EurJOC
European Journal of Organic Chemistry

A Journal of
ChemPubSoc Europe

Accepted Article

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To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.201800749

Link to VoR: http://dx.doi.org/10.1002/ejoc.201800749

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10.1002/ejoc.201800749

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Sulfinate-Organocatalyzed (3+2) Annulation Reaction of Propargyl or Allenyl Sulfones with Activated Imines

Thomas Martzel,[a] Jean-François Lohier,[a] Annie-Claude Gaumont,[a] Jean-François Brière,[b] and Stéphane Perrio*[a]

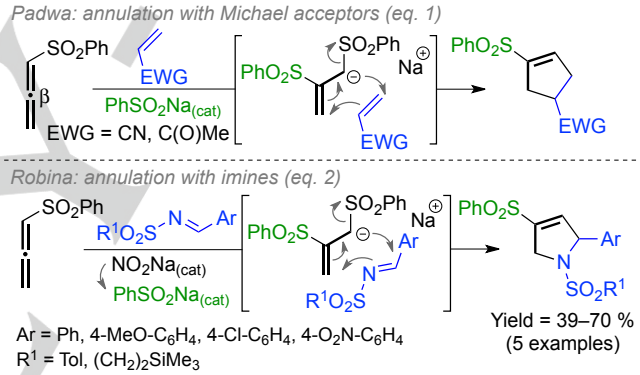
Dedication ((optional))

Abstract: An operationally simple methodology for the synthesis of 4-sulfonyl-3-pyrrolines is described using a propargylic sulfone and *N*-sulfonyl imines as substrates. This annulation process is initiated by an arenesulfinate organocatalyst, which allows a smooth isomerization of the alkynyl precursor into the corresponding allene, followed by the generation of a highly reactive allyl sulfone anion. An asymmetric version involving an unprecedented enantiopure sulfinate–ammonium cooperative ion pair ($PhSO_2^-$ R_4N^+*) was investigated. A proof-of-concept, with enantiomeric excesses of up to 41%, was obtained according to a preliminary screening of commercially available chiral phase transfer catalysts.

Introduction

Sulfinates RSO_2^- (sulfinic acid anions) are readily available, bench-stable, non-hygroscopic and easy to handle sulfur species, mainly associated to sodium cations.[1] Sulfinate salts exhibit a wide range of chemical reactivity, based on nucleophilic or radical pathways, thus acting as relevant precursors of sulfones. The pK_a value of about 2 for RSO_2H/RSO_2^- explains the good leaving group ability of sufinates.[2] This feature and the intrinsic nucleophilicity[3] of sulfinates afford an ideal combination for applications of these anions as Lewis bases in organocatalysis. However, to the best of our knowledge, very few example of sulfinate-organocatalyzed reactions have been reported so far in the literature.[4–6] The main approach in the area refers to the so-called Padwa reaction, which was introduced in the late 80's.[6] This strategy consists in a (3+2) annulation reaction between an allenyl sulfone and Michael acceptors to furnish 1-sulfonyl cyclopentenes (Scheme 1, eq. 1). The process is triggered by the nucleophilic attack of the sulfinate catalyst (probably through its soft sulfur centre) at the central carbon atom of the cumulative diene to generate an allyl sulfone anion intermediate. Diastereoselective versions were briefly developed by the group of García Ruano using chiral furanones as electrophilic reagents.[7] The group of Hale described also an example involving a chiral cyclohexenone, which resulted in the elaboration of a key precursor for the formal total synthesis of the naturally occurring (–)-echinosporin and (+)-brefeldin A.[8] To the best of our knowledge, enantioselective variants remain conspicuously absent.

Interestingly, the group of Robina disclosed an original approach to 4-sulfonyl 3-pyrrolines involving *N*-sulfonyl imines as electrophiles (Scheme 1, eq. 2).[9] Sodium nitrite ($NaNO_2$) was introduced as the initial reaction promoter but the authors speculated the intermediary formation of a sulfinate.[10] The reported protocol was tedious and required the use of a syringe pump, in order to generate small amounts of the key allyl sulfone anion intermediate and thus to minimize unwanted polymerisation events.



Scheme 1. Sulfinate-mediated (3+2) annulations with allenyl sulfones.

Considering the high interest of organic chemists for the development of synthetic approaches to original and medicinally-relevant five-membered nitrogen-containing heterocycles,[11] we believed that this annulation process which leads to unique functionalized pyrroline platforms deserves further attention.[12] The process could stand further improvements in terms of operational simplicity, substrate compatibility and reaction efficiency. Proving the intermediacy of a sulfinate catalyst could also open the way to an enantioselective version of the reaction.

In this respect, we conceived that the readily available propargylic sulfone isomer **1** could be a convenient source[13] of the allenyl sulfone **2** upon the influence of a sulfinate catalyst, to provide a user-friendly one-pot annulation procedure and to prevent, thereby side reactions such as polymerization (Figure 1). The introduced sulfinate catalyst would act both as a Brønsted base, thus permitting an *in situ* isomerisation of alkyne **1** into allene **2**, and as a Lewis base in the consecutive annulation pathway. Based on this hypothesis, the highly reactive allenyl sulfone **2** and allyl sulfone species **I** would be generated gradually in the reaction mixture. Furthermore, according to the anionic character of all intermediates, the use of

[a] T. Martzel, J.-F. Lohier, A.-C. Gaumont, and S. Perrio*
Normandie Univ, ENSICAEN, UNICAEN, CNRS, LCMT, 14000 Caen, France
E-mail: stephane.perrio@ensicaen.fr,
https://www.lcmt.ensicaen.fr/cv-stephane-perrio/
[b] J.-F. Brière
Normandie Univ, INSA Rouen, UNIROUEN, CNRS, COBRA, 76000 Rouen, France

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phase transfer conditions (PTC) could be an entry to an asymmetric version of the reaction.[14] Indeed, the fact that the incoming sulfinate remains on the products **4**, whereas the liberated one originates from the allenyl sulfone, implies the use of identical sulfonyl groups for the sulfinate catalyst and the allenic substrate and thus precludes to take profit of a chiral sulfinate.[7a] Alternatively, the use of an enantiopure sulfinate–ammonium salt $PhSO_2^-$ R_4N^{+}* (formed *in situ* in a catalytic amount from $PhSO_2Na_{cat}$ and $R_4N^*X_{cat}$), would allow the chiral ammonium cation R_4N^{+}* to influence the stereoselective issues of the anionic intermediates, meanwhile the sulfinate would still act as a Lewis base.[15–17] This methodology would design the first enantioselective version of a sulfinate-mediated annulation reaction, but also would highlight the unprecedented use of $PhSO_2^-$ R_4N^{+}* as a cooperative ion pair.[18] We are pleased to present herein the results of this investigation.

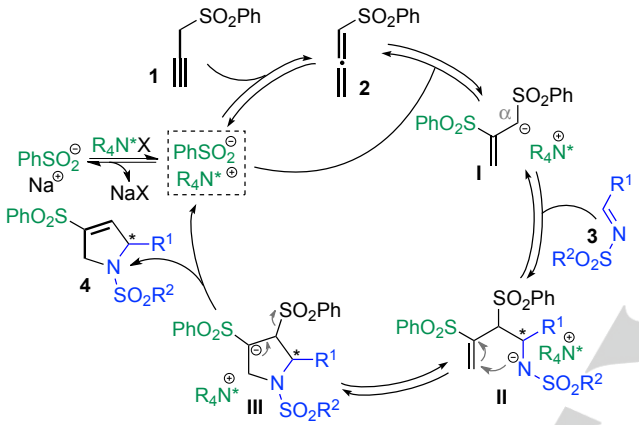
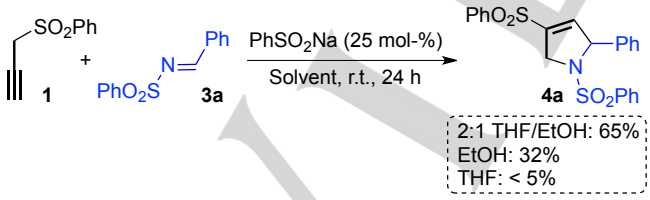


Figure 1. Proposed catalytic cycle from propargyl sulfone, mediated by a sulfinate-ammonium cooperative ion pair.

Results and Discussion

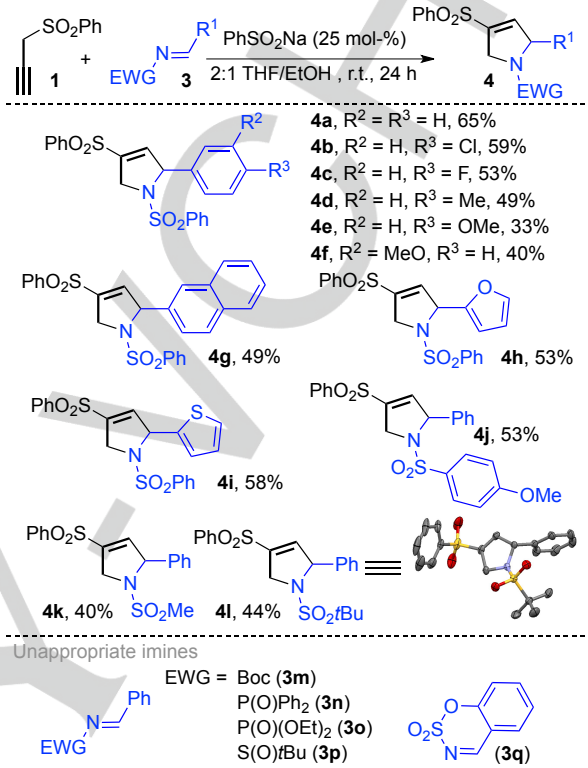
Investigation of the racemic version

The validation of our working hypothesis began with the reaction of propargyl sulfone **1** (1.5 equiv.) and *N*-sulfonyl imine **3a**, at room temperature, in the presence of a catalytic amount of sodium benzenesulfinate (25 mol-%) (Scheme 2).



Scheme 2. Optimization of the reaction conditions with imine **3a**.

The reaction was carried out in a 2:1 THF/EtOH mixture. This solvent combination was previously identified as an appropriate reaction medium in the inspiring Robina's report.[9] Pleasingly, the anticipated product **4a** was obtained in a 65% isolated yield after 24 h of reaction. Other conditions were tested but all of them led to inferior results (see Supporting Information). As the most representative examples, **4a** was produced in a 32% yield when the reaction was performed in EtOH alone, while only trace amounts of **4a** (< 5% yield)[19] were delivered in THF. We believe that the THF/EtOH mixture has a beneficial impact on the solubilization of the reagents (THF) and the stabilization of the highly reactive intermediates (EtOH) through hydrogen bonding.



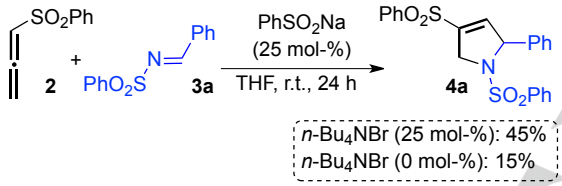
Scheme 3. Substrate scope with respect to the activated imine **3**.

Satisfied with the chemical efficacy of the process in the THF/EtOH system for the model reaction and its operational simplicity without the need of a syringe pump, these conditions were next used for the evaluation of the scope of the reaction (Scheme 3).[20] Imines derived from electron poor (**3b** and **3c**), as well as electron rich (**3d–f**) benzaldehydes provided the desired heterocycles **4b–f** with yields in the range of 33–59%. A 2-naphthyl group (imine **3g**) is also tolerated, leading to **4g** in a 49% yield. In addition, imines derived from heteroaromatic aldehydes such as **3h** (R^1 = 2-furyl) and **3i** (R^1 = 2-thienyl) were also good substrates, furnishing **4h** and **4i** in 53 and 58% yields, respectively. The influence of the sulfonyl group of the imine was then examined. A switch to the *N*-(4-methoxyphenyl)sulfonyl derivative **3j** allowed formation of **4j** in a 53% yield. Use of the *N*-methylsulfonyl analogue **3k** led to **4k** in a moderate 40% yield. A similar level of conversion was obtained with the *N*-*tert*-butylsulfonyl precursor **3l** (44% yield), and the structure of the target **4l** was confirmed by a single-crystal X-ray diffraction analysis.[21] The scope of the process was further examined through the investigation of imines activated by an *N*-*tert*-butoxycarbonyl (**3m**), an *N*-phosphinoyl (**3n**), an *N*-phosphoryl (**3o**), an *N*-sulfinyl (**3p**) or an *N*-sulfamoyl (**3q**) group.[22] Unfortunately, none of them furnished the desired cycloadducts. An unwanted hydrolytic reaction rapidly consumed imine **3m** (EWG = Boc), whereas a lack of reactivity and full recovery of **3n-q** was observed.

Having developed an operationally simple procedure giving rise to racemic 3-pyrrolines **4** through a (3+2) annulation reaction between *N*-sulfonyl imines **3** and allenyl sulfone, generated *in situ* from isomeric propargylic sulfone **1**, we turned our attention to the enantioselective version.

Investigation of the enantioselective version

A preliminary experiment was carried out with allenyl sulfone **2** and *N*-sulfonyl imine **3a** to embrace the question of the racemic background rate (Scheme 4). In order to favor tight ion pair species, the reaction was arbitrarily performed in pure THF. In the presence of $PhSO_2Na$ (25 mol-%) and *n*-Bu_4NBr (25 mol-%), a smooth annulation reaction took place to furnish, after 24 hours at a room temperature, the anticipated adduct **4a** in a 45% isolated yield.[23] By way of comparison, a slower transformation (< 15% yield with a similar reaction time) was observed without the ammonium catalyst. Unfortunately, attempts starting with the propargyl sulfone **1**, in the THF solution, failed to produce the annulation product **4a**, as a result of an ineffective alkyne-allene isomerisation. Pleasingly, the results obtained with the preformed allenyl sulfone **2** highlighted a marked effect of phase transfer conditions on the process efficiency and were encouraging for the development of the asymmetric version with chiral ammonium salts R_4N^{+}* X^{-}. On these grounds, the investigation was pursued with the preformed cumulene **2**.



Scheme 4. Effect of phase transfer conditions.

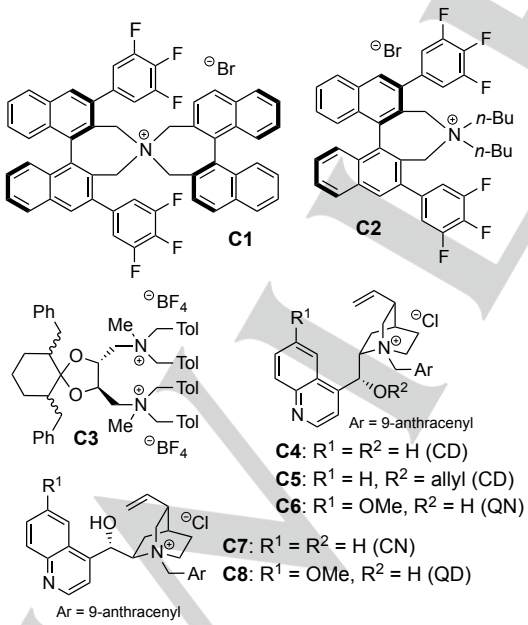
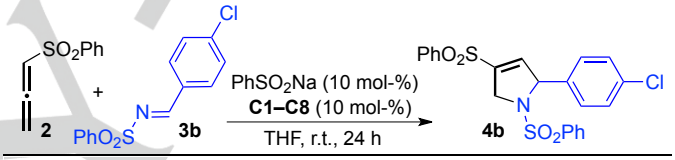


Figure 2. Enantiopure quaternary ammonium salts evaluated. CD: cinchonidinium, QN: quininium, CN: cinchoninium, QD: quinidinium.

At the outset, the evaluation of the asymmetric version was carried out with imine **3a**. The influence of various reaction parameters, including the solvent, the concentration, the catalytic $PhSO_2Na/R_4N^{+}$* X^{-} loading and the temperature, was examined.[24] Details of this seminal study are reported in Supporting Information. Et_2O, CH_3Cl and CH_2Cl_2 failed to promote the process[25] and the best reaction performance was obtained in THF[26] solution at an ambient temperature. Pleasingly, the catalyst loading could be reduced from 25 to 10 mol-%, without significant erosion of the reactivity. Furthermore, improved chemical yields were obtained when the allene and the imine were added together, via a syringe pump to the solution of the catalytic system. The slow addition of both reagents probably prevents polymerization of the highly reactive allyl sulfone anion and hydrolysis of the imine reagent.

These parameters being set, the screening of enantiopure quaternary ammonium salts **C1–C8**,[27] displaying architecturally distinct types, was then investigated (Figure 2). The reaction with the chloro-substituted imine **3b**, in the presence of 10 mol-% of the organocatalytic system ($PhSO_2Na$/**C1–C8**) was chosen as the model reaction (Table 2).

Table 2. Screening of enantiopure phase transfer catalysts towards an enantioselective version.[a]



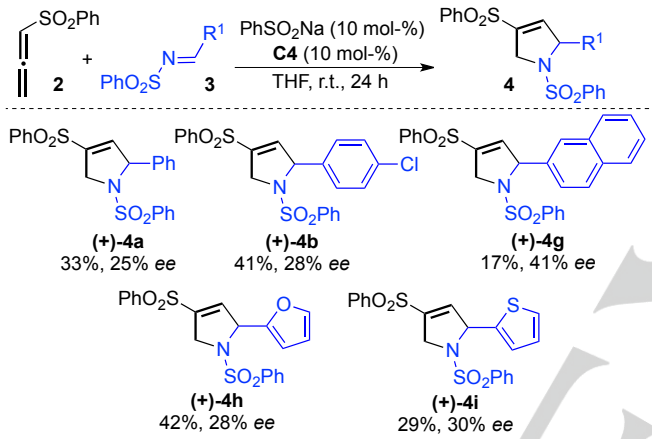
Entry	Catalyst	Yield (%)[b]	*ee* (%)[c]
1	**C1**	37	22
2	**C2**	59	–2
3	**C3**	41	–2
4	**C4**	41	28
5	**C5**	48	0
6	**C6**	32	13
7	**C7**	31	2
8	**C8**	20	0

[a] *Reaction conditions:* $PhSO_2Na$ (10 mol-%) and catalyst **C** (10 mol-%) in THF (0.1 M). A solution (THF, 0.1 M) of allenyl sulfone **2** (1.5 equiv.) and *N*-sulfonyl imine **3b** (1 equiv.) was slowly added to the previous suspension *via* a syringe pump (speed of 0.25 mL/h) at r.t. The mixture was stirred for 24 h. [b] Isolated yield. [c] Determined by HPLC: IA column, 1mL.min^{-1}, *n*-heptane/*i*PrOH/CH_2Cl_2 mixture (80:15:5 ratio) as eluent.

Use of the fully synthetic *N*-spiro C2-symmetric quaternary ammonium salt **C1** (first generation Maruoka's catalyst) led to the desired heterocycle **4b**, in 22% enantiomeric excess (*ee*) and 37% yield (entry 1). With the second-generation Maruoka's scaffold **C2**, a significant improvement of the yield to 59% (entry 2) was obtained but the product was almost racemic (*ee* = –2%). The tartrate-derived diammonium salt **C3** (TaDiAS) led to **4b** in a 41% yield (entry 3), but without enantioselectivity (*ee* = –2%). The *N*-anthracenylmethyl cinchonidinium chloride **C4** furnished a sample of **4b**, in 28% enantiomeric excess and 41% yield (entry 4). The analogous *O*-allyl cinchonidinium derivative **C5** allowed the formation of **4b** in an improved 48% yield, but unfortunately

in a racemic manner (entry 5). The results obtained with **C4** and **C5** highlight that the presence of the free 9-OH in the *Cinchona* alkaloid catalyst is crucial to achieve a reasonable enantioselectivity through ion-pairing interactions. The analogous 9-hydroxy quininium chloride **C6** allowed the isolation of **4b** in a 32% yield, but only in a 13% ee (entry 6). The pseudoenantiomeric derivatives **C7** (cinchoninium salt) and **C8** (quinidinium salt) appeared as completely inefficient in terms of enantioselectivity (entries 7 and 8). Finally, a range of other 9-hydroxy cinchonidinium salts, through the variation of the Ar group on the quinuclidine moiety, proved ineffectual, by comparison with the **C4** catalyst previously tested (see Supporting Information).

The proof of concept for the enantioselective version was next examined with various *N*-sulfonyl imines, under the established conditions in the presence of the currrently optimal cinchonidinium salt **C4** (Scheme 5).



Scheme 5. Proof of concept towards an enantioselective version.

3-Pyrroline **4a** was obtained in a 33% yield and an enantiomeric excess of 25% starting with parent imine **3a** (R^1 = Ph). The best *ee* value (41%) was obtained for compound **4g** containing a 2-naphthyl group, but at the expense of the yield (17%). Hetero-aromatic imines **3h** (R^1 = 2-furyl) and **3i** (R^1 = 2-thienyl) were also suitable substrates, providing the related enantioenriched products **4h** (*ee* = 28%) and **4i** (*ee* = 30%) in 42 and 29% yield, respectively. The major enantiomers produced were shown to be uniformly dextrorotatory and display also the shortest retention time on the HPLC chromatographs (see Supporting Information). We believe that the same sense of asymmetric induction with the phase transfer catalyst **C4** has taken place in all the cases.

Conclusions

In conclusion, we have developed an operationally simple procedure for the preparation of racemic 3-pyrrolines by a (3+2) annulation reaction between *N*-sulfonyl imines and parent allenyl sulfone, generated *in situ* from the isomeric propargylic sulfone. We also report an extension to enantioenriched products, under asymmetric phase transfer conditions, in which the preformed allenyl sulfone is the suitable substrate. Using the commercially available enantiopure cinchonidinium salt **C4**, the chiral 3-pyrrolines were obtained with *ee* ranging from 25 to 41%, and yield up to 42%. We believe that the evaluation of a library of alternative ammonium catalysts derived from the *Cinchona* chiral pool and displaying various substituents on the quinuclidine nitrogen center could infer improved levels of stereocontrol of the reaction. These proof-of-principle results also highlight the unprecedented use of an enantiopure sulfinate–ammonium (RSO_2^- R_4N^+*) cooperative ion pair through phase transfer conditions. This offers an attractive opportunity in asymmetric organocatalysis making use of sulfinates as Lewis bases. Future efforts aiming at broadening this strategy are currently underway in our laboratories.

Experimental Section

Typical Procedure for the Racemic Version: Propargylic sulfone **1** (1.5 equiv.), *N*–sulfonyl imine **3** (1.0 equiv.) and sodium benzenesulfinate (25 mol-%) were suspended in a THF/EtOH mixture (2:1 ratio). The reaction mixture was stirred at room temperature for 24 h, filtered on a syringe filter with a PTFE membrane (0.2 μm pore size) and concentrated under reduced pressure. The resulting crude product was then purified by column chromatography on silica gel [eluent: *n*-pentane/EtOAc/CH_2Cl_2 (7:1.5:1.5)] to afford the analytically pure pyrroline **4**.

Typical Procedure for the Enantioselective Version: Sodium benzenesulfinate (10 mol-%) and *N*-anthracenylmethyl cinchonidinium chloride **C4** (10 mol-%) were suspended in THF. *N*-sulfonyl imine **3** (1 equiv.) and allenyl sulfone **2** (1.5 equiv.) were dissolved in THF and slowly added to the previous suspension *via* a syringe pump (speed of 0.25 mL/h). The reaction mixture was stirred at room temperature until total disappearance of the allenyl sulfone (TLC) and concentrated under reduced pressure. The resulting crude product was purified by column chromatography on silica gel [eluent: *n*-pentane/EtOAc/CH_2Cl_2 (7:1.5:1.5)] to afford the analytically pure pyrroline **4**.

Supporting Information (see footnote on the first page of the article): Experimental procedures, optimization of reaction conditions, compound characterization data, copies of ^{1}H and ^{13}C NMR spectra, HPLC chromatographs, and crystallographic data for **2** and **4l**.

Acknowledgements

We acknowledge financial support from Region Normandie (CRUNCh network), CNRS, EFRD and Labex SynOrg (ANR-11-LABX-0029). This work has been also partially supported by INSA Rouen and Rouen Normandy University. We wish to thank C. Bellanger and D. Leparfait (Université de Caen Normandie) for contributing in the synthesis of starting materials and the optimization of the protocols.

Keywords: Sulfinates • Organocatalysis • Allenyl sulfones • Lewis base • Phase transfer

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[16] For our recent contributions in the field of asymmetric phase transfer catalysis: a) T. Cadart, C. Berthonneau, V. Levacher, S. Perrio, J.–F. Brière, *Chem. Eur. J.* **2016**, *22*, 15261–15264; b) T. Cadart, V. Levacher, S. Perrio, J.–F. Brière, *Adv. Synth. Catal.* **2018**, *360*, 1499–1509.

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[18] For reviews on asymmetric cooperative ion pairs, see: a) J. Godemert, S. Oudeyer, V. Levacher, *ChemCatChem* **2016**, *8*, 74–85; b) J. Novacek, M. Waser, *Eur. J. Org. Chem*. **2013**, 637–648; c) J.-F. Brière, S. Oudeyer, V. Dalla, V. Levacher, *Chem. Soc. Rev*. **2012**, *41*, 1696–1707; d) T. Ooi, K. Maruoka, *Acc. Chem. Res.* **2004**, *37*, 526–533.

[19] The reaction did not proceed better, under solid-liquid PT conditions (*n*-Bu_4NBr, 25 mol-%), in THF .

[20] 1.5 equiv. of allenyl sulfone **2** was routinely used for the application scope. A comparison of the reaction outcome, with instead an excess of imine **3** (1.5 equiv.), is provided in the Supporting Information for the synthesis of **4c, 4e**, **4f** and **4l**.

[21] CCDC 1511068 (for allene **2**) and CCDC 1511069 (for pyrroline **4l**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

[22] For a scale of electrophilicity of benzaldehyde-derived imines, see: R. Appel, S. Chelli, T. Tokuyasu, K. Troshin, H. Mayr, *J. Am. Chem. Soc.* **2013**, *135*, 6579–6587.

[23] A much lower yield was observed starting with (4-methylphenyl)sulfonyl allene ($TolSO_2$ group), in the presence of sodium (4-methylbenzene)sulfinate as catalyst ($TolSO_2Na$).

[24] Commercial *N*-benzyl and *N*-9-anthracenylmethyl cinchonidinium chloride were used as chiral phase transfer reagent.

[25] Liquid-liquid PT conditions were also critical for the process, because of the pronounced hydrolytic decomposition of the imine reagent in the presence of water.

[26] For the use of THF as solvent in solid liquid asymmetric phase transfer catalysed reactions, see ref. 16b and a) Y.-G. Wang, T. Kumano, T. Kano, K. Maruoka, *Org. Lett.* **2009**, *11*, 2027–2029; b) O. Mahé, I. Dez, V. Levacher, J.–F. Brière, *Angew. Chem. Int. Ed.* **2010**, *49*, 7072–7075. *Angew. Chem.* **2010**, *122*, 7226–7229; c) O. Mahé, I. Dez, V. Levacher, J.–F. Brière, *Org. Biomol. Chem.* **2012**, *10*, 3946–3954.

[27] Ammonium salts **C1–C5** are commercially available. The known *Cinchona* derivatives **C6–C8** were prepared by quaternarization of the appropriate alkaloid with the required benzylic chloride. **C6**: a) T. Perrard, J.–C. Plaquevent, J.–R. Desmus, D. Hébrault, *Org. Lett.* **2000**, *2*, 2959–2962; **C7**: b) B. Lygo, P. G. Wainwright, *Tetrahedron* **1999**, *55*, 6289–6300; **C8**: c) S. Arai, H. Tsuge, M. Oku, M. Miura, T. Shioiri, *Tetrahedron* **2002**, *58*, 1623–1630.

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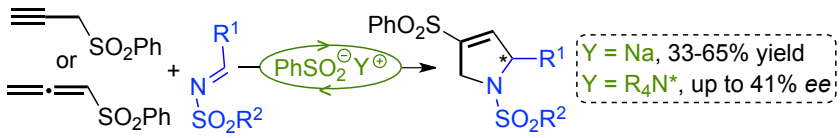
COMMUNICATION



The synthesis of 4-sulfonyl-3-pyrrolines, from a propargylic sulfone and activated imines, is described. The annulation is initiated by sodium benzenesulfinate as organocatalyst, which allows isomerization of the alkynyl precursor into the analogous allene. A proof of concept towards an asymmetric version involving an unprecedented enantiopure sulfinate–ammonium ($PhSO_2^-$ R_4N^+*) cooperative ion pair was then highlighted (*ee* up to 41%).

Lewis base organocatalysis

*Thomas Martzel, Jean-François Lohier, Annie-Claude Gaumont, Jean-François Brière and Stéphane Perrio**

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Sulfinate-Organocatalyzed (3+2) Annulation Reaction of Propargyl or Allenyl Sulfones with Activated Imines