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Tandem Asymmetric Michael Reaction−Intramolecular Michael Addition. An Easy Entry to Chiral Fluorinated 1,4-Dihydropyridines

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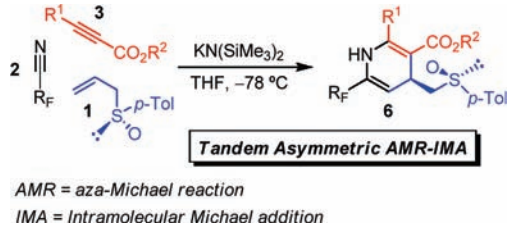
ABSTRACT



A novel one-pot tandem asymmetric Hantzsch-type process has been employed to generate fluorinated 1,4-dihydropyridines (1,4-DHPs) as single diastereoisomers. It involves the condensation of (*R*)-(+)-allyl *p*-tolyl sulfoxide, fluorinated nitriles, and alkyl propiolates, giving access to a new family of enantiomerically pure fluorine-containing 1,4-DHPs.

Dihydropyridines (DHPs) constitute an important class of biologically active heterocycles. They can be considered "privileged structures" in medicinal chemistry exhibiting a wide range of pharmacological and biological activities.[1] Probably, the best known family of 1,4-DHPs are calcium blockers, compounds used routinely in the treatment of a variety of vascular disorders.[2] In addition, 1,4-DHPs are NADH mimics and may be involved in hydrogen transfer reactions. These bioinspired transformations are extensively used in organocatalytic enantioselective hydrogenations, reductive aminations, and other enantioselective reductions of C=C, C=N, and C=O functionalities.[3] 1,4-DHPs have also proven to be valuable synthetic intermediates in the preparation of a large number of nitrogen heterocycles.[4]

One of the most straightforward routes to the synthesis of 1,4-DHPs is the Hantzsch condensation, which was first developed in 1882.[5] This process constitutes an emblematic example of a multicomponent reaction, allowing for the creation of molecular diversity and complexity and the synthesis of wide libraries of such important compounds.[6] The absolute configuration of the stereogenic center of chiral DHPs has a crucial

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influence on their biological activity.[7] In this respect, a classical example is compound (*R*)-(+)-Bay K 8644, which shows antihypertensive activity due to its calcium antagonist effect, whereas the *S* enantiomer induces the opposite response (Figure 1).

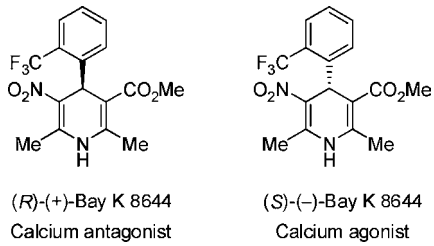

Figure 1. Influence of the chiral center on the biological activity of DHPs.

Despite the biological importance of enantiomerically pure DHPs, a general method for their asymmetric synthesis still remains an important challenge. Traditional strategies make use of either enzymatic[8] or chemical[9] resolutions of racemates or, alternatively, chiral auxiliaries. In this context, sugar-derived aldehydes,[10] chiral acetoacetate esters,[11] chiral amino aldehydes[12] (derived from the corresponding α-amino acids), and chiral sulfoxides[13] have been reported as asymmetry inducers for the synthesis of 1,4-DHPs in Hantzsch syntheses. Alternatively, chiral oxazoline-derived aryl lithiums[14] and chiral aminal-derived organocopper reagents[15] have been used in diastereoselective additions to the 4-position of pyridines. To date, only three examples of catalytic enantioselective syntheses of 1,4-DHPs have been described, both in an organocatalytic fashion.[16]

Chiral sulfoxides are reliable chiral synthons able to bring about important asymmetric transformations.[17] In this context, metalated allylic sulfoxides, despite the ambident reactivity of the carbanion, have been used as chiral inducers in their addition to conjugated enones.[18] The reaction takes place almost exclusively through the γ-position giving rise to the corresponding vinyl sulfoxides—a successfully applied strategy for the synthesis of natural products.[19] As part of our continued interest in the preparation of new fluorinated building blocks,[20] and taking advantage of the enhanced electrophilicity of fluorinated nitriles, we envisioned the possibility of using them as reaction partners with metalated allyl sulfoxides. The attack by the γ-position would provide enamino sulfoxides, which in turn could be treated with alkyl propiolates to afford fluorinated 1,4-DHPs. Herein, we report the development of this closely related asymmetric Hantzsch transformation by using allylic sulfoxides, fluorinated nitriles, and alkyl propiolates as the three components of the novel one-pot tandem reaction outlined in Scheme 1. This methodology allows for the preparation of a new family of enantiomerically pure fluorinated 1,4-DHPs.[21]

Our synthetic strategy starts with the reaction of allyl sulfoxide **1** through the γ-position with fluorinated nitriles **2** to generate enamino sulfoxides **4**. Upon treatment with alkyl propiolates **3**, a tandem intermolecular aza-Michael reaction (AMR)−intramolecular Michael addition (IMA) (over the previously formed vinyl sulfoxides **5**)[22] might render 1,4-DHPs **6** (Scheme 1).

We initially explored the preparation of enamino sulfoxides **4** to evaluate our synthetic proposal. After testing several bases and temperatures, we found that optimal reaction conditions involved the treatment of (*R*)-(+)-allyl *p*-tolyl sulfoxide **1** with $KN(SiMe_3)_2$ at −78 °C, followed by addition of fluorinated nitriles **2**. The reaction took place exclusively over the γ-carbon

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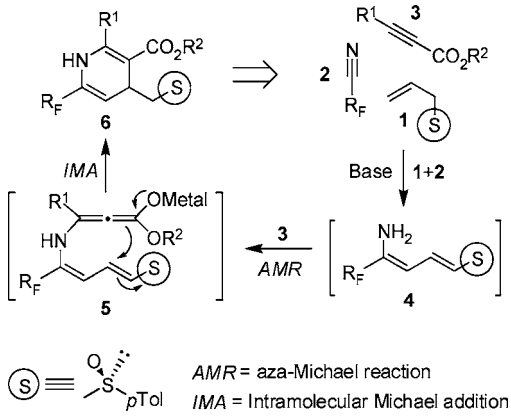
(20) For a recent review, see: Fustero, S.; Sanz-Cervera, J. F.; Aceña, J. L.; Sánchez-Roselló, M. *Synlett* **2009**, 525.

(21) Despite the relevance of fluorine in medicinal chemistry, only a few examples of fluorinated DHPs have been reported. In most of them, fluorine atoms are present as substituents in the aromatic rings of 4-aryl-1,4-DHPs.

(22) The conjugate addition of carbon nucleophiles over α,β-unsaturated sulfoxides has been extensively used in its intermolecular version, while examples of its intramolecular counterpart are very scarce. See reference 18a.

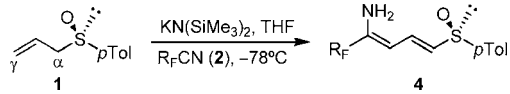
Scheme 1. Synthetic Strategy



of **1** giving rise to dienic sulfoxides **4** after tautomerization of the iminic double bond to the more conjugated enamine tautomer.

In all cases studied, the ^{1}H NMR spectra of the crude reaction mixtures were very clean, indicating that the reaction took place almost quantitatively. However, during the purification process, compounds **4** appeared to be partially unstable, thus decreasing the final isolated yields (Table 1).

Table 1. Preparation of Enamino Sulfoxides **4**



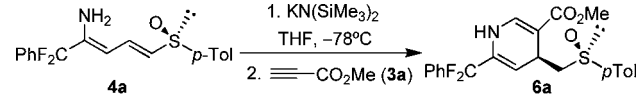
entry	**2**	R_F	**4**	% yield[a,b]
1	**2a**	$PhCF_2$	**4a**	65 (98)
2	**2b**	$allylCF_2$	**4b**	60 (95)
3	**2c**	2-naphtylCF_2	**4c**	66 (99)
4	**2d**	1-naphtylCF_2	**4d**	73 (99)

[a] Isolated yields after flash column chromatography. [b] In parentheses, yield determined by ^{1}H NMR on the crude reaction mixture.

The next step in our synthetic plan was the double Michael tandem sequence initiated by reaction of sulfoxides **4** with alkyl propiolates **3**. Again, $KN(SiMe_3)_2$ was chosen to generate the amine anion. Thus, when compound **4a** was treated with $KN(SiMe_3)_2$ at −78 °C followed by addition of methyl propiolate (**3a**), 1,4-DHP **6a** was obtained as a single diastereoisomer (determined by means of ^{19}F NMR in the crude reaction mixture) in 60% yield after flash chromatography (Scheme 2). As for sulfoxides **4**, ^{1}H NMR of the crude mixture was very clean. Most likely, the final compound **6a** partially decomposed under the purification conditions, thus diminishing the final isolated yield.

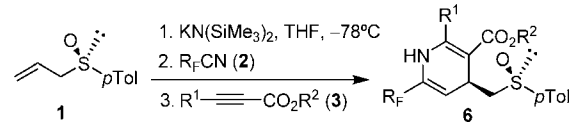
Once it was demonstrated that both Michael processes took place in a tandem manner, we decided to combine them with the formation of sulfoxides **4** in a one-pot sequence. To our delight, we found that after the initial reaction of the potassium anion of **1** with fluorinated nitriles **2** the addition of propiolates

Scheme 2. Double Michael Reaction of **4a** with Methyl Propiolate **3a**



3 to the reaction mixture led to the formation of the corresponding 1,4-DHPs **6** in moderate isolated yields. In most cases, a single diastereoisomer of **6** according to the ^{19}F NMR of the crude reaction mixtures (Table 2) was formed. This novel methodology gives access to a new family of enantiomerically pure fluorinated Hantzsch-type derivatives.

Table 2. One-Pot Tandem Process for the Synthesis of Enantiomerically Pure DHPs **6**



entry	**2**	**3**	R_F	R^1	R^2	**6**	% yield[a]
1	**2a**	**3a**	$PhCF_2$	H	Me	**6a**	60
2	**2a**	**3b**	$PhCF_2$	CO_2Et	Et	**6b**	62
3	**2a**	**3c**	$PhCF_2$	Ph	Et	**6c**	35 (45)[b]
4	**2a**	**3d**	$PhCF_2$	H	Et	**6d**	48
5	**2b**	**3a**	$allylCF_2$	H	Me	**6e**	53
6	**2b**	**3b**	$allylCF_2$	CO_2Et	Et	**6f**	55
7	**2b**	**3d**	$allylCF_2$	H	Et	**6g**	57
8	**2c**	**3a**	2-Naph-CF_2	H	Me	**6h**	60
9	**2d**	**3a**	1-Naph-CF_2	H	Me	**6i**	52[c]

[a] Isolated yields after flash column chromatography. [b] The conversion was 45%. [c] A 7:1 mixture of two diastereoisomers was obtained.

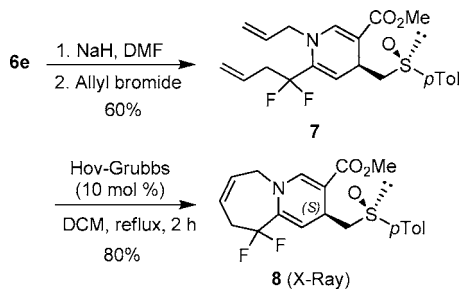
The absolute stereochemistry of the newly created stereocenter was determined by means of X-ray analysis of derivative **8** (Scheme 3). Thus, *N*-allylation of **6e** generated diene **7**, which smoothly cyclized in the presence of Hoveyda−Grubbs (II G) catalyst [Cl_2(IMes)Ru=CH(*o*-*i*-PrOC_6H_4)]. The bicyclic system **8** allowed us to prepare suitable crystals for X-ray diffraction. The absolute configuration of the chiral center was found to be *S* (Scheme 3),[23] and an identical stereochemical outcome was assumed for all examples in Table 2.

The stereochemical outcome of the overall process could be rationalized as depicted in Scheme 4. After the initial aza-Michael addition of the enaminic nitrogen to the propiolate, a potassium enolate bearing an allene functionality would be formed. Assuming that the *S*-lone pair should be coplanar to the C=C bond,[24] the most favored approach would be to the *Re* face in a 1,3-like-type addition, since the *p*-tolyl substituent would block the *Si* face.

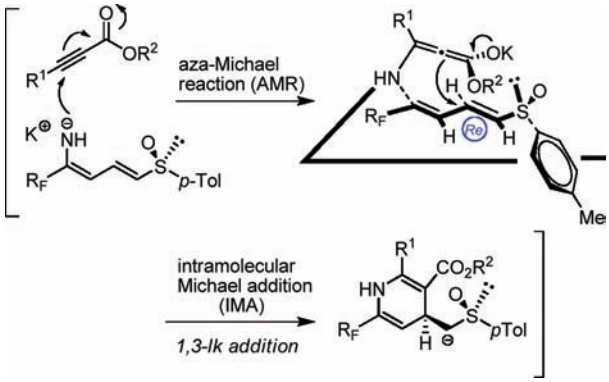
(23) For the X-ray structure of (+)-**8**, see Supporting Information.

(24) This coplanarity of the *S*-lone pair with aryl or dienic moieties was previously described by several authors: (a) Clayden, J.; Fletcher, S. P.; MacDouall, J. J. W.; RowBottom, S. J. M. *J. Am. Chem. Soc.* **2009**, *131*, 5331 and references cited therein. (b) Paley, R. S.; Berry, K. E.; Liu, J. M.; Sanan, T. T. *J. Org. Chem.* **2009**, *74*, 1611.

Scheme 3. Determination of the Absolute Configuration of the Newly Created Stereocenter



Scheme 4. Rationalization of the Stereochemical Outcome



The last step in our study was the removal of the chiral auxiliary from the final products. To this end, Pummerer-type reactions have been extensively used in synthesis.[25,18a] The non-oxidative variant of the Pummerer reaction (NOPR) enables the conversion of β-amino sulfoxides into the corresponding β-amino alcohols by reaction with TFAA and *sym*-collidine followed by $NaBH_4$ reduction.[26] In this context, when several *N*-Cbz-protected DHPs **9** were subjected to NOPR conditions, alcohols **10** were isolated in reasonable yields (Table 3).[27] However, a partial erosion of the ee was observed during the sulfoxide cleavage, as determined by means of chiral HPLC analysis of the dihydropyridine alcohols **10** (Table 3) (see Supporting Information for details). This was probably due to the acidity of the hydrogen present in the stereocenter, since it is located in a double allylic position, and therefore being susceptible to racemization under NOPR conditions.

(25) For a review of the applications of Pummerer reactions in total synthesis, see: Padwa, A.; Gunn, D. E., Jr.; Osterhout, M. H. *Synthesis* **1997**, 1353.

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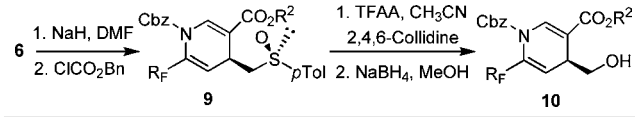
(27) A complex mixture was obtained when non-protected 1,4-DHPs **6** were subjected to NOPR conditions.

Table 3. *N*-Cbz Protection and Non-oxidative Pummerer Reaction

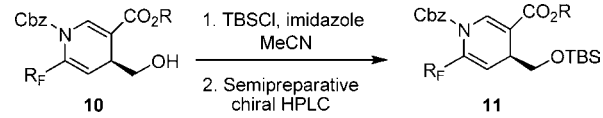


entry	**9**	% yield[a]	R_F	R^2	**10**	% yield[a] (er)[b]
1	**9a**	76	$PhCF_2$	Me	**10a**	70 (88:12)
2	**9b**	72	$PhCF_2$	Et	**10b**	68 (86:14)
3	**9c**	60	$allylCF_2$	Me	**10c**	65 (83:17)
4	**9d**	73	$allylCF_2$	Et	**10d**	67 (76:24)
5	**9e**	63	2-naph-CF_2	Me	**10e**	73 (85:15)

[a] Isolated yields after flash column chromatography. [b] Enantiomeric ratios were determined by chiral HPLC analysis.

Although several attempts directed toward avoiding the erosive process of the ee in the NOPR reaction were performed (by changing reaction conditions), they were unsuccessful. However, we found that the protection of the hydroxyl group of compounds **10** as *tert*-butyl dimethylsilyl ethers rendered DHPs **11**, which were susceptible to separation by means of semipreparative chiral HPLC (Scheme 5). In this manner, it was finally possible to access DHPs **11** in enantiomerically pure form (see Supporting Information for details).

Scheme 5. Obtention of Enantiomerically Pure DHPs **11**



In conclusion, a novel asymmetric tandem aza-Michael reaction (AMR)−intramolecular Michael addition (IMA) has been described. It involves the reaction of (*R*)-(+)-allyl *p*-tolyl sulfoxide, fluorinated nitriles, and alkyl propiolates. The reaction took place with complete selectivity allowing for the preparation of a new family of fluorinated 1,4-dihydropyridines (DHPs) as single diastereoisomers in moderate yields. The elimination of the sulfoxide group by means of a Pummerer-type process took place with partial erosion of the ee. However, it was possible to access the final DHPs in enantiomerically pure form after semipreparative chiral HPLC separation.

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Supporting Information Available: Experimental procedures and NMR spectra for all new compounds, as well as crystallographical data for compound **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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