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ARTICLE

Gold(I) catalysed regio- and stereoselective intermolecular hydroamination of internal alkynes: towards functionalised azoles

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Abstract: Gold(I) catalysed regio- and stereoselective intermolecular hydroamination of internal alkynes was developed for the effective synthesis of a series of (Z)-functionalised vinylazoles under solvent free conditions. The catalytic hydrogenation of the resulting enamines leads to substituted saturated azoles in good yields.

N-functionalised azoles are important molecular scaffolds for pharmaceuticals, bioactive compounds and natural products. They are useful in the treatment of various diseases as they exhibit antifungal (I),¹ antibacteria (II),² anxiolytic (III),³ analgesic (IV),⁴ antidepressant (IV)⁴ and anticancer (V)⁵ activities (Figure 1). If various methodologies including cycloaddition and multicomponent reactions focused on building these heterocycles,⁶ direct functionalisation of azoles has been much less explored. Considering that the hydroamination of alkenes and alkynes is the shortest synthetic route to secondary and tertiary amines, this reaction should be of practical interest for the preparation of azole derivatives. In this context, if the intermolecular hydroamination of alkenes remains a challenge, the inter- and intramolecular hydroamination of terminal alkynes has been broadly studied.⁷ The resulting substituted enamines, imines or functionalised heterocycles are obtained as Markovnikov or anti-Markovnikov products and are useful intermediates in organic synthesis. Although the intermolecular hydroamination of internal alkynes with primary amines has been effectively performed using Group 4-based catalysts,⁸ the use of other nucleophiles such as dialkylamines or heterocycles remains more challenging due to a lack of general synthetic method. Recently, Schaffer et al. have reported on the use of bis(amidate)bis(amido)titanium(IV) to catalyse the

selective anti-Markovnikov hydroamination of terminal and internal alkynes with *N*-silyl amines to afford *N*-silylenamines.⁹ The latter either led to primary amines, after desilylation, or to various pyridines through reactions with α,β -unsaturated carbonyls followed by oxidation.⁹ The versatility of rhodium(I) catalyst was also concomitantly highlighted by several contributions.¹⁰ Dong et al. and Sunoj et al. reported on the hydroamination of internal alkynes via tandem rhodium catalysis to yield branched *N*-allylic amines and more specifically *N*-allyl indolines with high regio- and enantioselectivities.^{10a,e} In parallel, Breit et al. have developed a rhodium catalyst allowing for the chemo-, regio-, and enantioselective allylation of pyrazoles and triazoles with internal alkynes.^{10b,d} Interestingly, Zhao et al. combined rhodium-catalysed hydroamination and C–H activation in a highly selective [4+2] imine/alkyne annulation to form multi-substituted 3,4-dihydroisoquinolines^{10c}. Regarding Group 11-based catalysts, Zhu et al. (Ag(I)) and later Kawatsura et al. (Cu(II)) reported the regioselective intermolecular hydroamination of internal alkynes functionalized with electron-withdrawing groups in the presence of various amines.¹¹

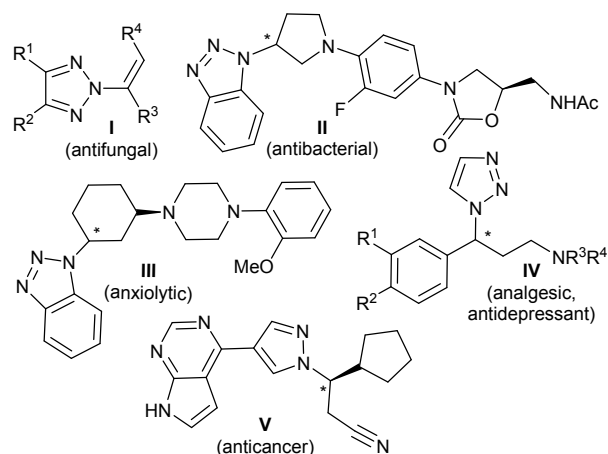


Figure 1. Azoles found in the pharmaceutical industry

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Electronic Supplementary Information (ESI) available: Figures S1 and S2, Table S1, synthetic and catalytic details, NMR spectra of all products. See DOI: 10.1039/x0xx00000x

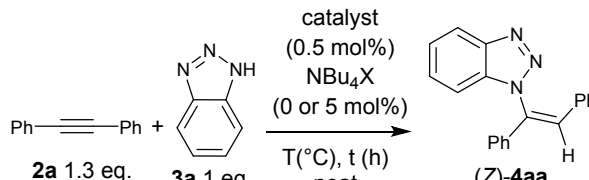
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ARTICLE

In parallel, gold-catalysed additions to CC multiple bonded substrates proved to be effective in intramolecular reactions though intermolecular versions have remained more challenging.¹² Interestingly, Bertrand et al. have developed gold(I) catalysts based on cyclic(alkyl)(amino)carbenes (CAACs) for the intermolecular hydroamination of alkynes with ammonia, hydrazine and amines.^{13a,d} This methodology was later applied to the one-pot three-component synthesis of 1,2-dihydroquinolines.^{13b,c} Thereafter, Stradiotto et al. reported *P,N*-ligand based gold(I) catalysts for the stereo- and regioselective hydroamination of internal alkynes using various dialkylamines.¹⁴ In parallel, triazole-gold(I) complexes developed by Shi et al. proved to be also valuable catalysts for the intermolecular hydroamination of internal alkynes with primary amines,^{15a} the reaction yields being improved by the use of an acid co-catalyst. Interestingly, this methodology was further extended to the synthesis of several vinyl-substituted triazoles.^{15b} Some related pyrazoles were later prepared by Chen et al. through a 1,4-conjugate addition to propiolates using gold(I) chloride as a catalyst.¹⁶ Following our interests in gold(I)-catalysed hydrophenoxylation, hydroalkoxylation and hydrocarboxylation of alkynes¹⁷ as well as in gold(I)-catalysed hydroamination of alkenes,¹⁸ we report here gold(I)-catalysed regio- and stereoselective intermolecular hydroamination of internal alkynes for the effective synthesis of a broad range of functionalised vinylazoles under solvent-free conditions. Interestingly, the subsequent catalytic hydrogenation of the resulting (Z)-enamines leads to the related saturated azoles in good yields.

Initially, diphenylacetylene **2a** and benzotriazole **3a** were selected as model substrates to test the three selected pre-catalysts, e.g. [Au(IPr)(OH)] **1a**,^{19a} [Au(IPr)][NTf₂] **1b**^{19b} and [(Au(IPr))₂(μ-OH)][BF₄] **1c**^{19c} and establish the best catalytic conditions (Table 1). Reactions were performed with 0.5 mol% catalyst loading, in closed vials containing 0.22 mmol of alkyne **2a** without any solvent. The mixtures were heated at 100°C for 72 hours using a sand bath (method A) or by using microwave heating at 150°C for 0.75 hour (method B). At first, none of the catalysts were active when the reaction was performed using method A (entries 1-3). However, we found the use of a catalytic amount (5 mol%) of NBu₄OTf as an additive allowed the reactions to proceed. Other ammonium salts bearing anions like BF₄ or OTos led also to hydroamination product **4aa** but yields were lower and some by-products were formed. The critical effect of NBu₄OTf (and of the OTf anion) can be explained by its role in the proto-deauration step (see Scheme 2 and the mechanism discussion below).^{20,21} Indeed, the hydroamination product **4aa** was obtained in a 22% yield while using catalyst **1a** (entry 4).

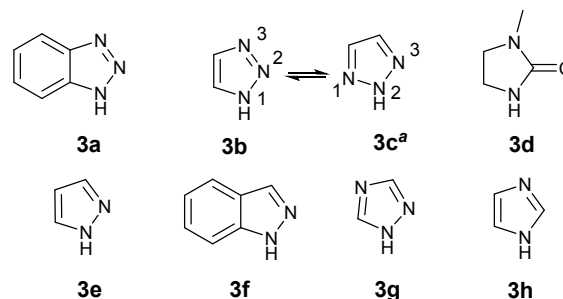
Table 1 Development of the catalytic reaction


Reaction scheme: Diphenylacetylene (**2a**, 1.3 eq.) + Benzotriazole (**3a**, 1 eq.) $\xrightarrow[\text{neat}]{\text{catalyst (0.5 mol\%), NBu}_4\text{X (0 or 5 mol\%), T (°C), t (h)}}$ (Z)-4aa

Catalysts shown: **1a** [Au(IPr)(OH)], **1b** [Au(IPr)][NTf₂], **1c** [(Au(IPr))₂(μ-OH)][BF₄]

Entry	Cat. (mol%)	NBu ₄ X (mol%)	T (°C) (method) ^a	time (h)	Yield (%) ^b
1	1a	0	100 (A)	72	-
2	1b	0	100 (A)	72	-
3	1c	0	100 (A)	72	-
4	1a	X = OTf (5)	100 (A)	72	22
5	1b	X = OTf (5)	100 (A)	72	61
6	1c	X = OTf (5)	100 (A)	72	66
7	1c	X = OTf (5)	100 (A)	72	44 ^c
8	1c	X = OTf (5)	150 (B)	0.75	66
9	1c	X = OTf (5)	150 (B)	0.75	96 ^c

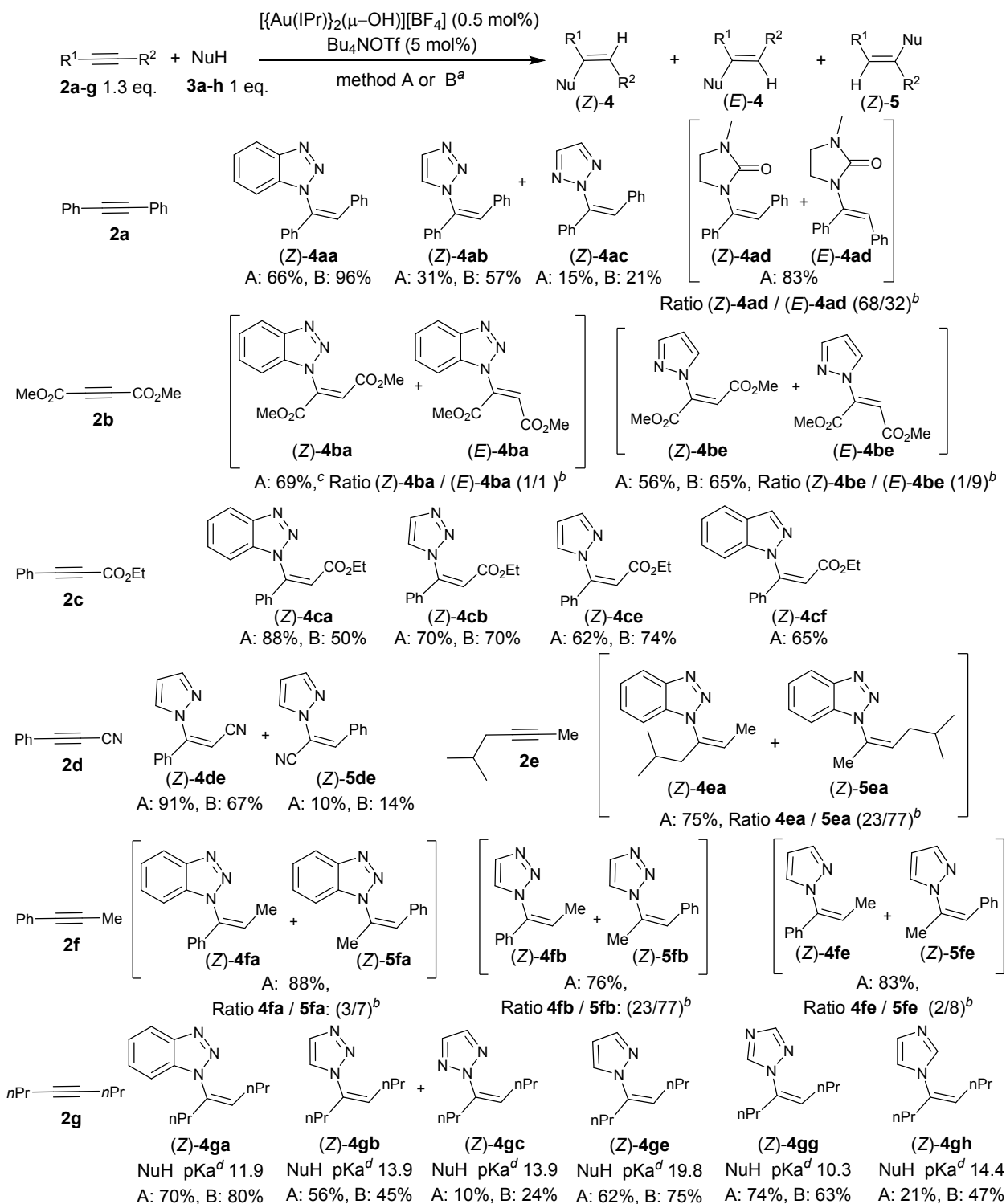
a) Method A using a sand bath at 100°C for 72 h, method B using microwave heating at 150°C for 0.75 h. b) 0.22 mmol of **3a** used, isolated yields. c) 1.10 mmol of **3a** used, isolated yields.

**Figure 2** Azole nucleophiles used in this study. ^a **3c** is the *N*² tautomer of **3b** in solution²²

Organic & Biomolecular Chemistry

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Scheme 1 Scope of the reaction. ^a Method A using a sand bath at 100°C for 72h, method B using microwave heating at 150°C for 45 min., isolated yields; ^b determined by ¹H NMR; ^c 6 h reaction; ^d pKa in reference to DMSO

Organic & Biomolecular Chemistry

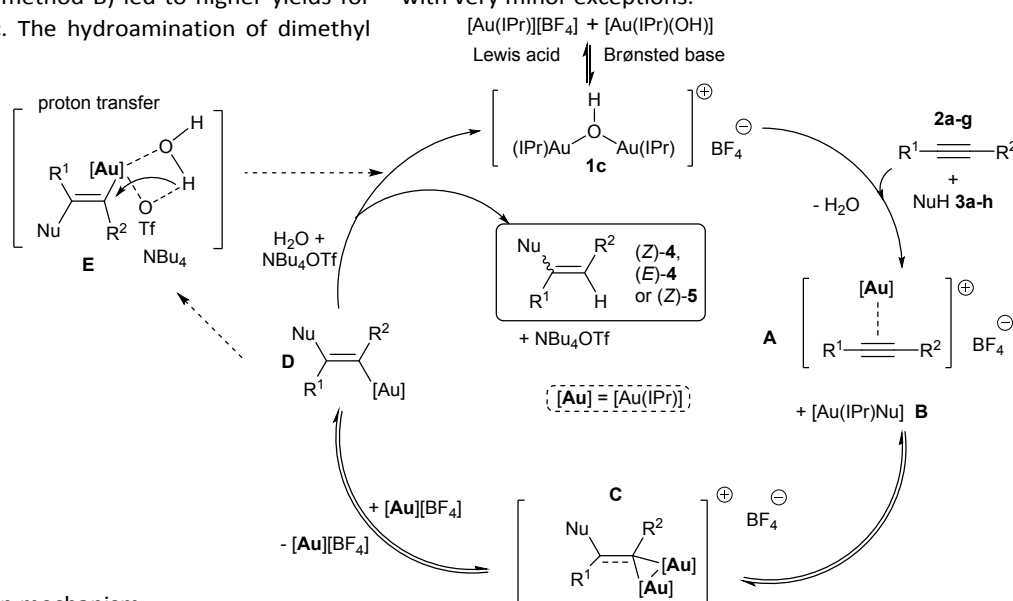
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A change to catalysts **1b** and **1c** led to a significant increase in yields of **4aa** to 61% and 66%, respectively (entries 5 and 6). Finally, the reaction was performed on a larger scale starting with 1.1 mmol of **2a**. While a decrease in product **4aa** yield was noticed using a sand bath for 72 hours (method A) (entry 7), we observed a nearly quantitative yield, e.g. 96%, of enamine **4aa** by employing microwave heating for 0.75 hour (method B) (entry 9). It is noteworthy that similar yields of **4aa** were obtained starting from 0.22 mmol of **2a** and applying method A or B (entries 6, 8).

The scope of the gold(I)-catalysed hydroamination was studied for a series of alkynes and azole nucleophiles by using method A and B (Scheme 1 and Figure 2). The (Z)/(E) (cis/trans) isomerism of pure or mixed isomers was established based on the observed and non-observed NOEs profiles after full assignment of $^1\text{H}/^{13}\text{C}/^{15}\text{N}$ chemical shifts (see the SI for details). By studying all hydroamination products **4**, we noticed the $^3J(^1\text{H}-^{15}\text{N})$ coupling constants were larger than or equal to 4.8 Hz for all (Z)-enamines and less than 2 Hz for the (E)-enamines in agreement with previous analyses²³ (see SI, Figures S1,S2). At first, diphenylacetylene **2a** was reacted with benzotriazole **3a** and triazoles **3b-c** to lead to the corresponding (Z)-products **4aa**, **4ab** and **4ac** in good yields. The reaction with triazole **3b** afforded preferentially the *N*¹ addition product **4ab**, the *N*² tautomer product **4ac** being minor. In spite of a high yield, the hydroamination of alkyne **2a** with 1-methylimidazolidin-2-one **3d** was not entirely (Z)-selective, a (Z)/(E) ratio of 68/32 was observed for **4ad**. As noticed during the development of the catalytic reaction, the use of microwave heating (method B) led to higher yields for products **4aa**, **4ab** and **4ac**. The hydroamination of dimethyl

acetylenedicarboxylate (DMAD) **2b** with benzotriazole **3a** afforded a 1/1 mixture of (Z) and (E) **4ba** isomers in a good yield. By comparison, the use of pyrazole **3e** led to a more selective reaction with a mixture of (Z)/(E) **4be** isomers in a 1/9 ratio. Unsymmetrical phenylpropiolate **2c** underwent hydroamination with azoles **3a-b** and **3e-f** with complete regio- and stereoselectivity and good isolated yields. In contrast, the hydroamination of 3-phenylpropionitrile **2d** with pyrazole **3e** led to isolated (Z)-regioisomers **4de** and **5de** in a 9/1 ratio and high yields. The reactions of unsymmetrical 5-methylhex-2-yne **2e** and phenylpropyne **2f** with azoles **3a,b** and **3e** gave mixtures of the corresponding (Z)-regioisomers **4** and **5** in high yields with ratios from 3/7 to 2/8. The hydroaminations of 4-octyne **2g** with azoles **3a-c**, **3e** and **3g-h** afforded the related enamines **4** with complete (Z)-stereoselectivity in average to good yields independently of the pK_a of the azole nucleophile. It is worth noting that the reaction of 4-octyne **2g** with triazole **3b** led to a mixture of the preferred *N*¹ addition product **4gb** and the minor *N*² tautomer product **4gc**. By comparison to the previous work of Shi et al. who reported the synthesis of several vinyl-substituted triazoles from terminal and internal alkynes using PPh_3AuOTf catalyst in toluene,^{15b} our synthetic methodology operates in solvent free conditions and therefore allows practical, simple, and scalable reactions using standard thermal heating or more convenient microwave heating. Moreover, the scope of our reactions is broader and allows the hydroamination of seven internal alkynes with eight heterocycles including triazoles, pyrazoles, imidazole and a cyclic urea to form (Z)-enamines with very minor exceptions.



Scheme 2 Proposed reaction mechanism

Finally, along our study, we observed triazole **3b** reacted preferentially to form the N^1 addition product, the N^2 tautomer product being minor or not formed.

Regarding the reaction mechanism, some of us have demonstrated that $[\{Au(IPr)\}_2(\mu-OH)][BF_4]$ **1c** is a highly efficient bifunctional catalyst for the hydrophenoxylation, hydroalkoxylation and hydrocarboxylation of internal alkynes.¹⁷ This complex can be regarded as a catalyst able to activate substrates in a dual-mode providing Lewis acid $[Au(IPr)][BF_4]$ and Brønsted base $[Au(IPr)(OH)]$ (Scheme 2). On the basis of previous mechanistic studies,¹⁷ we propose the Lewis acid $[Au(IPr)][BF_4]$ would coordinate to the alkyne to form species **A**²⁴ and the Brønsted base $[Au(IPr)(OH)]$ would deprotonate the azole nucleophile to generate the corresponding gold-azole complex **B** and release a water molecule (Scheme 2). Afterwards, the subsequent nucleophilic attack of gold-azole **B**^{15a} toward π -complex **A** in an anti-fashion would lead to the formation of gem-diaurated species **C**²⁵ or σ -monoaured species **D**²⁶ (most likely in equilibrium), **C** acting as an off-cycle species. Finally, protodeauration with H_2O and the assistance of OTf anion^{20,21} through intermediate **E** would deliver the vinylazole product **4** or **5** and catalyst **1c**. This assisted proton-transfer/protodeauration step underlines the prominent role of counterions during gold catalysed

selectivities as well as narrow substrate scopes.^{20,21} A rapid screening of the reaction conditions determined EtOAc to be the best solvent in order to reach high isolated yields (Scheme 3 and SI, Table S1). The Pd/C catalyst (5% Pd) loading was set at 1 mol% and other parameters, e.g. temperature, time and pressure, needed to be adjusted as a function of the substrate. Hydrogenation of enamines **4aa**, **4ad** and **4ce** proceeded smoothly within 15 hours at room temperature and 1 bar of H_2 . Under the same reaction conditions except heating at 60°C, triazole and pyrazole derivatives **4be** and **4cb** were reduced effectively in 15 and 30 hours, respectively. The hydrogenation of enamines **4ab** and **4ca** required 10 bar pressure of H_2 and 60°C heating to proceed in 15 and 72 hours. As previously observed by Pfaltz et al. and Hou et al. on other similar derivatives,²⁹ the hydrogenation of conjugated nitrile **4de** into saturated pyrazole **6de** required stronger reaction conditions, i.e. 80°C and 50 bar of H_2 , to reach a very good 85% yield. The vinyltriazole **4gb** was hydrogenated in a similar manner but required a longer reaction time, 72 hours.

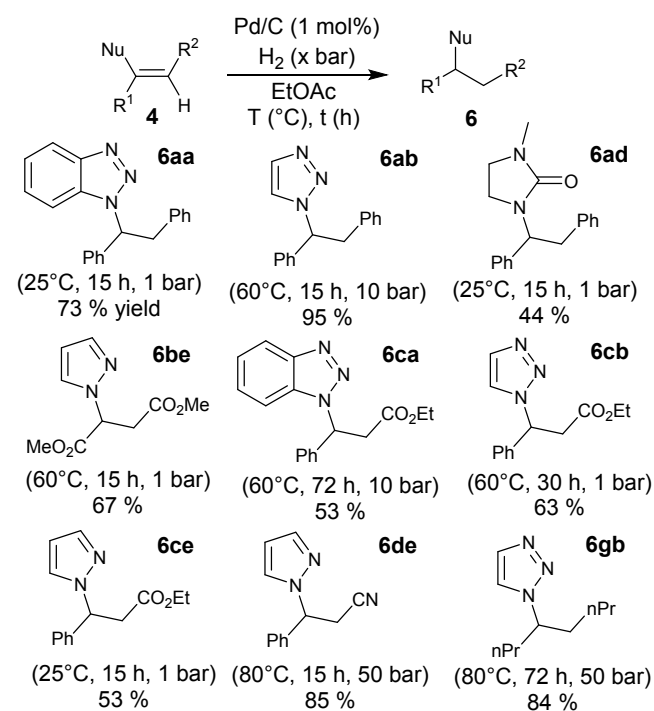
To summarise, we have developed a gold(I)-catalysed intermolecular hydroamination of internal alkynes for the effective synthesis of a broad range of functionalised vinylazoles with fair to high yields and high regio-, chemo-, and stereoselectivity. The use of solvent-free conditions allows a practical, simple, and scalable synthetic methodology using standard thermal heating or more convenient microwave heating. In addition, the catalytic hydrogenation of the resulting (Z)-enamines led to various substituted saturated azoles in good yields without the formation of significant by-products. The present process represents a practical and atom-economical alternative to existing synthetic methods to assemble a variety of functionalised azoles.

Conflicts of interest

There are no conflicts to declare

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reactions.^{20,21}

Scheme 3 Hydrogenation of enamines **4**

The catalytic hydrogenation of a series of vinylazoles **4** into saturated azoles **6** was then investigated (Scheme 3 and SI, Table S1). Although the hydrogenation of enamines has been well-studied,^{8b,n,16,27,28} it is also clear that it suffers from important limitations regarding the reaction activities and

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