C-H functionalization reactions of unprotected *N*-heterocycles by gold catalyzed carbene transfer

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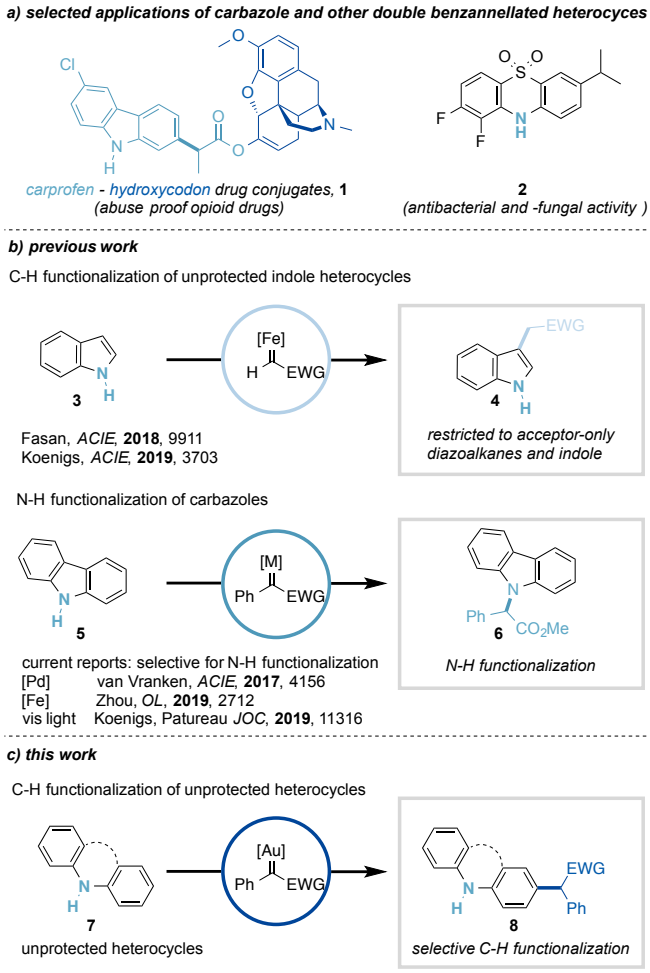
Abstract: *The C-H functionalization reaction of N-heterocycles with unprotected N-H group is one of the most step-economic strategies to introduce functional groups without the need of installation and removal of protecting groups. Despite recent significant advances in C-H functionalization chemistry, this strategy remains unsatisfactorily developed. In this report, we disclose a simple and straightforward protocol to allow for the selective C-H functionalization of unprotected double benzannellated N-heterocycles via gold catalyzed carbene transfer reactions (29 examples, up to 86% yield). The scope of the reaction can also be expanded to the corresponding protected heterocycles (37 examples, up to 98% yield), further demonstrating the generality of this method. Mechanistic studies by DFT calculations underpin the importance of the gold catalyst and reveal that the selectivity of this reaction is driven by trace amounts of water present in the reaction mixture.*

The site-selective direct functionalization reaction of heterocycles represents a straightforward, step-economic and atom-economic strategy to introduce new functional groups and to rapidly build up molecular complexity.[1,2] In this context, the C-H functionalization via carbene transfer reactions is widely recognized as one of the main strategies to decorate commonly encountered protected *N*-heterocycles such as pyrrole,[3] indole,[4] or others[2,6] in a highly selective fashion. In contrary, the direct, site-selective C-H functionalization of unprotected *N*-heterocycles is far more onerous as the free N-H group can readily undergo unwanted N-H functionalization or catalyst poisoning. Synthetic methods for the functionalization of unprotected *N*-heterocycles are thus rather underdeveloped.[6,7] Currently available processes are either low yielding[7] or limited to the reaction of unprotected indole heterocycles **3** with acceptor-only diazoalkanes as recently disclosed by our group[8] and the Fasan group (Scheme 1b).[9] The development of a general and simple synthesis method to directly introduce new functional groups onto unprotected *N*-heterocycles thus remains a major challenge in C-H functionalization chemistry.

Given the importance of carbazole heterocycles and other double benzannellated heterocycles in materials and drug discovery – for example in the development of highly demanded abuse proof opioid drugs (**1**, Scheme 1a)[10,11] – we envisioned that the strategic introduction of functional groups onto unprotected carbazole heterocycles **7** via C-H functionalization with metal carbene fragments (Scheme 1c) would be highly useful. This approach would open up an unprecedented pathway to selectively functionalize carbazoles without the need of protecting groups. Currently available strategies for the functionalization of unprotected carbazole **5** with carbene or metal-carbene intermediates via light-induced[12] or palladium-[13] or iron-catalyzed reactions generally afford products of N-H functionalization (**6**, Scheme 1b).[14] Even with an *N*-protecting group, Van Vranken *et al.* only observed selective C-H functionalization of the carbazole framework with moderate yields in their palladium-catalyzed reactions.[13]



Scheme 1. a) C-H functionalization of unprotected indole heterocycles, b) carbene transfer reactions of unprotected carbazole heterocycles, c) C-H functionalization of unprotected heterocycles.

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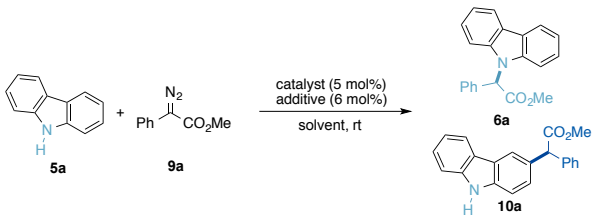
Gold catalysts recently emerged as promising catalysts to conduct C-H functionalization reactions via carbene transfer.[15,16] Inspired by recent literature in the field, we hypothesized that Au(I) catalysts might be suitable to promote selective C-H functionalization reactions of unprotected *N*-heterocycles. We therefore studied the reaction of carbazole **5a** with methyl phenyldiazoacetate **9a** using a pool of different carbene transfer catalysts. Among these, Rh(II), Cu(I), Ag(I), Fe(III), or Pd(II) catalysts all led to either selective N-H functionalization of the carbazole or decomposition of the diazoalkane reaction partner (see Table S1 in ESI).[17] Interestingly, a stark difference in reactivity was observed with Au(I) catalysts (Table 1). When using monodentate carbene, phosphine, or phosphite ligands, we could observe a chemo- and regio-selective C-H functionalization of the carbazole heterocycle **5a** with the N-H function remaining untouched and the best yields were obtained using tri-*t*-butylphosphine as ligand in only 15 min reaction time (Table 1, entry 7). Only in the case of the bidentate dppf ligand (Table 1, entry 6), a small amount of the N-H functionalization product could be isolated. Further investigations concerned the use of different solvents, stoichiometry, and additives, to give the optimized conditions (Table 1, entry 8-10 and Table S1 in ESI).[17]

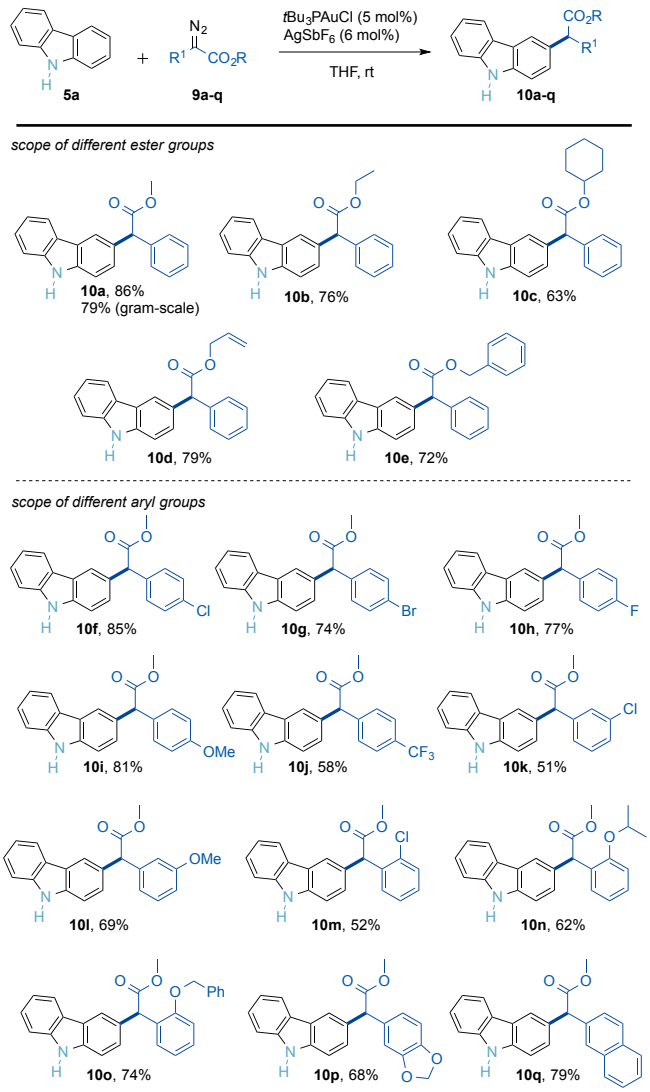
Table 1. Optimization of the C-H functionalization reaction.



entry[a]	catalyst	additive	solvent	yield%(**6a**/**10a**)[b]
1	(**L**$_1$)AuCl	$AgSbF_6$	DCM	- / 50
2	(**L**$_1$)AuCl	$AgSbF_6$	THF	- / 70
3	(IPr)AuCl	$AgSbF_6$	THF	- / 73
4	(IMes)AuCl	$AgSbF_6$	THF	- / 21
5	(XPhos)AuCl	$AgSbF_6$	THF	- / 48
6	dppf$(AuCl)_2$	$AgSbF_6$	THF	11 / 51
7	(*t*Bu_3P)AuCl	$AgSbF_6$	THF	- / 86
8	(*t*Bu_3P)AuCl	$AgBF_4$	THF	- / 51
9	(*t*Bu_3P)AuCl	$AgPF_6$	THF	- / 65
10	(*t*Bu_3P)AuCl	$AgNTf_2$	THF	- / 59

[a] *Reaction conditions*: 0.2 mmol **9a**, 0.4 mmol **5a**, 5 mol% catalyst, 6.0 mol% additive were dissolved in 4.0 mL solvent under N_2 atmosphere at room temperature, 15 min reaction time. [b] Yield of isolated products. IPr = 1,3-*Bis*(2,6-diisopropylphenyl)imidazol-2-ylidene, IMes = 1,3-Dimesitylimidazol-2-ylidene, XPhos = 2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl, dppf = 1,1'-*bis*(diphenylphoshino)ferrocene, **L**$_1$ = *tris*(2,4-*di-tert.*-butylphenyl)phosphite.

With the optimized conditions in hand, we next embarked on the applicability of this Au(I)-catalyzed C-H functionalization reaction. Different phenyldiazoacetates reacted smoothly to give the C-H functionalization products in good yields (Scheme 2, **10a** – **10e**). In the case of the sterically more demanding cyclohexyl ester **9c** a slightly diminished yield was observed. When studying the substitution pattern of aryldiazoacetates, we could observe a minor influence on the product yield in case of *para*-substitution (Scheme 2, **10f** – **10j**), which was most obvious with the strongly electron-withdrawing trifluoromethyl group. *Meta*- and *ortho*-substitution of the aromatic ring led to a slight decrease in product yield (Scheme 2, **10k** – **10q**). Overall, higher yields were observed with electron-donating substituents; even the sterically demanding *ortho*-ether aryldiazoacetates (**9n** and **9o**) gave high yields of the C-H functionalization products than their analogue **9m** with an electron-withdrawing substituent.



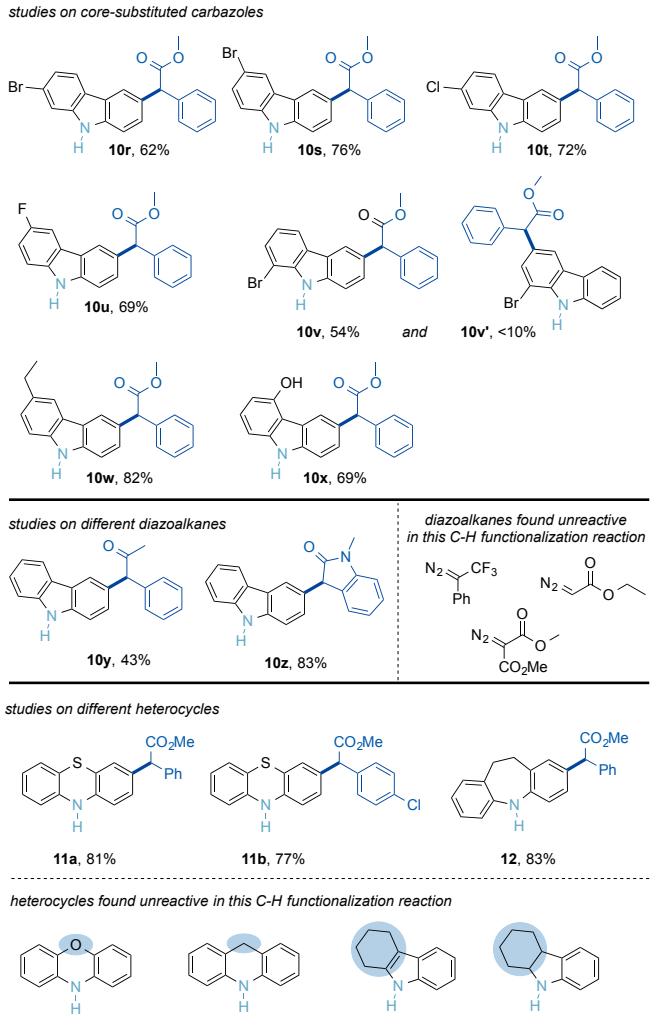
Scheme 2. Substrate scope of aryl diazoacetates.

We subsequently turned our attention to the functionalization of substituted carbazole heterocycles, which can give rise to different regioisomers depending on the nature of the substituents. Gratifyingly, all mono-halogenated or alkylated carbazole heterocycles reacted smoothly in this C-H functionalization reaction with high regioselectivity and only a single isomer was obtained in most cases (Scheme 3, **10r** – **10x**). The only exception was with 1-bromo carbazole, as a minor amount of a second regioisomer (**10v'**) was obtained. In the case of 4-hydroxy carbazole, much to our surprise, selective C-H functionalization occurred in the 6-position of the carbazole heterocycle in high yield without concomitant N-H or O-H functionalization (Scheme 3, **10x**). This intriguing reactivity further demonstrates the efficiency and selectivity of gold catalyzed carbene transfer reactions in C-H functionalization reactions.

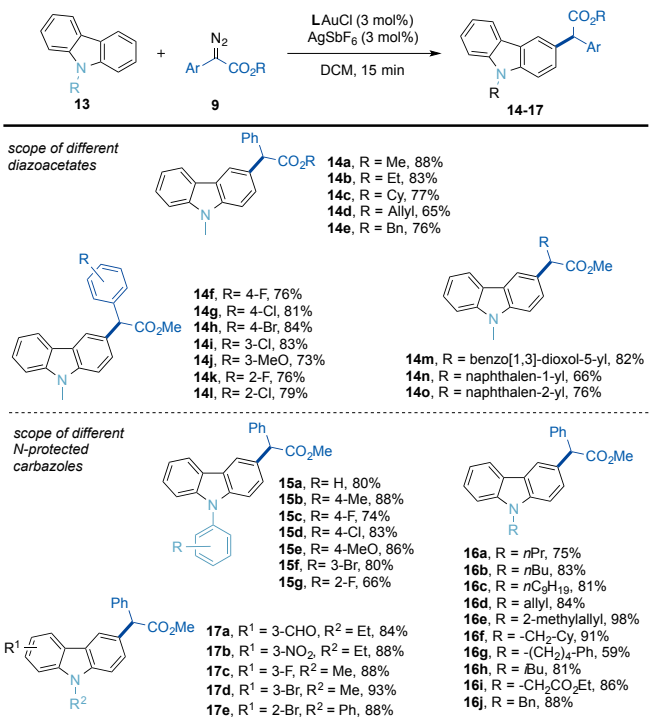
Further studies focused on the application of different diazoalkane reaction partners. In the reaction with a donor-acceptor diazoketone and a cyclic diazoamide, the C-H functionalization reaction of the unprotected carbazole proceeded smoothly without by-products from N-H functionalization (Scheme 3, **10y**, **10z**). Notably, acceptor-only, *bis*-acceptor substituted, or trifluoromethyl-substituted donor-acceptor diazoalkanes did not undergo C-H functionalization reaction and only the decomposition of the diazoalkane was observed under the reaction conditions (Scheme 3).

Next, we planned to showcase the potential of this C-H functionalization reaction with different unprotected *N*-heterocycles. Among these, unprotected phenothiazine is a particularly demanding *N*-heterocycle for C-H functionalization. Due to the electron-donating nature of both nitrogen and sulfur atoms, it can undergo different unwanted side reactions such as ylide formation with the sulfur atom, N-H functionalization with the free N-H group, or different C-H functionalization reactions. Gratifyingly, under our Au(I)-catalyzed reaction conditions, phenothiazine underwent selective C-H functionalization to give products **11a** and **11b** without observation of any aforementioned side-processes (Scheme 3). Similarly, 10,11-dihydro-dibenzo[b,f]azepine smoothly reacted to give the C-H functionalization product **12**. It is important to note that other *N*-heterocycles, such as phenoxazine, or different reduced forms of carbazole did not undergo the C-H functionalization under the present reaction conditions.

At this stage, it would be also of interest to study the applicability of our newly developed method to a broader substrate scope of protected *N*-heterocycles, as gold catalyzed carbene transfer has been rarely reported with these systems.[4e] Thus, we found



Scheme 3. Studies on substituted carbazoles, different diazoalkanes and heterocycles.

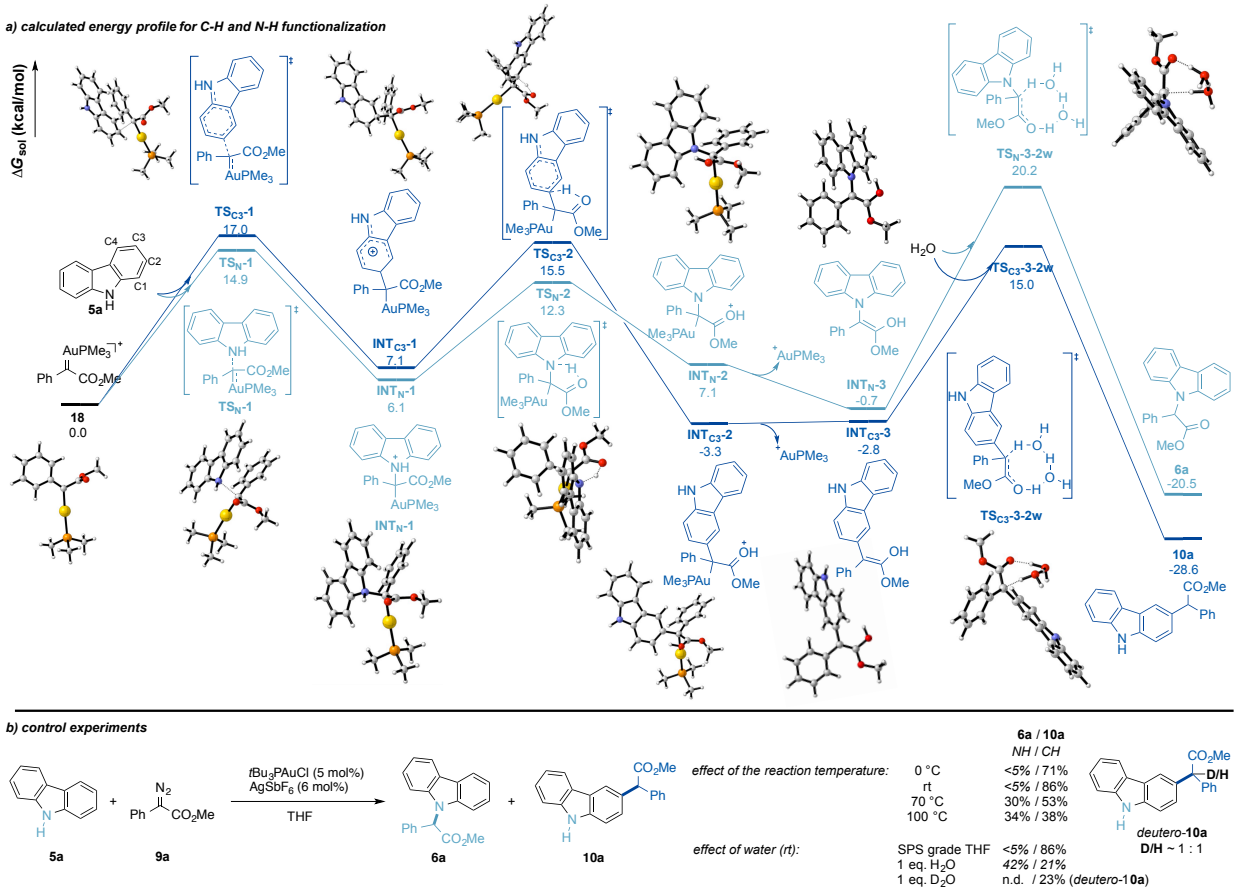


Scheme 4. Studies on protected carbazole heterocycles: *reaction conditions*: 1.5 eq. protected carbazole (**13**), 1.0 eq. aryl diazoacetate (**9**), 3 mol% **L**AuCl, 3 mol% $AgSbF_6$, 2.0 mL DCM, 15 min reaction time. Ligands used: for *N*-Alkyl carbazole **L** = *tris*(2,4-*di*-*tert*.-butylphenyl)phosphite; for *N*-aryl carbazole, **L** = XPhos.

that protected carbazoles **13** underwent selective C-H functionalization in the 3-position of the heterocyclic core (for the optimization of reaction conditions, please see Table S2 in ESI).[17] Different ester groups and different substituents in all positions of the aromatic ring of the aryldiazoacetates reaction partner were well tolerated (**14a**-**o**). In addition, different aliphatic and aromatic *N*-protecting groups at the carbazole heterocycle had only an insignificant effect on the reaction yield. When studying both electron-withdrawing or halogen substituents at the 2- and 3-position of the carbazole heterocycle, selective C-H functionalization at the pendant benzannelated ring occurred in good to excellent yield (Scheme 4, **15** – **17**).

To rationalize the selectivity of this C-H functionalization reaction, we calculated different reaction pathways of carbazole with Au(I)-carbene complexes (activation free energy for the Au(I)-carbene complex formation is 9.6 kcal/mol, please see Figure S1 in ESI for details),[17,18] to account for all possible C-H or N-H functionalization of the carbazole heterocycle. In all cases, the reaction of the Au(I)-carbene complex **18** with carbazole **5a** proceeds via nucleophilic attack of carbazole to the electrophilic gold carbene complex (for details, see Figure S2 in ESI).[17] There are two favorable pathways involving addition from N-H or C-3 of carbazole *via* $\mathbf{TS_N1}$ or $\mathbf{TS_{C3}1}$ with similar activation free energies, respectively (14.9 vs. 17.0 kcal/mol for N-H or C-H functionalization, Scheme 5a). Following the formation of the addition product $\mathbf{INT_N1}$ or $\mathbf{INT_{C3}1}$, a 1,4 proton migration step via low lying transition states $\mathbf{TS_N2}$ and $\mathbf{TS_{C3}2}$ gives $\mathbf{INT_N2}$ or $\mathbf{INT_{C3}2}$ (for details and discussion of other pathways, see Figure S3 in ESI).[17] Subsequent deauration, followed by a proton shuttle involving two water molecules, gives the product of either N-H or C-H functionalization.

The calculations can now rationalize for the selectivity of this reaction. The low activation free energies of transition states render the formation of both intermediates $\mathbf{INT_N2}$ or $\mathbf{INT_{C3}2}$ reversible. For the case of C-H functionalization, the final proton shuttle step proceeds from the low-energy $\mathbf{INT_{C3}2}$ via $\mathbf{TS_{C3}3\text{-}2w}$ with an activation free energy of only 15.0 kcal/mol, which accounts for the formation of the kinetic reaction product **10a**. Contrarily, the N-H functionalization product is formed only via a relatively high-lying intermediate $\mathbf{INT_N2}$ that reacts via a high-lying $\mathbf{TS_N3\text{-}2w}$ with an activation free energy of 20.2 kcal/mol to give the thermodynamic reaction product **6a**. Control experiments at different reaction temperatures are in accordance with this mechanism, as at 100 °C an almost 1:1 mixture of C-H and N-H functionalization is observed (Scheme 5b).



Scheme 5. a) Reaction pathways for the gold catalyzed C-H functionalization reaction of unprotected carbazole with methyl phenyldiazoacetate, PMe_3 was used as a ligand instead of P^tBu_3 to simplify calculations. Reaction pathway for C-H functionalization in dark blue; N-H functionalization in turquoise (level of theory M06/6-31(d)/LANL2DZ in THF). b) Control experiments on the selectivity of this reaction. Isolated yields are given. Yields in italics by ^{1}H-NMR of the crude reaction mixtures. SPS grade THF <100 ppm H_2O.

An intricacy of the present mechanism lies within the proton shuttle mechanism.[19] The activation free energy of this step is strongly dependent on residual amounts of water in the reaction mixture. The calculations indicate that in the presence of negligible residual water amounts in THF solvent (SPS grade THF, typical amount of remaining water: <100 ppm or <0.0013 mol/L or 0.02 eq. with respect to the diazoacatete **9a**) the activation free energy for the N-H functionalization reaction is significantly disfavored over the C-H functionalization reaction (20.2 kcal/mol for N-H vs. 15.0 kcal/mol for C-H functionalization). A large amount of water (1 eq. with respect to the diazoalkane reaction partner) promotes this proton shuttle mechanism for both pathways and results in a smaller activation free energy (18.0 kcal/mol for N-H vs. 12.8 kcal/mol for C-H functionalization).[17] Whilst the energy difference of the proton shuttle mechanism for N-H functionalization and C-H functionalization remains the same, N-H functionalization becomes more feasible in the presence of water, which leads to the formation of both reaction products. Indeed, a control experiment in the presence of 1 eq. of H_2O produced a 2:1 ratio of N-H vs. C-H functionalization product mixture. A similar experiment with 1 eq. of D_2O revealed deuterium incorporation in the reaction product, supporting the role of water in the proton shuttle step (Scheme 5b).

In summary, we report an unprecedented selective C-H functionalization of unprotected heterocycles via Au(I)-catalyzed carbene transfer reaction. This protocol allows for the efficient and direct C-H functionalization of a broad scope of carbazole and other unprotected double benzannellated heterocycles even on gram-scale. Detailed mechanistic calculations unveil the underlying reaction pathway leading to this exceptional selectivity, which proceeds via a reversible reaction of the gold carbene intermediate with the *N*-heterocycle. Residual amounts of water in THF solvent and kinetic reaction control drive the selective formation of the C-H functionalization product.

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Keywords: C-H functionalization • carbazole • carbene • gold

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