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Synthesis of Metallocene Analogues of the Phenethylamine and Tetrahydroisoquinoline Scaffolds via Regioselective Ring Opening of 2-Aryl-*N*-sulfonyl Aziridines

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Abstract: The Lewis (or Brønsted) acid-catalyzed reaction of 2-aryl-*N*-sulfonyl aziridines with ferrocene and ruthenocene provided new amino-functionalized metallocene derivatives arising from a regioselective ring opening of the aziridine. The functionalized metallocene derivatives available by this methodology are suitable precursors for the stereoselective synthesis of metallocene analogues of the relevant tetrahydroisoquinoline motif by a Pictet-Spengler type reaction. These isoquinoline analogues are also accessible by a TfOH-catalyzed three-component reaction of 2-aryl-*N*-sulfonyl aziridines, ferrocene (or ruthenocene) and formaldehyde.

Keywords: Cyclization; Metallocenes; Multicomponent reactions; Nitrogen heterocycles; Strained molecules

Introduction

Functionalized ferrocene derivatives have found a myriad of applications in different realms of chemistry.[1] In particular, the ferrocene moiety is of high interest in medicinal organometallic chemistry as a bioisostere for aromatic and heteroaromatic groups.[2] Although the introduction of a ferrocenyl group into an active molecule does not ensure an improvement in the activity at all, this bioisosteric replacement has allowed the access to ferrocene derivatives displaying not only promising properties but also alternative modes of action dependent on the metallocene moiety and hence unattainable by the purely organic parent drug. One such relevant example is ferroquine, a ferrocenyl analogue of the antimalarial drug chloroquine, active against chloroquine-resistant strains.[3] Similarly, ferrocifens, organometallic analogues of the anticancer drug tamoxifen, display promising broad spectrum antiproliferative activity.[4]

On the other hand, a number of nitrogen-containing compounds such as β-phenethylamines **A** and tetrahydroisoquinolines **B** (Figure 1, top) can be found not only in the structure of numerous natural products but also of bioactive compounds and for this reason they are considered valuable and highly sought-after frameworks in medicinal chemistry.[5]

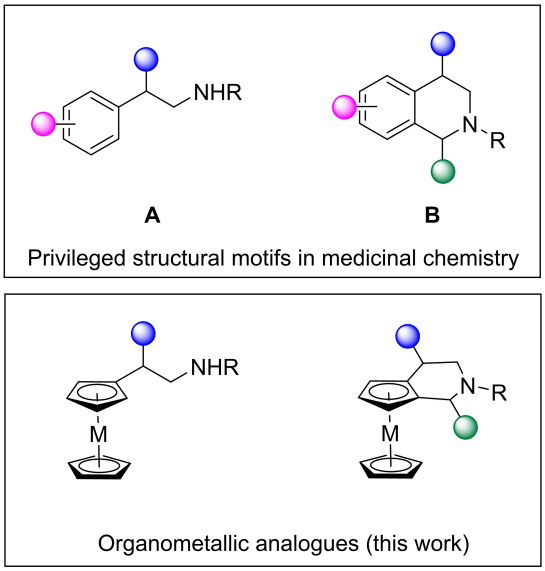


Figure 1. β-Phenethylamine and tetrahydroisoquinoline scaffolds **A** and **B** and their organometallic analogues.

Given the relevance of both β-phenethylamine and tetrahydroisoquinoline scaffolds, we became interested in the preparation of their metallocene analogues featuring a ferrocene moiety (Figure 1, bottom). Our synthetic plan to prepare such metallocene analogues is shown in Figure 2. We surmised that metallocene tetrahydroisoquinoline analogues could be accessed from the corresponding β-aminoethyl ferrocene derivatives through a Pictet-Spengler type reaction, the most commonly used tool for the preparation of tetrahydroisoquinolines.[6] However, unlike α-amino (m)ethyl ferrocene derivatives, which are readily available and have found numerous synthetic applications,[7] there are no suitable direct methodologies for the preparation of the required β-aminoethyl ferrocene starting materials. Based on our previous study on the TfOH-catalyzed ring opening of donor-acceptor cyclopropanes with ferrocene,[8] we reasoned that a related transformation involving aziridines could provide a straightforward route to β-aminoethyl ferrocenes, organometallic analogues of the β-phenethylamine scaffold with potential value for medicinal chemists.

Herein, we report the attainment of this goal; specifically, we describe the synthesis of new nitrogen-containing ferrocene (and ruthenocene) derivatives through regioselective ring opening of *N*-sulfonyl aziridines. As a preliminary exploration of the synthetic potential of the new amino-functionalized metallocene derivatives, formation of six-membered heterocyclic systems fused to the metallocene is also described. A straightforward multicomponent approach to these fused metallocene derivatives is furthermore reported.

Results and Discussion

Synthesis of amino-functionalized ferrocene derivatives. Using racemic 2-phenyl-1-tosylaziridine (**1a**) as model substrate, we initially studied its reaction with ferrocene (**2**) in the presence of a catalytic amount (10 mol%) of different Lewis and Brønsted acids. In accordance with our previous research,[8] trifluoromethanesulfonic acid (TfOH) in 1,2-dichloroethane (DCE) was initially selected as the catalytic system.

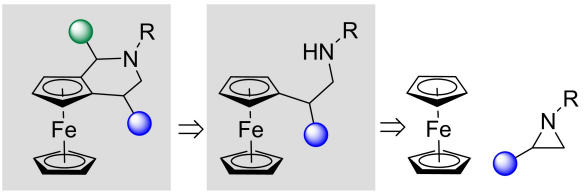


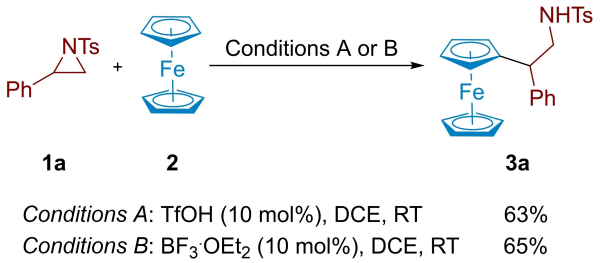
Figure 2. Our approaches to the synthesis of metallocene analogues of the β-phenethylamine and tetrahydroisoquinoline scaffolds.

Thus, stirring a solution of aziridine **1a**, ferrocene (**2**, 2 equiv.), and TfOH (10 mol%) in DCE at room temperature produced the desired ferrocene derivative **3a** in 63% isolated yield (Scheme 1, Conditions A). Alternatively, ferrocene **3a** can be obtained in 65% isolated yield by using boron trifluoride etherate as catalyst (Scheme 1, Conditions B). Other Brønsted and Lewis acids proved ineffective in the present ring opening transformation (see the Supporting Information for full details on the screening study). Furthermore, running the model reaction under conditions B on a 1 mmol scale had no detrimental effect affording compound **3a** in almost identical isolated yield (64%). Notably, this ring opening transformation takes place with complete regioselectivity.

Concerning the reaction scope, a range of sterically and electronically differentiated aryl-substituted aziridines **1** reacted smoothly with ferrocene (**2**) to produce the desired functionalized ferrocene derivatives **3** under conditions B (Table 1). For example, methyl substituents in the *ortho*, *meta* or *para* positions were well tolerated and furnished the desired ferrocene derivatives **3b–d** with comparable yields. An aziridine substrate bearing a *p*-$AcOC_6H_4$ group was also transformed into the desired ferrocene derivative **3e** in moderate yield (42%). 2-(4-Halophenyl)-*N*-tosylaziridines also undergo this ring opening reaction delivering the corresponding ferrocene derivatives **3f–h** in synthetically useful yields.

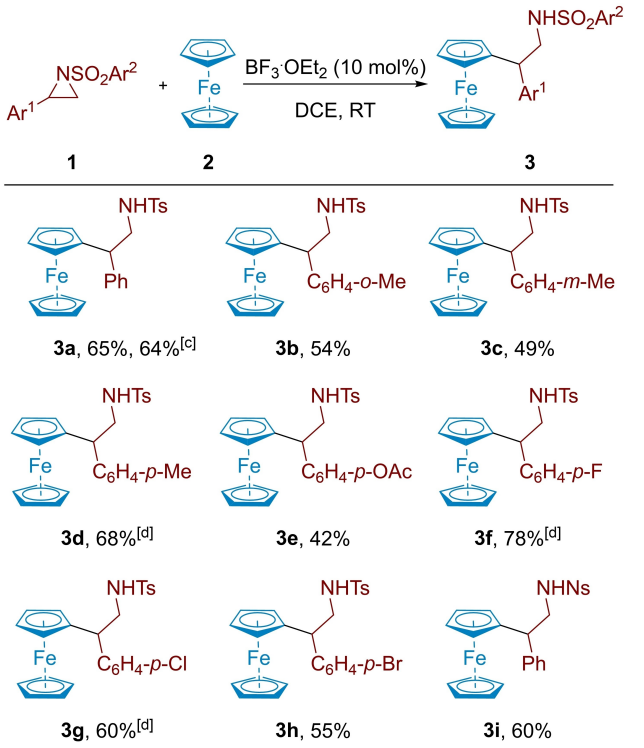
On the other hand, substitution on the aromatic ring Ar^2 appears to exert little influence on the reaction outcome. For example, under conditions B, 1-((4-nitrophenyl)sulfonyl)-2-phenylaziridine gave the desired functionalized ferrocene derivative **3i** in 60% yield.[9]

Some limitations of this ring-opening reaction were also revealed. For example, our studies indicate that an aryl group on the aziridine is paramount for reaction success. In fact, reaction of ferrocene with 1-tosylaziridine under conditions A or B did not proceed and the starting materials were recovered unchanged. Moreover, substrates bearing strong electron-withdrawing



Scheme 1. Reaction of aziridine **1a** and ferrocene (**2**); Initial findings. Reaction conditions A: **1a** (0.1 mmol), **2** (0.2 mmol), TfOH (10 mol%), DCE, RT. Reaction conditions B: **1a** (0.1 mmol), **2** (0.2 mmol), $BF_3{\cdot}OEt_2$ (10 mol%), DCE, RT.

Table 1. Reaction of *N*-sulfonyl aziridines **1** with ferrocene (**2**): Scope.[a,b]

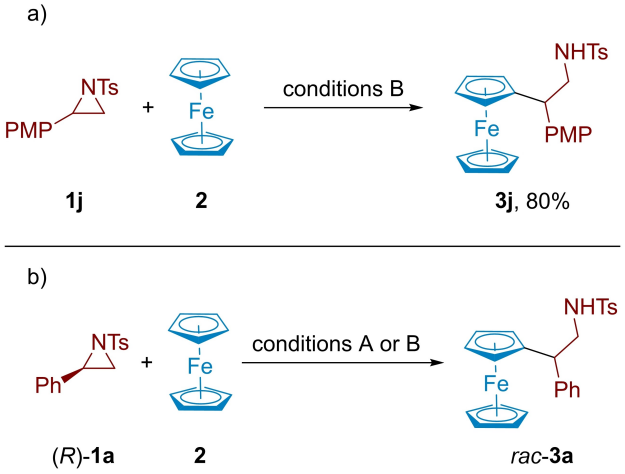


[a] Reaction conditions: **1** (0.1 mmol), **2** (0.2 mmol), $BF_3{\cdot}OEt_2$ (10 mol%), DCE, RT.
[b] Yields of isolated products after chromatographic purification.
[c] Reaction performed on a 1.0 mmol scale.
[d] TfOH (10 mol%) in DCE at RT was used.

groups such as *p*-nitrophenyl or pentafluorophenyl failed to undergo this acid-catalyzed ring opening reaction.

From a mechanistic point of view, the lack of reactivity of aryl-substituted aziridines bearing strong electron-withdrawing groups in this acid-catalyzed ring opening process would point to the participation of a benzylic carbocation intermediate, which would then undergo a Friedel-Crafts type electrophilic aromatic substitution with ferrocene.[10] Consistent with this mechanistic assumption, reaction of 2-(4-methoxyphenyl)-1-tosylaziridine (**1j**) with ferrocene under conditions B proceeded smoothly delivering the expected amino-functionalized ferrocene derivative **3j** in good isolated yield (80%) (Scheme 2, a).[11] Also in full agreement with the participation of a benzylic carbocation intermediate, enantiopure aziridine (*R*)-**1a** underwent the ring opening reaction with complete loss of stereochemical information to result in racemic **3a** (Scheme 2, b).

Notably, when 2-phenyl-1-tosylazetidine (**4**) and ferrocene (**2**, 2 equiv.) were subjected to reaction



Scheme 2. Evidences of participation of a benzylic cation intermediate: a) Reaction of a 2-aryl-1-tosylaziridine featuring an electron-donating methoxy group (PMP = C_6H_4-*p*-OMe). b) Reaction of optically active aziridine (*R*)-**1a** and ferrocene (**2**).

conditions A (TfOH 10 mol%, DCE, RT), homologated γ-amino-functionalized ferrocene **5** was obtained in moderate yield (42%), demonstrating that the regioselective ring-opening reaction of azetidine derivatives by ferrocene is also possible (Scheme 3).[12]

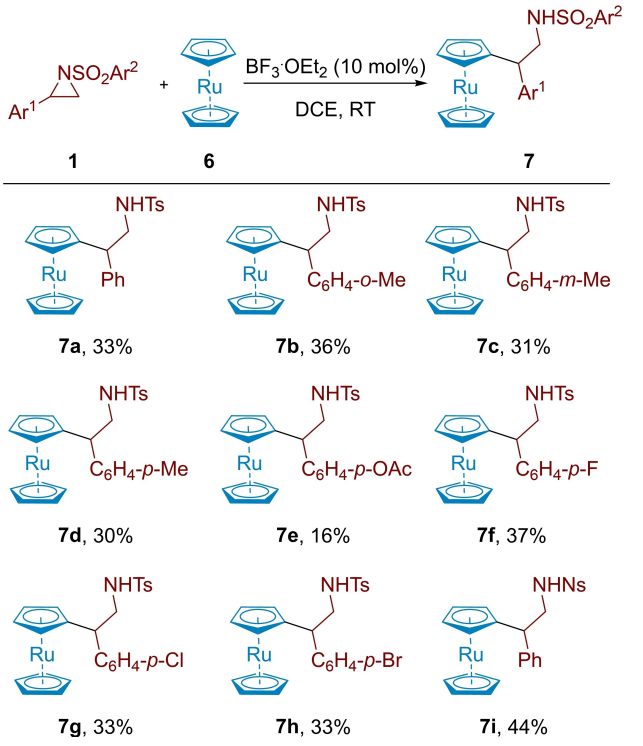
Synthesis of amino-functionalized ruthenocene derivatives. We found that this acid-catalyzed ring opening reaction was not limited to ferrocene. Indeed, ruthenocene (**6**) was likewise identified as viable a substrate yielding the corresponding ruthenocene derivatives **7** (Table 2). Thus, a variety of aryl-substituted aziridines **1** and ruthenocene (**6**) were subjected to the previously developed reaction conditions B ($BF_3{\cdot}OEt_2$ 10 mol%, DCE, RT) providing the corresponding functionalized ruthenocene derivatives **7a–i** in moderate yields. Both electron-donating and -withdrawing groups could be accommodated in the aryl moiety.

As shown, the reactions of aziridines **1** with ruthenocene (**6**) exhibited consistently lower yields than those involving ferrocene, which might be ascribed to the well documented diminished ability of ruthenocene to engage in electrophilic substitution reactions.[13]

Synthesis of metallocene analogues of the tetrahydroisoquinoline scaffold. Having developed a con-

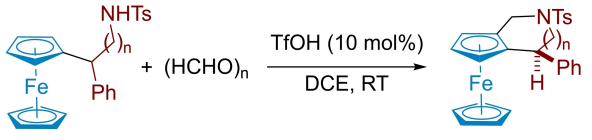
Scheme 3. TfOH-catalyzed reaction of 2-phenyl-1-tosylazetidine (**4**) and ferrocene (**2**).

Table 2. Reaction of *N*-sulfonyl aziridines **1** with ruthenocene (**6**): Scope.[a,b]



[a] Reaction conditions: **1** (0.1 mmol), **6** (0.2 mmol), $BF_3{\cdot}OEt_2$ (10 mol%), DCE, RT.
[b] Yields of isolated products after chromatographic purification.

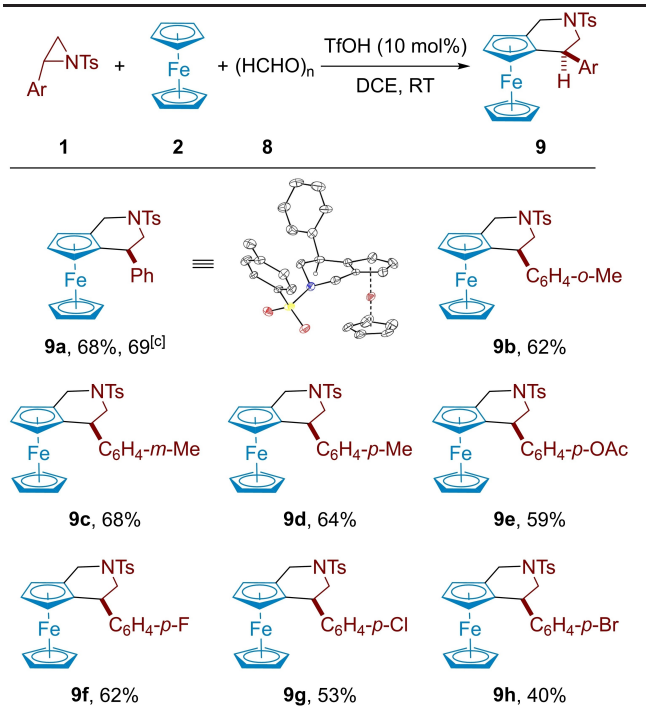
venient process for the preparation of β-aminoethyl ferrocenes **3** (and ruthenocenes **7**), we then explored their transformation into the target metallocene analogues of the tetrahydroisoquinoline scaffold through the planned Pictet-Spengler type reaction. To this end, ferrocene **3a** was initially reacted with an excess of paraformaldehyde (**8**) in the presence of a catalytic amount (10 mol%) of different Lewis and Brønsted acids. Pleasingly, we found that the use of TfOH allowed isolation of the corresponding ferrocene derivative **9a** in 62% yield after column chromatography (Scheme 4). Interestingly, compound **9a** featuring both central and planar chirality is formed as a single diastereoisomer, whose relative configuration was confirmed by X-ray diffraction.[14] The synthesis of a ferrocene derivative **9a′** containing a seven-membered heterocyclic system fused to the metallocene framework from functionalized ferrocene derivative **5** was also attempted, but unfortunately under the developed reaction conditions it was unsuccessful.



Scheme 4. TfOH-catalyzed Pictet-Spengler type reaction of ferrocene **3a** and paraformaldehyde (**8**).

After establishing a suitable stepwise method to access ferrocene **9a**, and considering the ability of TfOH to catalyze the ring opening reaction of *N*-sulfonyl aziridines **1** by ferrocene (See Scheme 1, Conditions A), we decided to investigate the feasibility of preparing compound **9a** and structurally related ferrocene derivatives in a more straightforward manner through a multicomponent reaction. The results compiled in Table 3 prove that this plan worked out reasonably well. Thus, stirring the corresponding aziridine **1**, ferrocene (**2**), and paraformaldehyde (**8**) in the presence of TfOH (10 mol%) in DCE at room temperature afforded the desired fused heterocyclic compounds **9a–h** in synthetically useful isolated yields (40–68%). In all the cases investigated, compounds **9** are formed as single diastereoisomers.[15,16]

Table 3. Three-component approach to disubstituted ferrocene derivatives **9**.[a,b]



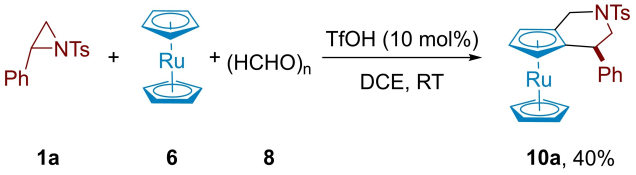
[a] Reaction conditions: **1** (0.1 mmol), **2** (or **4**, 0.2 mmol), **8** (0.5 mmol), TfOH (10 mol%), DCE, RT.
[b] Yields of isolated products after chromatographic purification.
[c] Reaction performed on a 1.0 mmol scale.

We also carried out the 3-component coupling of 2-phenyl-1-tosylaziridine (**1a**), ruthenocene (**6**) and paraformaldehyde (**8**) (Scheme 5). Consistent with the results previously seen for the ring-opening of *N*-sulfonyl aziridines by ruthenocene (see Table 2), this transformation proceeded sluggishly delivering the desired functionalized ruthenocene derivative **10a** in moderate yield (40%).[17]

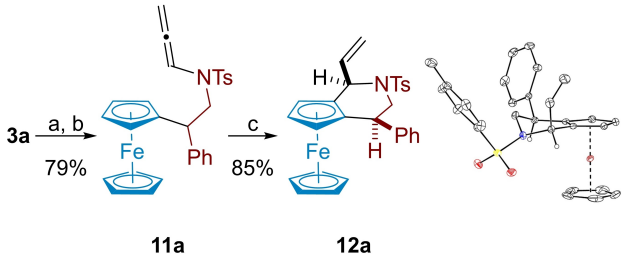
Unfortunately, under the above reaction conditions, substituted aldehydes (e.g. benzaldehyde, acrolein) were found to be unsuitable substrates, limiting the scope of this 3-component methodology. To partially overcome this limitation, we envisioned an alternative pathway to vinyl substituted derivatives based on the gold-catalyzed intramolecular cyclization of allenamides.[18,19] Thus, starting from amino-substituted ferrocene derivative **3a** and using a conventional two-step sequence consisting of initial propargylation and subsequent *t*-BuOK-catalyzed isomerization, *N*-tosylallenamide **11a** was prepared in good overall yield (Scheme 6). Pleasingly, exposure of allenamide **11a** to 5 mol% of [Au(IPr)(CH_3CN)][SbF_6] in dichloromethane at room temperature resulted in the formation of ferrocene derivative **12a** in high isolated yield (85%) as a single stereoisomer. The relative configuration of compound **12a** was established by X-ray diffraction.[14]

Conclusion

In summary, we have devised a convenient synthesis of new amino-functionalized metallocene derivatives based on the regioselective ring opening of *N*-sulfonyl aziridines. Both ferrocene and ruthenocene proved to be suitable substrates for this ring opening reaction. The amino-functionalized metallocene derivatives available by this method were transformed into heterocyclic compounds through a Pictet-Spengler type reaction. Furthermore, three-component reactions between ferrocene or ruthenocene, aziridines and formaldehyde also provided a rapid and efficient means to access these metallocene analogues of the medicinally relevant tetrahydroisoquinoline motif. To the best of our knowledge, this is the first example of synthesis of 1,2-disubstituted derivatives from the parent metallocene through a multicomponent reaction. Both stepwise and multicomponent fashions proceeded with complete regio- and stereoselectivity. An additional methodology for the stereoselective synthesis of vinyl substituted disubstituted ferrocene derivatives based on the gold-catalyzed intramolecular hydroarylation of an allenamide was also developed. Further investigations into the development of new synthetic applications of the amino-functionalized metallocene derivatives available by the present methodology are currently being pursued in our laboratory.



Scheme 5. Three-component approach to ruthenocene derivative **10a**.



Scheme 6. Synthesis of ferrocenyl allenamide **11a** and its transformation into ferrocene **12a** through a Au(I)-catalyzed cyclization. Reaction conditions: a) NaH, DMF, 15 min.; then, propargyl bromide; b) *t*-BuOK (10 mol%), THF, RT; c) [Au(IPr)(CH_3CN)][SbF_6] (5 mol%), DCE, RT.

Experimental Section

General Procedure for the Acid-catalyzed Reaction of Aziridine Derivatives 1 with Ferrocene (2): Synthesis of Ferrocene Derivatives 3. $BF_3{\cdot}OEt_2$ (1.3 µl, 0.01 mmol, 10 mol%) was added to a solution of the corresponding aziridine **1** (0.1 mmol) and ferrocene (**2**, 37.2 mg, 0.2 mmol) in DCE (1 mL). The resulting mixture was stirred at room temperature until the disappearance of the starting aziridine (monitored by TLC). The solvent was removed under reduced pressure and the resulting residue was purified by column chromatography (silica gel, hexanes/ethyl acetate 5:1) to afford ferrocene derivatives **3**. A similar protocol using ruthenocene (**6**, 46.3 mg, 0.2 mmol) instead of ferrocene provided amino-functionalized ruthenocene derivatives **7**.

General Procedure for the TfOH-Catalyzed Three-Component Reaction of Aziridine Derivatives 1, Ferrocene (2) and Formaldehyde (8): Synthesis of Ferrocene Derivatives 9. TfOH (0.9 µl, 0.01 mmol, 10 mol%) was added to a solution of the aziridine **1** (0.1 mmol), ferrocene (**2**, 37.2 mg, 0.2 mmol) and paraformaldehyde (**8**, 30 mg, 1.0 mmol) in DCE (1 mL). The resulting mixture was stirred at room temperature until the disappearance of the starting aziridine (monitored by TLC). The solvent was removed under reduced pressure and the resulting residue was purified by column chromatography (silica gel, hexanes/ethyl acetate 10:1) to afford ferrocene derivatives **9**. A similar protocol using ruthenocene (**6**) provided the ruthenocene derivative **10a**.

Acknowledgements

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Europeo de Desarrollo Regional (FEDER) (Grants CTQ2016-76840-R and PID2019-107469RB–I00) is gratefully acknowledged. S. G.-P. thanks the Principado de Asturias for a predoctoral grant (Severo Ochoa Program). We also thank Prof. J. M. González for helpful discussions. We are also grateful to Dr J. Perles (SIdI, Universidad Autónoma de Madrid) for her assistance in the collection of the X-ray date.

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[11] This mechanism would also account for the lack of reactivity of unsubstituted and 2-alkyl-substituted tosylaziridines.

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[14] CCDC numbers 2034262 (**9a**) and 2034263 (**12a**), contain the supplementary crystallographic data for these structures. These data are provided free of charge by the Cambridge Crystallographic Data Centre.

[15] The stereochemistry of compounds **9b-h** was assigned by analogy to **9a**, whose structure was determined by X-ray crystal structure analysis.

[16] We have attempted the removal of the N-sulfonyl group in ferrocene derivative **9a**. Toward this end, we conducted the reaction of **9a** with lithium/naphthalene in THF as solvent but no reaction occurred even at an elevated temperature (reflux for 8 hours). Alternatively, we also performed the reaction of **9a** with Mg in methanol under sonication conditions. However, no

reaction was observed and the starting ferrocene derivative was again recovered.
[17] Interestingly, the yield of ruthenocene derivative **10a** obtained by the three-component protocol is higher than that of its presumed precursor **7a** (40 vs 33%, see Table 2). A possible explanation for this observation would be the higher stability of compound **10a** relative to its precursor **7a** while chromatographic purification.
[18] For selected examples of gold(I)-catalyzed intramolecular hydroarylation of allenes, see: a) C. Liu, R. A. Widenhofer, *Org. Lett.* **2007**, *9*, 1935–1938; b) J. Barluenga, M. Piedrafita, A. Ballesteros, A. L. Suárez-Sobrino, J. M. González, *Chem. Eur. J.* **2010**, *16*, 11827–11831; c) Y. Wang, P. Zhang, X. Di, Q. Dai, Z.-M. Zhang, J. Zhang, *Angew. Chem.* **2017**, *129*, 16121–16125; *Angew. Chem. Int. Ed.* **2017**, *56*, 15905–15909.
[19] For general reviews on synthetic applications of allenamides, see: a) J. L. Mascareñas, I. Varela, F. López, *Acc. Chem. Res.* **2019**, *52*, 465–479; b) E. Manoni, M. Bandini, *Eur. J. Org. Chem.* **2016**, 3135–3142; c) T. Lu, Z. Lu, Z.-X. Ma, Y. Zhang, R. P. Hsung, *Chem. Rev.* **2013**, *113*, 4862–4904; d) L.-L. Wei, H. Xiong, R. P. Hsung, *Acc. Chem. Res.* **2003**, *36*, 773–782.