shown in Fig. 4, the use of deuterated triethylsilane, deuterated triflic acid, or both,

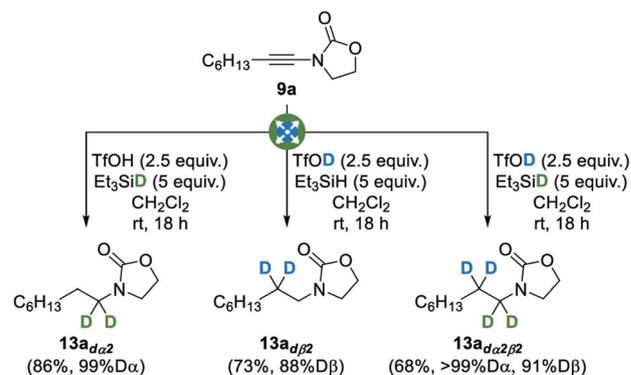


Fig. 4 Divergent and selective deuterative reduction of ynamides to amines.



resulted in a smooth reduction to the corresponding α -, β - or α,β -deuterated products **13a_{d α 2}**, **13a_{d β 2}** and **13a_{d $\alpha\beta$ 2}**, in good yields, excellent and good levels of deuteration at the α and β positions being respectively attained. Importantly, a complete regioselectivity was observed in these three trials, which is in sharp contrast with previously reported techniques.

Scope of the divergent synthesis of deuterated amines

We then moved to the study of the scope and limitations of this divergent synthesis of selectively deuterated amines, first focusing on α -deuterated ones **13_{d α 2}** resulting from the reduction of the corresponding ynamides **9** with deuterium-labelled triethylsilane (Fig. 5). A set of ynamides **9** with representative substitution patterns was therefore reacted under our optimized conditions: in all cases, the reduction was shown to be fully regioselective, with deuterium being selectively incorporated at the α position only, and remarkably high levels of deuteration (96 to >99% D) were systematically attained. The α -deuterated amines **13_{d α 2}** could be obtained in fair to good yields, with the major byproducts that could be detected and easily separated being the amides resulting from a competing trapping of the transient activated keteniminium ions by the triflate followed by hydrolysis of the resulting ketene *N,O*-acetals.^{28c} Oxazolidinone- and pyrrolidinone-derived ynamides were found to be suitable substrates, providing the corresponding deuterated *N*-alkyl oxazolidinones **13a–c_{d α 2}** and lactam **13d_{d α 2}**, respectively. Interestingly, *N*-tosyl-ynamides were also found to smoothly undergo the reductive deuteration to afford the corresponding

deprotectable *N*-tosyl-amines **13e–m_{d α 2}** in modest to good yields. As for the substitution pattern and electronic properties of the starting ynamides, both aryl (**13b–d_{d α 2}**, **13f–h_{d α 2}** and **13l,m_{d α 2}**) and alkyl (**13a_{d α 2}**, **13e_{d α 2}** and **13i_{d α 2}**) groups were found to be tolerated and even terminal and trifluoromethyl-substituted ynamides could be transformed into the corresponding selectively α -deuterated amines **13j_{d α 2}** and **13k_{d α 2}**, respectively, although with reduced efficiency yet excellent levels of deuteration. Interestingly, and which nicely highlights the efficacy and selectivity of our method, an alkyne (**13c_{d α 2}**) was found to be compatible with the reaction conditions and no competing reduction was observed in this case. As for the substituent on the nitrogen atom in the starting ynamides **9**, cleavable benzyl (**13e–k_{d α 2}**) and allyl (**13l_{d α 2}**) groups were tolerated and no products resulting from a competing Pictet–Spengler-type trapping of the transient keteniminium ions by the benzyl group, a reaction that is known to be fast and that would afford isoindolines,³⁴ were observed. Finally, even an acid-sensitive cyclopropyl group (**13m_{d α 2}**) was found to survive the reductive deuteration without competing ring-opening.

Having demonstrated the broad scope and the generality of our reductive deuteration for the synthesis of a range of amines selectively deuterated at the α position, we next moved to the study of the synthesis of their analogues selectively deuterated at the β position **13_{d β 2}**. The exact same set of ynamides **9** was therefore reacted under our optimized conditions but now using deuterated triflic acid instead of deuterated triethylsilane (Fig. 6). This simple switch in reagents enabled the synthesis of a variety of β -deuterated amines **13_{d β 2}** that could be obtained

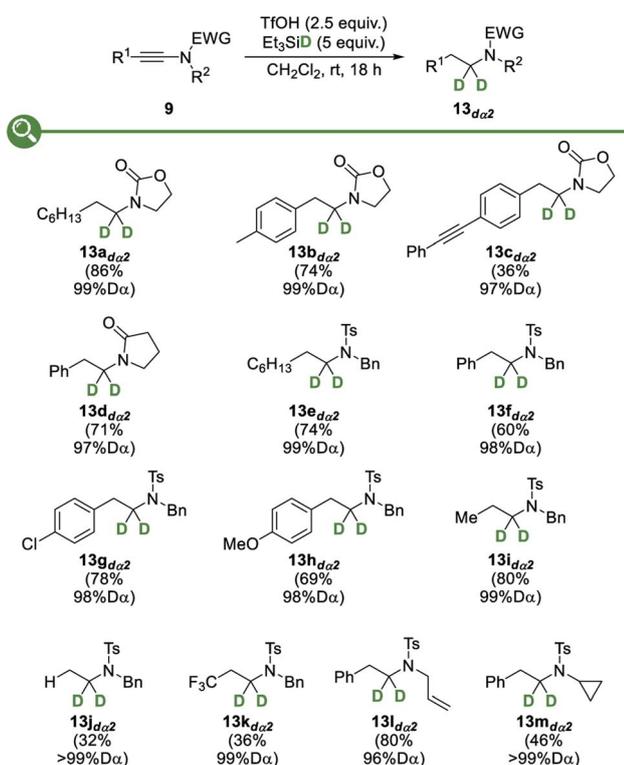


Fig. 5 Synthesis of selectively α -deuterated amines.

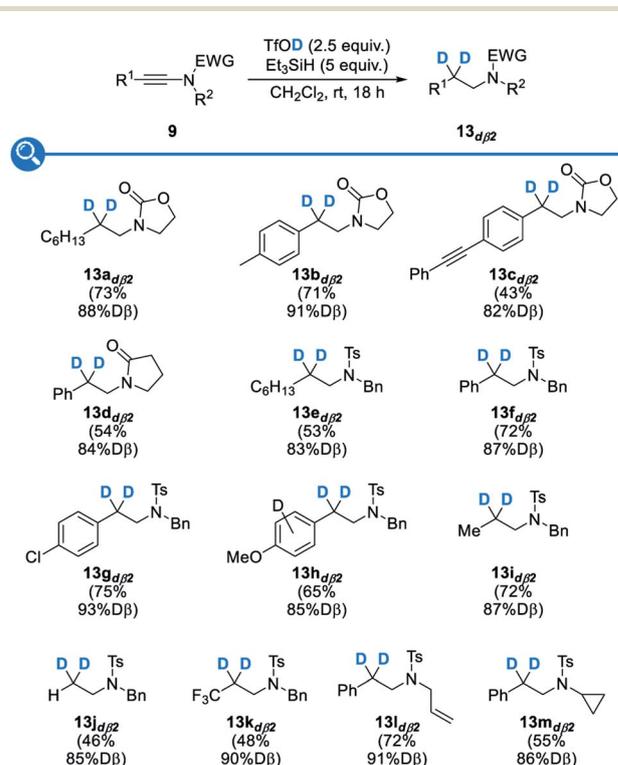


Fig. 6 Synthesis of selectively β -deuterated amines.



with similar efficiencies and good levels of deuteration (82–93% D), levels that were however somehow a bit lower than the ones obtained for the deuteration at the β -position but still in the high range and highly competitive with levels of deuteration that can be obtained with other methods. As for the yields, some are somehow lower than when using triflic acid, which might be attributed to the lower acidity of TfOD vs. TfOH. As a practical note, higher levels of deuteration were attained with freshly prepared deuterated triflic acid. Importantly, the reductive deuteration was not affected by the presence of aromatic substituents that could be competitively protonated by TfOD, resulting, after deprotonation, in the release of TfOH and therefore reduced levels of deuteration at the β -position, as observed only with an especially electron-rich anisole substituent that was partially deuterated in the course of the reaction and resulted in a reduced (85% D) level of β -deuteration (**13h_{da2 β 2}**). In a similar vein, no competing deuteration of the alkene (**13l_{da2 β 2}**) or cyclopropane (**13m_{da2 β 2}**) was noted, the deuteration being selective for the β position.

We finally focused our efforts on the synthesis of amines selectively deuterated at both their α and β positions, compounds that could be obtained using a combination of deuterated triflic acid and deuterated triethylsilane under our standard reaction conditions. Results summarized in Fig. 7 show the generality of this process that enables the preparation of a broad range of selectively deuterated amines – compounds that can be hardly prepared otherwise – with various protecting groups, substitution patterns and substituents. As for the trends in reactivity and deuteration levels, they logically follow

the ones discussed above for the synthesis of α - and β -deuterated amines.

Results from these studies highlight the efficiency and selectivity of our process for the divergent preparation of amines selectively deuterated at the α position, β position, or both. By simply selecting the appropriate deuterated reagent(s), all these selectively labelled molecules can be prepared in a fully divergent manner and with high functional group tolerance and levels of deuterium incorporation. These processes could have a significant impact in medicinal chemistry, a field in which amines are ubiquitous, and we therefore decided to apply them to the synthesis of representative deuterated biologically relevant amines. The corresponding results will be described in the next section.

Application to the synthesis of deuterated biologically relevant amines

In an effort to further highlight the synthetic potential of our divergent and selective synthesis of deuterated amines, we indeed next envisioned, as a proof of concept, its use for the synthesis of simple biologically relevant amines selectively deuterated at the α - and/or β -position(s) with respect to the nitrogen atom: phenethylamine **17** and dopamine **19** were selected for this study. Phenethylamine **17** is indeed a monoamine alkaloid found in low concentrations in the central nervous system of mammals. Along with other so-called “trace amines”, phenethylamine is a major one and is known to act as a neuromodulator for structurally related classical neurotransmitters such as dopamine **19**, norephedrine and serotonin.³⁵ Therefore, trace amines are known to affect the release and uptake of the latter neurotransmitters and have thus been linked to psychiatric and neurological pathologies such as depression, schizophrenia, Tourette's syndrome and Parkinson's disease. Accordingly, their use for the development of new therapeutics has been suggested and highlighted on multiple occasions.³⁶ Interestingly, the very first example of deuterium substitution in biologically relevant compounds, dating back to 1961, already described that the metabolism of two trace amines, *p*-tyramine and tryptamine, was significantly reduced when replacing α -hydrogens with deuterium atoms.³⁷ With this in mind, we envisioned the synthesis of phenethylamine **17** deuterated at the α - and/or β -position(s) from ynamide **9n**, itself readily synthesized by copper-catalyzed cross-coupling of bromoalkyne **15** with sulfonamide **16** (Fig. 8). Upon exposure of **9n** to combinations of triflic acid and triethylsilane, deuterated or not, and subsequent deprotection of the anisylsulfonyl and benzyl moieties, selectively deuterated phenethylamine **17_{da2}**, **17_{af2}** and **17_{da2 β 2}** could be obtained in good overall yields and with excellent deuteration levels of 97 to >99% at the α -position, and 84 to 95% at the β -position, further demonstrating the usefulness and versatility of our process for the synthesis of deuterated amines.

In an effort to go one step further, we next targeted a second biologically relevant amine, dopamine **19**, a major neurotransmitter that also plays a central role in various pathologies. It is notably involved in Parkinson's disease which is characterized

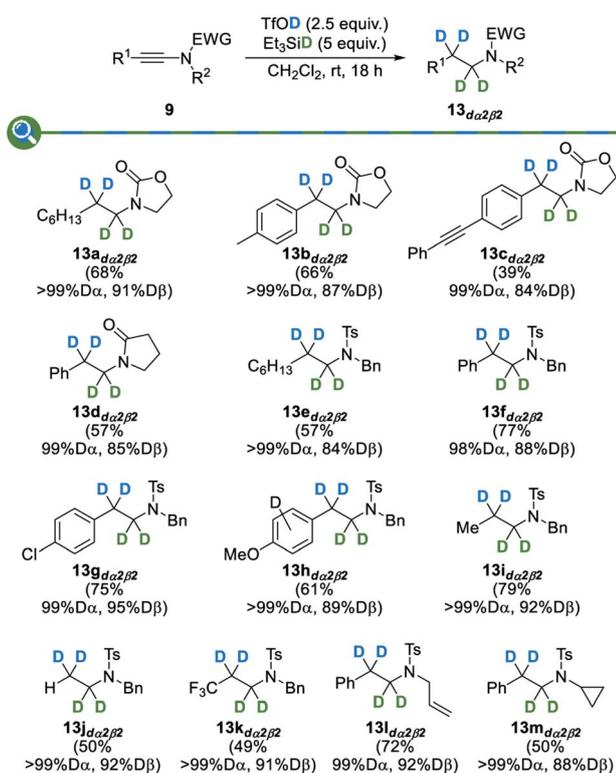


Fig. 7 Synthesis of selectively α,β -deuterated amines.



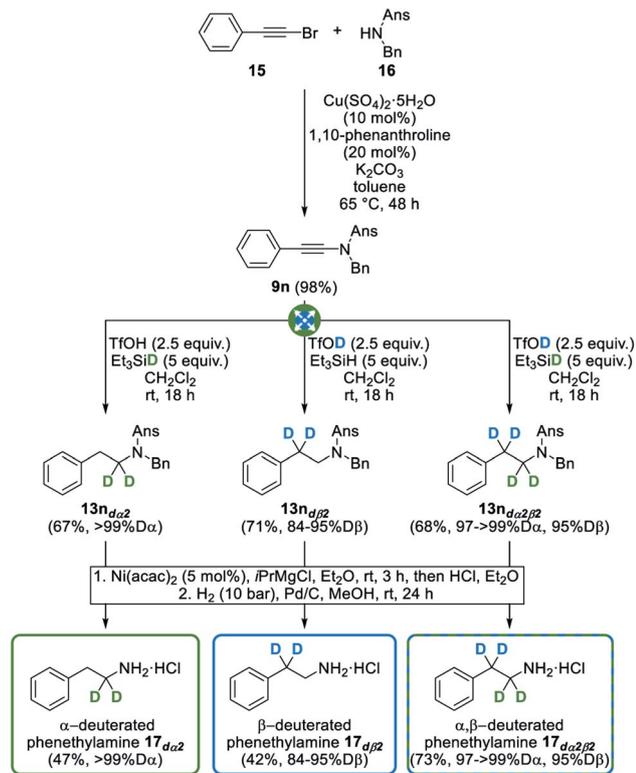


Fig. 8 Divergent synthesis of selectively α -, β - and α,β -deuterated phenethylamine.

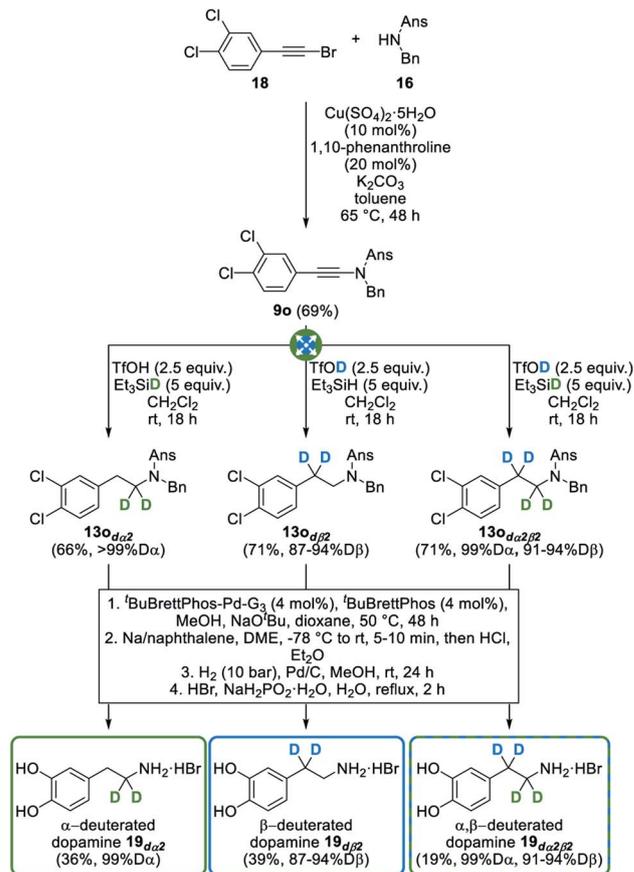


Fig. 9 Divergent synthesis of selectively α -, β - and α,β -deuterated dopamine.

by a progressive loss of dopaminergic neurons, causing decreasing dopamine levels and therefore a degeneration of motor skills in affected patients. To date, the most efficient symptomatic therapy for Parkinson's disease relies on the oral administration of L-DOPA (L-3,4-dihydroxyphenylalanine) as a precursor to dopamine.³⁸ Interestingly, and which further showcases the importance of selectively deuterated drugs, the introduction of deuterium atoms at the α - and β -positions of L-DOPA significantly slows down the metabolic breakdown of deuterated dopamine, thus improving its potency.³⁹ Indeed, and as mentioned in the introduction, the breaking of C-D bonds during metabolic oxidation is often more difficult than that of C-H bonds, meaning that the selective deuteration of bioactive compounds might allow for smaller or less frequent dosing. In this perspective, we decided to apply our method to the divergent synthesis of α - and/or β -deuterated dopamine from readily available dichlorinated ynamide **9o** that was chosen as the starting substrate to avoid a competing deuteration of its electron-rich dimethoxylated analogue with deuterated triflic acid. As shown in Fig. 9, this ynamide **9o** was readily converted into selectively deuterated amines **13o_{d α 2}**, **13o_{d β 2}** and **13o_{d α 2 β 2}** with good yields and deuteration levels of $\geq 99\%$ at the α -position and ranging from 87 to 94% at the β -position. Installation of the methyl-protected catechol moiety by a palladium-catalyzed Buchwald-Hartwig cross-coupling⁴⁰ and subsequent deprotection of the anisylsulfonyl, benzyl and methyl ether moieties next afforded selectively deuterated dopamine **19_{d α 2}**, **19_{d β 2}** and **19_{d α 2 β 2}** without affecting deuteration levels,

further highlighting the versatility and efficiency of our modular synthesis of deuterated amines.

After having successfully developed a straightforward and divergent access to α - and/or β -deuterated amines and applied it, as a proof of concept, to biologically relevant amines including phenethylamine and dopamine, we finally wanted to briefly evaluate the possibility of extending this strategy to the synthesis of selectively deuterated alcohols and ethers.

Extension to the synthesis of selectively deuterated ethers

In order to illustrate the generality of our method, we indeed envisioned that our strategy could be extended to other heteroatomic molecules and building blocks starting from other heterosubstituted alkynes. With this goal in mind, ynoyl ether **21**, readily obtained in a single step from commercially available ethyl ethynyl ether **20**,⁴¹ was subjected to our standard conditions and gratifyingly gave the corresponding selectively deuterated ethers **22_{d α 2}**, **22_{d β 2}** and **22_{d α 2 β 2}** with good to excellent levels of deuteration (Fig. 10). In this case, lower yields were however obtained due to the formation of an ester side-product resulting from the hydrolysis of the intermediate ketylenium ion. This side-product could however be easily removed by simply subjecting the crude reaction mixture to saponification conditions and subsequent acid-base wash. Despite lower yields,



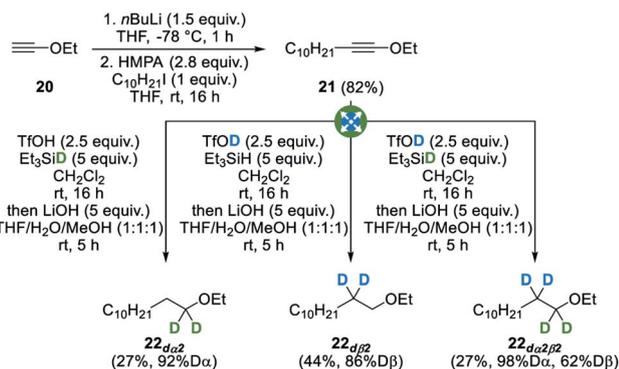


Fig. 10 Divergent synthesis of α -, β - and α,β -selectively deuterated ethers.

these examples again still highlight both the strong selectivity, as no residual deuteration was observed at untargeted positions, and versatility of this method. Other heterosubstituted alkynes such as thioynol ethers and bromoalkynes were however found to be reluctant substrates for this transformation.

Conclusions

In conclusion, we have developed a simple, user-friendly and general synthesis of amines selectively deuterated at their α and/or β positions. Upon simple treatment of readily available ynamides with a mixture of triflic acid and triethylsilane, either deuterated or not, a range of amines can be smoothly obtained with high levels of deuterium incorporation. Notable features of this process, for which we envision great acceptance due to the major and growing importance of selectively deuterated amines, particularly in medicinal chemistry, include its versatility, its generality and its user-friendliness. The extension of this process to the synthesis of selectively deuterated ethers and its use for the preparation of biologically relevant amines such as phenethylamine and dopamine, deuterated with surgical precision at their α and/or β positions, further highlight the potential of this rather unique method involving moreover an underrated novel domino keteniminium/iminium activation.

Data availability

All experimental procedures, characterization, copies of NMR spectra for all new compounds related to this study can be found in the ESI.

Author contributions

G. E. designed the study. Experimental work and data analysis were performed by M. Le., M. La., P. T., and A. E. B.; P. T. and G. E. co-wrote the manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Notes and references

- (a) J. S. Rigden and J. O'Connell, *Am. J. Phys.*, 2003, **71**, 189; (b) H. C. Urey, *Science*, 1933, **78**, 566–571.
- J. Yang, *Deuterium: Discovery and Applications in Organic Chemistry*, Elsevier, 2016.
- "Hydrogen" is commonly used in place of "protium" ¹H, the major isotope of hydrogen. For clarity, we have utilized "hydrogen" everywhere in this manuscript but it refers to "protium" in most cases.
- For a representative example, see: R. R. Gerona, T. J. Woodruff, C. A. Dickenson, J. Pan, J. M. Schwartz, S. Sen, M. W. Friesen, V. Y. Fujimoto and P. A. Hunt, *Environ. Sci. Technol.*, 2013, **47**, 12477–12485.
- (a) N. S. Isaacs, *Physical Organic Chemistry*, Longman Scientific & Technical, Burnt Mill, Harlow, Essex, England, 1995; (b) K. B. Wiberg, *Chem. Rev.*, 1955, **55**, 713–743.
- J. Rinkel and J. S. Dickschat, *Beilstein J. Org. Chem.*, 2015, **11**, 2493–2508.
- (a) M. Miyashita, M. Sasaki, I. Hattori, M. Sakai and K. Tanino, *Science*, 2004, **305**, 495–499; (b) K. W. Quasdorf, A. D. Hutters, M. W. Lodewyk, D. J. Tantillo and N. K. Garg, *J. Am. Chem. Soc.*, 2012, **134**, 1396–1399.
- T. Kaino, K. Jinguji and S. Nara, *Appl. Phys. Lett.*, 1983, **42**, 567–569.
- (a) H. Tsuji, C. Mitsui and E. Nakamura, *Chem. Commun.*, 2014, **50**, 14870–14872; (b) C. C. Tong and K. C. Hwang, *J. Phys. Chem. C*, 2007, **111**, 3490–3494.
- A. E. Mutlib, *Chem. Res. Toxicol.*, 2008, **21**, 1672–1689.
- (a) R. D. Tung, *Innovations Pharm. Technol.*, 2010, **32**, 24–28; (b) S. L. Harbeson and R. D. Tung, in *Annual Reports in Medicinal Chemistry*, ed. J. E. Macor, Elsevier, 2011, vol. 46, ch. 24, pp. 403–417; (c) N. A. Meanwell, *J. Med. Chem.*, 2011, **54**, 2529–2591; (d) S. L. Harbeson and R. D. Tung, *MedChem News*, 2014, **24**, 8–22; (e) G. S. Timmins, *Expert Opin. Ther. Pat.*, 2014, **24**, 1067–1075; (f) T. G. Gant, *J. Med. Chem.*, 2014, **57**, 3595–3611; (g) T. Pirali, M. Serafini, S. Cargnin and A. A. Genazzani, *J. Med. Chem.*, 2019, **62**, 5276–5297; (h) R. D. Tung, *Future Med. Chem.*, 2016, **8**, 491–494; (i) A. Mullard, *Nat. Rev. Drug Discovery*, 2016, **15**, 219–221; (j) B. Halford, *Chem. Eng. News*, 2016, **94**, 32–36; (k) G. S. Timmins, *Expert Opin. Ther. Pat.*, 2017, **27**, 1353–1361.
- (a) A. E. Mutlib, R. J. Gerson, P. C. Meunier, P. J. Haley, H. Chen, L. S. Gan, M. H. Davies, B. Gemzik, D. D. Christ,



- D. F. Krahn, J. A. Markwalder, S. P. Seitz, R. T. Robertson and G. T. Miwa, *Toxicol. Appl. Pharmacol.*, 2000, **169**, 102–113; (b) A. W. Czarnik, *US Pat.*, US 2009/0075991 A1, 2009.
- 13 F. Maltais, Y. C. Jung, M. Chen, J. Tanoury, R. B. Perni, N. Mani, L. Laitinen, H. Huang, S. Liao, H. Gao, H. Tsao, E. Block, C. Ma, R. S. Shawgo, C. Town, C. L. Brummel, D. Howe, S. Pazhanisamy, S. Raybuck, M. Namchuk and Y. L. Bennani, *J. Med. Chem.*, 2009, **52**, 7993–8001.
- 14 K. Sanderson, *Nature*, 2009, **458**, 269.
- 15 A. Sommer, C. Zhang, J. Carter, J. Arthur, M. Bradbury, T. Gant and M. Shahbaz, *US Pat.*, US 2016/0222008 A1, 2016.
- 16 (a) J. Siffert, *WO Pat.*, WO2016/040930 A1, 2016; (b) R. P. Garay and G. T. Grossberg, *Expert Opin. Invest. Drugs*, 2017, **26**, 121–132.
- 17 (a) U.S. National Library of Medicine, <https://clinicaltrials.gov/ct2/show/NCT02153502>, accessed May 11, 2021; (b) R. P. Garay, C. A. Zarate, T. Charpeaud, L. Citrome, C. U. Correll, A. Hameg and P.-M. Llorca, *Expert Rev. Neurother.*, 2017, **17**, 593–609.
- 18 V. Braman, *US Pat.*, US 2018/0353500 A1, 2018.
- 19 R. M. Moslin, D. S. Weinstein, S. T. Wroblewski, S. J. Tokarski and A. Kumar, *WO Pat.*, WO 2014/074661 A1, 2014.
- 20 C. Schmidt, *Nat. Biotechnol.*, 2017, **35**, 493–494.
- 21 J. F. Liu, S. L. Harbeson, C. L. Brummel, R. Tung, R. Silverman and D. Doller, in *Annual Reports in Medicinal Chemistry*, ed. R. A. Goodnow, Elsevier, 2017, ch. 14, vol. 50, pp. 519–542.
- 22 Y. Zhou, J. Wang, Z. Gu, S. Wang, W. Zhu, J. L. Aceña, V. A. Soloshonok, K. Izawa and H. Liu, *Chem. Rev.*, 2016, **116**, 422–518.
- 23 B. J. Simmons, M. Hoffmann, J. Hwang, M. K. Jackl and N. K. Garg, *Org. Lett.*, 2017, **19**, 1910–1913.
- 24 (a) B. Zhang, H. Li, Y. Ding, Y. Yan and J. An, *J. Org. Chem.*, 2018, **83**, 6006–6014; (b) Y. Ding, S. Luo, A. Adijiang, H. Zhao and J. An, *J. Org. Chem.*, 2018, **83**, 12269–12274; (c) Y. Ding, S. Luo, C. Weng and J. An, *J. Org. Chem.*, 2019, **84**, 15098–15105; (d) R. Mészáros, B.-J. Peng, S. B. Ötvös, S.-C. Yang and F. Fülöp, *ChemPlusChem*, 2019, **84**, 1508–1511; (e) A. Kurimoto, R. S. Sherbo, Y. Cao, N. W. X. Loo and C. P. Berlinguette, *Nat. Catal.*, 2020, **3**, 719–726.
- 25 (a) For a review, see: A. Michelotti and M. Roche, *Synthesis*, 2019, **51**, 1319–1328; (b) M. Maeda, O. Ogawa and Y. Kawazoe, *Chem. Pharm. Bull.*, 1977, **25**, 3329–3333; (c) M. Takahashi, K. Oshima and S. Matsubara, *Chem. Lett.*, 2005, **34**, 192–193; (d) E. Alexakis, M. J. Hickey, J. R. Jones, L. P. Kingston, W. J. S. Lockley, A. N. Mather, T. Smith and D. J. Wilkinson, *Tetrahedron Lett.*, 2005, **46**, 4291–4293; (e) L. Neubert, D. Michalik, S. Bähn, S. Imm, H. Neumann, J. Atzrodt, V. Derdau, W. Holla and M. Beller, *J. Am. Chem. Soc.*, 2012, **134**, 12239–12244; (f) G. Pieters, C. Taglang, E. Bonnefille, T. Gutmann, C. Puente, J.-C. Berthet, C. Dugave, B. Chaudret and B. Rousseau, *Angew. Chem., Int. Ed.*, 2014, **53**, 230–234; (g) T. Maegawa, A. Akashi, H. Esaki, F. Aoki, H. Sajiki and K. Hirota, *Synlett*, 2005, **2005**, 0845–0847; (h) F. T. Jere, D. J. Miller and J. E. Jackson, *Org. Lett.*, 2003, **5**, 527–530; (i) C. Taglang, L. M. Martínez-Prieto, I. del Rosal, L. Maron, R. Poteau, K. Philippot, B. Chaudret, S. Perato, A. Sam Lone, C. Puente, C. Dugave, B. Rousseau and G. Pieters, *Angew. Chem., Int. Ed.*, 2015, **54**, 10474–10477; (j) K. Moozeh, S. M. So and J. Chin, *Angew. Chem., Int. Ed.*, 2015, **54**, 9381–9385; (k) L. V. A. Hale and N. K. Szymczak, *J. Am. Chem. Soc.*, 2016, **138**, 13489–13492; (l) S. Bhatia, G. Spahlinger, N. Boukhumseen, Q. Boll, Z. Li and J. E. Jackson, *Eur. J. Org. Chem.*, 2016, **2016**, 4230–4235; (m) A. Michelotti, F. Rodrigues and M. Roche, *Org. Process Res. Dev.*, 2017, **21**, 1741–1744; (n) C. Taglang, D. E. Korenchan, C. von Morze, J. Yu, C. Najac, S. Wang, J. E. Blecha, S. Subramaniam, R. Bok, H. F. VanBrocklin, D. B. Vigneron, S. M. Ronen, R. Sriram, J. Kurhanewicz, D. M. Wilson and R. R. Flavell, *Chem. Commun.*, 2018, **54**, 5233–5236; (o) B. Chatterjee, V. Krishnakumar and C. Gunanathan, *Org. Lett.*, 2016, **18**, 5892–5895; (p) Y. Y. Loh, K. Nagao, A. J. Hoover, D. Hesk, N. R. Rivera, S. L. Colletti, I. W. Davies and D. W. C. MacMillan, *Science*, 2017, **358**, 1182; (q) Y. Hu, L. Liang, W.-t. Wei, X. Sun, X.-j. Zhang and M. Yan, *Tetrahedron*, 2015, **71**, 1425–1430.
- 26 Y. Chang, A. Yesilcimen, M. Cao, Y. Zhang, B. Zhang, J. Z. Chan and M. Wasa, *J. Am. Chem. Soc.*, 2019, **141**, 14570–14575.
- 27 For review articles, see: (a) K. A. DeKorver, H. Li, A. G. Lohse, R. Hayashi, Z. Lu, Y. Zhang and R. P. Hsung, *Chem. Rev.*, 2010, **110**, 5064–5106; (b) G. Evano, A. Coste and K. Jouvin, *Angew. Chem., Int. Ed.*, 2010, **49**, 2840–2859; (c) G. Evano, C. Theunissen and M. Lecomte, *Aldrichimica Acta*, 2015, **48**, 59–70.
- 28 For representative contributions from our group, see: (a) W. Gati, M. M. Rammah, M. B. Rammah, F. Couty and G. Evano, *J. Am. Chem. Soc.*, 2012, **134**, 9078–9081; (b) W. Gati, F. Couty, T. Boubaker, M. M. Rammah, M. B. Rammah and G. Evano, *Org. Lett.*, 2013, **15**, 3122–3125; (c) C. Theunissen, B. Métayer, N. Henry, G. Compain, J. Marrot, A. Martin-Mingot, S. Thibaudeau and G. Evano, *J. Am. Chem. Soc.*, 2014, **136**, 12528–12531; (d) H. A. Laub, G. Evano and H. Mayr, *Angew. Chem., Int. Ed.*, 2014, **53**, 4968–4971; (e) M. Lecomte and G. Evano, *Angew. Chem., Int. Ed.*, 2016, **55**, 4547–4551; (f) P. Thilmann and G. Evano, *Angew. Chem., Int. Ed.*, 2020, **59**, 242–246.
- 29 For review articles, see: (a) C. Madelaine, V. Valerio and N. Maulide, *Chem.-Asian J.*, 2011, **6**, 2224–2239; (b) G. Evano, M. Lecomte, P. Thilmann and C. Theunissen, *Synthesis*, 2017, **49**, 3183–3214.
- 30 (a) G. Evano, K. Jouvin and A. Coste, *Synthesis*, 2013, **45**, 17–26; (b) Y. Zhang, R. P. Hsung, M. R. Tracey, K. C. M. Kurtz and E. L. Vera, *Org. Lett.*, 2004, **6**, 1151–1154; (c) T. Hamada, X. Ye and S. S. Stahl, *J. Am. Chem. Soc.*, 2008, **130**, 833–835; (d) A. Coste, G. Karthikeyan, F. Couty and G. Evano, *Angew. Chem., Int. Ed.*, 2009, **48**, 4381–4385; (e) K. Jouvin, F. Couty and G. Evano, *Org. Lett.*, 2010, **12**, 3272–3275; (f) K. Jouvin, J. Heimbürger and G. Evano, *Chem. Sci.*, 2012, **3**, 756–760.
- 31 X. Zeng, *Chem. Rev.*, 2013, **113**, 6864–6900.
- 32 For examples of ionic reduction of enamides, see: (a) M. M. Hinman and C. H. Heathcock, *J. Org. Chem.*, 2001,



- 66, 7751–7756; (b) M. N. Masuno and T. F. Molinski, *Tetrahedron Lett.*, 2001, **42**, 8263–8266.
- 33 For the partial reduction of alkynes with silanes, see: (a) M. Yan, T. Jin, Y. Ishikawa, T. Minato, T. Fujita, L.-Y. Chen, M. Bao, N. Asao, M.-W. Chen and Y. Yamamoto, *J. Am. Chem. Soc.*, 2012, **134**, 17536–17542; (b) J. Chen, X. Shen and Z. Lu, *J. Am. Chem. Soc.*, 2020, **142**, 14455–14460.
- 34 Y. Zhang, R. P. Hsung, X. Zhang, J. Huang, B. W. Slafer and A. Davis, *Org. Lett.*, 2005, **7**, 1047–1050.
- 35 (a) M. D. Berry, *J. Neurochem.*, 2004, **90**, 257–271; (b) A. H. Lewin, *AAPS J.*, 2006, **8**, E138–E145; (c) L. Lindemann and M. C. Hoener, *Trends Pharmacol. Sci.*, 2005, **26**, 274–281.
- 36 (a) M. D. Berry, *Rev. Recent Clin. Trials*, 2007, **2**, 3–19; (b) T. A. Branchek and T. P. Blackburn, *Curr. Opin. Pharmacol.*, 2003, **3**, 90–97.
- 37 B. Belleau, J. Burba, M. Pindell and J. Reiffenstein, *Science*, 1961, **133**, 102–104.
- 38 W. G. Meissner, M. Frasier, T. Gasser, C. G. Goetz, A. Lozano, P. Piccini, J. A. Obeso, O. Rascol, A. Schapira, V. Voon, D. M. Weiner, F. Tison and E. Bezard, *Nat. Rev. Drug Discovery*, 2011, **10**, 377–393.
- 39 (a) T. Malmjöf, D. Rylander, R.-G. Alken, F. Schneider, T. H. Svensson, M. A. Cenci and B. Schilström, *Exp. Neurol.*, 2010, **225**, 408–415; (b) F. Schneider, L. Erisson, H. Beygi, M. Bradbury, O. Cohen-Barak, I. D. Grachev, S. Guzy, P. S. Loupe, M. Levi, M. McDonald, J.-M. Savola, S. Papapetropoulos, W. G. Tracewell, M. Velinova and O. Spiegelstein, *Br. J. Clin. Pharmacol.*, 2018, **84**, 2422–2432.
- 40 C. W. Cheung and S. L. Buchwald, *Org. Lett.*, 2013, **15**, 3998–4001.
- 41 P. J. Kociński, B. Pelotier, J.-M. Pons and H. Prideaux, *J. Chem. Soc., Perkin Trans. 1*, 1998, 1373–1382.

