Manganese-Catalyzed Multicomponent Synthesis of Tetrasubstituted Propargylamines: System Development and Theoretical Study

Stavros P. Neofotistos,[a] Nikolaos V. Tzouras,[a] Martin Pauze,[b] Enrique Gómez-Bengoa,[b] and Georgios C. Vougioukalakis*[a]

Dedicated to Professor Robert H. Grubbs, on the occasion of the 50-year anniversary of his independent research.

[a] S. P. Neofotistos, N. V. Tzouras, Prof. Dr. G. C. Vougioukalakis
Department of Chemistry, Laboratory of Organic Chemistry
National and Kapodistrian University of Athens
Panepistimiopolis, 15771 Athens, Greece
E-mail: vougiouk@chem.uoa.gr
[b] Martin Pauze, Prof. Dr. E. Gómez-Bengoa
Department of Organic Chemistry I, Faculty of Chemistry
University of the Basque Country
UPV/EHU, 20018 Donostia-San Sebastián, Spain

Supporting information for this article containing copies of the ^{1}H and ^{13}C NMR spectra, as well as the Cartesian coordinates to which the present manuscript refers, is given via a link at the end of the document.

Abstract: *The importance of multicomponent reactions as an efficient tool in organic synthesis is widely recognized, as the need for sustainable, practical, atom- and step-economic methodologies is becoming a crucial concept in contemporary research. In this context, the synthesis of propargylamines via multicomponent protocols holds great promise, because of their biological action and their potential as synthons. Ketone-derived, tetrasubstituted propargylamines are a relatively unexplored subclass of compounds, while protocols to access them have only been described in the past decade, owing to the challenging nature of ketones as multicomponent coupling partners. Herein, we report a catalytic system based on the earth-abundant manganese for the ketone, amine, alkyne (KA^2) reaction. The efficiency of manganese, combined with sustainable reaction conditions, comprise a useful new method for accessing various interesting propargylamines. Additionally, the use of computational methods reveals mechanistic aspects of this reaction, for the first time, raising important points regarding the reactivity of both manganese and ketones.*

Introduction

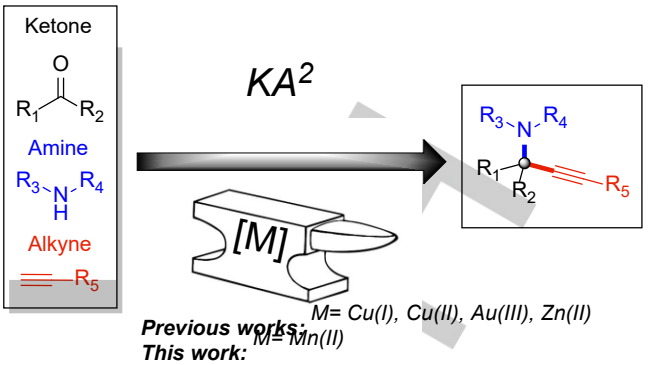
Propargylamines are a versatile family of organic compounds that have found numerous applications in the fields of organic synthesis and pharmaceutical chemistry.[1,2] The biological activity of various members of their family renders them inherently valuable in drug development, mostly against neurodegenerative diseases.[1–9] In addition, propargylic amines are useful building blocks in organic synthesis, providing access to diverse molecular architectures.[1,2] The unique structure of these compounds is based on the existence of an amine group in *β*-position to an alkyne moiety, which leads to diverse reactivity.[1] These characteristics make propargylamines susceptible to a variety of chemical transformations, thus fulfilling the conditions which have been established by the diversity-oriented synthesis strategy and natural product synthesis.[1,2,10–17] Moreover, through the integration of carbon dioxide or other small molecules, propargylamines can serve as intermediates or precursors for the synthesis of various heterocyclic compounds,[1] such as oxazolidinones,[18,19] same as their propargylic alcohol congeners.[20] Amongst others, propargylamines can be accessed in a facile manner through catalytic, multicomponent reaction protocols,[1,2,21–25] thus minimizing the required effort, time, and the generation of waste related to multistep processes.[26–33]

The development of various catalytic systems, based on sustainable and biorelevant transition metals,[34] as well as the ever increasing interest related to atom- and step-economy arising from multicomponent synthesis combined with C-H activation,[35] allows the discovery of novel and green methodologies.[26–33] The A^3 coupling (aldehyde, amine, alkyne) is a well-known example of such a methodology.[2,36,37] Various sustainable and highly efficient catalytic protocols have been employed for the synthesis of trisubstituted propargylamines based on this multicomponent coupling.[36–45] Remarkably, not long after the initial discovery of this reaction, enantioselective versions were also developed, utilizing chiral ligands.[46,47]

Ketimines exhibit lower reactivity than aldimines, a fact that stems from both their stereochemical and electronic features.[48,49] Nucleophilic addition to ketimines is in general challenging, although ketimines obtained from cyclohexanone are relatively reactive, due to the release of torsional strain.[50–52] Along these lines, employing ketones instead of aldehydes in the A^3 coupling remained a challenge until almost a decade ago. The synthesis of ketone-derived, tetrasubstituted propargylamines, through a catalytic, multicomponent coupling strategy, was attempted by several research teams, considering the great abundance of different natural products that possess *α*-tertiary amine moieties,[53] along with the inherent value of propargylamines and the scarcity of synthetic strategies leading to such molecular

scaffolds.[54–57] An early related example was demonstrated by Ramón and co-workers in 2010, when the desired product was obtained in 38% yield after 7 days of reaction between piperidine, 3-pentanone, and phenylacetylene, catalyzed by Cu(OH)$_x$-Fe$_3$O$_4$ as the catalyst.[58] Nonetheless, the first breakthrough was made when the research group of Van der Eycken successfully prepared various tetrasubstituted propargylamines, derived from cyclohexanones, benzylamines and phenylacetylene, using a homogeneous, CuI-based and microwave-assisted catalytic system, under neat conditions. This discovery was made possible by taking advantage of the high reactivity of cyclohexanones, whilst they named the reaction "KA^2 coupling" (ketone, amine, alkyne – Scheme 1).[59] In a later work, the same research group utilized azoles instead of alkynes, along with secondary amines and cyclic ketones, under a similar, copper-catalyzed/microwave-irradiated protocol.[60] A catalytic system based on AuBr$_3$ in 4.0 mol% loading was also developed, using for the most part secondary amines, cyclohexanones, and phenylacetylene.[61] In a similar manner, a homogeneous *N*-heterocyclic carbene-Au(I)-based protocol was employed towards polysubstituted dihydropyrazoles *via* a three-component annulation of alkynes with *N, N´*-disubstituted hydrazines and aldehydes/ketones.[62] Larsen and co-workers developed additional efficient systems for the KA^2 coupling, based on CuCl$_2$ or Cu(OTf)$_2$.[63-65] Further expansion of the scope of the reaction was achieved when Ti(OEt)$_4$ was employed as an additive, thereby allowing the integration of prochiral, linear ketones as coupling partners.[66] Likewise, a Cu(I) based system developed by Ma and co-workers was also very efficient for the KA^2 coupling of secondary amines, various ketones and terminal alkynes, in toluene, along with molecular sieves to assist with water removal.[67] The same research group was the first to report the successful integration of aromatic ketones, in the KA^2 coupling, which was mediated by a catalytic system based on CuBr$_2$, along with the use of Ti(OEt)$_4$ and sodium ascorbate.[68] Naturally, the increasing interest in this reaction and its potential has led to the development of a multitude of heterogeneous catalytic systems. Some leading examples include the use of Cu$_2$O nanoparticles on titania,[69] nano Cu$_2$O-ZnO,[70] Cu$_2$O/nano-CuFe$_2$O$_4$,[71] CuO/Fe$_2$O$_3$ nanoparticles,[72] Cu(II)-hydromagnesite,[73] polystyrene-supported, *N*-phenylpiperazine-CuBr$_2$,[74] Cu(II)@furfural imine-decorated Halloysite,[75] CuI on Amberlyst A-21,[76] as well as semi-heterogeneous, magnetically recoverable graphene oxide-supported CuCl$_2$.[77] Catalytic systems based on other metals have been also developed, such as Ag-doped nanomagnetic *γ*-Fe$_2$O$_3$@DA core-shell hollow spheres,[78] Fe$_2$O$_3$@SiO$_2$-IL/Ag hollow spheres,[79] and polystyrene-supported *N*-heterocyclic carbene-Au(III).[80]

More recently, our research group reported a robust catalytic system for the KA^2 reaction, introducing Zn(OAc)$_2$ as a reliable catalyst under neat conditions.[81] Additionally, we found that a catalytic system based on ZnI$_2$ can mediate the tandem formation of allenes from the *in situ* generated propargylamines in a one-pot procedure. This work highlighted that there is substantial reason to investigate new metals in this reaction, in order to gain more insight into its underlying principles, and, more importantly, that the choice of reaction conditions can lead to new and/or improved reactivity.



Scheme 1. The metal-catalyzed KA^2 coupling reaction.

Manganese is a particularly attractive metal on account of its high natural abundance (the 3rd transition metal in the earth's crust after iron and titanium) and biocompatibility, which is particularly valuable for the pharmaceutical industry.[82] According to a recent report of the European Medicine Agency, manganese and copper are considered metals of low safety concern.[83] Therefore, manganese is a prominent candidate for the mediation of all kinds of chemical transformations.[82] In this regard, a plethora of manganese-based homogeneous catalytic systems have been developed,[82] successfully catalyzing the hydrosilylation of carbonylic compounds,[84,85] the electrochemical CO_2 reduction,[86–92] as well as the oxidation and allene epoxidation reactions.[93–99] A well-known example of manganese catalysis is the Katsuki reaction, which utilizes a Mn(I)-salen complex for the epoxidation of allenes.[98] Similarly, Mn(I)-based catalytic protocols utilizing porphyrin,[93,95,96] phthalocyanine,[97] or polyamine ligands,[100] have been reported. Mn-catalyzed C-H activation approaches have been also developed.[101–105] More specifically, Wang and co-workers introduced the first manganese-catalyzed aromatic C−H alkenylation with terminal alkynes.[102] Exploiting various pyridine derivatives as directing groups, they successfully accomplished the alkenylation of aromatic rings, mediated by a MnBr(CO)$_5$ complex and dicyclohexylamine as the base, at high chemo-, regio-, and stereo-selectivity. Interestingly, the same group proposed the formation of a *σ*-alkynyl intermediate in the catalytic cycle, based on Density Functional Theory (DFT) studies.[102] The formation of a Mn-acetylide was also proposed by Takai and co-workers as an intermediate.[106] Specifically, they reported that the mechanism for the hydantoin synthesis included an oxidative addition of a terminal alkyne to form an Mn-acetylide, followed by the insertion of an iso-cyanate into the manganese–carbon bond of the manganese acetylide.[106] Given that the formation of Mn-acetylides had been well established, a novel, MnCl$_2$-based protocol for the mediation of the A^3 coupling, along with a tandem intramolecular [3 + 2] dipolar cycloaddition, was reported by Lee and co-workers, introducing an efficient, one-pot strategy for the synthesis of propargylamines, as well as fused triazoles.[107]

To the best of our knowledge, manganese catalysis has not yet been tested in the KA^2 coupling. Inspired by the applications of sustainable metal catalysis in green organic transformations,[35,108–111] as well as our recent work on zinc catalysis,[81] we became interested in studying the potential of manganese catalysis in the KA^2 reaction. Our primary goal was the development of a highly-efficient, green, and user-friendly

catalytic system based on a widely-available and cost-efficient manganese source, which could mediate the KA^2 coupling reaction of various challenging and synthetically intriguing substrates, under solvent-free conditions. Ideally, our KA^2 coupling protocol would be also viable under air, improving the sustainable aspects of this transformation even further. Finally, this provided an opportunity to study the reaction mechanism using computational tools for the first time, in order to further understand and more accurately pinpoint the reasons why ketone functionalization is significantly more challenging than that of aldehydes.

Results and Discussion

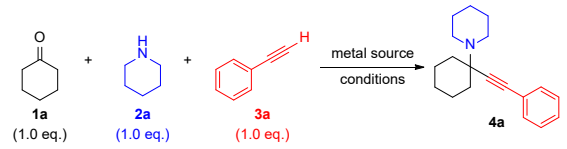
Based on our experience with the zinc-based catalytic protocol we have recently developed,[81] we chose cyclohexanone (**1a**), piperidine (**2a**) and phenylacetylene (**3a**) as model substrates for the optimization of the novel, manganese-based catalytic system. When $Mn(OAc)_2$ was employed in 20 mol% loading and the reaction was carried out under neat, inert conditions at 120 °C for 20 hours, propargylamine **4a** was obtained in 21% GC yield (Entry 1, Table 1). Despite this result, proving that manganese is able to mediate this reaction, a substantial amount of by-products were detected by GC/MS analysis.[20] Repetition of the reaction in toluene (1 M) at 120 °C, resulted in a 12% GC yield, which is considerably lower than the neat conditions (Entry 2, Table 1). This was a first indication that the reaction is favored under neat conditions. Then, we decided to proceed with the study of manganese halides. MnF_2 in 20 mol% loading under inert, neat conditions at 120 °C for 20 hours, resulted in a 52% yield (Entry 3, Table 1). When the same reaction was performed in toluene (1 M), the product was obtained with only 8% yield (Entry 4, Table 1). A significant increase in the reaction yield was observed, under neat conditions, at 120 °C using $MnCl_2$ as a catalyst, resulting in a 58% isolated yield (Entry 5, Table 1), suggesting that the counter ions of the manganese catalyst have a significant impact on the reaction. When the same reaction was performed in toluene (1 M), it resulted in an 18% GC yield (Entry 6, Table 1). When $MnBr_2$ was employed in 20 mol% loading at 120 °C, under neat, inert conditions, the desired product was obtained in 74% isolated yield (Entry 7, Table 1). Importantly, the formation of side products was also significantly reduced. The same reaction, when performed in toluene (1 M), resulted in the desired propargylamine **4a** in 45% GC yield (Entry 8, Table 1). When MnI_2 was used in 20 mol% loading at 120 °C, under neat, inert conditions, the desired product was obtained in 55% GC yield (Entry 9, Table 1). Besides being very difficult to handle because of its hydroscopic nature, MnI_2 is also characterized by reduced solubility in the reaction mixture. Therefore, the same reaction was performed in toluene, which efficiently dissolves MnI_2, affording propargylamine **4a** in 79% GC yield (Entry 10, Table 1). Furthermore, a blank test, using only molecular sieves, was performed, but, as anticipated, the product was not observed, as judged by GC-MS analysis (Entry 11, Table 1). Based on the above results, we decided that the best manganese source is $MnBr_2$, as it is easy to handle and it also affords very high product yields. The use of molecular sieves was deemed unnecessary, since their use only increased the complexity of the protocol (*vide infra*), while the use of solvent under these conditions negatively affects the reaction outcome. More importantly, the employment of solvent-free conditions is in line with the principles of green chemistry.

Then, we tested our protocol at various temperatures, using $MnBr_2$ at 20 mol% loading under an inert atmosphere and neat conditions for 20 hours. At 80 °C, the product was formed in 14% GC yield (Entry 1, Table 2). Performing the same reaction at 100 °C allowed the formation of propargylamine **4a** in 44% GC yield. When the reaction was repeated under the same conditions at 120 °C, it led to the formation of the desired product in 77% GC yield (Entry 3, Table 2). This result also suggested that the use of molecular sieves is not necessary, given that the results are practically the same with or without their presence (compare Entry 3, Table 2 with Entry 7, Table 1). When we performed the reaction employing $MnBr_2$ at 20 mol% loading under inert atmosphere and solvent-free conditions at 130 °C for 20 hours, the product was formed in 99% GC yield and 94% isolated yield (Entry 4, Table 2). Expanding our investigation, the same reaction was performed in the presence of molecular sieves, giving exactly the same results (Entry 5, Table 2), reaffirming the needlessness of molecular sieves.

We were also interested in shedding some light on the mechanism of the reaction. Besides carrying out a series of theoretical calculations (*vide infra*), we performed the transformation using $MnBr_2$, under the thus far optimal conditions (Entry 6, Table 2), by also adding 2.0 equivalents of (2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl (TEMPO), a well-known free radical scavenger. Again, the product was formed in 98% GC yield. This suggests that the catalytic mechanism does not involve radical intermediates.

Finally, we investigated the impact of the catalyst loading on the reaction outcome (Table 3). To our surprise, the reaction can be very efficiently carried out even at 5 mol% $MnBr_2$ (Entry 3, Table 3) affording the desired product in 98% GC yield and 95% isolated yield. This very low catalyst loading, along with the solvent-free conditions, the sustainable nature of Mn, and the fact that this is a multicomponent reaction, render this protocol highly appealing and "green".

Table 1. Metal sources screening and solvent tests.

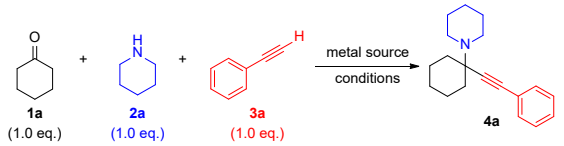


Entry	Metal source	mol%	Solvent	% GC yield[a] (isol. yield)[b]
1	$Mn(OAc)_2$	20	Neat & m. sieves	21
2	$Mn(OAc)_2$	20	Toluene (1M)	12
3	MnF_2	20	Neat & m. sieves	52
4	MnF_2	20	Toluene (1M)	8
5	$MnCl_2$	20	Neat & m. sieves	63 (58)

6	$MnCl_2$	20	Toluene (1M)	18
7	$MnBr_2$	20	Neat & m. sieves	78 (74)
8	$MnBr_2$	20	Toluene (1M)	45
9	MnI_2	20	Neat & m. sieves	55
10	MnI_2	20	Toluene (1M)	79
11	-	-	Neat & m. sieves	Traces

All reactions were performed on a 2.0 mmol scale, running at 120 °C for 20 hours. [a] Yield determined by GC/MS analysis, using *n*-octane as the internal standard. [b] After column chromatography.

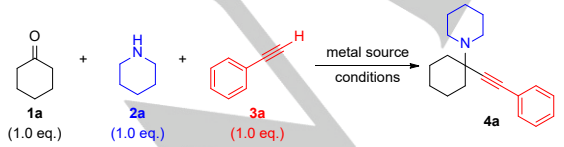
Table 2. Optimization studies.



Entry	Metal source	Temp. (°C)	Solvent	% GC yield[a] (isol. yield)[b]
1	$MnBr_2$	80	Neat	14
2	$MnBr_2$	100	Neat	40
3	$MnBr_2$	120	Neat	77
4	$MnBr_2$	130	Neat	99 (94)
5	$MnBr_2$	130	Neat & m. sieves	99
6	$MnBr_2$	130	Neat TEMPO (2eq)	98

All reactions were performed on a 2.0 mmol scale, with 20 mol% catalyst loading for 20 hours. [a] Yield determined by GC/MS analysis, using *n*-octane as the internal standard. [b] After column chromatography.

Table 3. Optimization studies.



Entry	Metal source	mol%	Solvent	% GC yield[a] (isol. yield)[b]
1	$MnBr_2$	20	Neat	99
2	$MnBr_2$	10	Neat	98
3	$MnBr_2$	5	Neat	98 (95)

All reactions were performed on a 2.0 mmol scale, running at 130 °C for 20 hours. [a] Yield determined by GC/MS analysis, using *n*-octane as the internal standard. [b] After column chromatography.

For the last part of our investigation we studied the progress of the reaction over time (Table 1, see Supporting Information). $MnBr_2$ was used at 5 mol% loading under an inert atmosphere at 130 °C and solvent-less conditions, while the reaction was repeated for different reaction times and analysed by GC/MS. Based on these results, we were able to construct a reaction profile plot (Figure 1). The reaction reaches a yield plateau in 12 hours, proceeding to completion after 18 to 20 hours. Based on this result, we decided to run our substrate scope investigation studies that follow for 20 hours, given that some of the substrates we were planning to utilize are considered demanding coupling partners.

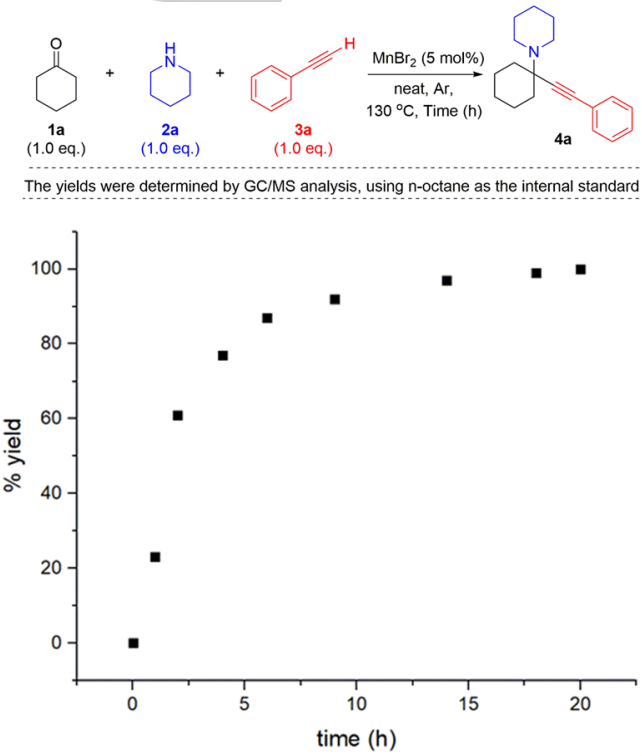
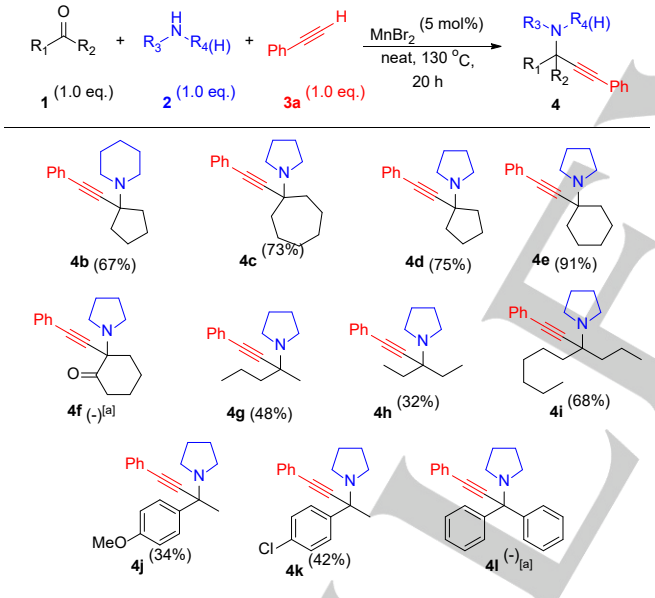


Figure 1. Kinetic profile of the reaction.

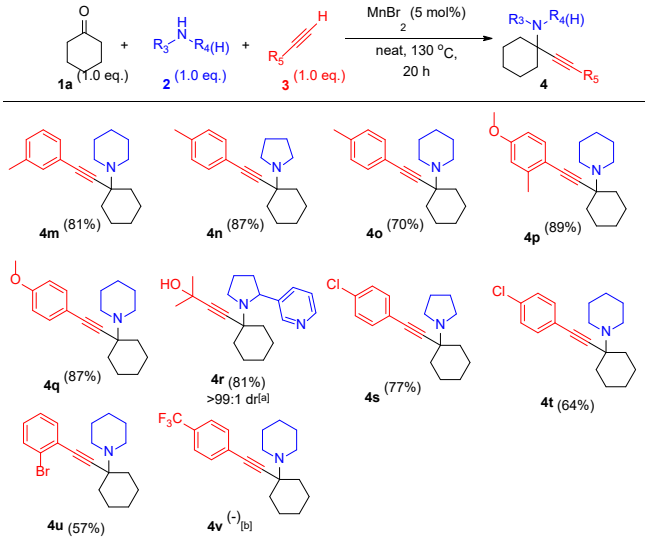
While investigating the scope of ketones (Scheme 2), phenylacetylene was used in combination with primarily pyrrolidine, as well as piperidine (Scheme 2). It was quickly determined that besides cyclohexanone a variety of different ketones can be successfully employed in this reaction under our protocol, with cyclopentanone and piperidine leading to propargylamine **4b** in 67% isolated yield. When cycloheptanone was used, propargylamine **4c** was obtained in 73% yield. Propargylamines **4d** or **4e** were obtained, in 75 or 91% isolated yield, respectively, when cyclopentanone or cyclohexanone were used along with pyrrolidine. The respective propargylamine **4f**, stemming from cyclohexane-1,2-dione, was not obtained. A drop

in the yield was observed when linear ketones were employed. More specifically, 2-pentanone and 3-pentanone resulted in propargylamines **4g** and **4h** in 38% and 48% isolated yields, respectively. On the contrary, when 4-decanone was used, propargylamine **4i** was obtained in 68% isolated yield. The increased steric hindrance and the lack of torsional strain release during the acetylide attack on the *in-situ* formed ketiminium ion are most probably the reasons for this reactivity pattern.[50–52,64] Additionally, the lower boiling points of 2-pentanone and 3-pentanone may have a negative impact on the outcome of the reaction, which was not observed when 4-decanone was deployed. Surprisingly, our catalytic protocol was also able to successfully mediate the KA^2 coupling reaction of aromatic ketones. This result is of outmost importance, since, thus far, only one other example has been reported in the literature.[68] Specifically, we screened aromatic ketones bearing both electron-withdrawing (EWGs) and electron-donating groups (EDGs). When 4-methoxy-acetophenone was used, propargylamine **4j** was isolated in 34% isolated yield. Similarly, when 4-chloro-acetetophenone was employed, the respective propargylamine **4k** was obtained in 42% isolated yield. When benzophenone was utilized, propargylamine **4l** was not observed, which may be because of the increased steric hindrance imparted from the two phenyl moieties in the *α*-position of the carbonyl group.



Scheme 2. The manganese-catalyzed KA^2 coupling: Scope of ketones. All reactions were performed on a 2.0 mmol scale and isolated yields are reported in parentheses. [a] The desired product was not observed by GC/MS analysis.

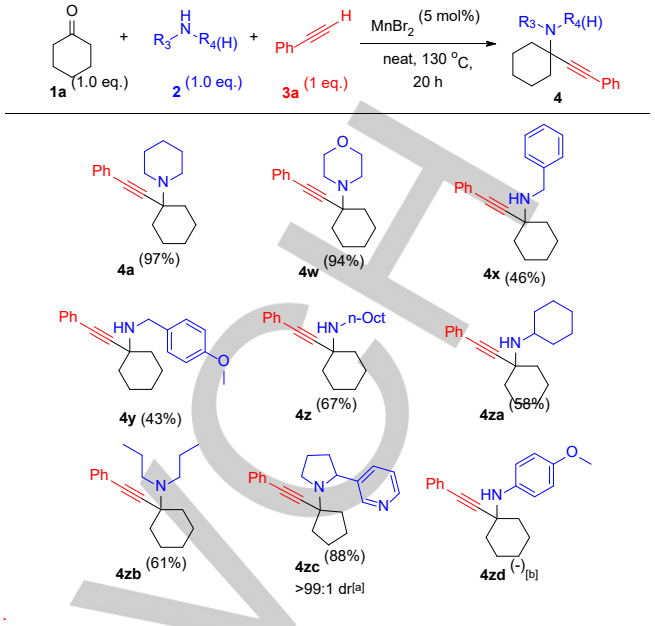
To study the scope of alkynes (Scheme 3), cyclohexanone, along with piperidine or pyrrolidine, were coupled with various terminal alkynes, leading to the formation of the corresponding propargylamines. The presence of electron-donating groups (EDGs) on the aromatic ring of the aromatic terminal alkynes leads to the generation of propargylamines in high to excellent yields. Specifically, 3-ethynyl-toluene couples with cyclohexanone and piperidine to afford propargylamine **4m** in 81% isolated yield. Similarly, when 4-ethynyl-toluene was employed along with pyrrolidine and cyclohexanone, propargylamine **4n** was isolated in 87% yield. Propargylamine **4o** was obtained in 70% isolated yield when *p*-methyl-phenylacetylene along piperidine and cyclohexanone were used. The coupling between 4-methoxy-2-methyl-phenylacetylene, piperidine and cyclohexanone led to the synthesis of **4p** in 89% isolated yield. Moreover, propargylamine **4q** was synthesized in 87% isolated yield using *p*-methoxy-phenylacetylene along with cyclohexanone and piperidine. We also became interested in the use of nornicotine, along with 2-methylbut-3-yn-2-ol and cyclohexanone, which allowed the synthesis of product **4r** as a single diastereoisomer (see ESI) in 81% isolated yield. Nornicotine is a natural, biologically-active molecule, bearing a pyridine moiety on the pyrrolidine heterocycle. Additionally, the pyrrolidine moiety is especially useful for derivatization of propargylic amines, taking into account their role as precursors to allenes.[112,113] Similarly, 2-methylbut-3-yn-2-ol is a useful handle for various applications,[114–119] providing access to terminal alkynes *via* a variety of deprotection techniques.[120,121] Alkynes bearing halide-containing moieties were also tested under our catalytic protocol. First, 4-chloro-ethynylbenzene was employed, along with pyrrolidine and cyclohexanone, leading to propargylamine **4s** in 77% isolated yield. When piperidine was used instead of pyrrolidine, the desired propargylamine (**4t**) was isolated in 64% yield. When 2-bromo-phenylacetylene was coupled with cyclohexanone and piperidine, the resulting propargylamine (**4u**) was obtained in 57% isolated yield. This decrease in yield may stem from the increased steric hindrance, because of the presence of the bromine atom in the *ortho* position of the aromatic ring, obstructing the nucleophilic attack of the manganese acetylide. Additionally, upon using *p*-trifluomethyl-phenylacetylene, propargylamine **4v** was observed by GC/MS analysis in low yields, but its isolation proved extremely difficult. This result suggests that strongly electron-withdrawing substituents reduce the ability of the corresponding acetylides to act as effective nucleophilic species. Furthermore, this observation agrees with the existing literature, in which the use of highly electron-deficient alkynes is rarely reported in similar studies, due to the decreased nucleophilicity of the respective acetylides.[68]



Scheme 3. The manganese-catalyzed KA^2 coupling: Scope of alkynes. All reactions were performed on a 2.0 mmol scale and isolated yields are reported in parentheses. [a] The diastereomeric ratio was determined by ^{1}H-NMR

analysis (see ESI). [b] This compound was detected by GC/MS analysis; however, it decomposed during column chromatography.

A wide variety of amines was also used, along with phenylacetylene and cyclohexanone (Scheme 4). As mentioned above, propargylamine **4a** was obtained 97% isolated yield during the optimization studies of our catalytic protocol. When morpholine was used, propargylamine **4w** was obtained in 94% isolated yield, while GC/MS analysis showed complete conversion. Benzylamine was also found to be a suitable coupling partner; propargylamine **4x** was obtained in 46% isolated yield. This decreased yield may be attributed to the increased stability of the intermediate ketimine. Similarly, when *p*-methoxy-benzylamine was used, the resulting propargylamine **4y** was isolated in 43% yield. We also tested the efficiency of our catalytic protocol on aliphatic amines. *N*-octylamine, along with cyclohexanone and phenylacetylene, furnished propargylamine **4z** in 67% isolated yield. Along the same lines, utilization of cyclohexylamine led to the desired product (**4za**) in 58% yield. Upon using the secondary amine di-*n*-propylamine, the desired product **4zb** was formed in 61% yield. Interestingly, the coupling between nornicotine, cyclopentanone and phenylacetylene led to the formation of the corresponding propargylamine (**4zc**) as a single diastereoisomer in 88% isolated yield, without the need of purification *via* column chromatography, since crystallization of the product was achieved using a simple, green protocol (described in the experimental section), developed from our research group in previous studies.[81] Aromatic amines have not been successfully utilized in the KA^2 coupling reaction thus far. Indeed, although the product of the coupling reaction of *p*-methoxy-aniline (**4zd**) was observed by GC/MS analysis, it rapidly decomposes in light and, despite our efforts, could not be isolated. We continued by testing our protocol under ambient conditions, performing the reaction under air. More specifically, we studied the coupling between morpholine, phenylacetylene and piperidine, which, under inert conditions, affords the synthesis of the desired product (**4w**) in 94% yield. To our surprise, our protocol furnished product **4w** in 89% isolated yield under air, after chromatographic purification. According to GC/MS analysis, the presence of air only slightly increased the formation of by-products. Additionally, we performed the synthesis of **4w** on large scale under air, to evaluate the scalability of our protocol. Upon using 10 mmols of morpholine, along with equimolar amounts of cyclohexanone and phenylacetylene, the desired product was obtained in 93% isolated yield.

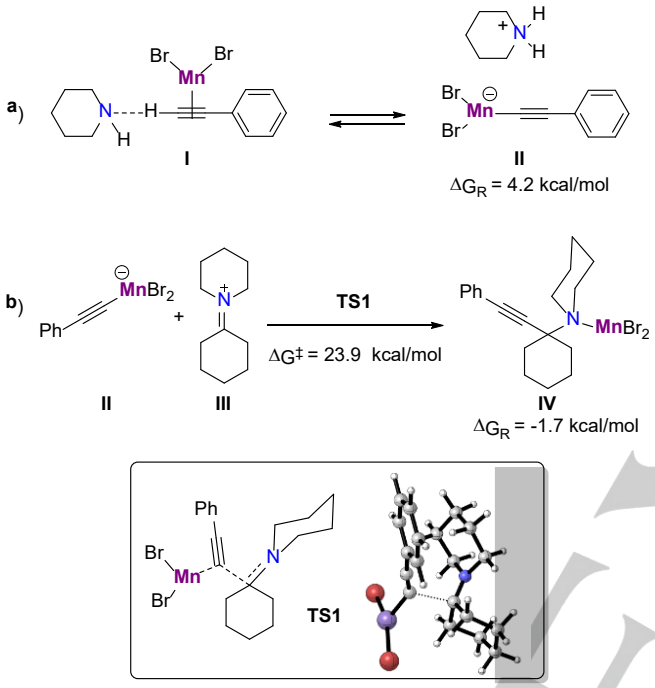


Scheme 4. The manganese-catalyzed KA^2 coupling: Scope of amines. All reactions were performed on a 2.0 mmol scale and isolated yields are reported in parentheses. [a] The diastereomeric ratio was determined by ^{1}H-NMR analysis (see Supporting Information). [b] The compound was detected by GC/MS analysis; however, it decomposes rapidly under ambient light. Despite our efforts, we could not isolate and characterize it.

To gain some insight into the reaction mechanism, we carried out DFT calculations with the Gaussian 16 set of programs, using the B97-D functional for the structure optimizations, together with the 6-31G(d,p) basis sets for all the atoms. Experimentally, the reactions are run in neat conditions, and we used cyclohexanone in an implicit solvent model (IEFPCM) for the best description of the reaction medium during the energy refinements.[122] We wanted to get information particularly about the role of the manganese salts during the process and also about the high temperatures needed in the reaction. As reagent models for the calculations, we used $MnBr_2$, cyclohexanone (**1a**), piperidine (**2a**) and phenylacetylene (**3a**).

The first interesting data is that the manganese dibromide and its complexes with the substrates have lower energy in the quartet spin state than in the doublet for every computed structure (usually > 10 kcal/mol difference), showing that the metal contains three unpaired electrons in degenerate orbitals, along the entire reaction coordinate. Initially, the coordination of $MnBr_2$ to the triple bond in **I** increases the acidity of the alkyne, and activates it for the deprotonation by piperidine.[ref] Upon proton abstraction, slippage of the metal fragment from the π-coordination to the terminal position produces the ate complex **II**, which is 4.2 kcal/mol higher in energy than **I** (Scheme 5a). Therefore, the reactive species **II** must be in a small concentration in the reaction medium. Then, the attack of the alkynyl-manganese **II** species to the immonium electrophile **III** presents an affordable activation energy (23.9 kcal/mol), in a transition state (**TS1**, Scheme 5b) that does not present any interaction between the manganese and the immonium moiety. After the final product is formed, a stable complex **IV** was located, containing the expected N-Mn coordination. Taken both steps together (from **I** to **TS1**), the overall activation energy is 28.1 kcal/mol, which is in agreement with the high temperatures needed in the process. In other words,

the nucleophilic attack of **II** to **III** could be moderately fast (23.9 kcal/mol), but is probably unfavourably affected by the small concentration of the nucleophile in the reaction medium. As detailed in the experimental section, $MnBr_2$ proved to be the most efficient catalyst, followed by MnI_2 and $MnCl_2$ (Table 1). Indeed, the activation energy of **TS1** in the presence of MnI_2 is higher (25.7 kcal/mol) than with $MnBr_2$. Meanwhile, $MnCl_2$ decreases the barrier to 22.8 kcal/mol, but its lower efficiency seems to be linked to a decreased coordination energy with the triple bond (>4 kcal/mol worse than $MnBr_2$), inducing a lower concentration of **II** in the reaction medium.



Scheme 5. a) Deprotonation equilibrium between $MnBr_2$-activated alkyne and alkynyl-Mn complex. b) C-C bond formation by nucleophilic attack of the alkyne to the immonium cation.

Conclusion

A sustainable catalytic system based on manganese has been developed for the challenging KA_2 coupling. The efficiency of $MnBr_2$ is reflected on the low catalyst loading needed and the range of substrates that can be derivatized. DFT calculations show that the coordination of $MnBr_2$ activates the alkyne to facilitate its deprotonation by the amine, forming an anionic complex, which is nucleophilic enough to attack the imminium species. The moderate activation energy of the C-C bond forming process, together with the low concentration of the alkynyl-manganese bromide, make this step rate limiting, explaining the range of temperatures used experimentally. This result suggests that the reaction rate should increase, even at lower temperatures, if appropriate ligand design enables the stabilization of the generated acetylide species, in order for its concentration to be higher, and also enhances its nucleophilicity. Further investigation based on these observations is ongoing in our laboratories.

Experimental Section

General reagent information

All chemicals were purchased from commercial sources and were used as received, with the exception of cyclohexanone and piperidine, which were distilled before use. All metal sources were in anhydrous form and their purity grade was at least 98%. Toluene purification was carried out according to published procedures, and the solvent was distilled and stored under inert atmosphere prior to use. The reactions were set up in a fume hood and allowed to proceed under an atmosphere of argon, in Teflon seal screw-cap pressure tubes which were flame-dried prior to use. The course of the reactions was followed by thin layer chromatography (TLC), using aluminium sheets (0.2 mm) coated with silica gel 60 with fluorescence material absorbing at 254 nm (silica gel 60 F254) or by GC-MS analysis of aliquots. The purification of the products was carried out by flash column chromatography, using columns packed with silica gel 60 (230-400 mesh) and the corresponding eluting system.

Computational Methods

All reported structures were optimized at Density Functional Theory level by using the unrestricted B97-D[123] functional, which includes Grimme´s dispersion, as implemented in Gaussian 16.[124] Optimizations were carried out with the 6-31G(d,p) basis set taking into account the doublet and quartet spin states for the Mn-containing species. The reported energy values correspond to Gibbs Free energies, including a solvent model (IEFPCM, cyclohexanone).[125] The critical stationary points were characterized by frequency calculations in order to verify that they have the right number of imaginary frequencies, and the intrinsic reaction coordinates (IRC)[126] were followed to verify the energy profiles connecting the key transition structures to the correct associated local minima.

General analytical information

^1H, ^{13}C and ^{19}F NMR spectra were measured on a Varian Mercury 200 MHz, or a Brucker Avance 400 MHz instrument, using $CDCl_3$ as the solvent and its residual solvent peak as a reference. ^1H-NMR spectroscopic data are given in the following order: chemical shift, multiplicity (s, singlet, d, doublet, t, triplet, q, quartet, m, multiplet), the *J* coupling constant in Hertz (Hz), and the number of protons. The GC-MS spectra were recorded with a Shimandzu® GCMS-QP2010 Plus, Chromatograph Mass Spectrometer using a MEGA® (MEGA-5, F.T: 0.25 µm, I.D.: 0.25 mm, L: 30 m, Tmax: 350 °C, Column ID# 11475) column, using *n*-octane as the internal standard. HRMS spectra were recorded in a QTOF maxis Impact (Bruker®) spectrometer with Electron Spray Ionization (ESI)

General procedure

Unless otherwise noted, the following procedure was used for all reactions: In a Teflon seal screw-cap pressure tube which had been flame-dried and was equipped with a stirring bar and a rubber septum was added 5 mol% $MnBr_2$ (21.5 mg, 0.1 mmol). Under an argon flow, 2.0 mmol of the amine were added and the mixture was stirred. Subsequently, 2.0 mmol of the corresponding alkyne were added and the mixture was stirred at room temperature and under an argon flow until the solid was either completely or partially dissolved. Briefly after the dissolution of the inorganic material, 2.0 mmol of the ketone were added and the rubber septum was replaced by a Teflon seal screw-cap under an argon flow. The reaction mixture was stirred in an oil bath, preheated at 130 °C, for 20 hours. After removal from the heating apparatus and cooling to room temperature, ethyl acetate was added (10 mL) and the mixture was stirred for 5 minutes in order to completely remove and dissolve the viscous mixture from the vessel's inner walls (this procedure was done twice, with 5 mL of solvent each time). The resulting mixture was filtered through a short silica gel plug in order to filter off inorganic materials, the filtrate was concentrated under vacuum and then loaded onto a silica gel column (if the compound was insoluble into the eluents' system, dry loading of the crude mixture was performed). Gradient column chromatography (usually of 15.0 cm length and 3.5 cm width and eluents' flow set at 2.0 cm/min) with ethyl acetate/petroleum

ether provided the desired products. All products were characterized by ^{1}H NMR, $^{13}C\{^{1}H\}$ NMR, and HRMS, which were all in agreement with the assigned structures.

Modified procedure for the synthesis of 3-(1-(1-(phenylethynyl)cyclopentyl)pyrrolidin-2-yl)pyridine (4zc single diastereoisomer).

The general reaction setup was carried out. After cooling the reaction to room temperature, crystals started to form. Ethyl acetate was added (2x5 mL), the mixture was stirred rapidly until all viscous materials were removed from the reaction vessel and inorganic materials were filtered off by passing the mixture through a short silica gel plug. The yellow solution was allowed to cool overnight, and pale-yellow crystals precipitated. The solid was filtered on a frit, washed with cold ethyl acetate and dried under vacuum. The final product was obtained as yellow crystals in 88% yield (557 mg, 1.76 mmol). ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.65 – 8.59 (s, 1H) , 8.49 – 8.38 (d, *J* = 8.6 Hz, 1H), 7.82 – 7.69 (d, *J* = 12.8 Hz, 1H), 7.51 – 7.37 (m, 2H), 7.34 – 7.13 (m, 4H), 4.30 – 4.22 (dd, *J* = 7.4, 17.7 Hz, 1H), 3.28 – 3.16 (s, 1H), 3.12 – 2.92 (q, *J* = 16.8 Hz, 1H), 2.42 – 2.09 (p, *J* = 16.4 Hz, 2H), 2.05 – 1.42 (m, 10H, overlapping peaks). $^{13}C\{^{1}H\}$ NMR (50 MHz, $CDCl_3$) δ 149.2, 147.9, 143.9, 134.8, 132.0, 128.5, 128.0, 123.8, 123.3, 92.2, 84.1, 67.0, 62.5, 51.7, 40.9, 40.8, 36.7, 24.2, 23.3, 22.8. HRMS (ESI-TOF) m/z $[M+H]^+$ calcd for $C_{22}H_{25}N_2$ 317.2012; Found 317.2018.

Modified procedure for the synthesis of 4-(1-(phenylethynyl)cyclohexyl)morpholine (4w) under air.

A Teflon seal screw-cap pressure tube equipped with a stirring bar was charged with 5 mol% $MnBr_2$ (21.5 mg, 0.1 mmol). Under air, 2.0 mmol of morpholine (174 mg, 175 µL) were added and the mixture was stirred until the solid was partially dissolved. 2.0 mmol of phenylacetylene (204 mg, 220 µL) were added and the mixture was stirred at room temperature until the solid was completely dissolved. Afterwards, 2.0 mmol of cyclohexanone (196 mg, 207 µL) were added and the pressure tube was quickly sealed by a Teflon seal screw-cap. The reaction mixture was stirred in an oil bath in an oil bath, preheated at 130 ºC, for 20 hours. After allowing the mixture to cool to room temperature, ethyl acetate was added and the mixture was stirred rapidly for 5 minutes. The crude product was filtered through a short silica gel plug using 5.0 mL of ethyl acetate. The mixture was concentrated under vacuum, and loaded atop a silica gel column. Eluting with mixtures of EtOAc:PE – 1:30 and gradual change until 1:9 and then flashed with EtOAc afforded the sufficiently pure product as a yellow oil in 89% yield (480 mg, 1.78 mmol). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.52 – 7.37 (m, 2H), 7.31 – 7.23 (m, 3H), 3.81 – 3.70 (t, *J* = 4.4 Hz, 4H), 2.79 – 2.65 (t, *J* = 4.9 Hz, 4H), 2.07 – 1.95 (d, *J* = 12.2 Hz, 2H), 1.73 – 1.40 (m, 8H, overlapping peaks). $^{13}C\{^{1}H\}$ NMR (50 MHz, $CDCl_3$) δ 132.0, 128.5, 128.0, 123.6, 89.9, 86.7, 67.6, 59.0, 46.8, 35.6, 25.9, 22.9.[61]

Modified procedure for the synthesis of 4-(1-(phenylethynyl)cyclohexyl)morpholine (4w) on a gram scale under air.

A Teflon seal screw-cap pressure tube equipped with a stirring bar was charged with 5 mol% $MnBr_2$ (107.3 mg, 0.5 mmol). Under air, 10.0 mmol of morpholine (0.871 g, 0.875 mL) were added and the mixture was stirred. 10.0 mmol of phenylacetylene (1.02 g, 1.10 mL) were added and the mixture was stirred at room temperature until the solid was completely dissolved. Finally, 10.0 mmol of cyclohexanone (0.981 g, 1.04 mL) were added and the pressure tube was quickly sealed by a Teflon seal screw-cap. The reaction reaction mixture was stirred in an oil bath, preheated at 130 ºC, for 20 hours. After allowing the mixture to cool to room temperature, ethyl acetate was added (2x10 mL) and the mixture was stirred rapidly for 5 minutes before being transferred to a round bottom flask. The mixture was concentrated under vacuum, and loaded atop a silica gel column. Eluting with mixtures EtOAc/PE – 1 : 30 and gradual change until 1 : 9 and then flashed with EtOAc afforded the sufficiently pure product as a yellow oil in 93% yield (2.50 g, 9.30 mmol). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.52 – 7.37 (m, 2H), 7.31 – 7.23 (m, 3H), 3.81 – 3.70 (t, *J* = 4.4 Hz, 4H), 2.79 – 2.65 (t, *J* = 4.9 Hz, 4H), 2.07 – 1.95 (d, *J* = 12.2 Hz, 2H), 1.73 – 1.40 (m, 8H, overlapping peaks).[122]

Characterization data for new compounds

1-(1-((4-chlorophenyl)ethynyl)cyclohexyl)pyrrolidine (**4s**): Prepared according to the general procedure and obtained as pale yellow crystals in 77% yield (440 mg, 1.53 mmol). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.40 – 7.25 (d, *J* = 8.5 Hz, 2H), 7.22 – 7.14 (d, *J* = 8.5 Hz, 2H), 2.76 – 2.67 (t, J = 5.8 Hz, 4H), 2.00 – 1.88 (d, *J* = 8.0 Hz, 2H), 1.81 – 1.38 (m, 12H, overlapping peaks). $^{13}C\{^{1}H\}$ NMR (50 MHz, $CDCl_3$) δ 133.78, 133.14, 128.65, 122.38, 91.85, 85.17, 59.45, 47.24, 38.02, 25.90, 23.72, 23.22. HRMS (ESI-TOF) m/z $[M+H]^+$ calcd for $C_{18}H_{23}ClN$ 288.1514; Found 288.1510.

2-methyl-4-(1-(2-(pyridin-3-yl)pyrrolidin-1-yl)cyclohexyl)but-3-yn-2-ol (**4r**, single diastereoisomer): Prepared according to the general procedure and obtained as pale yellow crystals in 81% yield (506 mg, 1.66 mmol) and >99:1 d.r. according to ^{1}H NMR. ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.55 (s, 1H), 8.37 (d, *J* = 4.8 Hz, 1H), 7.71 (d, *J* = 7.8 Hz, 1H), 7.16 (t, *J* = 6.4 Hz, 1H), 4.21 (d, *J* = 9.4 Hz, 1H), 3.41 (s, 1H), 3.12 (t, *J* = 6.0 Hz, 1H), 2.81 (q, *J* = 8.3 Hz, 1H), 2.15 – 1.93 (m, 1H), 1.93 – 1.74 (m, 2H), 1.80 – 1.60 (m, 3H), 1.55 (s, 6H), 1.49 – 1.32 (m, 5H), 1.34 – 1.15 (m, 2H), 1.10 – 0.83 (m, 3H). $^{13}C\{^{1}H\}$ NMR (50 MHz, $CDCl_3$) δ 148.2, 147.0, 145.3, 134.8, 123.2, 90.6, 82.7, 64.7, 60.3, 60.0, 49.8, 39.4, 38.2, 36.2, 32.5, 25.6, 23.8, 23.1, 23.0. HRMS (ESI-TOF) m/z $[M+H]^+$ calcd for $C_{20}H_{29}N_2O$ 313.2274 ; Found 313.2275.

1-(phenylethynyl)-N, N-dipropylcyclohexan-1-amine (4zb): Prepared according to the general procedure and obtained as a pale - yellow oil in 61% yield (346 mg, 1.22 mmol). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.54 – 7.37 (m, 2H), 7.34 – 7.20 (m, 3H), 2.75 – 2.51 (t, *J* = 7.8 Hz, 4H), 2.23 – 1.99 (d, *J* = 11.2 Hz, 2H), 1.78 – 1.37 (m, 12H, overlapping peaks), 1.02 – 0.70 (t, *J* = 7.3 Hz, 6H). $^{13}C\{^{1}H\}$ NMR (50 MHz, $CDCl_3$) δ 131.8, 128.4, 127.7, 124.3, 93.3, 85.1, 59.8, 52.7, 37.5, 29.9, 26.0, 23.5, 23.3, 12.2. HRMS (ESI-TOF) m/z $[M+H]^+$ calcd for $C_{20}H_{30}N$ 284.2373; Found 284.2374.

1-(1-((4-chlorophenyl)ethynyl)cyclohexyl)piperidine (4t): Prepared according to the general procedure and obtained as pale yellow crystals in 64% yield (380 mg, 1.26 mmol). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.39 – 7.29 (d, *J* = 8.7 Hz, 2H), 7.26 – 7.19 (d, *J* = 8.7 Hz, 2H), 2.63 (t, *J* = 5.0, 3.6 Hz, 4H), 2.03 (d, *J* = 9.9 Hz, 2H), 1.53 (m, 14H, overlapping peaks). $^{13}C\{^{1}H\}$ NMR (50 MHz, $CDCl_3$) δ 133.8, 133.1, 128.7, 122.5, 92.1, 85.2, 59.5, 47.4, 35.9, 26.8, 25.9, 24.9, 23.3. HRMS (ESI-TOF) m/z $[M+H]^+$ calcd for $C_{19}H_{25}ClN$ 302.1670; Found 302.1670.

1-(1-(p-tolylethynyl)cyclohexyl)pyrrolidine (4n): Prepared according to the general procedure and obtained as pale yellow crystals in 87% yield (465 mg, 1.74 mmol). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.36 – 7.29 (d, *J* = 8.1 Hz, 2H), 7.14 – 7.06 (d, *J* = 8.1 Hz, 2H), 2.89 (d, *J* = 6.0 Hz, 4H), 2.34 (s, 3H), 2.03 (t, *J* = 5.2 Hz, 2H), 1.84 (p, *J* = 3.3 Hz, 4H), 1.73 – 1.66 (t, 8H, overlapping peaks). $^{13}C\{^{1}H\}$ NMR (50 MHz, $CDCl_3$) δ 138.2, 131.9, 129.2, 120.4, 88.7, 87.0, 60.5, 47.5, 37.7, 25.7, 23.8, 23.3, 21.7. HRMS (ESI-TOF) m/z $[M+H]^+$ calcd for $C_{19}H_{26}N$ 268.2060; Found 268.2064.

Characterization data for known compounds

1-(1-(phenylethynyl)cyclohexyl)piperidine (**4a**): Prepared according to the general procedure and obtained as a yellow oil in 97% yield (519 mg, 1.94 mmol). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.47 – 7.36 (m, 2H), 7.28 – 7.23 (m, 3H), 2.66 (s, 4H), 2.11– 2.05 (m, 2H), 1.83 – 1.34 (m, 14H, overlapping peaks). $^{13}C\{^{1}H\}$ NMR (50 MHz, $CDCl_3$) δ 131.9, 128.4, 127.8, 124.0, 91.1, 86.3, 59.5, 47.4, 36.0, 26.9, 26.0, 25.0, 23.3.[63,70,76]

1-(1-(phenylethynyl)cyclopentyl)piperidine (**4b**): Prepared according to the general procedure and obtained as a yellow oil in 67% yield (339 mg, 1.34 mmol). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.41 (dd, *J* = 6.5, 3.2 Hz, 2H),

7.31 – 7.25 (m, 3H), 2.65 – 2.62 (m, 4H), 2.13 – 2.10 (m, 2H), 1.87 – 1.44 (m, 12H, overlapping peaks). $^{13}C\{^{1}H\}$ NMR (50 MHz, $CDCl_3$) δ 131.9, 128.4, 127.8, 124.0, 91.6, 85.4, 67.7, 50.5, 40.1, 26.4, 24.7, 23.6.[70]

1-(1-(phenylethynyl)cycloheptyl)pyrrolidine (**4c**): Prepared according to the general procedure and obtained as a yellow oil in 73% yield (390 mg, 1.46 mmol). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.42 (dd, *J* = 6.6, 3.1 Hz, 2H), 7.28 (dd, *J* = 6.6, 2.7 Hz, 3H), 2.79 (t, *J* = 6.0 Hz, 4H), 2.10 – 1.83 (m, 4H, overlapping peaks), 1.78 (p, *J* = 3.2 Hz, 4H), 1.71 – 1.46 (m, 8H, overlapping peaks). $^{13}C\{^{1}H\}$ NMR (50 MHz, $CDCl_3$) δ 132.0, 128.4, 128.0, 123.7, 91.4, 85.3, 63.3, 48.2, 40.0, 28.2, 24.0, 22.4.[70]

1-(1-(phenylethynyl)cyclopentyl)pyrrolidine (**4d**): Prepared according to the general procedure and obtained as an orange/yellow oil in 75% yield (359 mg, 1.50 mmol). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.48 – 7.35 (m, 2H), 7.33 – 7.17 (m, 3H), 2.88 – 2.61 (t, *J* = 6.7 Hz, 4H), 2.21 – 1.98 (m, 2H), 1.93 – 1.64 (m, 10H, overlapping peaks). $^{13}C\{^{1}H\}$ NMR (50 MHz, $CDCl_3$) δ 131.9, 128.4, 127.9, 123.9, 91.4, 85.1, 65.9, 49.5, 40.7, 23.9, 23.7.[70]

1-(1-(phenylethynyl)cyclohexyl)pyrrolidine (**4e**): Prepared according to the general procedure and obtained as an orange/yellow oil in 91% yield (461 mg, 1.82 mmol). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.44 (dd, *J* = 6.7, 3.1 Hz, 2H), 7.30 (m, 3H), 2.82 (t, *J* = 5.9 Hz, 4H), 2.13 – 1.94 (m, 2H), 1.91 – 1.41 (m, 12H, overlapping peaks). $^{13}C\{^{1}H\}$ NMR (50 MHz, $CDCl_3$) δ 131.7, 128.1, 127.6, 123.6, 90.3, 86.1, 59.3, 47.0, 37.8, 25.7, 23.5, 23.0.[76]

1-(3-methyl-1-phenylhex-1-yn-3-yl)pyrrolidine (**4g**): Prepared according to the general procedure and obtained as an orange/brown oil in 48% yield (232 mg, 0.96 mmol). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.45 – 7.36 (m, 2H), 7.28 – 7.25 (m, 3H), 2.79 (t, *J* = 5.4 Hz, 4H), 1.85 – 1.74 (m, 4H), 1.73 – 1.47 (m, 4H), 1.43 (s, 3H), 0.95 (t, *J* = 7.1 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (50 MHz, $CDCl_3$) δ 132.0, 128.4, 127.9, 123.8, 91.5, 84.7, 58.3, 48.0, 44.0, 26.1, 23.9, 18.0, 14.8.[76]

1-(3-ethyl-1-phenylpent-1-yn-3-yl)pyrrolidine (**4h**): Prepared according to the general procedure and obtained as a yellow oil in 32% yield (154 mg, 0.64 mmol). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.41 (dd, *J* = 6.7, 3.1 Hz, 2H), 7.32 – 7.23 (m, 3H), 2.78 (s, 4H), 1.88 – 1.66 (m, 8H, overlapping peaks), 0.96 (t, *J* = 7.4 Hz, 6H). $^{13}C\{^{1}H\}$ NMR (50 MHz, $CDCl_3$) δ 131.9, 128.3, 127.7, 123.8, 91.5, 85.0, 62.2, 47.6, 29.0, 23.7, 8.3.[81]

1-(4-(phenylethynyl)decan-4-yl)pyrrolidine (**4i**): Prepared according to the general procedure and obtained as a yellow oil in 68% yield (424 mg, 1.36 mmol). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.41 (dd, *J* = 6.6, 3.1 Hz, 2H), 7.32 – 7.24 (m, 3H), 2.76 (s, 4H), 1.88 – 1.58 (m, 8H, overlapping peaks), 1.51 – 1.18 (m, 10H), 1.00 – 0.77 (m, 6H). $^{13}C\{^{1}H\}$ NMR (50 MHz, $CDCl_3$) δ 131.7, 128.2, 127.6, 123.7, 91.6, 84.7, 61.3, 47.5, 39.4, 37.1, 31.9, 29.8, 23.6, 22.8, 17.2, 14.6, 14.2.[81]

1-(2-(4-methoxyphenyl)-4-phenylbut-3-yn-2-yl)pyrrolidine (**4j**): Prepared according to the general procedure and obtained as a yellow oil in 34% yield (208 mg, 0.68 mmol). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.76 – 7.63 (d, *J* = 8.7 Hz, 2H), 7.59 – 7.46 (dd, *J* = 2.7, 6.1 Hz, 2H), 7.41 – 7.29 (m, 3H), 6.95 – 6.83 (d, *J* = 8.7 Hz, 2H), 3.91 – 3.76 (s, 3H), 2.83 – 2.69 (m, 2H), 2.69 – 2.54 (m, 2H), 1.91 – 1.75 (m, 4H), 1.78 – 1.69 (s, 3H). $^{13}C\{^{1}H\}$ NMR (50 MHz, $CDCl_3$) δ 158.9, 138.2, 132.1, 128.6, 128.2, 127.8, 123.7, 113.6, 89.9, 87.4, 62.3, 55.5, 48.7, 32.6, 24.1.[68]

1-(2-(4-chlorophenyl)-4-phenylbut-3-yn-2-yl)pyrrolidine (**4k**): Prepared according to the general procedure and obtained as a yellow oil in in 42% yield (260 mg, 0.84 mmol). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.87 – 7.71 (d, *J* = 8.3 Hz, 2H), 7.66 – 7.53 (m, 2H), 7.47 – 7.30 (m, 5H, overlapping peaks), 2.87 – 2.75 (m, 2H), 2.72 – 2.59 (m, 2H), 1.91 – 1.79 (m, 4H), 1.82 – 1.70 (s, 3H). $^{13}C\{^{1}H\}$ NMR (50 MHz, $CDCl_3$) δ 144.7, 133.0, 132.2, 128.6, 128.5, 128.4, 128.2, 123.5, 89.1, 87.8, 62.5, 48.7, 32.8, 24.2.[68]

1-(1-(*m*-tolylethynyl)cyclohexyl)piperidine (**4m**): Prepared according to the general procedure and obtained as a yellow oil in 81% yield (456 mg, 1.64 mmol). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.25 – 7.03 (m, 4H), 2.77 – 2.61 (t, *J* = 3.0, 3.9 Hz, 4H), 2.36 – 2.30 (s, 3H), 2.15 – 2.03 (d, *J* = 12.1 Hz, 2H), 1.85 – 1.34 (m, 14H, overlapping peaks). $^{13}C\{^{1}H\}$ NMR (50 MHz, $CDCl_3$) δ 137.9, 132.3, 128.8, 128.6, 128.1, 123.6, 90.3, 86.4, 59.5, 47.2, 35.8, 26.6, 25.8, 24.8, 23.2, 21.3.[81]

1-(1-(*p*-tolylethynyl)cyclohexyl)piperidine (**4o**): Prepared according to the general procedure and obtained as a yellow oil in 70% yield (394 mg, 1.40 mmol). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.33 (d, *J* = 6.5 Hz, 2H), 7.09 (d, *J* = 6.5 Hz, 2H), 2.69 (s, 4H), 2.33 (s, 3H), 2.14 – 2.07 (m, 2H), 1.73 – 1.44 (m, 14H, overlapping peaks). $^{13}C\{^{1}H\}$ NMR (50 MHz, $CDCl_3$) δ 137.9, 131.8, 129.2, 120.8, 90.1, 86.4, 59.9, 47.3, 35.9, 26.6, 25.9, 24.9, 23.4, 21.6.[70]

1-(1-((4-methoxy-2-methylphenyl)ethynyl)cyclohexyl)piperidine (**4p**): Prepared according to the general procedure and obtained as a yellow crystals in 89% yield (554 mg, 1.78 mmol). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.34 (d, *J* = 8.4 Hz, 1H), 6.73 (s, 1H), 6.66 (d, *J* = 8.5 Hz, 1H), 3.77 (s, 3H), 2.73 – 2.63 (m, 4H), 2.42 (s, 3H), 2.11 (d, *J* = 11.5 Hz, 2H), 1.75 – 1.52 (m, 10H, overlapping peaks), 1.55 – 1.37 (m, 4H, overlapping peaks). $^{13}C\{^{1}H\}$ NMR (50 MHz, $CDCl_3$) δ 159.1, 141.5, 133.3, 116.0, 115.0, 111.1, 92.9, 84.8, 59.7, 55.3, 47.2, 36.0, 26.6, 25.8, 24.8, 23.3, 21.5.[81]

1-(1-((4-methoxyphenyl)ethynyl)cyclohexyl)piperidine (**4q**): Prepared according to the general procedure and obtained as yellow crystals in 87% yield (517 mg, 1.74 mmol). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.48 – 7.22 (d, *J* = 8.9 Hz, 2H), 6.92 – 6.70 (d, *J* = 8.9 Hz, 2H), 3.98 – 3.47 (s, 3H), 2.68 – 2.62 (t, *J* = 5.3 Hz, 4H), 2.31 – 1.91 (d, *J* = 12.7 Hz, 2H), 1.80 – 1.37 (m, 14H, overlapping peaks). $^{13}C\{^{1}H\}$ NMR (50 MHz, $CDCl_3$) δ 159.3, 133.2, 116.2, 114.0, 89.3, 86.0, 59.4, 55.4, 47.3, 36.1, 26.9, 26.0, 25.0, 23.3.[127]

1-(1-((2-bromophenyl)ethynyl)cyclohexyl)piperidine (**4u**): Prepared according to the general procedure and obtained as an orange oil in 57% yield (395 mg, 1.14 mmol). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.67 – 7.37 (m, 2H, overlapping peaks), 7.29 – 7.06 (m, 2H, overlapping peaks), 2.83 – 2.64 (t, *J* = 5.5 Hz, 4H), 2.25 – 2.09 (d, *J* = 11.6 Hz, 2H), 1.89 – 1.35 (m, 14H, overlapping peaks). $^{13}C\{^{1}H\}$NMR (50 MHz, $CDCl_3$) δ 133.7, 132.5, 129.0, 127.1, 126.0, 125.7, 96.1, 85.0, 59.9, 47.4, 35.9, 26.8, 25.9, 25.0, 23.4.[81]

***N*-benzyl-1-(phenylethynyl)cyclohexanamine** (**4x**): Prepared according to the general procedure and obtained as a yellow oil in 46% yield (266 mg, 0.92 mmol). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.56 – 7.16 (m, 10H, overlapping peaks), 3.97 (s, 2H), 2.01 – 1.95 (m, 2H), 1.77 – 1.41 (m, 8H, overlapping peaks). $^{13}C\{^{1}H\}$ NMR (50 MHz, $CDCl_3$) δ 141.1, 132.0, 128.9, 128.4, 128.2, 127.9, 127.0, 124.0, 90.7, 86.4, 59.6, 47.3, 38.1, 26.0, 23.8.[59]

***N*-(4-methoxybenzyl)-1-(phenylethynyl)cyclohexanamine** (**4y**): Prepared according to the general procedure and obtained as an orange oil in 43% yield (275 mg, 0.86 mmol). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.53 – 7.40 (m, 2H), 7.36 – 7.27 (m, 5H, overlapping peaks), 6.86 (d, *J* = 8.7 Hz, 2H), 3.91 (s, 2H), 3.79 (s, 3H), 2.00 – 1.94 (m, 2H), 1.75 – 1.39 (m, 8H, overlapping peaks). $^{13}C\{^{1}H\}$ NMR (50 MHz, $CDCl_3$) δ 158.9, 133.3, 132.0, 130.0, 128.6, 128.1, 124.0, 114.1, 93.9, 85.1, 55.6, 55.5, 47.7, 38.5, 26.2, 23.3.[59]

***N*-octyl-1-(phenylethynyl)cyclohexanamine** (**4z**): Prepared according to the general procedure and obtained as a yellow oil in 67% yield (417 mg, 1.34 mmol). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.42 (dd, *J* = 6.7, 3.1 Hz, 2H), 7.33 – 7.23 (m, 3H), 2.79 (t, *J* = 7.1 Hz, 2H), 1.94 (d, *J* = 11.6 Hz, 2H), 1.74 – 1.07 (m, 20H, overlapping peaks), 0.88 (dd, *J* = 9.7, 6.6 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (50 MHz, $CDCl_3$) δ 131.6, 128.1, 127.7, 123.6, 93.3, 84.6, 55.2, 43.2, 38.1, 31.8, 30.5, 29.5, 29.3, 27.5, 25.9, 23.1, 22.7, 14.1.[81]

***N*-cyclohexyl-1-(phenylethynyl)cyclohexan-1-amine** (**4za**): Prepared according to the general procedure and obtained as a yellowish oil in 58% yield (326 mg, 1.16 mmol). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.46 – 7.35 (m, 2H), 7.33 – 7.23 (m, 3H), 2.98 – 2.71 (dt, *J* = 6.6, 10.2 Hz, 1H), 2.04 – 1.84 (d, *J* = 10.2 Hz, 4H), 1.79 – 1.49 (m, 6H), 1.50 – 1.01 (m, 10H, overlapping peaks). ^{13}C{^{1}H} NMR (50 MHz, $CDCl_3$) δ 131.7, 128.5, 127.9, 124.1, 94.6, 84.1, 55.4, 52.8, 39.5, 36.8, 26.0, 26.0, 26.0, 23.4.[128]

Acknowledgements

This work was supported by the Hellenic Foundation for Research and Innovation (H.F.R.I.) under the "First Call for H.F.R.I. Research Projects to support Faculty members and Researchers and the procurement of high-cost research equipment grant" (Project Number: 16 – Acronym: SUSTAIN), as well as by European Funding: Horizon 2020-MSCA (ITN-EJD CATMEC 14/06-721223). The contribution of COST Action CA15106 (C-H Activation in Organic Synthesis - CHAOS) is also gratefully acknowledged. Moreover, we are thankful to the human and technical support provided by the IZO-SGI SGIker of UPV/EHU.

Keywords: manganese catalysis • ketone-amine-alkyne coupling • sustainability • multicomponent reactions • DFT calculations

[1] K. Lauder, A. Toscani, N. Scalacci, D. Castagnolo, *Chem. Rev.* **2017**, *117*, 14091-14200.
[2] V. A. Peshkov, O. P. Pereshivko, E. V. Van der Eycken, *Chem. Soc. Rev.* **2012**, *41*, 3790-3807.
[3] J. W. Langston, I. Irwin, E. B. Langston, L. S. Forno, *Science* **1984**, *225*, 1480−1482.
[4] J. J. Chen, D. M. Swope, *J. Clin. Pharmacol.* **2005**, *45*, 878−894.
[5] I. Bolea, A. Gella, M. Unzeta, *J. Neural. Transm.* **2013**, *120*, 893−902.
[6] F. T. Zindo, J. Joubert, S. F. Malan, *Future Med. Chem.* **2015**, *7*, 609−629.
[7] M. Baranyi, P. F. Porceddu, F. Gölöncsér, S. Kulcsár, L. Otrokocsi, Á. Kittel, A. Pinna, L. Frau, P. B. Huleatt, M.-L. Khoo, C. L. L. Chai, P. Dunkel, P. Mátyus, M. Morelli, B. Sperlágh, *Mol. Neurodegener.* **2016**, *11*, 1−21
[8] J. Marco-Contelles, M. Unzeta, I. Bolea, G. Esteban, R. R. Ramsay, A. Romero, R. Martínez-Murillo, M. C. Carreiras and L. Ismaili, *Front. Neurosci.* **2016**, *10*, 294.
[9] A. Albreht, I. Vovk, J. Mavri, J. Marco-Contelles, R. R. Ramsay, *Front. Chem.* **2018**, *6*, 169.
[10] D. S. Ermolat'ev, J. B. Bariwal, H. P. L. Steenackers, S. C. J. De Keersmaecker, E. V. Van der Eycken, *Angew. Chem. Int. Ed.* **2010**, *49*, 9465−9468.
[11] N. Sharma, U. K. Sharma, N. M. Mishra, E. V. Van der Eycken, *Adv. Synth. Catal.* **2014**, *356*, 1029-1037.
[12] F. Nie, D. L. Kunciw, D. Wilcke, J. Stokes, W. R. J. D. Galloway, S. Bartlett, H. F. Sore, D. R. Spring, *Angew. Chem. Int. Ed.* **2016**, *55*, 11139-11143.14
[13] B. Jiang, M. Xu, *Angew. Chem. Int. Ed.* **2004**, *43*, 2543-2646.
[14] J. J. Fleming, J. Du Bois, *J. Am. Chem. Soc.* **2006**, *128*, 3926-3927.
[15] V. K.-Y. Lo, Y. Liu, M.-K. Wong and C.-M. Che, *Org. Lett.*, **2006**, *8*, 1529-1532.
[16] S. Arshadi, E. Vessally, L. Edjlali, R. Hosseinzadeh-Khanmiri and E. Ghorbani-Kalhor, *Beilstein J. Org. Chem.*, **2017**, *13*, 625-638.
[17] X.-B. Zhao, W. Ha, K. Jiang, J. Chen, J.-L. Yang and Y.-P. Shi, *Green Chem.*, **2017**, *19*, 1399-1406.
[18] W.-J. Yoo, C.-J. Li, *Adv. Synth. Catal.* **2008**, ***350***, 1503-1506.
[19] X. Liu, M. Wang, S. Wang, Q.Wang, L. He, *ChemSusChem* **2016**, *10*, 1210-1216.
[20] Y. Yuan, Y. Xie, D. Song, C. Zeng, S. Chaemchuen, C. Chen, F. Verpoort, *Appl. Organomet. Chem.* **2017**, *31*, e3867.
[21] B. B. Touré, D. G. Hall, *Chem. Rev.* **2009**, *109*, 4439-4486.
[22] B. Ganem, *Acc. Chem. Res.* **2009**, *42*, 463-472.
[23] Dömling, W. Wang, K. Wang, *Chem. Rev.* **2012**, ***112***, 3083-3135.
[24] C. Chen, P. Liu,, J. Tang, G. Deng, X. Zeng, *Org. Lett.* **2017**, *19*, 2474–2477.
[25] R. Afshari, A. Shaabani, *ACS Comb. Sci.* **2018**, *20*, 499-528.
[26] B. M. Trost, *Science* **1991**, *254*, 1471-1476.
[27] R. Noyori, *Chem. Commun.* **2005**, 1807-1811.
[28] R. A. Sheldon, *Green Chem.* **2005**, *7*, 267-268.
[29] C.-J. Li, B. M. Trost, *Proc. Natl. Acad. Sci. U. S. A.*, **2008**, *105*, 13197-13202.
[30] P. G. Jessop, *Green Chem.* **2011**, *13*, 1391-1398.
[31] R. A. Sheldon, *Chem. Soc. Rev.* **2012**, *41*, 1437-1451.
[32] R. A. Sheldon, *Green Chem.* **2017**, *19*, 18-43.
[33] R. A. Sheldon, *Chem. Commun.* **2008**, 3352-3365.
[34] M. S. Holzwarth and B. Plietker, *ChemCatChem* **2013**, *5*, 1650-1679.
[35] N. V. Tzouras, I. K. Stamatopoulos, A. T. Papastavrou, A. A. Liori and G. C. Vougioukalakis, *Coord. Chem. Rev.* **2017**, *343*, 25-138.
[36] L. Zani, C. Bolm, *Chem. Commun.* **2006**, 4263-4275.
[37] C. Wei, Z. Li, C.-J. Li, *Synlett* **2004**, 1472-1483.
[38] M. Kidwai, V. Bansal, A. Kumar, S. Mozumdar, *Green Chem.* **2007**, *9*, 742-745.
[39] T. Zeng, W.-W. Chen, C. Cirtiu, A. Moores, G. Song, C.-J. Li, *Green Chem.*, **2010**, *12*, 570-573.
[40] C. Wei, Z. Li, C. J. Li, *Org. Lett.*, **2003**, *23*, 4473-4475.
[41] C. M. Wei, C. J. Li, *J. Am. Chem. Soc.*, **2003**, *125*, 9584-9585.
[42] C.-J. Li, C. Wei, *Chem. Commun.* **2002**, 268-269.
[43] S. Sakaguchi, T. Kubo, Y. Ishii, *Angew. Chem. Int. Ed.*, **2001**, *40*, 2534-2536.
[44] A. B. Dyatkin, R. A. Rivero, *Tetrahedron Lett.* **1998**, *39*, 3647-3650.
[45] W. J. Yoo, L. Zhao, C.-J. Li, *Aldrichimica Acta* **2011**, *44*, 43-52.
[46] C. Wei, C.-J. Li, *J. Am. Chem. Soc.* **2002**, *124*, 5638-5639.
[47] N. Gommermann, C. Koradin, K. Polborn, P. Knochel, *Angew. Chem. Int. Ed.* **2003**, *42*, 5763-5766.
[48] W. Zhuang, S. Saaby, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2004**, *43*, 4476-4478.
[49] R. Wada, T. Shibuguchi, S. Makino, K. Oisaki, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2006**, *128*, 7687-7691.
[50] H. C. Brown, J. Muzzio, *J. Am. Chem. Soc.* **1966**, *88*, 2811-2822.
[51] M. Cherest, H. Felkin, N. Prudent, *Tetrahedron Lett.* **1968**, 2199-2204.
[52] M. Cherest, H. Felkin, *Tetrahedron Lett.* **1968**, 2205-2208.
[53] A. Hager, N. Vrielink, D. Hager, J. Lefranc, D. Trauner, *Nat. Prod. Rep.* **2016**, *33*, 491-522.
[54] M. Biyikal, M. Porta, P. Roesky, S. Blechert, *Adv. Synth. Catal.* 2010, **352**, 1870-1875.
[55] C. J. Pierce, H. Yoo, C. H. Larsen, *Adv. Synth. Catal.* **2013**, *355*, 3586-3590.
[56] Z. Palchak, D. Lussier, C. Pierce, H. Yoo, C. H. Larsen, *Adv. Synth. Catal.* **2015**, *357*, 539-548.
[57] M. Periasamy, P. O. Reddy, I. Satyanarayana, L. Mohan, A. Edukondalu, *J. Org. Chem.* **2016**, *81*, 987-999.
[58] M. J. Aliaga, D. J. Ramón, M. Yus, *Org. Biomol. Chem.* **2010**, *8*, 43-46.
[59] O. P. Pereshivko, V. A. Peshkov, E. V. Van der Eycken, *Org. Lett.* **2010**, *12*, 2638-2641.
[60] D. D. Vachhani, A. Sharma, E. V. Van der Eycken, *Angew. Chem. Int. Ed.* **2013**, *52*, 2547-2550.
[61] M. Cheng, Q. Zhang, X.-Y. Hu, B.-G. Li, J.-X. Ji, A. C. Chan, *Adv. Synth. Catal.* **2011**, *353*, 1274-1278.
[62] Y. Suzuki, S. Naoe, S. Oishi, N. Fujii, H. Ohno, *Org. Lett.* **2011**, *14*, 326-329.
[63] C. J. Pierce and C. H. Larsen, *Green Chem.* **2012**, *14*, 2672-2676.
[64] Z. L. Palchak, D. J. Lussier, C. J. Pierce, C. H. Larsen, *Green Chem.* **2015**, *17*, 1802-1810.
[65] C. E. Meyet, C. J. Pierce, C. H. Larsen, *Org. Lett.* **2012**, *14*, 964-967.
[66] C. J. Pierce, M. Nguyen C. H. Larsen, *Angew. Chem.* **2012**, *124*, 12455-12458.
[67] X. Tang, J. Kuang, S. Ma, *Chem. Commun.* **2013**, *49*, 8976.
[68] Y. Cai, X. Tang and S. Ma, *Chem. Eur. J.* **2016**, *22*, 2266-2269.

[69] M. J. Albaladejo, F. Alonso, Y. Moglie, M. Yus, *Eur. J. Org. Chem.* ***2012***, *2012*, 3093-3104.
[70] M. Hosseini-Sarvari, F. Moeini, *New J. Chem.* **2014**, *38*, 624-635.
[71] F. Nemati, A. Elhampour, H. Farrokhi, M. Bagheri Natanzi, *Catal. Commun.* **2015**, *66*, 15-20.
[72] . Chinna Rajesh, U. Gulati, D. S. Rawat, *ACS Sustainable Chem. Eng.* **2016**, *4*, 3409-3419.
[73] U. Gulati, U. Chinna Rajesh, D. S. Rawat, *Tetrahedron Lett.* **2016**, *57*, 4468-4472.
[74] P. C. Perumgani, S. Keesara, S. Parvathaneni and M. R. Mandapati, *N. J. Chem.* **2016**, *40*, 5113-5120.
[75] S. Sadjadi, T. Hosseinnejad, M. Malmir, M. M. Heravi, *N. J. Chem.* **2017**, *41*, 13935-13951.
[76] G. Bosica, R. Abdilla, *J. Mol. Catal. A: Chem.* **2017**, *426*, 542-549.
[77] X. Xiong, H. Chen, X. Liao, S. Lai, L. Gao, *ChemistrySelect*, **2018**, 3, 8819-8825.
[78] A. Elhampour, M. Malmir, E. Kowsari, F. Boorboor ajdari, F. Nemati, *RSC Adv.*, **2016**, *6*, 96623-96634.
[79] S. Sadjadi, M. M. Heravi, M. Malmir, *Appl. Organomet. Chem.* **2017**, *32*, e4029.
[80] J. Cao, P. Li, G. Xu, M. Tao, N. Ma, W. Zhang, *Chem. Eng. J.* **2018**, *349*, 456-465.
[81] N. V. Tzouras, S. P. Neofotistos, G. C Vougioukalakis, *ACS Omega* **2019**, *4*, 10279–10292.
[82] D. A.Valyaev, G. Lavigne, N. Lugan, *Coord. Chem. Rev.* **2016**, *308*, 191–235.
[83] European Medicies Agency. Guideline on the specification limits for residues of metal catalysts or metal reagents. In *Commitee for medicinal products for human use*; 2008; pp 6–7.
[84] T. K. Mukhopadhyay, M. Flores, T. L. Groy, R. J. Trovitch, *J. Am. Chem. Soc.* **2014**, *136*, 882–885.
[85] J. Zheng, S. Chevance, C. Darcela, J. Sortaisa, *Chem. Commun.* **2013**, *49*, 10010–10112.
[86] M. Bourrez, F. Molton, S. Chardon-Noblat, A. Deronzier, *Angew. Chem. Int. Ed.* **2011**, *50*, 9903–9906.
[87] J. M. Smieja, M. D. Sampson, K. A. Grice, E. E. Benson, E. J. D. Froehlich, C. P. Kubiak, *Inorg. Chem.* **2013**, *52*, 2484–2491.
[88] J. Agarwal, T. W. Shaw, C. J. Stanton, G. F. Majetich, A. B. Bocarsly, H. F. Schaefer, *Angew. Chemie Int. Ed.* **2014**, *53*, 5152–5155.
[89] M. D. Sampson, A. D. Nguyen, K. A. Grice, C. E. Moore, C. E. A. L. Rheingold, C. P. Kubiak, *J. Am. Chem. Soc.* **2015**, *137*, 3718–3718.
[90] F. Franco, C. Cometto, F. Ferrero Vallana, F. Sordello, E. Priola, C. Minero, C. Nervi, R. Gobetto, *Chem. Commun.* **2014**, *50*, 14670–14673.
[91] H. Takeda, H. Koizumi, K. Okamoto, O. Ishitani, *Chem. Commun.* **2014**, *50*, 1491–1493.
[92] J. J. Walsh, G. Neri, C. L. Smith, A. J. Cowan, *Chem. Commun.* **2014**, *50*, 12698–12701.
[93] B. Meunier, *Chem. Rev.* **1992**, *92*, 1411–1456.
[94] J. Luo, S. Preciado, S. O. Araromi, I. Larrosa,. *Chem. Asian J.* **2016**, *11*, 347–350.
[95] C.-M. Che, V. K.-Y. Lo, C.-Y. Zhou, J.-S. Huang, *Chem. Soc. Rev.* **2011**, *40*, 1950-1975.
[96] H. Lu, X. P. Zhang, *Chem. Soc. Rev.* **2011**, *40*, 1899–1909.
[97] A. B. Sorokin, *Chem. Rev.* **2013**, *113*, 8152–8191.
[98] T. Katsuki, *Coord. Chem. Rev.* **1995**, *140*, 189–214.
[99] E. M. McGarrigle, D. G. Gilheany, *Chem. Rev.* **2005**, *105*, 1563-1602
[100] P. Saisaha, J. W. De Boer, W. R. Browne, *Chem. Soc. Rev.* **2013**, *42*, 2059–2074.
[101] Y. Kuninobu, Y. Nishina, T. Takeuchi, K. Takai, *Angew. Chem. Int. Ed.* **2007**, *46*, 6518–6520.
[102] B. Zhou, H. Chen, C. Wang, *J. Am. Chem. Soc.* **2013**, *135*, 1264–1267.
[103] R. He, Z. T. Huang, Q. Y. Zheng, C. Wang, *Angew. Chem. Int. Ed.* **2014**, *53*, 4950–4953.
[104] B. Zhou, P. Ma, H. Chen, C. Wang, *Chem. Commun.* **2014**, *50*, 14558–14561.
[105] W. Liu, D. Zell, M. John, L. Ackermann, *Angew. Chem. Int. Ed.* **2015**, *54*, 4092–4096.
[106] Y. Kuninobu, K. Kikuchi, K. Takai, *Chem. Lett.* **2008**, *37*, 740–741.
[107] S. N. Afraj, C. Chen, G. H. Lee, *RSC Adv.* **2014**, *4*, 26301–26308.
[108] E. Voutyritsa, I. Triandafillidi, N. V. Tzouras, N. F. Nikitas, E. K. Pefkianakis, G. C. Vougioukalakis, C. G. Kokotos, *Molecules* **2019**, *24*, 1644.
[109] A. T. Papastavrou, M. Pauze, E. Gómez-Bengoa, G. C. Vougioukalakis, *ChemCatChem* **2019**, *11,* 5379–5386.
[110] A. A. Liori, I. K. Stamatopoulos, A. Pinaka, G. C. Vougioukalakis, *Eur. J. Org. Chem.* **2018**, *2018*, 6134–6139.
[111] A. Pinaka, G. C. Vougioukalakis, *Coord. Chem. Rev.* **2015**, *288*, 69–97.
[112] X. Tang, C. Zhu, T. Cao, J. Kuang, W. Lin, S. Ni, J. Zhang, S. Ma, *Nat. Commun.* **2013**, *4*, 2450.
[113] J. Kuang, X. Tang, S. Ma, *Org. Chem. Front.* **2015**, *2*, 470–475.
[114] J. H. Park, D. H. Lee, H. Kong, M. J. Park, M. I. H. Jung, C. E. Park, H K. Shim, *Org. Electron.* **2010**, *11*, 820–830.
[115] A. C. Grimsdale, K. L. Chan, R. E. Martin, P. G. Jokisz, A. B. Holmes, *Chem. Rev.* **2009**, *40*, 897–1091.
[116] G. Mao, A. Orita, L. Fenenko, M. Yahiro, C. Adachi, J. Otera, *Mater. Chem. Phys.* **2009**, *115*, 378–384.
[117] X. Cheng, A. Heyen, W. Ver; Mamdouh, H. Uji-i, F. De Schryver, S. Höger, S. De Feyter, *Langmuir* **2007**, *23*, 1281–1286.
[118] K. Königsberger, G. P. Chen, R. R. Wu, M. J. Girgis, K. Prasad, O. Repič, T. J. Blacklock, *Org. Proc. Res. Dev.* **2003**, *7*, 733–742.
[119] A. Caporale, S. Tartaggia, A. Castellin, O. De Lucchi, *Beilstein J. Org. Chem.* **2014**, *10*, 384–393.
[120] J. Li, P. Huang, *Beilstein J. Org. Chem.* **2011**, *7*, 426–431.
[121] T. A. Gschneidtner, K. Moth-Poulsen, *Tetrahedron Lett.* **2013**, *54*, 5426–5429.
[122] For Computational Details, see the Supporting Information.
[123] S. Grimme, *J. Comp. Chem.* **2006**, *27*, 1787-1799
[124] Gaussian 16, Revision A.03; M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, T. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, and D. J. Fox, Gaussian, Inc., Wallingford CT, **2016**.
[125] a) E. Cancès, B. Mennucci, J. Tomasi, *J. Chem. Phys.* **1997**, *107*, 3032–3047; b) M. Cossi, V. Barone, B. Mennuci, J. Tomasi, *Chem. Phys. Lett.* **1998**, *286*, 253–260; c) J. Tomasi, B. Mennucci, E. Cancès, *J. Mol. Struct. (Theochem)*, **1999**, *464*, 211–226.
[126] C. Gonzalez, H. B. Schlegel, *J. Phys. Chem.* **1990**, *94*, 5523–5527.
[127] A. P. Shah, A. S. Sharma, S. Jain, N. G. Shimpi, *N. J. Chem.* **2018**, *42*, 8724–8737.
[128] T. Sugiishi, H. Nakamura, *J. Am. Chem. Soc.* **2012**, *134*, 2504–2507.

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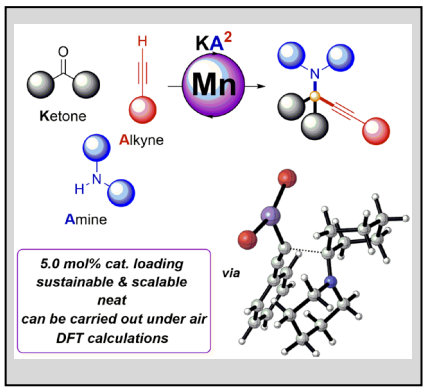

Manganese catalysis: A novel, user-friendly, sustainable catalytic system for the multicomponent coupling of ketones, amines and alkynes is described. Optimization studies show that higher temperatures unlock the potential of manganese as an efficient catalyst for this reaction, and functionalization of diverse and interesting substrates ensues. Computational investigation assists in explaining the catalytic behavior of manganese and sets the stage for further advancements.

Institute and/or researcher Twitter usernames: @Vougioukalakis, @HenryBengoa_, @uoaofficial