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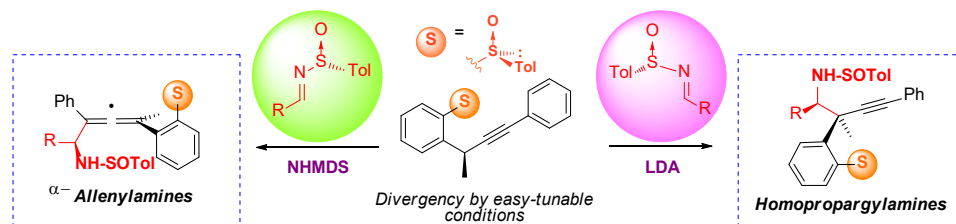
Stereocontrolled Addition of Scrambling *ortho*-Sulfinyl Carbanions: Easy Access to Homopropargylamines and α -Allenylamines

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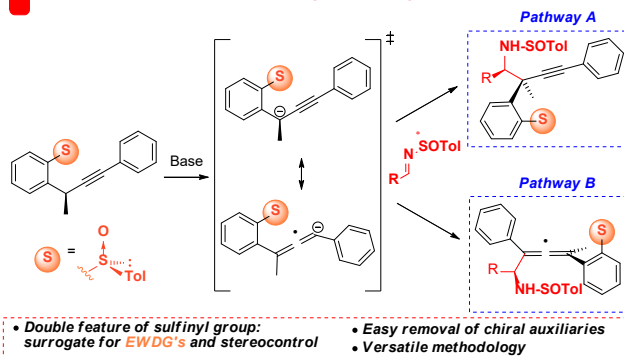
ABSTRACT: An unprecedented behavior of *ortho*-sulfinylpropargyl carbanions in the presence of optically active sulfinylimines affording two different families of compounds: this peculiar chemodivergency is importantly affected by the nature of the employed base, and assisted by the configuration of the electrophile, displaying no alteration in the stereocontrol of both reactions. α -Allenylamines are formed exclusively using *R*-sulfinyl aldimines as electrophiles, while homopropargylamines result when *S*-sulfinyl aldimines are employed.

Homopropargyl amines hold a preferred position in organic synthesis due to their versatility as building blocks in synthesis of terpenoid derivatives and other biologically active compounds.¹ Meanwhile, allenyl derivatives in their optically active form have received great attention in the synthetic chemist's community because of their ubiquitous presence among different natural products and pharmaceuticals.² However, the asymmetric construction of axially chiral allene derivatives and the design of acyclic molecules containing vicinal quaternary carbon centers, constitute some of the most challenging modern synthetic transformations. Unsurprisingly, a powerful arsenal of strategies that lead to these architectures continuously enriches the synthetic chemist's toolbox as a consequence of its trending demand. According to the literature,^{3a} the most invoked methodologies that enable the synthesis of enantioenriched allenes, consist in the resolution of racemates³ and chirality transfer from optically pure propargyl derivatives,⁴ among others.⁵ Related to the present work, Yin and co-workers have described an asymmetric copper-catalyzed alkynylogous aldol addition of propargyl esters to aldehydes, giving access to the corresponding enantioenriched α -allenyl alcohols.⁶ Regarding the preparation of homopropargyl amines,⁷ the most frequently employed procedures rely on the use of Schiff bases in the presence of propargyl or allenyl moieties.⁷ In this regard, Qiu and Hu,⁸ reported earlier this year an enantioselective multicomponent strategy enabling the preparation of optically active homopropargyl amines.

In a different context, the use of optically active sulfoxides as chiral auxiliaries has been exploited over the last decades,

Scheme 1. Proposed Strategy

Site-Selective Functionalization through Scrambling Anion Addition:

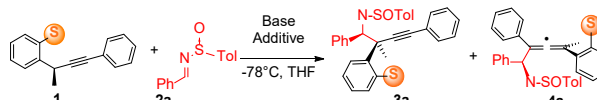


and due to their great stability and high stereocontrol in several synthetic transformations. Over the last years, our group has highlighted the peculiar behavior of the *ortho*-sulfinyl carbanions generated by the use of bases, such as LDA or diverse MHMDS, towards the stereocontrolled generation of new carbon-carbon single bonds between sterically hindered nucleophile-electrophile pairs.⁹ Taking this information into account, we considered the possibility of taking advantage of the delicate equilibrium of *ortho*-sulfinyl propargyl carbanions, designing a chemodivergent procedure based on a remotely controlled activation, to selectively achieve the γ -functionalization (Scheme 1, pathway A, top) or the ϵ -functionalization (Scheme 1, pathway B, bottom) of the described benzyl-propargyl scaffolds in presence of the same electrophile. Sulfinyl aldimines¹⁰ were chosen as the amino- source in this process considering a) its

easy preparation, b) their successful use in numerous asymmetric transformations, c) the latent possibility of modulating the chiral information at the sulfur atom, and d) the facile reported procedures to remove the chiral auxiliary after transformation, leading to two different families of amine derivatives.

Despite the brilliant strategies that are currently employed to synthesize α -allenylamines and homopropargyl amines, the lack of a general procedure that enables the selective preparation of each of these skeletons starting from a common substrate; encouraged us to design a tunable methodology to tackle this challenge in a stereoselective fashion. Herein, we present, the first chemodivergent functionalization of aryl propargyl moieties *remotely controlled* by a chiral sulfoxide to the best of our knowledge, which provides efficient access to two different families of amine-bearing compounds exhibiting high stereocontrol in both cases.

Table 1. Optimization of the reaction^a



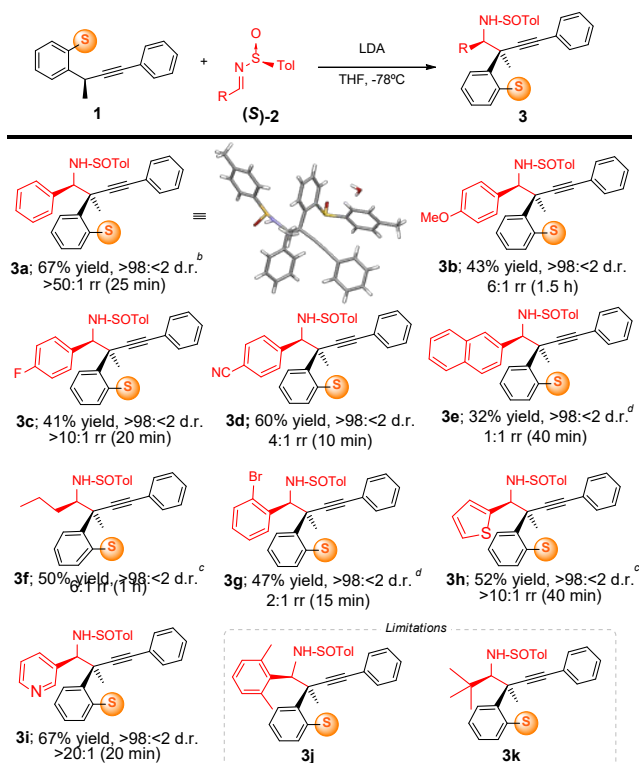
Entry	Base	2	Additive	3a (% yield)	4a (% yield)	d.r.
1	LDA	(S)-2a	---	67	0	>98:<2
2	KHMDS	(S)-2a	---	<20	0	---
3	NHMDS	(S)-2a	---	40	15 ^d	>98:<2
4 ^b	LDA	(S)-2a	12-crown-4	<10	0	---
5 ^c	LDA	(S)-2a	HMPA	22	43 ^d	90:10
6	LDA	(R)-2a	---	0	0	---
7	LHMDS	(R)-2a	---	0	18	90:10
8	KHMDS	(R)-2a	---	0	45	90:10
9	NHMDS	(R)-2a	---	0	73	>98:<2

^a Reaction conditions: **1** (0.1 mmol), **2** (0.12 mmol), base (0.12 mmol), 0.15 M. ^b Isolated yield is shown in all cases. Diastereomeric ratio of the major product is indicated and calculated by NMR crude. ^c 12-crown-4 (0.4 mmol). ^d HMPA (0.4 mmol). ^e Epimer of **4a** at the sulfur atom (N-S).

We started our studies with the optimization of the addition of alkyne **1** to aldimines **2**. In previous reports,⁹ we have established the use of LDA as an efficient deprotonating reagent, triggering the formation of the corresponding benzyl carbanion. Therefore, we carried out the reaction of **1** in front of aldimine (S)-2a, observing the formation of **3a** as the only product with an extraordinary diastereomeric ratio (Table 1, entry 1). Considering this result, and aiming to improve the yield, the temperature was increased. Despite multiple efforts, any attempt led to complete degradation of the starting materials, as -78 °C proved to be the optimal temperature to carry out this reaction. Screening different metal-organic bases with lower coordinative character, namely KHMDS and NHMDS afforded **3a** in lower yields (entries 2 and 3). In order to gather more information about the role of the cation (Li, Na, K), 12-crown-4 ether was evaluated as additive, recovering the entire unreacted starting materials (entry 4). Interestingly, the use of HMPA afforded **3a**, along with the corresponding allene, as a major product for the first time (entry 5). This result suggested an important contribution from a plausible association between the base and the recently generated carbanion,⁹ favoring the generation of one over the other product. Subsequently, we decided to change the configuration of the aldimine to the corresponding (R)-2a; rendering **4a** with high diastereoselectivity when LHMDS or

KHMDS were used (entries 7 and 8), while no conversion with LDA was observed (entry 6). Nevertheless, NHMDS was remarkably efficient in terms of yield and diastereomeric ratio (compare entries 3 and 9), and to our delight, complete suppression of **3a**, showing a synergistic behavior between the base and the configuration of the imine. With these optimized conditions in our hands, we proceeded to explore the scope of the propargylation reaction (Scheme 2).

Scheme 2. Scope of the propargylation reaction^a



^a Reaction conditions: **1** (0.1 mmol), (S)-2 (0.12 mmol), LDA (0.15 mmol), 0.015 M.

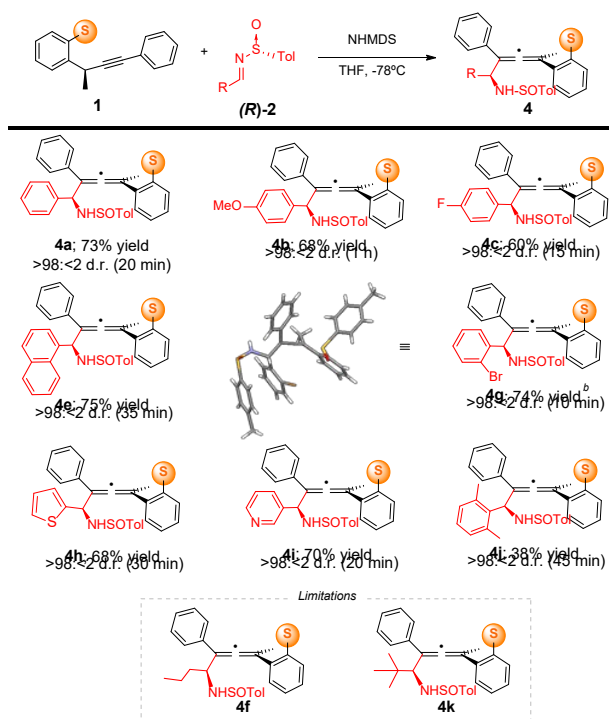
M. Isolated yields shown in all cases, unless otherwise noted. Diastereomeric ratios (d.r.) and regioisomer ratio (r.r.) were measured by NMR. ^b Reaction was run in 1.2 mmol scale. ^c Yield measured by NMR crude.

As expected, the reaction proved to work faster when electron-poor aromatic rings were present in the aldimines (**3c**, **3d** and **3g**), in contrast to electron-rich ones. The experimental trials disclosed that when bulkier substituents were used (**3e** and **3j**), the yield severely diminished, enhancing the formation of the allenyl adducts. Nonetheless, the diastereoselectivity remained unaltered in the desired products. Conversely, the use of a *tert*-butyl substituted aldimine, suppressed the formation of the target amine. The reaction conditions also proved to be successful when using an aliphatic aldimine (*n*-Pr) leading to **3f**, and heterocyclic substrates also gave good results, giving rise to the products **3h** and **3i**. To our delight, compound **3a** resulted to be a crystalline solid that allowed its study by X-ray diffraction in order to elucidate the absolute configuration of the two stereogenic centers,^{11a} wherein the α -amino center as *R* configuration and *S* at the benzylic position. Considering that the products were obtained under the same reaction conditions (see S.I. for further details), we assumed the same stereocourse of the reaction, and stereochemical outcome for the compounds.

After studying the synthetic scope of the above described homopropargylation reaction, we replaced the chiral information of the electrophile by inverting the configuration from the (S)-*p*-tolylsulfinyl aldimines to their enantiomeric forms

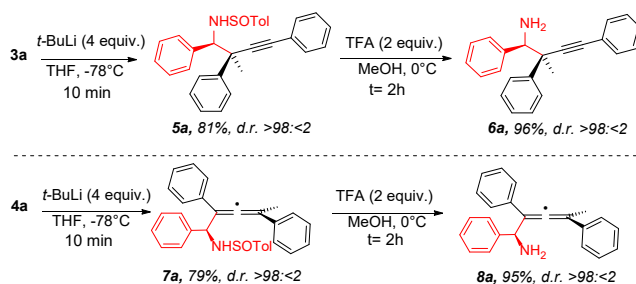
(*R*)-*p*-tolylsulfinyl aldimines. Taking into account the previously screened parameters, we carried out the formation of the diastereomeric enriched allenes. Various aromatic aldimines showed to undergo the desired transformation, affording the products with high levels of diastereoselectivity (Scheme 3). Additionally, substrates containing electron-donating (**4b**) and -withdrawing (**4c** and **4g**) substituents were tested, proving that the reaction works smoothly regardless of the electronic nature of the aryl motif. Moreover, the use of thienyl and pyridyl aldimines led to the corresponding allenes **4h** and **4i**, showing efficient results overall. Unfortunately, aliphatic aldimines were found to be unsuitable in this transformation (**4f** and **4k**), affording only complex reaction crudes. As previously stated, the use of bulky substituted aromatic rings resulted deleterious under the quaternization conditions. Therefore, in order to gather more information about this trend, a 2,6-disubstituted aromatic ring under this reaction conditions was tested, furnishing product **4j** in low yield, although maintaining the high stereocontrol. To our convenience, suitable crystals of compound **4g** were obtained, allowing the determination of the architecture at the axially chiral allenes (*R_a*) and absolute configuration of the new stereogenic center^{11b} via X-ray analysis.

Scheme 3. Scope of the allenylation reaction^a



In addition, to fulfil the chiral auxiliaries' role in the described transformations, the treatment of **3a** and **4a** (independently) with *t*-BuLi furnished the cleavage of the sulfoxide at the aromatic ring, leading to **5a** and **7a** respectively in good yield (Scheme 4). Subsequently, the acidolysis of the *N*-sulfinyl group gave the corresponding free amino group in each case: the homopropargylamine **6a** and the α -allenylamine **8a** in excellent yield without observing erosion of the optical purity.¹²

Scheme 4. Removal of the chiral auxiliaries

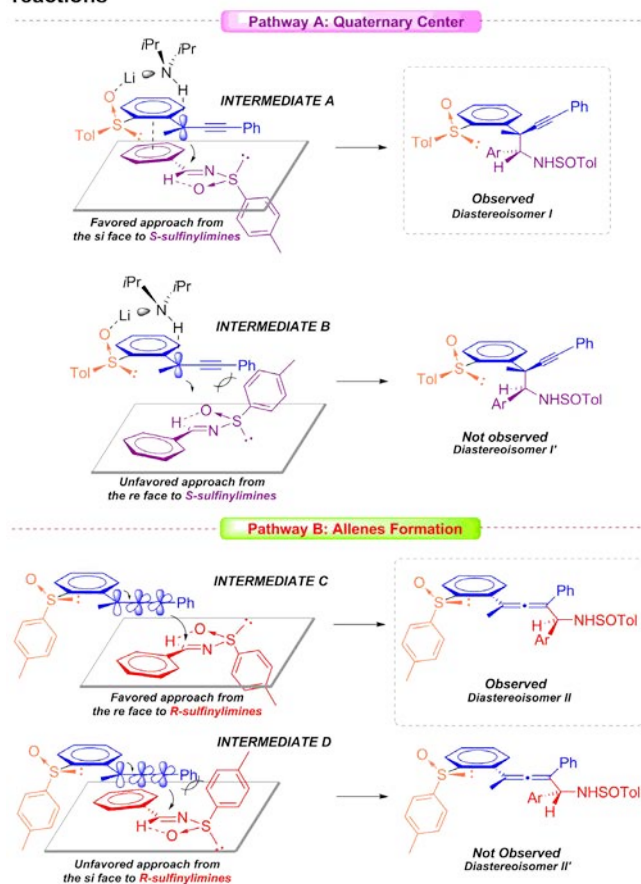


In light of the experimental data presented herein, and taking into account previously described theoretical evidence,^{9c,d} we propose a plausible mechanism for the present asymmetric transformations. The chemodivergent behavior of the generated benzyl carbanions derived from **1** may be correlated with the nature of the employed base (LDA vs NHMDS), unshackling a different disposition of the *ortho*-sulfinyl motif at an early transition state, and a “match-mismatch” relationship with the *N*-sulfinylimines. When lithium diisopropylamide is used, the resulting planar *sp*² benzyl carbanion is stabilized by an intramolecular association with the oxygen atom of the sulfoxide (Scheme 5, Pathway A) thus, generating a coordination through the O—[LDA]⁺—benzyl carbanion, that blocks the upper face of the planar system, favoring the approach of the aldimines from the bottom face as it was previously supported by DFT calculations.^{9c} In the case where NHMDS is used, the resulting “naked” anion, is prompted to delocalize more easily (compared to the coordination proposal) throughout the aromatic ring and the triple bond system (Scheme 5, Pathway B). Therefore, the more compromised the charge is, the less reactive the anion will be. Due to this high conjugation phenomenon, the so-called “scrambling” anion is observed, enabling two activated sites, the propargylic C(*sp*³) and the alkynyl C(*sp*), being the latter one more susceptible to carry out the nucleophilic attack to the “matched” imine. This previous statement can be supported with the fact that when using HMPA as additive and LDA as base, the major product of the reaction was the allenyl derivative. However, the d.r. was not entirely satisfactory due to the “mismatched” imine used (Table 1, entry 5).

Regarding the high stereoselectivity observed for both families of products, we propose that in the case of the homopropargyl amines (as shown in Scheme 5, intermediate **A**), the nucleophilic attack is executed by the *si* face of the aldimine, as the tolyl group of the electrophile is oriented at the bottom face, avoiding any kind of steric hindrance. Moreover, a plausible π - π stabilization could be contributing to this model (not feasible in intermediate **B**), leading to the formation of diastereoisomer **I**. This proposal is in accordance with the observed diminished yields when a bulkier substituent was employed (Scheme 2, **3g**) and the failure when using the 2,6-disubstituted aromatic ring **3j** and the aliphatic *tert*-Bu **3k**. Regarding the allenylamines, the stereoselectivity can be explained mainly by a desymmetrization process of the two π bonds forming the triple bond produced by the conjugation with the recently generated carbanion, as only the π bond oriented in parallel with respect to the orbital

containing the lone electron pair, will be suitable to perform a nucleophilic attack. In order to avoid steric interactions between the nucleophile and the electrophile, the approach is favored by the *re* face of the imine (Scheme 5, intermediate C), leading to the observed diastereoisomer **II**. As a complementary reactivity test, both procedures were carried out using as electrophile the racemic sulfinylimine (\pm)-**2a**. When LDA was used, the yield of **3a** decreased from 67% (as depicted in Scheme 3) to 30%, isolating unreacted starting material **1** and optically enriched *N*-sulfinylimine (–)-**2a**. In agreement with the previous observation, NHMDS conducted to the formation of **4a** in 33% yield,¹³ and in this case obtaining optically enriched (+)-**2a** with opposite configuration. This fact displays the importance of the right base-imine combination to achieve the targeted amine selectively.

Scheme 5. Proposed stereochemical outcome of the reactions



To conclude, we have developed a stereocontrolled chemodivergent strategy that selectively enables the generation of propargylic or allenic intermediates starting from a common substrate in front of optically active sulfinylimines. The nature of the employed base proved to be crucial to trigger one over the other activated species, as the configuration of the imine played a synergistic role to enhance the diastereoselectivity in the presented transformations. This method represents an elegant approach for the synthesis of two different families of amino compounds and is intended to inspire the development of new procedures to extend its scope and complete its limitations.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental details, supplementary figures, characterization of ¹H and ¹³C spectra for all compounds and X-Ray data for **3a** and **4g**. (PDF)

Crystallographic data for compounds **3a** and **4g** (CIF)

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(11) (a) CCDC 1969083 of compound **3a** and (b) Obtained via slow evaporation from a solvent mixture (hexane/DCM 4:1) CCDC 1969084 of compound **4g** contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccd.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

(12) Steps order of the transformation was inverted looking for the best global yield from **3a** and **4a** to **6a** and **8a** respectively. It was found that the most suitable order is the one presented in the manuscript in terms of yield. It is worth to note that in both cases, the diastereoselectivity is preserved.

(13) Standard conditions were employed when performing these tests (0.1 mmol of **1**, and 0.12 mmol of *rac*-**2a**). It was possible to recover the unreacted **2a** after flash column chromatography, in both cases with optical rotation nearly to the optically pure *N*-sulfinylimine, indicating that a kinetic resolution process has occurred. See: F. A. Davis, R. E. Reddy, J. M. Szweczyk, P. S. Portonovo, *Tetrahedron Lett.* **1993**, *34*, 6229.

