Metal-free intermolecular formal cycloadditions enable an orthogonal access to nitrogen heterocycles

Lan-Gui Xie\textsuperscript{1}, Supaporn Niyomchon\textsuperscript{1}, Antonio J. Mota\textsuperscript{2}, Leticia González\textsuperscript{2} & Nuno Maulide\textsuperscript{1}

Nitrogen-containing heteroaromatic cores are ubiquitous building blocks in organic chemistry. Herein, we present a family of metal-free intermolecular formal cycloaddition reactions that enable highly selective and orthogonal access to isoquinolines and pyrimidines at will. Applications of the products are complemented by a density functional theory mechanistic analysis that pinpoints the crucial factors responsible for the selectivity observed, including stoichiometry and the nature of the heteroalkyne.
Heteroarenes constitute one of the privileged core structural motifs in organic chemistry. Among them, isoquinolines and pyrimidines represent two big families in pharmaceutical agents, natural products and functional materials. Therefore, continued effort is devoted to the exploration of new and efficient synthetic strategies for these backbones.

The classical strategies to prepare isoquinolines (Fig. 1a) generally focus on the crucial textbook disconnections C1–C8a (Bischler–Napieralski and Pictet–Spengler syntheses) or C4–C4a (Pomeranz–Fritsch synthesis). Recently developed routes centred on the bond-forming events N2–C3 or N2–C3/C4–C4a, employing electrophile-triggered annulation and transition metal-catalysed C–H or C–halogen bond activation, respectively. A strategy relying on the simultaneous formation of N2–C3/C1–C8a is much less documented.

Conversely, most of the known avenues towards pyrimidine synthesis rely on the condensation of N–C–N subunits (mostly amidines or guanidines) with 1,3-dicarbonyl derivatives or the stoichiometric activation of carbonyl moieties with triflic anhydride (Fig. 1a). Ynamides have recently shown to be suitable candidates for regioselective cycloaddition with nitriles in the presence of a gold catalyst, leading to 4-aminopyrimidine cores. Although the reactivity of ynamides has received considerable recent attention, analogous investigation of the potential enclosed in the triple bond of thioalkynes is surprisingly rare, even though the resulting sulfide is a useful and versatile substituent.

Herein we report a family of reactions that enable a high yielding, orthogonal access to either isoquinolines or pyrimidines at will (Fig. 1b), by Brønsted acid-mediated regioselective formal cycloaddition of ynamides and thioalkynes with nitriles (for a review of transition-metal mediated [2 + 2 + 2] cycloadditions). Mechanistic studies reveal the subtle differences that are responsible for selectivity.

**Results**

**Synthesis.** Initial experiments involving the reaction of ynamide 1a with various Brønsted acids in the presence of varying amounts of acetonitrile led to moderate yields of isoquinoline 3aa. After optimization of conditions (see Supplementary Table 1 for details), we found that essentially equimolar amounts of 1a, 2a and TfOH in dichloroethane as solvent sufficed to enable preparation of 3aa in 89% yield (for a discussion of stoichiometry, vide infra).

Holding suitable conditions in hand, we then examined several nitriles 2a–j under the optimized conditions. As shown in Fig. 2a, this direct formal cycloaddition is applicable to a broad range of substrates, generally affording good to excellent yields of isoquinoline products. Remarkably, alkyl nitriles bearing...
functional groups such as an ester (2c), aryl rings (2h and 2i) or C–C double bonds (2j) are compatible with the reaction conditions. It is worth mentioning that the isolated double bond in product 3aj does not migrate into conjugation with the isoquinoline ring under these conditions. Aryl nitriles (2a–j) were also amenable to this transformation delivering isoquinoline products ripe for subsequent divergent functionalization. Thienopyridine skeletons could be obtained in reasonable yields (3ga and 3gh). Interestingly, N-tosyl-N-benzyl ynamide (1j) directly generated the corresponding debenzylated product: the tosyl-protected, pharmacologically relevant 3-aminoisoquinoline (3ja) (refs 44,45). Moreover, the use of an alkyl-substituted ynamide (1k) led to the annulated pyridine product (3ke). After this initial success, we hypothesized that other heteroatom-substituted alkynes might prove amenable to a similar modular assembly of isoquinolines. In particular, we were drawn to the use of thioalkynes such as 4b, with the expectation of obtaining an (alkythio)-isoquinoline 6ba where the sulfur residue could serve as a useful synthetic handle (Fig. 3a).

Much to our surprise, treatment of 4b with acetonitrile 2a under conditions identical to those employed previously led exclusively to the pyrimidine 5ba in 52% yield (Fig. 3a). Remarkably, product 5ba is the result of a formal, regioselective cycloaddition of one molecule of 4b with two molecules of 2a. This dramatic shift in product selectivity between ynamides and thioalkynes eventually presented us with a versatile cycloaddition Figure 3b depicts the full scope of nitriles 2b–v compatible with this metal-free pyrimidine synthesis. Secondary aliphatic (2k) and alicyclic (2m–2p) carbonitriles smoothly coupled with thioalkyne 4a under the reaction conditions. This formal cycloaddition was also tolerant of nitriles bearing triple (2q) and double bonds (2j), including conjugated olefins (2f). Both electron-rich (2d and 2s) and electron-deficient (2t and 2u) substituted benzonitriles could be employed, providing the desired pyrimidine products in good to excellent yields. It is worth noting that heteroaryl nitriles such as 3-cyanothiophene (2r) were also tolerated. The possibility...
of using dimethylcyanamide (2v), delivering an aminated pyrimidine in excellent yield, further highlighting the generality of this synthetic method. Pyrimidine 5ae yielded crystals suitable for X-ray diffraction analysis, unambiguously confirming its structure (see Supplementary Fig. 64 and Supplementary Tables 4 and 5 for details).

Further studies focused on the scope of heteroalkynes for this pyrimidine synthesis (Fig. 4a). We were pleased to find that a cyclopropyl substituent (4c) was tolerated, as a cyclopropyl appended to a pyrimidine ring is a common feature in drug-like, biologically active cores46–48. Both electron-rich (4e and 4g) and electron-poor (4d and 4f) arylalkynes afforded the corresponding pyrimidine products in good yields. Furthermore, considerable flexibility can be exerted, concerning the location of substituents on the aryl ring (4d–g).

Strikingly, we found that 4-aminosubstituted pyrimidines can also be obtained by exposing ynamides (1l, 1a and 1m) to the standard conditions developed for pyrimidine synthesis. A distal nitrile group carried by the ynamide partner could be successfully introduced into the pyrimidine product (7ma). Remarkably, when phenyl-substituted ynamide 1a was submitted to these conditions, a 4-amino-5-aryl pyrimidine product (7aa) was obtained in good yield (Fig. 4b). Together with the reactions described previously (cf. Figures 2–3), these results offer an entirely new orthogonal access to either isoquinoline or pyrimidine motifs at will, while unifying this novel, powerful family of formal cycloaddition reactions.

Density functional theory study. We approached the mechanistic study of this reaction performing density functional theory (DFT) calculations of two reaction manifolds: the first leading to isoquinoline products (by modelling the entire pathway introducing a single acetonitrile molecule, see Fig. 5a) and the second leading to pyrimidine adducts (by computing the mechanism with two acetonitrile molecules, see Fig. 5b). The first question that arises is what occurs when all these species are in the presence of the TfOH promoter, as there are many potential protonation sites. DFT calculations (see Computational details in the Supplementary Figs 65–67) show that protonation would take place preferably on the heteroalkyne partner. Indeed, calculated transition states for the oxazolidinone ( + 7.6 and + 6.0) and methylthio (+ 5.3 and + 10.7) derivatives (in the presence of either one or two acetonitrile molecules, IIi and IIip, respectively) are much lower than the acetonitrile protonation (+ 17.0 Kcal mol$^{-1}$). Furthermore, we confirmed that this protonation takes place regioselectively β- to the heteroatom as anticipated, leading to either a keteniminium IIIi or ketenethionium IIIip species, as the TiO$^{-}$ anion is stabilized by acetonitrile (which in these reactions coincides with the nucleophilic species). In the second mechanistic step, a nucleophilic attack by acetonitrile takes place stereoselectively from the face opposite to the β-proton due to shielding by TiO$^{-}$ (see IVi and IVip in Fig. 5). In fact, in both cases the introduction of acetonitrile, giving respectively $V_i$ and $V_{ip}$, is more stable than the corresponding TiO$^{-}$ bonded derivative by 6.1 and 7.7 Kcal mol$^{-1}$ for

Figure 3 | Synthesis of pyrimidine. (a) Unexpected synthesis of pyrimidine 5ba. (b) Scope of nitriles in the synthesis of pyrimidines 5.
organic and methylthio derivatives, respectively. Interestingly, and very important for the reaction outcome, in the absence of acetonitrile the TIO\(^-\) species easily adds to the positively charged intermediate effectively blocking further reaction with acetonitrile. Moreover, we verified that nucleophilic attack by acetonitrile can only take place after the first protonation event as the highest occupied molecular orbital of acetonitrile (∼0.3264 H) and the neutral ynamide’s lowest unoccupied molecular orbital (∼0.0242 H) are energetically too far apart. The protonation process, however, results in an alkyne-centred molecular orbital (−0.208 and −0.210 e\(^-\)) and the neutral ynamide’s lowest unoccupied molecular orbital of the TIO\(^-\) counteranion lies at −0.0742 H (see Supplementary Figs 65 in the Computational details section of the Supplementary Information). A similar trend is observed for the methylthio derivatives, (as the former lost its prior stabilization by acetonitrile) delivering rather stable intermediates (VII\(_p\)) giving rise to rather stable intermediates (VII\(_p\)). Once the second molecule is added, the system could conceivably undergo a polymerization process with continued further addition of more acetonitrile molecules to the newly generated carbocationic species (∼0.546 and ∼0.529 e\(^-\)), respectively, for the oxazolidinone and methylthio derivatives). Instead, the negatively charged (∼0.208 and ∼0.210 e\(^-\)), for the oxazolidinone and methylthio derivatives, respectively) β-carbon atom can attack (VIII\(_p\)) the newly generated carbocation to form an entropically favoured, six-membered pyrimidine ring (after a very exothermic re-aromatization promoted by TIO\(^-\), IX\(_p\)→X\(_p\)). This is the driving force for pyrimidine formation.

Pyrimidine formation. In this case, with two acetonitrile molecules (used for simplicity of the model, although the experimentally optimized molar ratio is higher), a different situation arises as a second addition becomes a more probable event. In fact, this process takes place through low energy-transition states (∼+6.5 and ∼+7.1 Kcal mol\(^{-1}\), respectively, for the oxazolidinone and methylthio derivatives), VI\(_p\), giving rise to rather stable intermediates (VII\(_p\), see Fig. 5b). Once the second molecule is added, the system could conceivably undergo a polymerization process with continued further addition of more acetonitrile molecules to the newly generated carbocationic species (∼+0.546 and ∼+0.529 e\(^-\)), respectively, for the oxazolidinone and methylthio derivatives). Instead, the negatively charged (∼0.208 and ∼0.210 e\(^-\)), for the oxazolidinone and methylthio derivatives, respectively) β-carbon atom can attack (VIII\(_p\)) the newly generated carbocation to form an entropically favoured, six-membered pyrimidine ring (after a very exothermic re-aromatization promoted by TIO\(^-\), IX\(_p\)→X\(_p\)). This is the driving force for pyrimidine formation.

A comparative analysis of both calculated mechanisms reveals at a glance that those involving the oxazolidinone derivative proceed generally with lower energies than the thioalkyne one. The main reason for that is the greater stabilization of the positive charge in the former case. In addition, although pathways for

The main reason for that is the greater stabilization of the positive charge in the former case. In addition, although pathways for

the oxazolidinone and methylthio derivatives, respectively. Interestingly, and very important for the reaction outcome, in the absence of acetonitrile the TIO\(^-\) species easily adds to the positively charged intermediate effectively blocking further reaction with acetonitrile. Moreover, we verified that nucleophilic attack by acetonitrile can only take place after the first protonation event as the highest occupied molecular orbital of acetonitrile (∼0.3264 H) and the neutral ynamide’s lowest unoccupied molecular orbital (∼0.0242 H) are energetically too far apart. The protonation process, however, results in an alkyne-centred molecular orbital (−0.208 and −0.210 e\(^-\)) and the neutral ynamide’s lowest unoccupied molecular orbital of the TIO\(^-\) counteranion lies at −0.0742 H (see Supplementary Figs 65 in the Computational details section of the Supplementary Information). A similar trend is observed for the methylthio derivatives, (as the former lost its prior stabilization by acetonitrile) delivering rather stable intermediates (VII\(_p\)) giving rise to rather stable intermediates (VII\(_p\)). Once the second molecule is added, the system could conceivably undergo a polymerization process with continued further addition of more acetonitrile molecules to the newly generated carbocationic species (∼0.546 and ∼0.529 e\(^-\)), respectively, for the oxazolidinone and methylthio derivatives). Instead, the negatively charged (∼0.208 and ∼0.210 e\(^-\)), for the oxazolidinone and methylthio derivatives, respectively) β-carbon atom can attack (VIII\(_p\)) the newly generated carbocation to form an entropically favoured, six-membered pyrimidine ring (after a very exothermic re-aromatization promoted by TIO\(^-\), IX\(_p\)→X\(_p\)). This is the driving force for pyrimidine formation.

Pyrimidine formation. In this case, with two acetonitrile molecules (used for simplicity of the model, although the experimentally optimized molar ratio is higher), a different situation arises as a second addition becomes a more probable event. In fact, this process takes place through low energy-transition states (∼+6.5 and ∼+7.1 Kcal mol\(^{-1}\), respectively, for the oxazolidinone and methylthio derivatives), VI\(_p\), giving rise to rather stable intermediates (VII\(_p\), see Fig. 5b). Once the second molecule is added, the system could conceivably undergo a polymerization process with continued further addition of more acetonitrile molecules to the newly generated carbocationic species (∼+0.546 and ∼+0.529 e\(^-\)), respectively, for the oxazolidinone and methylthio derivatives). Instead, the negatively charged (∼0.208 and ∼0.210 e\(^-\)), for the oxazolidinone and methylthio derivatives, respectively) β-carbon atom can attack (VIII\(_p\)) the newly generated carbocation to form an entropically favoured, six-membered pyrimidine ring (after a very exothermic re-aromatization promoted by TIO\(^-\), IX\(_p\)→X\(_p\)). This is the driving force for pyrimidine formation.

A comparative analysis of both calculated mechanisms reveals at a glance that those involving the oxazolidinone derivative proceed generally with lower energies than the thioalkyne one. The main reason for that is the greater stabilization of the positive charge in the former case. In addition, although pathways for
Figure 5 | Energy profiles. Isoquinoline (a, up, i subscript in roman numerals) and pyrimidine (b, down, p subscript in roman numerals) formation for the oxazolidinone (blue) and methylthio (red) derivatives. The corresponding three-dimensional structure sequence is exemplified for the methylthio derivative, for both a and b pathways, in Supplementary Figs 66 and 67, respectively.
formation of either heterocycle could exist for both heteroalkynes, the pathway for isoquinoline formation through the thioalkyne derivative (Fig. 5a) has a prohibitive energy barrier when considering the addition of a single acetonitrile molecule. This barrier is much lower in the case of pyrimidine formation (Fig. 5b). This is due to the fact that in the latter case, there is a significant stabilization of the corresponding transition state introduced by the presence of the second acetonitrile molecule. Yet, the transition state for the first acetonitrile attack is 5.2 Kcal mol\(^{-1}\) higher in the case of isoquinoline formation. In this value, 3.2 Kcal mol\(^{-1}\) are purely due to the stabilization offered by the second acetonitrile molecule, as calculations made considering cationic structures (namely just the substrate and the acetonitrile molecule(s) without the TfO\(^{-}\) species) show this same energy difference. Therefore, the remaining 2 Kcal mol\(^{-1}\) should derive from stabilization by the counteranion (which is present in our mechanistic studies) through cooperative Cyclic \(\delta^+ \cdot \delta^-\) interactions between the different molecular units (see Fig. 6). In fact, we expect this transition state to be very low-lying, taking into account more solvent molecules. The preceding mechanistic analysis also permits a rationalization of why isoquinoline synthesis (formal \([4 + 2]\); (refs 49–52)) requires high temperatures (highest energy barriers), whereas pyrimidine formation (formal \([2 + 2 + 2]\)) typically occurs at room temperature.

In both cases, stoichiometry plays a crucial role and imposes the final result, as both pathways are irreversible. In the presence of several molecules of acetonitrile (Fig. 5b), the corresponding transition state for a real \([2 + 2 + 2]\) approximation is either transition state \(\text{IV}_p\) or \(\text{VI}_p\), depending on the initial geometry conditions. These transition state also appear in a sequential pathway (as described in Fig. 5), thus indicating a natural direction for this molecular set. In the case of isoquinoline formation (Fig. 5a), the reaction of the unique acetonitrile molecule (imposed by stoichiometry) creates a positive charge that is readily neutralized by the negatively charged triflate present in the surrounding (as a remnant from the initial protonation event). The latter reaction should be faster than the time required for another acetonitrile molecule to approach, to

![Figure 6](image_url)  
**Figure 6 | Transition states for the first acetonitrile addition.** Isoquinoline (left) and pyrimidine (right) pathways, the latter presenting additional cyclic, electrostatic stabilizing interactions.

**Figure 7 | Synthetic application and modification.** (a) Preparation of norlaudanosine 8 by hydrogenation of 3di. (b) Transformations of compound 5ba. (c) Reductive desulfurization of compound 5aa. (d) Pyrimidine 7aa can be prepared in gram scale.
follow pathway B. Once triflate blocks this position, a quite stable intermediate (V₃) is formed and no additional acetonitrile molecules can be added.

It is noteworthy that although all the computed reaction pathways would only require a catalytic amount of TfOH to proceed (owing to its regeneration on aromatization, vide supra), the most stable final product in either pathway is the corresponding nitrogen-protonated heterocycle (readily converted into the experimentally isolated products following basic workup). This neatly accommodates the experimental need for stoichiometric amounts of acid, to obtain high yields.

Further studies. Given the prevalence of isoquinoline motifs in the core of bioactive molecules⁵³–⁵⁵, we were eager to showcase Further studies.

computational details can be found in the Supplementary Information. Full experimental details, characterization of compounds, Cartesian coordinates of the methods enables the preparation of either family of pyrimidine motifs has been developed, by Brønsted acid-promoted regioselective merger of alkynes and nitriles. These metal-free formal cycloadditions is illustrated by the large scope of alkynes and nitriles that can be employed. DFT calculations reveal the crucial role of TfOH and the reaction stoichiometry in these processes. With one equivalent of acetonitrile, the preferred pathway leads to isoquinoline products through a Friedel–Crafts-like process; with larger amounts of nitrile, a second addition is allowed en route to the formation of a pyrimidine derivative. Furthermore, subtle differences between the classes of heteroalkynes employed control which products can be formed. We believe that the simple yet powerful heterocycle syntheses presented here will be eagerly adopted into the repertoire of synthetic chemistry.

Methods

Discussion

A family of reactions selectively leading to isoquinoline and pyrimidine motifs has been developed, by Bronsted acid-promoted regioselective merger of alkynes and nitriles. These methods benefit from the strategic use of readily available nitriles as the C–N sources. Most importantly, the orthogonality of the heterocycles enables the preparation of either family of heterocycles from the same starting materials. The practicality of these metal-free formal cycloadditions is illustrated by the large scope of alkynes and nitriles that can be employed. DFT calculations reveal the crucial role of TfOH and the reaction stoichiometry in these processes. With one equivalent of acetonitrile, the preferred pathway leads to isoquinoline products through a Friedel–Crafts-like process; with larger amounts of nitrile, a second addition is allowed en route to the formation of a pyrimidine derivative. Furthermore, subtle differences between the classes of heteroalkynes employed control which products can be formed. We believe that the simple yet powerful heterocycle syntheses presented here will be eagerly adopted into the repertoire of synthetic chemistry.

Methods

Figures 7a, this can be achieved by the action of alcohols, amines or Grignard reagents, delivering substituted pyrimidines 10–12 in very good to excellent yields. In addition, Raney-Ni-mediated hydrogenation of 5aa smoothly excises the sulfide residue to afford the 2,5,6-trisubstituted pyrimidine 13 in 87% yield (Fig. 7c). These simple transformations outline the versatility and usefulness of the methods reported herein. Moreover, the reaction can be readily carried out in gram scale (Fig. 7d).

References

1. Joule, J. A. & Mills, K. Heterocyclic Chemistry 5th edn 194–200 (John Wiley & Sons, Ltd, 2010).
2. Iranshahi, M., Quinn, R. J. & Iranshahi, M. Biologically active isoquinoline alkaloids with drug-like properties from the genus Corydalis. RSC Adv. 4, 15990–15913 (2014).
3. Bentley, K. W. β-Phenylethylamines and the isoquinoline alkaloids. Nat. Prod. Rep. 23, 444–463 (2006).
4. Su, Y. J. et al. Highly efficient red electrophosphorescent devices based on iridium isoquinoline complexes: remarkable external quantum efficiency over a wide range of current. Adv. Mater. 15, 884–888 (2003).
5. Ho, C.-L. et al. Light-red-emitting iridium complexes with hole-transporting 9-arylcarbazole moieties for electrophosphorescence efficiency/color purity trade-off optimization. Adv. Funct. Mater. 18, 319–331 (2008).
6. Walker, S. R., Carter, E. J., Huff, B. C. & Morris, J. C. Variolins and related alkaloids. Chem. Rev. 109, 3080–3098 (2009).
7. Lagoa, I. M. Pyrimidines as constituent of natural biologically active compounds. Chem. Biodivers. 2, 1–50 (2005).
8. Köytepe, S., Paşahanoğlu, E., Ekinci, E. & Seckin, T. Synthesis, characterization and H₂O₂-sensing properties of pyrimidine-based hyperbranched polylactones. Eur. Polym. J. 41, 121–127 (2005).
9. Gompper, R., Mair, H. J. & Polborn, K. Synthesis of oligo(diazaphenyls). Tailor-made fluorescent heteroaromatics and pathways to nanostructures. Synthesis (Mass) 696–718 (1997).
10. He, R., Huang, Z.-T., Zheng, Q.-Y. & Wang, C. Isoquinoline skeleton synthesis via chelation-assisted C-H activation. Tetrahedron Lett. 55, 5705–5713 (2014).
11. Shi, Z., Koester, D. C., Boultadakis-Arapinis, M. & Glorius, F. Rh(III)-catalyzed synthesis of multisubstituted isoquinoline and pyridine N-oxides from oximes and dioxo compounds. J. Am. Chem. Soc. 135, 12204–12207 (2013).
12. Zhao, D., Lied, F. & Glorius, F. Rh(III)-catalyzed C–H functionalization/ aromatization cascade with 1,3-dienes: a redoxneutral and regioselective access to isoquinolines. Chem. Sci. 5, 2869–2873 (2014).
13. Roesch, K. R., Zhang, H. & Laroc, R. C. Synthesis of isoquinolines and pyridines by the palladium-catalyzed iminoannulation of internal alkynes. J. Org. Chem. 66, 8042–8051 (2001).
14. Fischer, D. et al. Iodine-mediated electrocyclic cyclization of 2-alkynyl-1-methylene azide aromatics leading to highly substituted isoquinolines and its application to the synthesis of Norchelerythrine. J. Am. Chem. Soc. 130, 15720–15725 (2008) and references therein.
15. Gilmore, C. D., Allan, K. M. & Soltz, B. M. Orthogonal synthesis of indolines and isoquinolines via azirine annulation. J. Am. Chem. Soc. 130, 1558–1559 (2008).
16. Castillo, J.-C., Quiroga, J., Abonia, R., Rodríguez, I. & Coquerel, Y. The aryleneaza-Diels–Alder reaction: flexible syntheses of isoquinolines. Org. Lett. 17, 3374–3377 (2015).
17. Coppola, A., Sucunza, D., Burgos, C. & Vaquero, J. J. Isoquinoline synthesis by heterocyclization of tosylmethyl isocyanide derivatives: total synthesis of mansouramycin B. J. Org. Chem. 66, 8042–8051 (2001).
18. Martínez, A. G., Fernández, A. H., Vilchez, D. M., Güiterrez, M. L. L. & Subramanian, L. R. A new easy one-step synthesis of isoquinoline derivatives from substituted phenylacetic esters. Synlett. 1993, 229–230 (1993).
19. Hill, M. D. & Movassaghi, M. New strategies for the synthesis of pyrimidine derivatives. Chem. Eur. J. 14, 6836–6844 (2008) and references therein.
20. Movassaghi, M. & Hill, M. D. Single-step synthesis of pyrimidine derivatives. J. Am. Chem. Soc. 128, 14254–14255 (2006).
21. Martínez, A. G. et al. On the mechanism of the reaction between ketones and trifluoromethanesulfonic anhydride. An improved and convenient method for the preparation of pyrimidines and condensed pyrimidines. J. Org. Chem. 57, 1627–1630 (1992) and references therein.
22. Herrera, A., Martínez-Álvarez, R., Chioa, M., Chioa, R. & Sánchez, Á. On the regioselectivity in the reaction of aliphatic ketones and aromatic nitriles. Regiospecific synthesis of alkylypyrimidines. Tetrahedron 58, 10053–10058 (2002).
23. Martínez, A. G. et al. Sterically hindered bases. Synthesis of 2,4,6-trisubstituted pyrimidine. Synthesis (Mass) 881–882 (1990) and references therein.
24. Karad, S. N. & Liu, R.-S. Regiocontrolled gold-catalyzed [2 + 2 + 2] cycladditions of ynamides with two discrete nitriles to construct 4-aminopyrimidine cores. Angew. Chem. Int. Ed. 53, 9072–9076 (2014).
25. Evanu, G., Coste, A. & Jouvin, K. Ynamides: versatile tools in organic synthesis. Angew. Chem. Int. Ed. 49, 2840–2859 (2010).
26. DeKovor, K. A. et al. Ynamides: a modern functional group for the new millennium. Chem. Rev. 110, 5064–5106 (2010).
27. Wang, X.-N. et al. Ynamides in ring forming transformations. Acc. Chem. Res. 47, 560–578 (2014).
28. Li, L. et al. Zinc-catalyzed alkyne oxidation/C–H functionalization: highly site selective synthesis of versatile isoquinolones and β-carbolines. Angew. Chem. Int. Ed. 54, 8245–8249 (2015).
29. Shu, C. et al. Generation of α-imino gold carbones through gold-catalyzed intermolecular reaction of azides with ynamides. J. Am. Chem. Soc. 137, 9567–9570 (2015).

30. Theumissen, C. et al. Keteniminium ion-initiated cascade cationic polycyclization. J. Am. Chem. Soc. 136, 12528–12531 (2014).

31. Peng, B., Huang, X., Xie, L.-G. & Maulide, N. A Brønsted acid-catalyzed redox arylation. Angew. Chem. Int. Ed. 53, 8718–8721 (2014).

32. Xie, L.-G., Kramer, S., Overgaard, J. & Skyllstrøm, T. Access to 1,2-dihydroisoquinolines through gold-catalyzed formal [4+2] cycloaddition. Chem. Eur. J. 20, 7926–7930 (2014).

33. Minko, Y., Pasco, M., Lercher, L., Botoshansky, M. & Marek, I. Forming all-carbon quaternary stereogenic centres in acyclic systems from alkynes. Nature 490, 522–526 (2012).

34. Ding, S. et al. Highly regio- and stereoselective hydrosilylation of internal thioketiminium ions under mild conditions. Angew. Chem. Int. Ed. 53, 1877–1880 (2014).

35. Ding, S., Jia, G. & Sun, J. Iridium-catalyzed intermolecular azide–alkyne cycloaddition of internal thioketimines under mild conditions. Angew. Chem. Int. Ed. 53, 1877–1880 (2014).

36. Huang, K.-H. & Isebe, M. Highly regioselective hydrosilylation of unsymmetric alkynes using a phenylthio directing group. Eur. J. Org. Chem. 4733–4740 (2014) and references therein.

37. Frei, R. et al. Fast and highly chemoselective alkynylation of thiols with hypervalent iodine reagents enabled through a low energy barrier concerted mechanism. J. Am. Chem. Soc. 136, 16563–16573 (2014).

38. Favre, A. & Fourrey, J.-L. Structural probing of small endonucleolytic ribozymes in solution using thio-substituted nucleobases as intrinsic photolabels. Acc. Chem. Res. 28, 375–382 (1995).

39. Dubbaka, S. R. & Vogel, P. Organosulfur compounds: electrophilic reagents in transition-metal-catalyzed carbon–carbon bond-forming reactions. Angew. Chem. Int. Ed. 44, 7674–7684 (2005).

40. Prokopcová, H. & Kappe, C. O. The Liebeskind–Srogl C–C cross-coupling reaction. Angew. Chem. Int. Ed. 48, 2276–2286 (2009).

41. Pan, F. & Shi, Z.-J. Recent advances in transition-metal-catalyzed C–S activation: from thioester to (hetero)aryl thioether. ACS Catal. 4, 280–288 (2014).

42. Melzig, L., Metzger, A. & Knochel, P. Dd and Ni-catalyzed cross-coupling reactions of functionalized organozinc reagents with unsaturated thioethers. Chem. Eur. J. 17, 2948–2956 (2011) and references therein.

43. Chopade, P. R. & Louie, J. [2+2+2] Cycloaddition reactions catalyzed by transition metal complexes. Adv. Synth. Catal. 348, 2307–2327 (2006).

44. Suzuki, H. & Abe, H. A simple cyclization route to some 4-substituted 3-aminoisoquinolines. Synthesis (Mass) 763–765 (1995) and references therein.

45. Neumeyer, J. L., Weinhardt, K. K., Carrano, R. A. & McCurdy, D. H. Isoquinolines 3. 3-aminoisoquinoline derivatives with central nervous system depressant activity. J. Med. Chem. 16, 808–813 (1973).

46. Straub, A. et al. NO-independent stimulators of soluble guanylate cyclase. Bioorg. Med. Chem. Lett. 11, 781–784 (2001).

47. Achorn, J., Chakravarty, S., Dugar, S., Mcerroe, G. & Murphy, A. Inhibitors of TFGbeta. PCT Int. Appl. WO 2004/024159 A1 (2004).

48. Moyer, E. G. et al. Pyrimidine derivatives capable of inhibiting one or more kinases. PCT Int. Appl. WO 2009/122180 A1 (2009).

49. Barluenga, J., Fernández-Rodríguez, M. Á., García-García, P. & Aguilar, E. Gold-catalyzed intermolecular hetero-dehydro-diels – alder cycloadditions of captodative dienynes with nitrides: a new reaction and regioselective direct access to pyridines. J. Am. Chem. Soc. 130, 2764–2765 (2008).

50. Wessig, P. & Müller, G. The dehydro-diels – alder reaction. Chem. Rev. 108, 2051–2063 (2008).

51. Fernández-García, J. M., Fernández-Rodríguez, M. A. & Aguilar, E. Catalytic intermolecular hetero-dehydro-Diels–Alder cycloadditions: regio- and diastereoselective synthesis of 5,6-dihydropyrindin-2-ones. Org. Lett. 13, 5172–5175 (2011).

52. Hoye, T. R., Baire, B., Niu, D., Willoughby, P. H. & Woods, B. P. The hexadehydro-Diels–Alder reaction. Nature 490, 208–212 (2012).

53. Chrzanowska, M. & Rozwadowska, M. D. Asymmetric synthesis of isoquinoline alkaloids. Chem. Rev. 104, 3341–3370 (2004).

54. Scott, J. D. & Williams, R. M. Chemistry and biology of the tetrahydroisoquinoline antitumor antibiotics. Chem. Rev. 102, 1669–1730 (2002).

55. Kartsev, V. G. Natural compounds in drug discovery. Biological activity and new trends in the chemistry of isoquinoline alkaloids. Med. Chem. Res. 13, 325–336 (2004).

56. Glorius, F., Spielkamp, N., Holle, S., Goddard, R. & Lehmann, C. W. Efficient asymmetric hydrogenation of pyridines. Angew. Chem. Int. Ed. 43, 2850–2852 (2004).

57. Heitbaum, M., Frchlich, R. & Glorius, F. Diastereoselective hydrogenation of substituted quinolines to enantiomerically pure decahydroquinolines. Adv. Synth. Catal. 352, 357–362 (2010).

Acknowledgements
We are grateful to the European Research Council (ERC SIG 278872 to N.M.) and the University of Vienna for support of this work. We acknowledge Dr Michael J. Fink and Professor Marko D. Mihovilovic (Vienna University of Technology) for hydrogenation reactions and helpful discussions. The computational results have been achieved in part using the Vienna Scientific Cluster (VSC).

Author contributions
L.-G.X. and N.M. planned the project. L.-G.X. and S.N. carried out the experiments and analysed the data. A.J.M. and L.G. carried out the DFT analysis. L.-G.X., A.J.M., S.N., L.G. and N.M. wrote the manuscript.

Additional information
Accession codes: The X-ray crystallographic coordinates for structures reported in this study have been deposited at the Cambridge Crystallographic Data Centre (CCDC), under deposition numbers CCDC 1423496. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supplementary Information accompanies this paper at http://www.nature.com/naturecommunications

Competing financial interests: The authors declare no competing financial interests.

Reprints and permissions information is available online at http://npg.nature.com/reprintsandpermissions/

How to cite this article: Xie, L.-G. et al. Metal-free intermolecular formal cycloadditions enable an orthogonal access to nitrogen heterocycles. Nat. Commun. 7:10914 doi: 10.1038/ncomms10914 (2016).

This work is licensed under a Creative Commons Attribution 4.0 International License. The images or other third party material in this article are included in the article's Creative Commons license, unless indicated otherwise in the credit line; if the material is not included under the Creative Commons license, users will need to obtain permission from the license holder to reproduce the material. To view a copy of this license, visit http://creativecommons.org/licenses/by/4.0/