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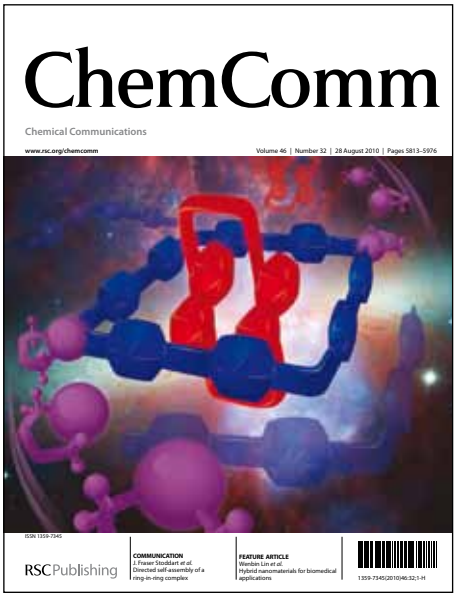

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Kinetic Resolution of Propargylamines via a Highly Enantioselective Non-enzymatic *N*-Acylation Process†

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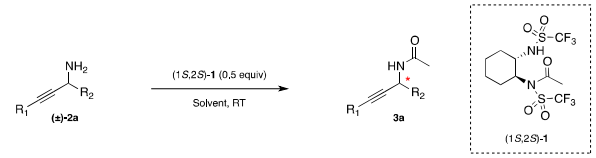
The non-enzymatic kinetic resolution of diversely substituted primary propargylic amines is reported featuring a highly selective acetyl transfer using (1*S*,2*S*)-1 in conjunction with Aliquat™ 336, affording the corresponding enantio-enriched *N*-acetylated propargylic amines with unprecedented levels of selectivity (*s*-factors up to 193 at 50% conversion).

Enantio-enriched propargylic amines are particularly useful building blocks in synthetic organic chemistry finding use in the preparation of various nitrogen-containing compounds such as allylamines and pyrrolidines.[1] In addition, they are also valuable intermediates in the synthesis of complex natural products[2] as well as several pharmaceuticals[3] and agrochemicals.[4] In this context, a number of synthetic tools have been developed to access this specific structural motif. These methods generally involve the enantioselective addition of alkyne nucleophiles to imines and afford the corresponding enantio-enriched secondary amines.[5] Another practical approach to optically active propargylic amines consists of the kinetic resolution (KR) of the corresponding racemic amines. In this field however, only one example has to the best of our knowledge been reported so far.[6] The strategy is based on a particularly elegant dual catalytic approach involving a chiral thiourea-acylpyridinium catalyst which affords the KR of primary propargylic amines with *s*-factors[7] up to 56 at –78 °C.

Interestingly, since the pioneering work of Murakami *et al.*,[8] the development of effective non-enzymatic processes for the KR of racemic amines has become the focus of tremendous work,[9] mostly from the groups of Fu,[10] Mioskowski,[11] Krasnov[12] and, more recently, by Birman,[13] Miller,[14] Bode[15] and Seidel.[6,16,17] In this context, Arseniyadis, Mioskowski and co-workers established that (1*S*,2*S*)-*N*-acetyl-1,2-bis-trifluoromethanesulfonamidocyclohexane (1*S*,2*S*)-**1** could be used as a highly selective acetylating agent for the KR of primary benzylic amines affording the corresponding acetamides with up to 84% ee at room temperature (*s*-factor up to 30 at 50% conv.) and displaying a unique solvent-induced reversal of stereoselectivity.[11a] Following these initial results, a spectacular salt effect was also reported, allowing to increase both the reactivity and the selectivity of the reagent an afford the KR of primary benzylic amines with *s*-factors up to 115 (up to 94% ee at –20 °C and 50% conv.).[11b] Finally, a fully recyclable and particularly effective solid-supported version of the reagent was developed capable of resolving primary benzylic- and homobenzylic amines with useful levels of selectivity at room temperature (*s*-factors up to 12).[11c]

Table 1. Evaluation of the reaction parameters[a]



Entry	Solvent	ee (%)[b] without Aliquat™ 336	ee (%)[b] with Aliquat™ 336
1	THF	46 (*R*[c])	85 (*S*) [91[d] (*S*)]
2	Cyclohexane	51 (*R*)	80 (*S*)
3	Toluene	46 (*R*)	81 (*S*)
4	Dioxane	36 (*R*)	73 (*S*)
5	α,α,α-Trifluorotoluene	32 (*R*)	77 (*S*)
6	CH_2Cl_2	38 (*R*)	80 (*S*)
7	$CHCl_3$	37 (*R*)	61 (*S*)
8	NMP	74 (*S*)	76 (*S*)
9	DMPU	76 (*S*)	78 (*S*)

[a] All reactions were carried out on a 0.25 mmol scale using 0.5 equiv of (1*S*,2*S*)-**1** at rt with or without Aliquat™ 336 [0.7M]. [b] Enantiomeric excess of compound **3a** determined by chiral SFC analysis. [c] Absolute configuration of the major enantiomer. [d] Reaction run at –20 °C. Aliquat™ 336 = trioctylmethylammonium chloride. DMPU=1,3-dimetyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone. NMP = *N*-methyl-2-pyrrolidone.

In this paper, we wish to report a new benchmark in the KR of primary propargylic amines using (1*S*,2*S*)-**1**.

On the basis of the previous results,[11a] we decided to initiate our study by screening various solvents at room temperature using (±)-methyl-3-phenyl-prop-2-ynylamine **2a** as a model substrate. The results of this survey are summarized in Table 1.

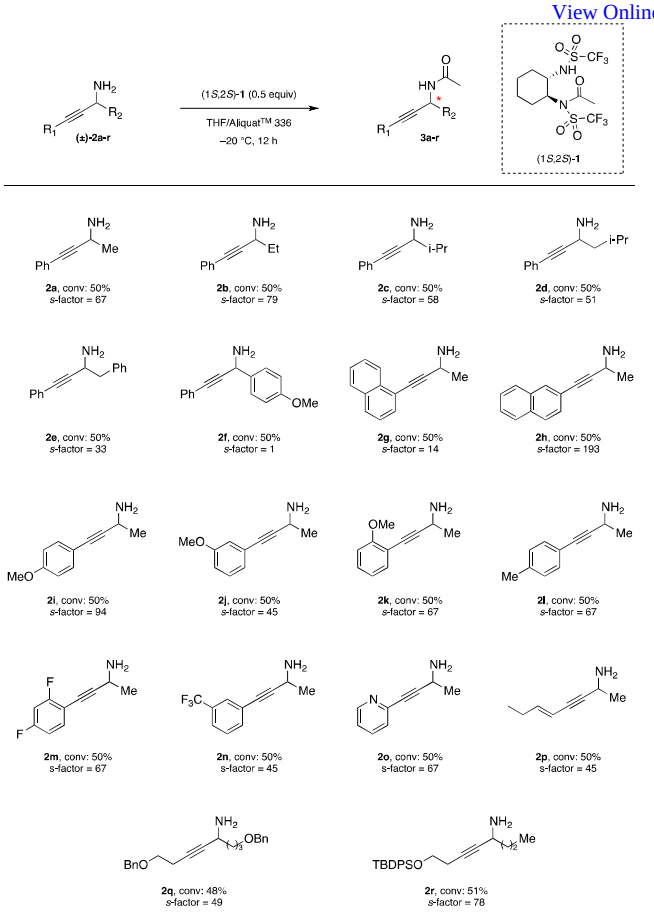
As expected, a solvent-induced reversal of selectivity was observed when switching from solvents such as THF, cyclohexane, toluene, dioxane, trifluorotoluene, dichloromethane or chloroform (Table 1, entries 1-7) to solvents exhibiting a higher relative permittivity such as NMP and DMPU (Table 1, entries 8 and 9). Interestingly, we also observed a particularly important salt effect similar to the one witnessed when performing the KR of primary benzylic amines, leading to an increase in both reactivity and selectivity in conjunction with a reversal of the overall stereoselectivity. Hence, by performing the

reaction in the presence of Aliquat^{TM} 336 under otherwise identical conditions, we were able to isolate acetamide **3a** in quantitative yield and 85% ee ($s = 33$, Table 1, entry 1). Optimizing the reaction conditions by simply reducing the temperature to –20 °C produced an additional increase in selectivity affording the desired acetamide in 91% ee ($s = 67$, Table 1, entry 1) which compared favourably with the result obtained by Seidel *et al*. ($s = 39$ at 48% conv.) on the same substrate.[6]

With this set of conditions in hand, we next examined the scope and limitations of the reaction (Scheme 1). A number of racemic propargylic amines were therefore prepared and resolved under our optimized conditions [(1*S*,2*S*)-**1** (0.5 equiv), Aliquat^{TM} 336 (0.7M in THF) at –20 °C] affording the corresponding acetamides with good to excellent selectivities. Hence, whereas an exchange of the methyl for an ethyl in the parent substrate led to a small increase in selectivity from $s = 67$ to $s = 79$, substrates bearing a bulkier substituent such as an isopropyl (**2c**, $s = 58$), an isobutyl (**2d**, $s = 51$) or a benzyl (**2e**, $s = 33$) were resolved with slightly lower *s*-factors. Aryl propargylic amines bearing substituents on different positions (**2i-n**) of the aryl ring were also effectively resolved regardless of the electronic nature of the substituents on the aromatic ring (*s*-factors ranging from 45 to 94) and with *p*-methoxy-substituted arylpropargylic amine **3j** giving rise to the highest selectivity ($s = 94$). Remarkably, introducing the propargylamine on either the C1- (**2g**) or the C2-position (**2h**) of a naphthalene ring had a profound impact on the selectivity as *s*-factors ranged from $s = 13$ (C1: 73% ee at 50% conv.) to $s = 193$ (C2: 96% ee at 50% conv.). In addition, substrates with extended π-systems such as enyne **2p** or heteroaryl propargylic amines such as **2o** were also effectively resolved with *s*-factors of 45 and 67, respectively. Finally, propargylic amines with two aliphatic residues such as compounds **2q** and **2r** proved to be viable substrates as well, as the corresponding acetamides were obtained in 90% ee ($s = 49$ at 48% conv.) and 91% ee ($s = 78$ at 51% conv.), respectively.

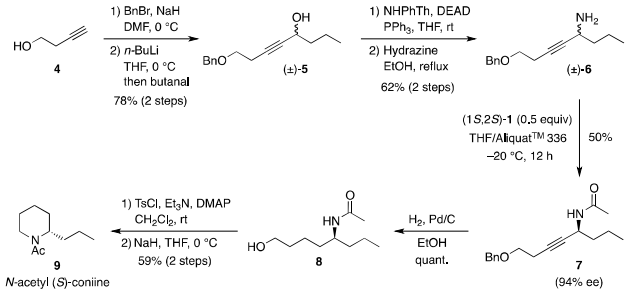
Unfortunately, our system was not capable of distinguishing between two different π-systems, as exemplified by the resolution of substrate **2f**. Indeed, the corresponding acetamide **3f** was obtained in only 7% ee ($s = 1$) albeit in quantitative yield. Our concern was that the enantio-enriched product could undergo epimerization under the reaction conditions or during the purification step. We therefore ran a few control experiments to test for this possibility. The enantio-enriched acetamide **3f** was thus re-subjected to the same reaction conditions, but no racemization could be detected even after stirring for 48 h at temperatures ranging from +20 °C to +60 °C. Compound **3f** was also exposed to (1*S*,2*S*)-1,2-bis-trifluoromethanesulfonamido-cyclohexane, which is the by-product formed during the reaction, but once again no erosion of the ee was observed. Likewise, treating **3f** with silica gel did not modify the ee thus indicating the considerable configurational stability of the product and therefore confirming the lack of selectivity of our reagent in front of such compounds.

In order to confirm the absolute configuration of the acetylated product obtained through the KR process and also demonstrate the synthetic utility of this method, we undertook the synthesis of coniine,[18,19] a toxic alkaloid present in poison hemlock.



Scheme 1. Scope and limitations of the reaction

The synthesis began with the benzylation of 3-butyn-1-ol **4** under standard conditions (BnBr, NaH, DMF, 0 °C) (Scheme 2). The corresponding benzyl ether was then treated with *n*-BuLi and the resulting propargyl lithium species was added to butanal to afford propargyl alcohol **5** as a racemic mixture in 78% overall yield. The latter was then engaged in a two-step sequence featuring a Mitsunobu reaction with phthalimide (DEAD, PPh_3, THF, rt) followed by a hydrazine-mediated cleavage to afford the corresponding propargyl amine **6** in 62% yield over two steps. The resulting propargyl amine was eventually engaged in the KR process under our optimized conditions [(1*S*,2*S*)-**1** (0.5 equiv), Aliquat^{TM} 336 (0.7M in THF) at –20 °C] to afford the corresponding acetamide **7** in 94% ee and 50% yield. Reduction of the alkyne moiety concomitantly with the cleavage of the benzyl ether was possible under hydrogenation conditions (H_2, Pd/C, EtOH, rt), affording the corresponding hydroxyamide **8** in quantitative yield. Tosylation of the primary alcohol (TsCl, Et_3N, DMAP, CH_2Cl_2, rt) followed by ring-closure through a nucleophilic substitution (NaH, THF, 0 °C) finally afforded the piperidine ring. To facilitate product-isolation due to the inherent volatility of coniine, and considering the fact that *N*-acetyl coniine had already been reported in the literature,[19] we decided to stop the synthesis at this stage. Gratifyingly, the spectroscopic and physical data of **9** were identical with those reported in the literature for *N*-acetyl (*S*)-coniine {$[\alpha]^{20}_D$ +46.0 (*c* 0.65, $CHCl_3$); lit. $[\alpha]^{22}_D$ +46.9 (*c* 0.4, $CHCl_3$)}[19b] confirming that under our optimized conditions (1*S*,2*S*)-**1** reacts preferentially on the



Scheme 2. Application of the KR to the synthesis of *N*-acetyl (*S*)-coniine **9**.

S-enantiomer, which is consistent with the results previously obtained in the KR of primary benzylic amines.[11]

In summary, we have described a highly selective process for the KR of propargylic amines. The reaction itself is operationally simple, proceeds under mild conditions and affords enantio-enriched propargylic amines with unprecedented levels of selectivity (*s*-factor up to 193) setting a new benchmarck in the field of non-enzymatic amine KR. Further applications of this method are currently under investigation and will be reported in due course.

This communication is dedicated to the memory of Dr. Charles Mioskowski.

Notes and references

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† Electronic Supplementary Information (ESI) available: [details of experimental procedures and ^{1}H NMR, ^{13}C NMR spectra for all new compounds. This material is available free of charge via the internet at http://pubs.rsc.org]. See DOI: 10.1039/b000000x/

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Abstract

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