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Introducing 1,3-Enyne Functionalization by Nitrene Transfer Reaction

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SUMMARY

In the context of carbon-nitrogen bond formation, metal-catalyzed nitrene transfer reactions constitute a powerful transformation. Albeit many saturated and unsaturated substrates can be modified with this strategy, the incorporation of nitrene to enynes yet remains undescribed. Herein we report the first example of this transformation, leading to the formation of propargyl aziridines or to unsaturated sulfinamides, corresponding to the attack of a copper-nitrene intermediate onto the *ene* or *yne* sites. DFT studies have provided an explanation to this diverse reactivity, which is sustained on the interactions of the enyne substituent with the pyrazolyl rings of the trispyrazolylborate ancillary ligand of the catalyst.

enynes functionalization nitrene transfer copper catalysis aziridines sulfinamides

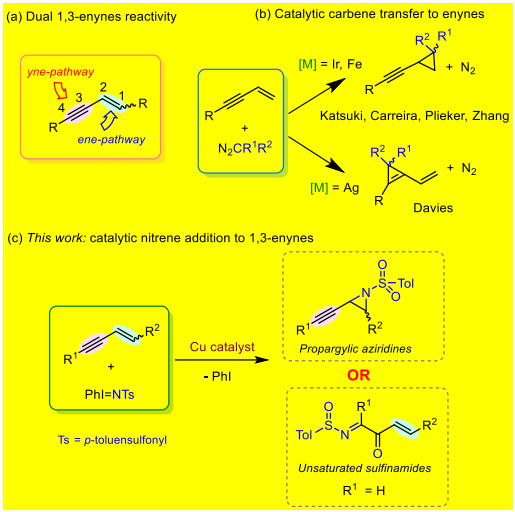
INTRODUCTION

Enynes are molecules bearing both double and triple carbon-carbon bonds which originate a very rich reactivity, with a considerable number of transformations being reported.[1] Conjugate 1,3-enynes are commonly used as the prototypical examples of such compounds, which may undergo, among others, 1,2- and 3,4-functionalization (Scheme 1a).[2-6] For example, the addition of a carbene group from a diazo compound may lead to the formation of three member rings at the alkene (1,2) or alkyne (3,4) sites. The few examples known to date correspond to independent reports by Katsuki (2008),[7] Carreira (2012),[8] Plietker (2020),[9] and Zhang,[10,11] which showed the selective cyclopropanation of the C=C bond, whereas Davies disclosed[12] the cyclopropenation of the alkyne moiety (Scheme 1b).

In contrast with the above, and to the best of our knowledge, the metal-catalyzed incorporation of nitrene (NR) units[13-20] to enynes remains unreported. Herein we describe the first example of such transformation, using 1,3-enynes, which employs a copper-based catalyst and PhI=NTs as the nitrene source. This system shows a remarkable behavior in terms of selectivity: the reaction can be directed towards the alkene or the alkyne groups upon tuning the substituents at those functionalities (Scheme 1c). This is not only a novel transformation with 1,3-enynes but also a simple and general protocol for the synthesis of propargylic aziridines[21] or unsaturated sulfinamides.[22].

THE BIGGER PICTURE

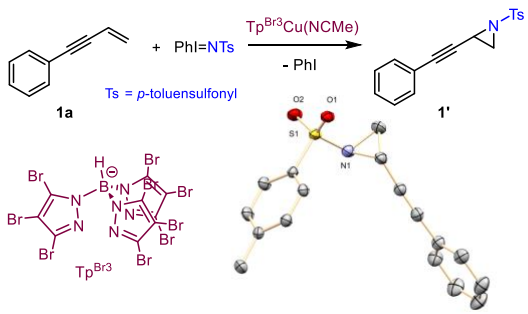
The formation of carbon-nitrogen bonds constitutes one of the main areas of synthetic chemistry nowadays due to its relevance in the preparation of a plethora of applied chemicals. One of the strategies toward that end consists in the catalytic transfer of a nitrene (NR) group from a metal center, which has been applied to many substrates. However, 1,3-enynes, molecules bearing two unsaturated, double and triple carbon-carbon bonds, remain unexplored within this methodology. Herein we describe the first example of an efficient catalytic system that allows not only functionalizing 1,3-enynes upon nitrene incorporation but also directing the reaction towards the double or the triple bond depending on-the substrate design.



Scheme 1. Introducing the 1,3-enyne functionalization by copper-catalyzed nitrene transfer.

RESULTS AND DISCUSSION

Our initial approach employed but-3-en-1-yn-1-ylbenzene (**1a**) as the model substrate and PhI=NTs as nitrene precursor (Scheme 2). We first employed $Tp^{Br3}Cu(NCMe)$ as catalyst, given the previously described excellent activity towards nitrene transfer to unsaturated bonds.[22-25] A 1:20:60 mixture of [Cu]:[PhI=NTs]:[enyne] (0.005 mmol of catalyst) was employed. A solution of the catalyst in dichloromethane at room temperature first incorporates the enyne and then solid NMR studies of the reaction crude revealed the presence of a unique product in a quantitative manner, which has been identified as the propargylic aziridine **1'** based on spectroscopic data (see Supplemental Information). Yellowish single crystals of **1'** were obtained upon cooling ether:n-hexane solutions, allowing the determination of the solid-state structure (Scheme 2),[26] which confirmed the proposal of the propargyl aziridine, in a novel route toward this type of compounds.



Scheme 2. The catalytic functionalization of 1,3-enyne with PhI=NTs using $Tp^{Br3}Cu(NCMe)$ as the catalyst.

ORTEP plot (50% thermal ellipsoids) of the X-ray structure of **1'** with hydrogens omitted for clarity.

Reaction conditions were further optimized in terms of stoichiometry, nitrene precursors, solvents and temperature (see Supplemental Information), leading to the use of PhI=NTs in dichloromethane and a 1:3 [PhI=NTs]:[enyne] ratio as the most productive conditions, affording **1'** in 95% yield. $TsNH_2$ accounted for the remaining of the initial PhI=NTs. When a 1:1 ratio of PhI=NTs and enyne was employed, the yield in **1'** dropped to 33%.

In view of this unprecedented transformation, we wondered about the use of other catalysts to promote it and performed a catalyst screening study with several group 11 metal complexes as well as Al- and Fe-halides with demonstrated effectiveness in nitrene

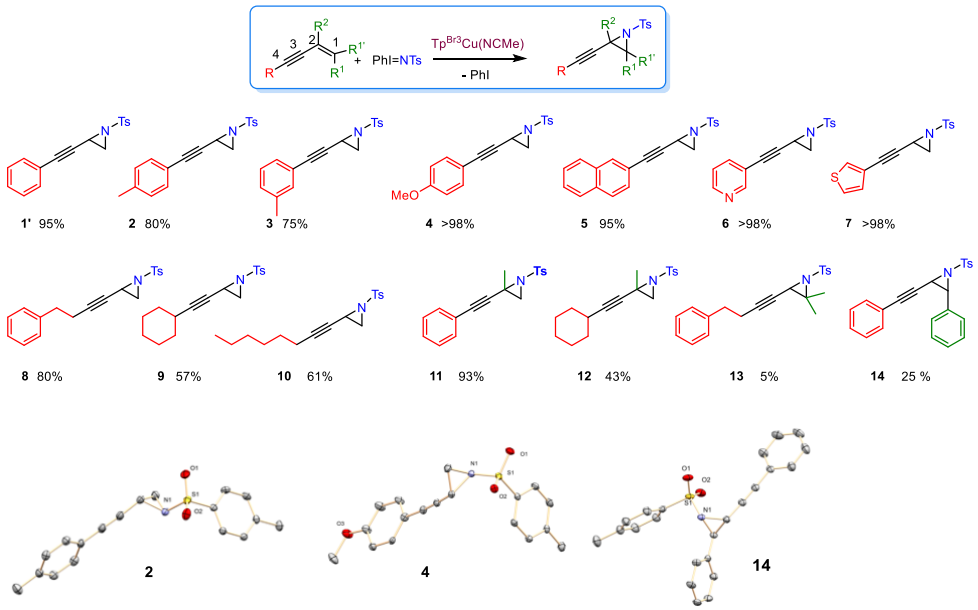
transfer reactions.[13-16] As shown in Table 1, the most efficient catalysts were, in this order, $Tp^{Br3}Cu(NCMe)$, IPrCuCl (+ $NaBAr^F_4$), $[Tp^{*,Br}Ag]_2$ and CuCl. However, it is worth mentioning that, albeit at lower yields, all the catalyst employed led to detectable amounts of aziridines with the exception of AgOTf.

Table 1. Catalyst screening for the reaction of 1a with PhI=NTs.[a,b]

Catalyst	Yield **1'** [b]	Catalyst	Yield **1'**[b]
$AlCl_3$	10	$Cu(acac)_2$	25
CuI	55	AgOTf	<1
$Fe(OTf)_2$	10	$IPrAuCl/NaBAr^F_4$	10
$[Tp^*Cu]_2$	50	$IPrAgCl/NaBAr^F_4$	10
$Tp^{Ms}Cu(thf)$	35	$IPrCuCl/NaBAr^F_4$	94
$[Tp^*Cu]_2$		$Tp^{Br3}Cu(NCMe)$	>98%

[a][Cat]:[PhINTs]:[1,3-Enynes] = 1:20:60, r.t., DCM, 2 h.
[b]Determined by 1H NMR using 1,3,5-trimethoxybenzene as internal standard.

The scope of the reaction has been first developed with enynes maintaining substitution at position 4 and modifying the degree of substitution at positions 1 and/or 2. The results are displayed in Scheme 3, leading in all cases to the formation of the propargylic aziridines **1**-**14** as the main product in moderate to high yields. Substitution at position 4 with aryl groups and with unsubstituted positions 1,2 led to very high yields (**1**-**5**), a behavior also observed for heterocycles such as pyridine and thiophene as substituents (**6**-**7**). Benzyl-substituted enyne provided high yields (**8**), whereas cyclohexyl or n-hexyl-substituted enynes (**9**-**10**) were functionalized at a lower extent.

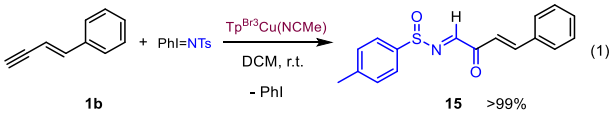


Scheme 3. Reaction scope with 4-substituted enynes.

Reaction conditions: [Cat]/[PhI=NTs]/[enyne] = 1:20:60, r.t., DCM, 2h. Yields determined by NMR using 1,3,5-trimethoxybenzene as internal standard. $TsNH_2$ accounted for 100% of initial PhI=NTs not converted in aziridine. ORTEP plots (50% thermal ellipsoids) of the X-ray structures of **2**, **4** and **14** with hydrogens omitted for clarity.

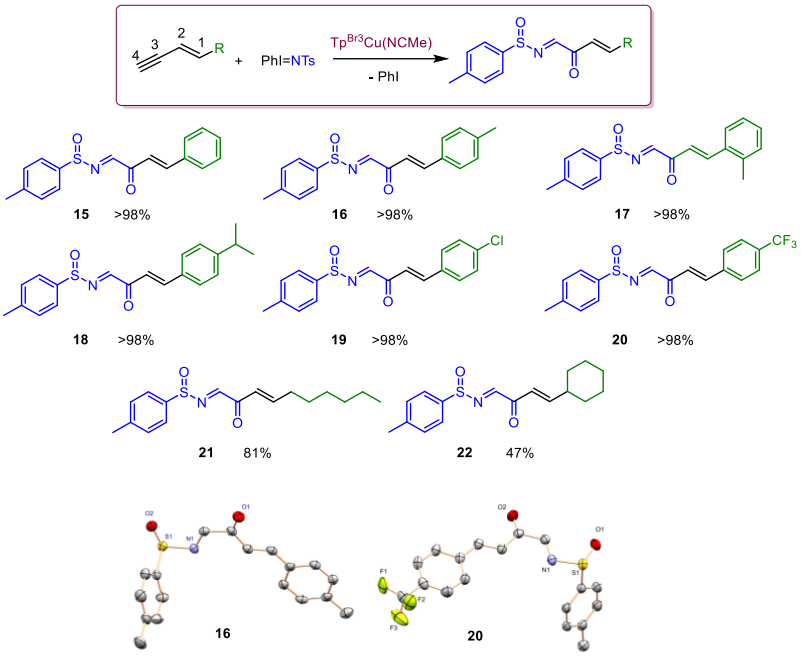
The incorporation of substituents at the 1 and/or 2 positions of the enyne led to drastic changes in the reaction outcome. Thus, with a Me group at 2, and a Ph substituent at 4, 93% yield of **11** was obtained, which decreased to 43% upon replacing the aryl with a cyclohexyl group (**12**). Substitution at position 1 is also relevant since the presence of one Ph or two methyl groups induced significant decrease in the yield. We assumed these latter results indicate a certain steric effect governing the nitrene transfer process. In fact, when we employed the bulkier $Tp^{Ms}Cu(THF)$[27] complex as the catalyst, **14** was obtained in 5% yield, assessing such steric effect. $TsNH_2$ was obtained as the major by-product in these transformations, due to PhI=NTs decomposition Compounds **2**, **4**, **5** and **14** have been characterized by X-ray studies (see Scheme 3 and Supplemental Information).[26] It is worth mentioning that the use of $IPrCuCl/NaBAr^F_4$ as catalyst using other 1,3-enynes different than **1a** led to mixtures of products, showing poor selectivity than $Tp^{Br3}Cu(NCMe)$ as the catalyst. We think this is the result of a less sterically protected copper-nitrene unit, that induces undesired side reactions.

The use of 4-unsubstituted enynes led to a completely distinct behavior. In a first experiment, (*E*)-but-1-en-3-yn-1-ylbenzene (**1b**) was employed, under identical reaction conditions to those employed above (eq 1), leading to the observance in the reaction crude of a unique set of resonances that allowed proposing the formation of compound **15**, which contains the olefinic bond intact. This compound corresponds to the formal reduction of the sulfone group into sulfoxide and the corresponding transfer of an oxygen atom to one of the alkyne carbon atoms. A similar transformation has been independently described by Fokin[28] and by our group.[25] Optimization studies led to experimental conditions similar to those previously found for the set of 1,3-enynes shown in Scheme 3 (see Supplemental Information).



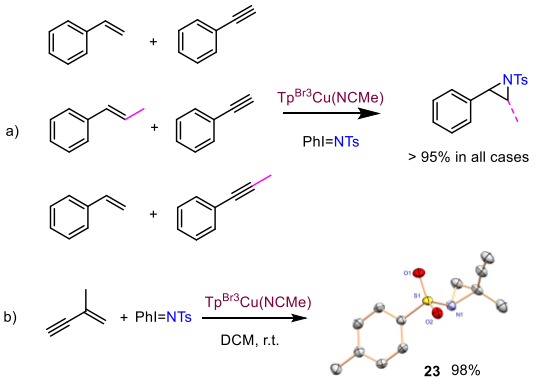
1b **15** >99% (1)

Several 4-unsubstituted enynes were employed to investigate the scope of this transformation (Scheme 4). 1-Aryl substituted 1,3-enynes led to quantitative formation of the sulfinamides **15**-**20**, the presence of electron-donating or electron-withdrawing groups in the aromatic ring not affecting the reaction outcome. Replacement of aryl with cyclohexyl or n-hexyl substituents at that position decreased yields to 81% (**21**) and 47% (**22**), respectively. Single crystals of sulfinamides **16**, **18**, and **20** served to verify the proposed structures through X-ray studies (see Scheme 4 and Supplemental information).[26]



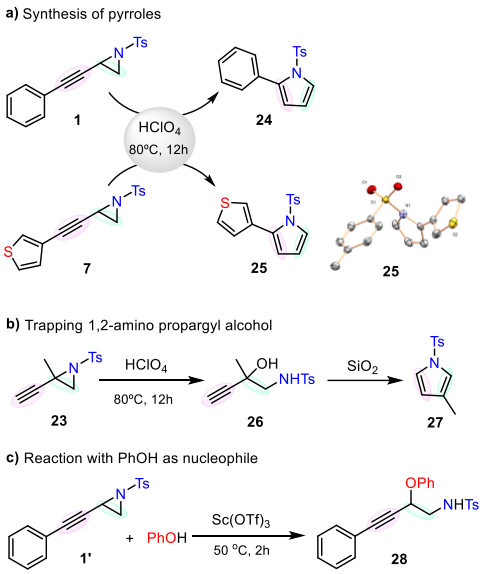
Scheme 4. Reaction scope with 4-unsubstituted enynes.
Reaction conditions: [Cat]/[PhI=NTs]/[enyne] = 1:20:100, r.t., DCM, 2h. Yields determined by NMR using 1,3,5-trimethoxybenzene as internal standard. $TsNH_2$ accounted for 100% of initial PhI=NTs not converted in aziridine. ORTEP plot (50% thermal ellipsoids) of the X-ray structure of **16** and **20** with hydrogens omitted for clarity (see Supplemental Information for X-ray data for **19**).

To compare the above results, corresponding to an ene-yne intramolecular competition, with the intermolecular competition between olefins and alkynes, several experiments using mixtures of styrenes and phenylacetylenes led to the same outcome (Scheme 5a): only the aziridines derived from styrenes were formed in nearly quantitative yields. Moreover, the use of 2-methylbut-1-en-3-yne, lacking substituents at the terminal olefin and alkyne carbons, also led to aziridine **23** (Scheme 5b).



Scheme 5. Alkene/alkyne competition experiments.
Reaction conditions: a) [Cat]/[PhI=NTs]/[olefin]:[alkyne] = 1:20:50:50, r.t., DCM, 2h. Yields determined by NMR using 1,3,5-trimethoxybenzene as internal standard. $TsNH_2$ accounted for 100% of initial PhI=NTs not converted in product. b) [Cat]/[PhI=NTs]/[enyne] = 1:20:60, r.t., DCM, 2h. Yields determined by NMR using 1,3,5-trimethoxybenzene as internal standard. $TsNH_2$ accounted for 100% of initial PhI=NTs not converted in aziridine. ORTEP plot (50% thermal ellipsoids) of the X-ray structure of **23** with hydrogens omitted for clarity.

The propargylic aziridines are direct precursors of propargylic amines, which are building blocks in pharmaceutical and bioactive compounds and are present in many natural products.[29-32] We have explored the ring-opening of the propargylic aziridines **1'** and **7**. Under acid conditions,[33] pyrroles **24** and **25**, respectively, were formed in a quantitative manner (Scheme 6a, see Supplemental Information for experimental details). The pyrrole formation must occur through two consecutive steps, ring-opening and intermolecular rearrangement. Aiming at detecting the propargylic amino alcohol intermediate, aziridine **23** led, under the same reaction conditions, to a 90:10 mixture of amino alcohol **26** and pyrrole **27**. Treating the reaction crude with silica gel, full conversion of **26** into **27** was observed (Scheme 6b). Ring-opening reaction of **1'** through S_N2 process with PhOH as nucleophile in the presence $Sc(OTf)_3$[34] led to compound **28** in 55% (Scheme 6c).



Scheme 6. Propargylic aziridines functionalization via ring-opening reaction.

DFT studies.

Reaction conditions are given in the Supplemental Information. ORTEP plot of **25** is represented with 50% thermal ellipsoids, and hydrogens being omitted for clarity.

The results collected with this copper-based system for the unprecedented 1,3-enyne functionalization by nitrene incorporation can be summarized as follows: (a) substrates with substitution at position 4 undergo ene-reactivity, leading to aziridines; (b) substrates with no substitution at position 4, and with substitution at position 1 verify yne-reactivity, leading to sulfinamides; (c) intermolecular experiments support the preference for ene-reactivity for this catalytic system. On these bases, we decided to perform DFT studies (B3LYP-D3 on DCM solvent, see Supplemental Information for full details) to ascertain the intimate pathways that govern this transformation.

We had previously characterized the mechanism of the ene reactivity leading to aziridine[35] and the yne- reactivity leading to sulfinamide[25]. In the case of enynes, bearing either the alkene or the alkyne functionalities, both species can be reached depending on the unsaturated bond involved in the transfer (Scheme 1c). We evaluated both possibilities based on the previous multistep mechanisms for the **1a** and **1b** as models for C1 and C4-substituted enynes, finding similar behaviors (see Supplemental Information). We will not discuss here the full mechanism, reported previously by our group in closely related systems,[25,35] instead we will focus on the key steps for the competition between the two reactions are those leading to the formation of the first C-N bond, and we will focus on this part (Figure 1). The reaction starts with a triplet ground state for the metallonitrene active species, $Tp^{Br3}Cu(NTs)$. The enyne approaches this complex to give rise to a supramolecular adduct. The $\Delta G^{\ddagger}$(DCM) values show a stabilization of those arrangements bearing the phenyl

substituent stacked to the Tp^{Br3} ligand, namely **Ia** and **I'b**. After the formation of the substrate-catalyst adduct, the cycle follows by C-N bond formation, **TSI-IIa/b** and **TSI-II'a/b**, in an irreversible process. We explored for this specific TS paths involving bond formation with either C1 or C2 (see Figure S4), and found an energetic preference for the path going through the C2 internal carbon, which is the one discussed below. The stabilization observed in intermediates **Ia** and **I'b** is enhanced along the transition states **TSI-IIa** and **TSI-II'b** making this process the selectivity-determining step of the reaction. The $\Delta\Delta G^{\ddagger}$(DCM) values of 4.9 kcal·mol^{-1} for pro-aziridine and 5,2 kcal·mol^{-1} for pro-sulfinamide pathways, in the reaction of **1a** and **1b** enynes, respectively, reproduce the 100% selectivity of the transformation. After the formation of the C-N bond, both pathways proceed through minimum energy crossing points (MECP) which connect the triplet and the singlet spin state surfaces. The detailed mechanisms for this part are presented and discussed in the Supplemental Information (Figures S5 and S6), as the energy differences involved indicate they play no role on the selectivity of the process. We will only mention here that the aziridinated product is reached directly, while the sulfinamide product formation goes through an intermediate containing a five-member cycle.

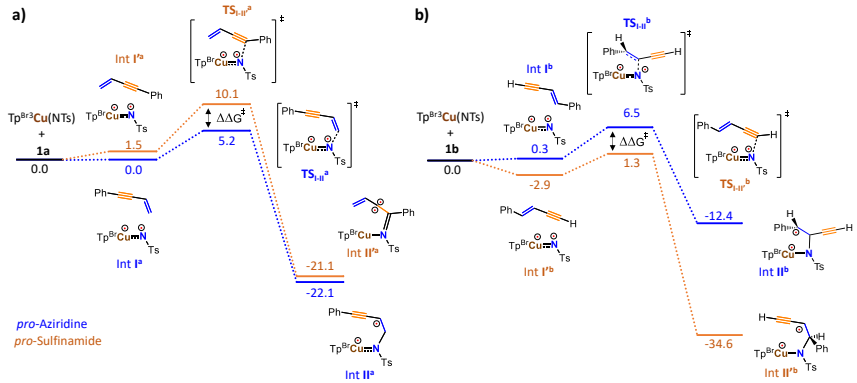


Figure 1. Comparison of the triplet Gibbs energy profiles (B3LYP-D3 in DCM) for the regioselective C-N bond formation process leading to aziridine (blue profiles) and sulfinamide (orange profiles).

A) For enyne **1a**. B) For enyne **1b**. Energy values in kcal·mol^{-1}. The separated catalytically active species Tp^{Br3}Cu(NTs) and enynes are taken as energy reference. The complete profiles are shown in the Supplemental Information.

The factors discriminating between the key transition states were investigated by Non Covalent Interaction (NCI) analysis (Figure 2).[36] In the case of the C4-substituted enyne **1a**, the C4-substituent is acting as a directing group favoring the interaction of those orientations displaying the Ph stacked with the Tp^{Br3} ligand (**IntI^{a}** and **TS$_{I\text{-}II}^{a}$**). In the case of the C1-substituted enyne **1b**, the more favorable interaction between the Ph and the Tp^{Br3} ligand leads to the sulfinamide product. It is very likely that for the alkyl-substituted enynes, related, albeit weaker interactions between the Csp3-H bonds and the pyrazolyl rings might take place. The key role of the substituents as director groups if further confirmed by an additional set of calculations on a hypothetical unsubstituted but-1-en-3-yne substrate. For the substrate with no substituents neglectable ene/yne selectivity is predicted by the calculation ($\Delta\Delta G^{\ddagger}$(DCM)=0.01 kcal·mol^{-1}).

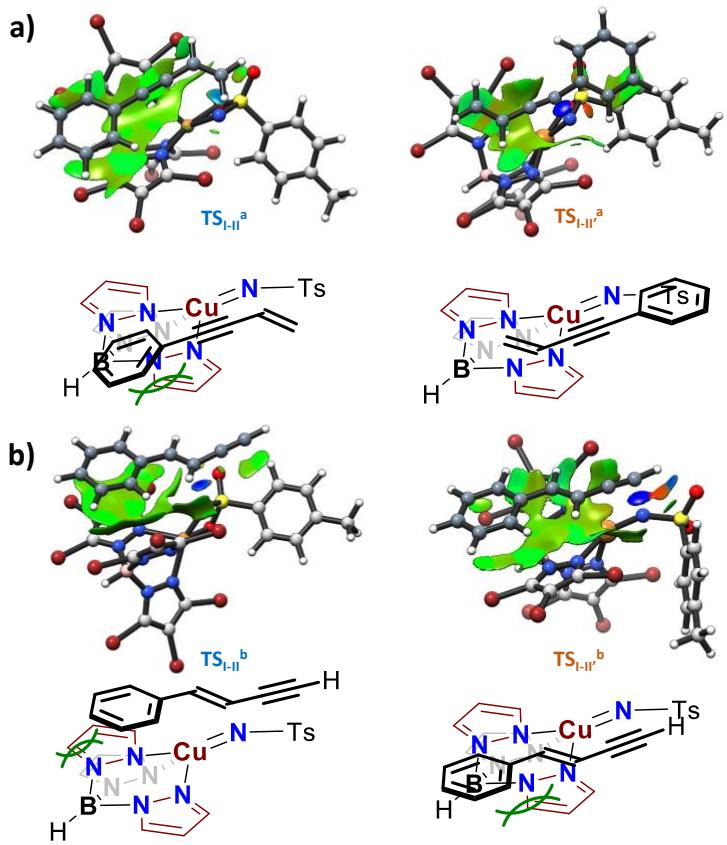


Figure 2. Optimized geometries along with their schematic representations. Comparison of the triplet Gibbs energy profiles (B3LYP-D3 in DCM) for the regioselective C-N bond formation process leading to aziridine (blue profiles) and sulfinamide (orange profiles).

a) For *pro* aziridine **TS$_{I-II}$^{a}**, *pro* sulfinamide **TS$_{I-II'}$^{a}**. b) For *pro* aziridine **TS$_{I-II}$^{b}**, *pro* sulfinamide **TS$_{I-II'}$^{b}**. NCIs surfaces computed by NCIPlot are depicted as blue (strong attractive), green (wdW) and red (repulsive) blobs.

Conclusions

We have developed the first catalytic system for the functionalization of 1,3-enynes upon incorporation of nitrene units. The reaction can be directed toward ene or yne modification upon the appropriate election of the substituents. DFT studies have provided a mechanistic picture, where the interaction between the substituents of enynes and the pyrazolyl ring of the trispyrazolylborate ligand are shown to be the main factor governing the selectivity.

Resource availability

Lead contact

Further information and requests for resources should be directed to and will be fulfilled by the lead contact, Pedro J. Pérez (perez@dqcm.uhu.es).

Materials availability

All materials generated in this study are available from the lead contact without restriction.

Data and code availability

The datasets generated during this study are available at the Supplemental Information, accessible via web from...

SUPPLEMENTAL INFORMATION

Document SI is the main supplemental PDF, and includes all experimental procedures and characterization data, computational data, and Cartesian coordinates of the optimized structures. The authors have cited additional references within the Supplemental Information.

ACKNOWLEDGMENTS

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AUTHOR CONTRIBUTIONS

M.M.D.R. and P.J.P. designed the experiments and wrote the paper. F.M. designed the DFT studies and wrote the paper. A.M.R. conducted the experiments. G.S. and L.M.-G. performed the DFT calculations. F.M. carried out X-ray experiments.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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