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Enantioselective organocatalytic formal allylation of α-branched aldehydes†

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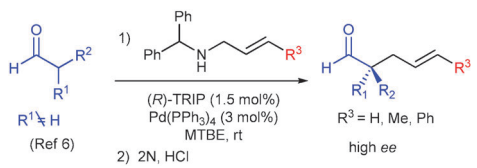
Heteroarylvinyl sulfone 1 has been successfully used as a new sulfonyl Michael acceptor in aminocatalytic reactions with branched aldehydes. Subsequent one-pot Julia–Kocienski olefination allows the challenging preparation of enantiomerically pure α-allylated aldehydes bearing C-α quaternary carbons.

The direct asymmetric intermolecular α-alkylation of aldehydes remains a hot topic which has been even considered the "Holy Grail" of organocatalysis.[1] Although some brilliant strategies have been described,[2] there are a wide variety of substrates still out of range of these methodologies. This is also the case of the α-allylation of aldehydes. The formation of quaternary stereogenic centers has also been recognized as one of the most challenging tasks in organic chemistry.[3] Thus, although several purely organocatalytic[4] or organocatalytic combined methods[5,6] have provided bright solutions for the α-allylation of aldehydes, the synthesis of enantiomerically pure α-allylated aldehydes bearing quaternary stereogenic centers at C-α remains elusive. This is an important task since there are many natural and non-natural products with interesting pharmaceutical properties containing quaternary carbon centres,[7] many of them prepared in racemic form from allylated aldehydes.[8]

The only organocatalytic method reported so far for the α-allylation of branched aldehydes involving the creation of quaternary α-carbons is due to Mukherjee and List (Scheme 1).[6] It is a powerful procedure that employs allylamines as electrophiles and chiral Brønsted acids in combination with a Pd-catalyst. The method is quite efficient for R^3 = H, but only two examples with $R^3 \neq$ H (Me, Ph) were reported, with slightly lower yields and enantioselectivities.



Scheme 1 Allylation of branched aldehydes using chiral Brønsted acid and palladium-catalyst.

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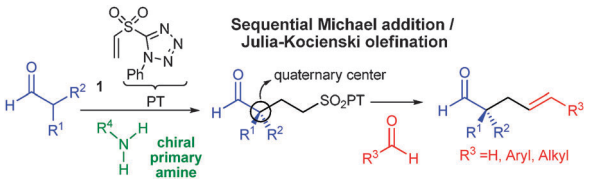


Scheme 2 Formal regio- and enantioselective method for the allylation of α-branched aldehydes by a sequential procedure.

We envisioned a complementary and fully organocatalytic strategy based on the alkylation of branched aldehydes through a Michael addition[9] yielding compounds with moieties easily transformed into allylic fragments. It would provide a flexible method for the synthesis of α-allylated aldehydes containing a quaternary centre and a wide range of substitutions using aminocatalysis. In order to develop this modular approach, heteroaryl vinyl sulfone **1**[10] was identified as an appropriate electrophile since the resulting heterosulfone moiety has been successfully used in Julia–Kocienski olefinations,[11] thus making possible the introduction of a variety of substituents R^3 from only one common electrophile (Scheme 2).

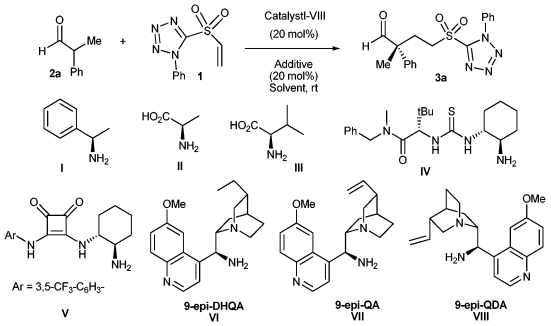
α,β-Unsaturated sulfones have proven to be excellent Michael acceptors under different organocatalytic conditions,[12] such as base promoted conjugate additions,[13] phase transfer type reactions,[14] and Michael additions involving *thiourea* activation.[15] Activation of aldehydes *via enamine* has been the most prolific method,[16] although an additional electron-withdrawing group (EWG) is mandatory in the alkene so that the Michael addition takes place, hampering the possibility of using the obtained adducts as substrates for olefination reactions.

We initiated the studies with the heteroarylvinyl sulfone **1** with the hope that its higher electron-withdrawing character[17] was enough to confer to the double bond the appropriate electrophilicity to react with branched aldehydes *via enamine* activation without requiring the presence of additional EWG groups at the alkene, thus making possible the sequential Michael/Julia–Kocienski process shown in Scheme 2.

We present herein the results obtained in these studies that have allowed us to synthesise a variety of γ,δ-unsaturated aldehydes containing a quaternary C-α and R^3 = alkyl, aryl, H, which constitutes a regio- and enantioselective indirect method for the α-allylation of branched aldehydes.

In order to find the optimal reaction conditions, we started our research using phenylpropionaldehyde **2a** as a model

Table 1 Screening of different catalysts for the conjugate addition of 2-phenylpropionaldehyde **2a** to heteroaryl vinyl sulfone **1**



Entry[a]	Catalyst	Solvent	Additive	Time/h	Conv. (%)	*ee*[b] (%)
1	**I**	$CHCl_3$	—	24	100	20[c]
2	**II**	DMSO	—	24	100	30[c]
3	**III**	DMSO	—	48	95	2[c]
4	**IV**	CH_2Cl_2	—	1	100	74[c]
5	**IV**	Toluene[d]	—	1	100	68[c]
6	**IV**	DMF	—	No reaction	—	—
7	**IV**	$CHCl_3$	—	1	100	78[c] (86)[e]
8	**V**	$CHCl_3$	—	4	100	18[c]
9	**VI**	$CHCl_3$	—	16	100	92
10	**VII**	$CHCl_3$	—	16	100	95
11	**VIII**	$CHCl_3$	—	16	100	86[c]
12	**VII**	$CHCl_3$	BzOH	36	74[f]	96
13	**VII**	$CHCl_3$	*p*-NO_2-BzOH	16	100	96
14[g]	**VII**	$CHCl_3$	*p*-NO_2-BzOH	48	76	94

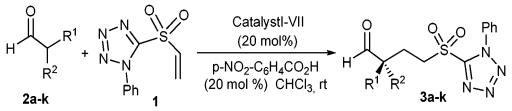
[a] Reactions carried out with 30 equiv. of aldehyde **2a** unless otherwise stated. [b] *ee* determined by HPLC. [c] Opposite enantiomer of **3a** was obtained. [d] With 5 equivalents of water. [e] Reaction performed at −30 °C. [f] Yield. [g] 5 equiv. of aldehyde **2a** were used.

aldehyde and testing a variety of primary amines as catalysts such as (*S*)-methylbenzylamine (**I**), aminoacids[18,19] L-alanine (**II**) and L-valine (**III**). The conjugate addition took place effectively but with low enantioselectivity (Table 1, entries 1–3). Higher enantioselectivities were obtained with Jacobsen's thiourea **IV**[20] (entries 4–7). After testing several solvents and temperatures the best result was achieved using $CHCl_3$ as solvent at −30 °C (entry 7). Under similar conditions squaramide **V** gave poorer enantioselectivities (entry 8). Catalysts derived from cinchona alkaloids (**VI–VIII**)[21] afforded better enantiocontrol (entries 9–11). In search of additives to enhance both reactivity and selectivity, we found the optimal balance when *p*-nitrobenzoic acid (20 mol %)[22] and 9-amino-(9-deoxi)-*epi*quinine **VII** were used (entry 14).

The optimized conditions, which were also scaled up to 500 mg of sulfone **1**, were applied to a series of aldehydes (Table 2). It is important to note that in all the cases the excess of aldehyde can be recovered by flash chromatography.

Substituted aromatic aldehydes **2a–e** afforded the Michael adducts **3a–e** in good yields (60–83%) and *ee*s (86–94%) regardless of the electronic nature of the substituents (entries 1–5). The reaction seems to be sensitive to the *ortho* substitution and aldehyde **2f** afforded the corresponding adduct **3f** with high *ee* but lower yield (entry 6). The Michael addition of aldehyde with 2-thiophenyl substituent **2g** was sluggish affording moderate enantioselectivity (entry 7). Even the more challenging branched aldehydes with two aliphatic substituents were suitable

Table 2 Scope of the conjugate addition of aldehydes **2** to heteroaryl vinyl sulfone **1**



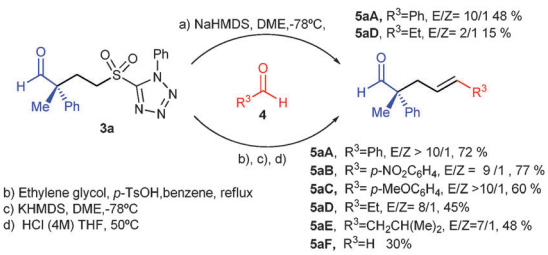
Entry[a]	R^1	R^2	Aldehyde	Time/h	Yield (%)	*ee* (%)
1	Me	Ph	**3a**	48	76	94
2	Me	*p*-Br–C_6H_4–	**3b**	48	71	93
3	Me	*p*-CN–C_6H_4–	**3c**	48	65	86
4	Me	*p*-CH_3–C_6H_4–	**3d**	48	60	93
5	Me	2-Naphthyl	**3e**	48	83	89
6	Me	*o*-F–C_6H_4–	**3f**	72	30	92
7	Me	2-Thiophenyl	**3g**	72	68	58
8[b]	Me	*n*-Pr	**3h**	96	48	40
9[b]	Me		**3i**	96	46	42
10[b]	Me	Bn	**3j**	96	62	71
11[b]	Et	Ph	**3k**	120	50[c]	75–80[c]

[a] Reactions carried out with 5 equiv. of aldehyde **2** unless otherwise stated. [b] 10 equiv. of aldehyde **2** and 50% of *p*-NO_2–$C_6H_4CO_2H$. [c] See ESI.†

substrates in the Michael addition to sulfone **1**. As it is the case in other organocatalytic examples,[23] reactivity and enantiomeric ratios were significantly lower (entries 8–9) but they improved when R^2 is Bn (entry 10). Not only 2-arylpropanals were used and 2-phenylbutanal **2k** was also tolerated (R^1 = Et, entry 11).

Once compounds **3** were obtained, we studied their transformation into the α-allylated aldehydes using the model aldehyde **3a**. We thought that the low reactivity of the α-dibranched aldehydes **3**, due to steric hindrance, would make unnecessary their protection before reacting with other aldehydes under the mild conditions of the Julia–Kocienski olefination. In fact, **3a** reacts with benzaldehyde (**4A**) and propanal (**4D**) to afford olefins **5aA** (*E*/*Z* = 10 : 1) and **5aD** (*E*/*Z* = 2 : 1) in 48% and 15% yields, respectively. However, both yields and stereoselectivities were improved starting from protected aldehydes in the Julia-Kocienski reaction, as indicated in Scheme 3. The easy protocol involving protection/Julia–Kocienski olefination[11]/deprotection was satisfactorily applied to a variety of aldehydes with only one final chromatography.

The best results were obtained with aromatic aldehydes. Aldehyde **5aF**, which has been used in the preparation of a potential pharmaceutical agent for the treatment of depression and related disorders,[24] was obtained in lower yield (R^3 = H). However, it is noteworthy that formaldehyde is not a common aldehyde used in Julia–Kocienski olefination.[25] Furthermore, we have used **5aF** for establishing the absolute configuration at



Scheme 3 Julia one-pot reaction of adduct **3a** with different aldehydes.

the stereogenic center by chemical correlation as *R* (see ESI†). The configurations of the rest of aldehydes **3a–k** and **5aA–5aF** were assigned by analogy.

In conclusion, we have developed a new modular method for the enantioselective α-allylation of branched aldehydes involving their Michael addition to heteroarylvinyl sulfone **1** catalyzed by 9-amino-(9-deoxi)-*epi*quinine **VII** followed by a Julia–Kocienski olefination. We anticipate that this easy to perform new flexible retrosynthetic disconnection—complementary to that reported by List—will find application in the preparation of a variety of allylated aldehydes **5** bearing quaternary centers, which are interesting building blocks in the synthesis of biologically active molecules. Moreover, this communication describes for the first time the synthetic usefulness of a monoactivated vinyl sulfone in organocatalysis *via* enamine activation.

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