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Asymmetric alkylation of 5-alkyl-2-aminothiazolones using a C_2-symmetric chiral tetraamine base

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ABSTRACT

The diastereoselective alkylation of a series of 5-alkyl-2-aminothiazolones utilizing a C_2-symmetric chiral tetraamine base is reported.

Introduction

AMG 221 (**1a**, Scheme 1) is an inhibitor of 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1). Inhibitors of 11β-HSD1 are potential therapeutic agents for the treatment of type 2 diabetes.[1]

The first-generation synthesis of **1** involved alkylation of 5-isopropylthiazolone **2** (>98% ee for the norbornyl moiety) using LDA as base to afford a 1.1:1 mixture of diastereomers which were separated by chiral chromatography.[1a] Importantly, this procedure afforded the 5,5′-dialkylthiazolones **1a** and **1b** in the absence of O-, N- and N′-alkylated by-products. While this procedure was sufficient to support early preclinical studies, an asymmetric process was sought to control the stereochemical outcome of the C–C bond forming event. We hoped to use a chiral lithium amide base to introduce facial selectivity into this already chemo- and regioselective reaction.

Results and Discussion

In 1990, Koga reported that a chiral lithium amide base (e.g., **8**) could be used to direct the approach of an electrophile selectively to one face of an achiral tetralone enolate.[2] We sought to explore a similar approach for alkylation of **2**.[3]

As shown in Table 1, an initial screen of chiral bases (**3–8**, Scheme 1) revealed that the dilithium enolate of (*S,S*)-**8** afforded significant selectivity for the desired isomer (**1a**).[4] Further optimization studies focused on the base structure revealed that the initial base **8** was optimal for selectivity. Modifying the length of the tether (Table 1, entries 10 and 11) afforded worse selectivity, as did replacement of the piperidine ring in **8** with a tetrahydroisoquinoline (Table 1, entry 12). Alkyl iodides afforded better selectivity than the corresponding bromide and sulfate (Table 1, entries 13 and 14). Finally, a significant improvement in both rate and selectivity was observed by the use of TMEDA as an additive, presumably by affecting the active lithium aggregate.[5] Other ethylenediamine ligands (i.e., TMPDA and TMBDA, entries 18 and 19) did not produce a similar effect. One drawback to the use of methyl iodide as alkylating agent was the methylation of (*S,S*)-**8** itself during the course of the reaction, which rendered recycle of (*S,S*)-**8** impossible. In an effort to avoid alkylation of the chiral base and enable recycle, we evaluated the alkylation with isopropyl iodide, 5-methylthiazolone 12, and the antipode of the chiral base, (*R,R*)-**8** (Scheme 2).

To our delight, the alkylation proceeded with a similar level of selectivity and without alkylation of (*R,R*)-**8**, which could now be recycled via a simple acid/base extraction procedure followed by crystallization.[4] The success of the alkylation of **12** led us to

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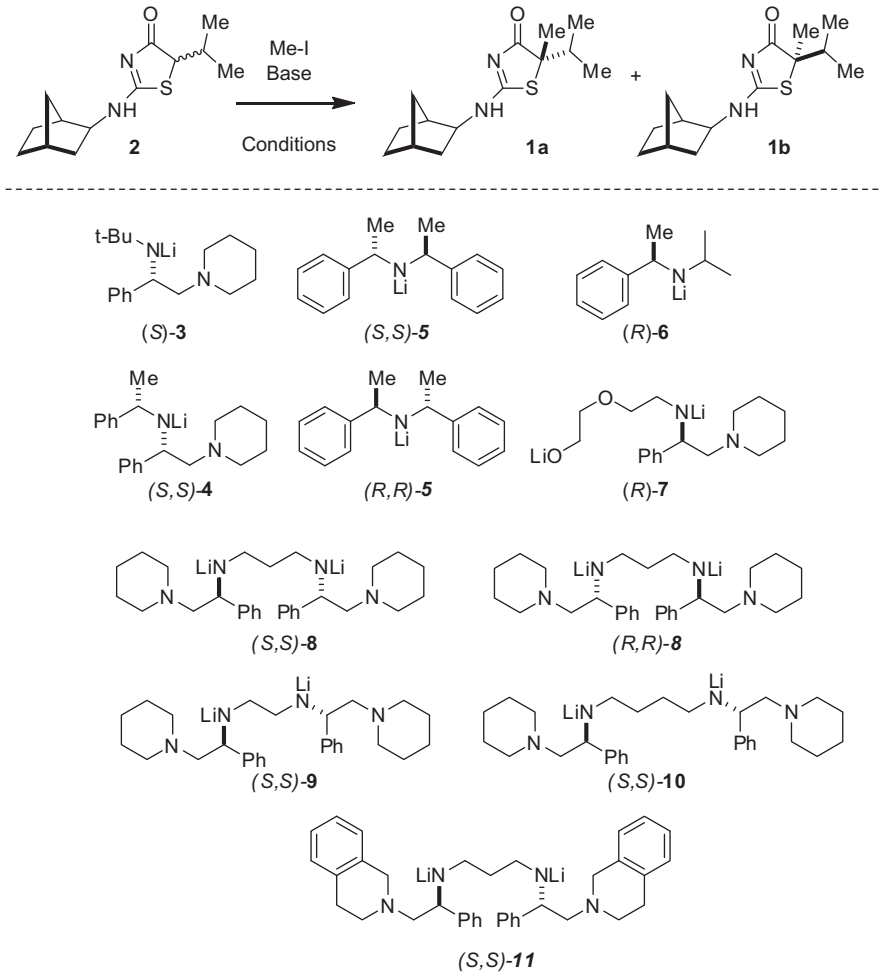


Scheme 1. Chiral bases screened for asymmetric alkylation of **2**.

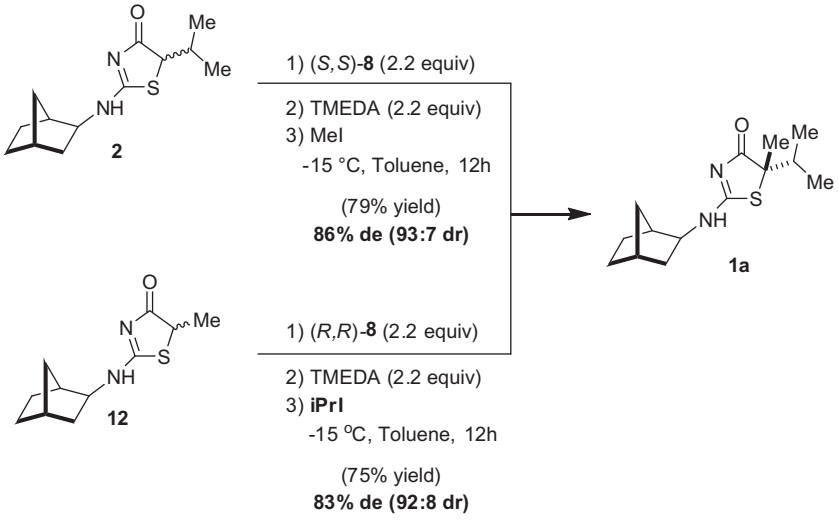
Table 1
Alkylation of **2** under various conditions

Entry	Base[a]	Conditions	Electrophile	Additive	**1a** Diastereoselectivity[b] (%)	% Conversion (HPLC)
1	LDA	Toluene, −45 to 0 °C	MeI	–	5	>95
2	(*S*)-**3**	THF, −78 to 0 °C	MeI	–	0	79
3	(*S,S*)-**4**	THF, −78 to 0 °C	MeI	–	−1.5	42
4	(*S,S*)-**5**	THF, −78 to 0 °C	MeI	–	9	85
5	(*R,R*)-**5**	THF, −78 to 0 °C	MeI	–	−24	90
6	(*R*)-**6**	THF, −78 to 0 °C	MeI	–	−5	94
7	(*R*)-**7**	THF, −78 to 0 °C	MeI	–	12	42
8	(*S,S*)-**8**	THF, −78 to 0 °C	MeI	–	32	90
9	(*S,S*)-**8**	Toluene, −45 to 0 °C	MeI	–	58	93
10	(*S,S*)-**9**	Toluene, −45 to 0 °C	MeI	–	19	87
11	(*S,S*)-**10**	Toluene, −45 to 0 °C	MeI	–	0	83
12	(*S,S*)-**11**	Toluene, −45 to 0 °C	MeI	–	20	75
13	(*S,S*)-**8**	Toluene, −45 to 0 °C	MeBr	–	49	88
14	(*S,S*)-**8**	Toluene, −45 to 0 °C	Me_2SO_4	–	34	89
15	(*S,S*)-**8**	Toluene, −45 to 0 °C	MeI	TMEDA (1.0 equiv)	66	>95
16	(*S,S*)-**8**	**Toluene, −45 to 0 °C**	**MeI**	**TMEDA (2.0 equiv)**	**86**	**>95**
17	(*S,S*)-**8**	Toluene, −45 to 0 °C	MeI	TMEDA (4.0 equiv)	64	>95
18	(*S,S*)-**8**	Toluene, −45 to 0 °C	MeI	TMPDA (2.0 equiv)	64	89
19	(*S,S*)-**8**	Toluene, −45 to 0 °C	MeI	TMBDA (2.0 equiv)	59	84

[a] 3 equiv of chiral bases 3–7 were used, 2 equiv of chiral bases 8–1 were used.
[b] Determined by Chiral HPLC.

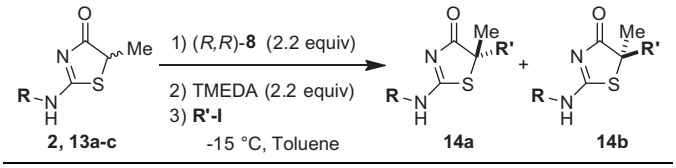
explore other substrates under similar conditions. As can be seen from Table 2, (*R,R*)-**8** affords good selectivity with a range of substituted 5-alkylthiazolones.[6] In general, secondary alkyl iodides afforded better selectivity than primary alkyl iodides.

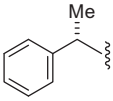
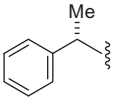
In conclusion, C_2-symmetric chiral base (*R,R*)-**8** enables efficient reagent-controlled alkylation of 5-alkyl-2-aminothiazolones with a high degree of regio-, chemo-, and stereochemical control, overriding any intrinsic stereocontrol element. Importantly, use



Scheme 2. Use of (*R*,*R*)-**8** with isopropyl iodide to alkylate **12**.

Table 2
Scope of 5-alkylthiazolone alkylations using (*R*,*R*)-**8**



Substrate	R	R′	% de **14a**[a]	Yield[b] (%)
12		2-Propyl	86	79
12		1-Propyl	27	76
13a		2-Propyl	81	86
13a		1-Propyl	43	71
13b		2-Propyl	89	70
13b		1-Propyl	86	65

[a] Determined by Chiral HPLC.
[b] Isolated yields as diastereomeric mixture.

of electrophiles more sterically hindered than methyl iodide prevents alkylation of the chiral base itself, enabling facile recycle of the chiral controller.

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3. The initial disclosure of this work can be found in: Moniz, G. A.; Frizzle, M. J.; Bernard, C.; Martinelli, M. J.; Faul, M. M.; Nani, R. R.; Larrow, J. F. PCT Int. Appl. WO2009002445, 2008. This reference also describes the synthesis of **2.**
4. For a large-scale preparation of the C_2-symmetric tetraamine used to generate (*R*,*R*)-**8**, see: Frizzle, M. J.; Caille, S.; Marshall, T.; McRae, K.; Guo, G.; Wu, S.; Martinelli, M. J.; Moniz, G. A. *Org. Process Res. Dev.* **2007**, *11*, 215.
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6. A typical large-scale alkylation procedure is as follows: A 20 L reactor was placed under a nitrogen sweep. (*R*,*R*)-chiral amine (**8**, 1610 g, 3.59 mol, 2.2 equiv) was charged to the reactor. This was followed by a nitrogen sweep for 50 min. Anhydrous toluene (5.42 L) was then charged and agitation was initiated. The reaction mixture was allowed to stir under a nitrogen sweep for an additional 10 min, after which the reaction mixture was cooled to −7.5 °C over 45 min. A dropping funnel was charged with *n*-BuLi solution (2.7 M in toluene, 2.66 L, 7.18 mol, 4.4 equiv), and dropwise addition of the *n*-BuLi was initiated. During this addition, the addition rate and jacket temperature were adjusted to ensure that internal temperature did not rise above 0 °C. Once the addition was complete, the dropping funnel was rinsed with anhydrous toluene (100 mL). The reaction mixture was cooled to −15 °C and TMEDA (540 mL) was then added via cannula. 5-methylthiazolone (**13a**, 361.6 g, 1.63 mol, 1.0 equiv) was slurried in anhydrous toluene (1.45 L) in a separate 5 L, 3-neck round-bottom flask under a nitrogen sweep for 30 min. The resulting slurry was charged portionwise to the reactor via cannula, adjusting addition rate and jacket temperature so as to maintain the internal temperature below 0 °C. The round-bottom flask used to prepare the substrate slurry was rinsed with toluene (2 × 468 mL) and the washes were charged to the reactor. The reaction mixture was warmed to 15 °C over 1.5 h, and aged at this temperature for 30 min. The mixture was then re-cooled to −15 °C over 1 h. 2-Iodopropane (1.3 L, 13.0 mol, 8.0 equiv) was charged via cannula at such a rate as to maintain temperature below −12.5 °C, adjusting the jacket temperature as needed to control the resulting exotherm. The reaction mixture was allowed to age at −15 °C until >93% conversion was obtained, and then quenched by dropwise addition of saturated NH_4Cl solution (3.62 L), again adjusting addition rate and jacket temperature to control the resulting exotherm. The reaction mixture was warmed to room temperature and agitation was halted. Phases were allowed to separate and the lower aqueous layer was drained. 4.82 L of saturated NH_4Cl solution was added and the mixture agitated for 20 min. The phases were allowed to separate and the lower aqueous

layer was drained. Acetic acid solution (2 M, 3 L) was charged to the reactor and the mixture agitated for 30 min. The phases were allowed to separate and the lower aqueous layer was drained. The acetic acid wash was repeated. Saturated $NaHCO_3$ (3 L) was charged to the reactor slowly while agitating for 20 min. The phases were allowed to separate (at least 20 min). The lower aqueous phase was drained. The toluene layer was solvent-exchanged into octane, with the final ratio of solvents 20:1 octane–toluene. After the desired solvent ratio was reached, with a final volume of 3.9 L, the slurry was filtered through a medium-porosity sintered glass funnel, rinsing with two portions of octane (1400 mL total). The solids were dried on the filter for 1–1.5 h, and then transferred to a drying dish and dried in a vacuum oven at 45–55 °C, 3–30 torr for 18–42 h. Obtained 370 g of a white solid, 86% yield, 80.5% de.