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Asymmetric Synthesis of 1- ,3- or 4-Alkyl- or Aryl-Tetrahydro-Benzo[c]azepines

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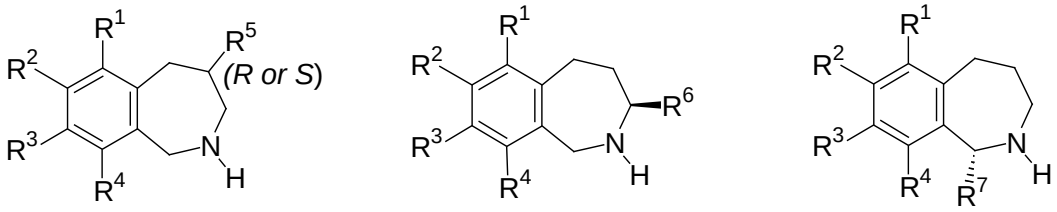
Abstract: Flexible routes for the stereoselective synthesis of a variety of structurally diverse 1-, 3- or 4-alkyl and aryl-tetrahydrobenzo[c]azepines have been developed. The key steps are the highly diastereoselective 1,2-addition process or metallation/alkylation sequence applied to stereopure hydrazones. Subsequent cyclomethylenation or ring-closing metathesis reaction to secure the formation of the seven-membered azaheterocycle ring system complete the assembly of the targeted titled compounds.

Introduction

Benzazepines play an important role in heterocyclic chemistry because this ring system lies at the heart of a great variety of poly and diversely functionalized models endowed with profound chemotherapeutic properties [1].
Thus compounds containing the benzazepine skeleton, mainly at the tetrahydro level, display important physiological properties and are known to exhibit strong neuroleptic and neurotropic activities [2]. Some representatives have been found to display anti-HIV activity [3], to promote healing of skin wounds [4] and to treat cardiovascular diseases, especially glaucoma and hypertension [5]. Compounds of this class are also used as antiarrythmic [6] and CNS agents [7], as inhibitors of PNMT [8] and are recommended for the treatment of stomach disorders [9]. Finally the benzazepine nucleus represents the main structural unit of many naturally occurring molecules, namely those extracted from *Cephalotaxus Harringtonia*, *Papaveraceae* and *Amaryllidaceae* alkaloids which could be used in the treatment of Alzheimer disease [10], the most common cause of elderly dementia.

Due to the diverse biological activities of many of their derivatives the chemistry of 2-benzazepines has been the focus of new synthetic methodologies during the past decades [1] but only few of them allowed the control of stereogenic centers on the seven-membered azaheterocyclic unit. Therefore the development of synthetic methodologies which may find generality for constructing a variety of tetrahydrobenzo[*c*]azepines with alkyl or aryl appendages at C1, C3 and C4 in a stereo and enantioselective manner constitutes an area of current interest.
Herein we report straightforward, feasible and highly stereoselective routes to these alkylated and arylated tetrahydrobenzo[*c*]azepines **1**-**3** (Fig. 1).

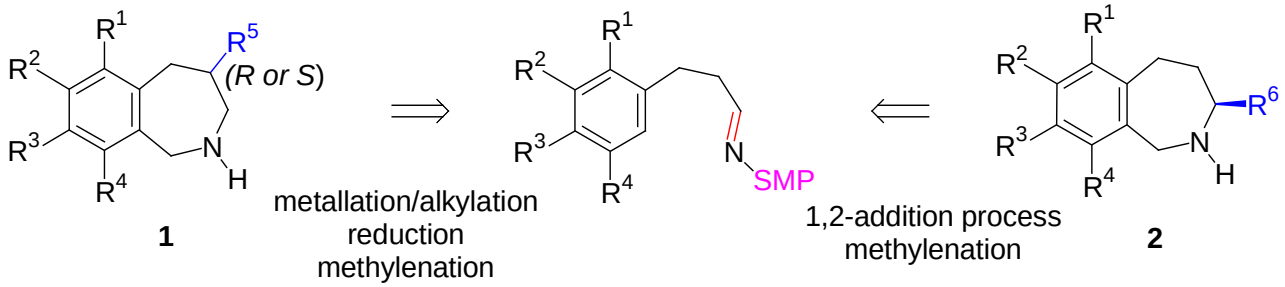


1 **2** **3**

Figure 1.

The Synthetic Strategy

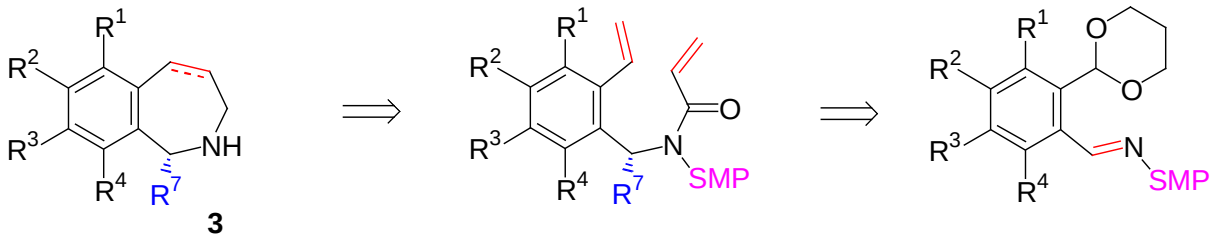
The new synthetic route to 4- or 3-alkyl(aryl)tetrahydrobenzo[*c*]azepines **1**, **2** hinges upon the combination of the highly diastereoselective metallation/alkylation reaction or nucleophilic 1,2-addition reaction to chiral aliphatic hydrazones with a cyclomethylenation reaction (Scheme 1).



1 **2**

Scheme 1.

For the assembly of the 1-alkyltetrahydrobenzo[*c*]azepines **3** the key step is a highly diastereoselective 1,2-addition process applied to a stereopure aromatic hydrazone combined with a ring-closing metathesis (Scheme 2).



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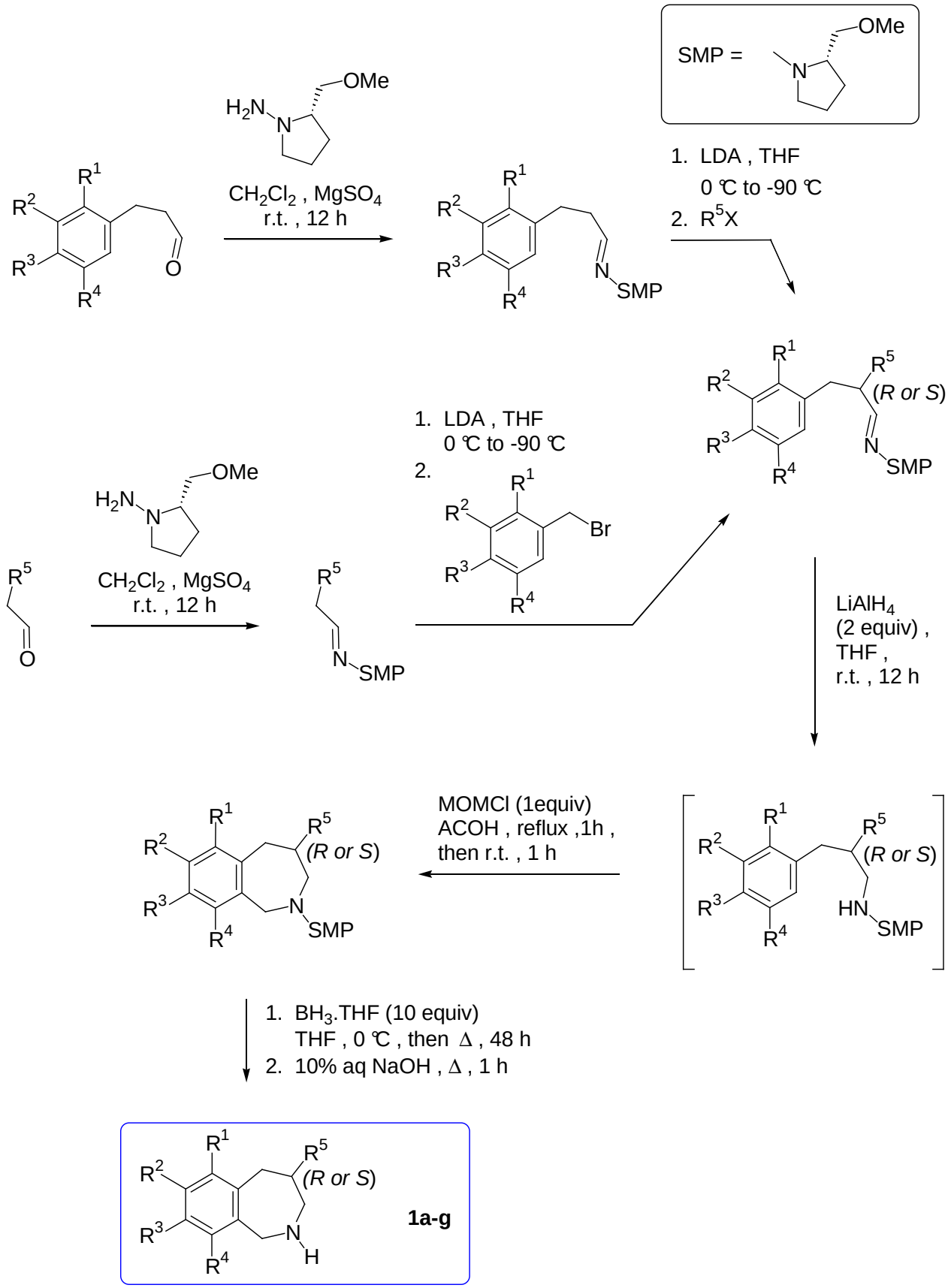
Scheme 2.

Asymmetric Synthesis of 4-Aryl or Alkyl-Tetrahydro-Benzo[*c*]azepines (1).

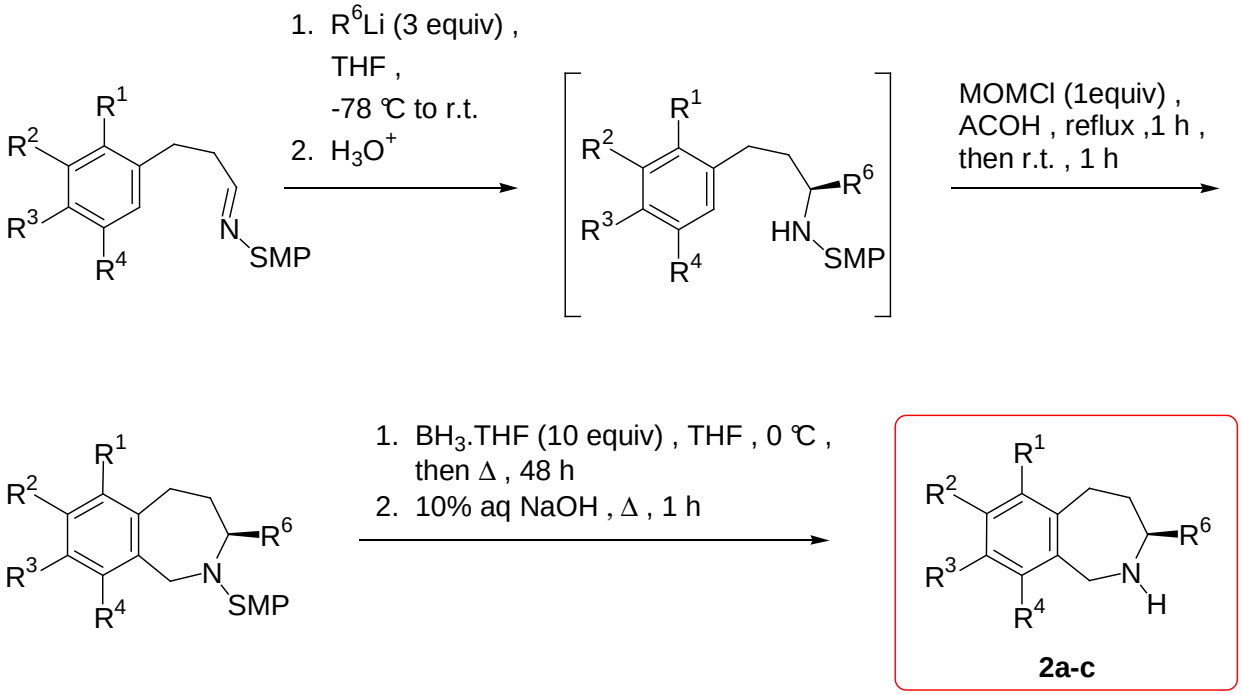


Scheme 3.

Table 1. Tetrahydrobenzazepines **1a-g** Prepared.

R^1	R^2	R^3	R^4	R^5	Benzazepines **1a-g**	(Yield)
H	MeO	MeO	MeO	Me	(*R*)-**1a**	(58%)
H	MeO	MeO	MeO	Bn	(*R*)-**1b**	(48%)
H	MeO	MeO	MeO	CH_2OMe	(*R*)-**1c**	(49%)
H	MeO	MeO	H	Me	(*R*)-**1d**	(53%)
H	MeO	MeO	H	Me	(*S*)-**1d**	(55%)
H	MeO	MeO	MeO	Ph	(*R*)-**1e**	(48%)
MeO	MeO	H	H	C_5H_{11}	(*S*)-**1f**	(52%)
H	OCH_2O		H	$(CH_2)_2OBn$	(*R*)-**1g**	(51%)

Asymmetric Synthesis of 3-Alkyl-Tetrahydro-Benzo[*c*]azepines (2).



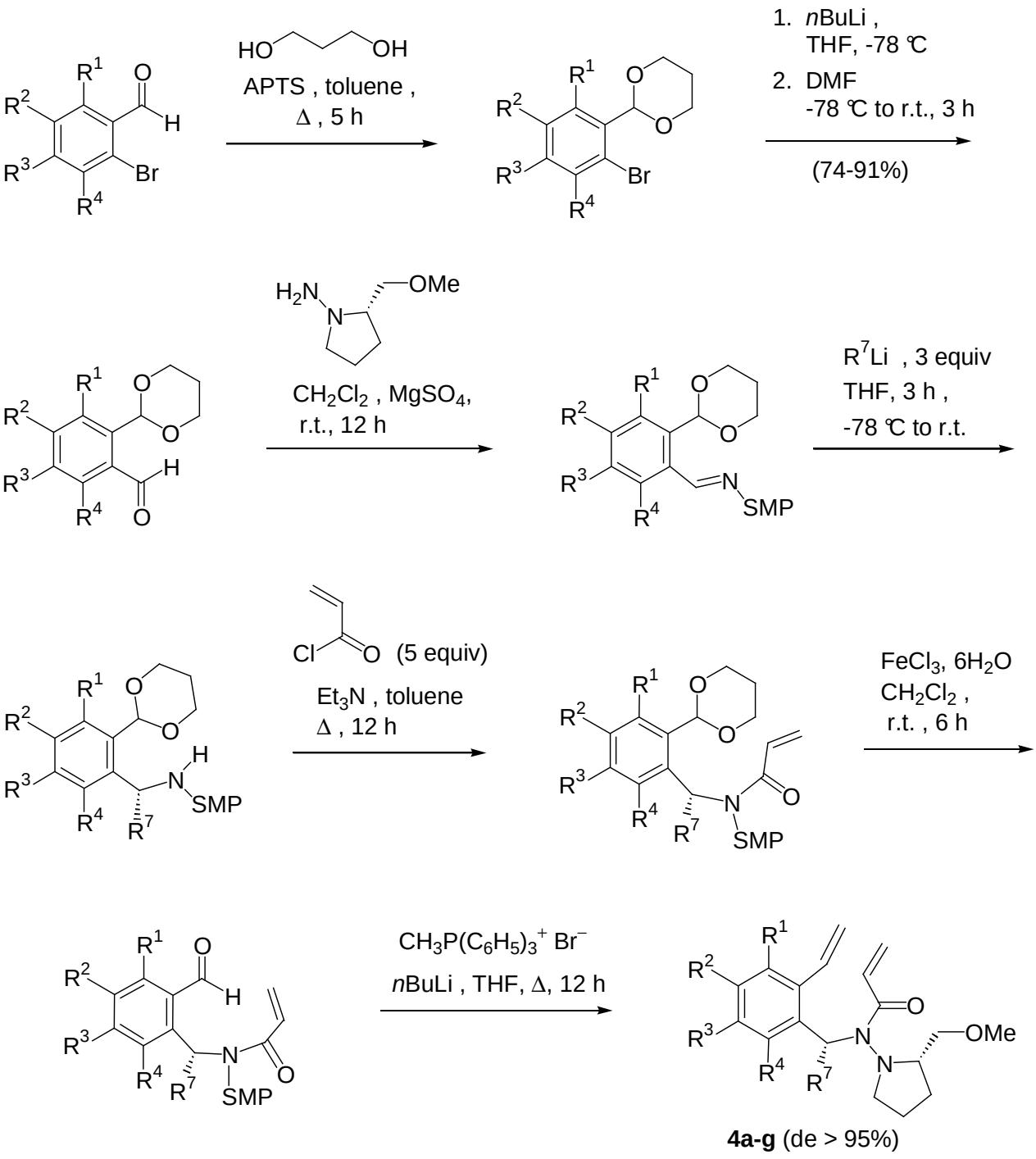
Scheme 4.

Table 2. Tetrahydrobenzazepines **2a-c** Prepared.

R^1	R^2	R^3	R^4	R^6	R^6Li	Benzazepines **2a-c**	(Yield)
H	MeO	MeO	MeO	Me	CH_3Li	(*R*)-**2a**	(58%)
H	MeO	MeO	H	Me	CH_3Li	(*R*)-**2b**	(53%)
H	MeO	MeO	H	C_6H_{13}	$C_6H_{13}Li$	(*R*)-**2c**	(56%)

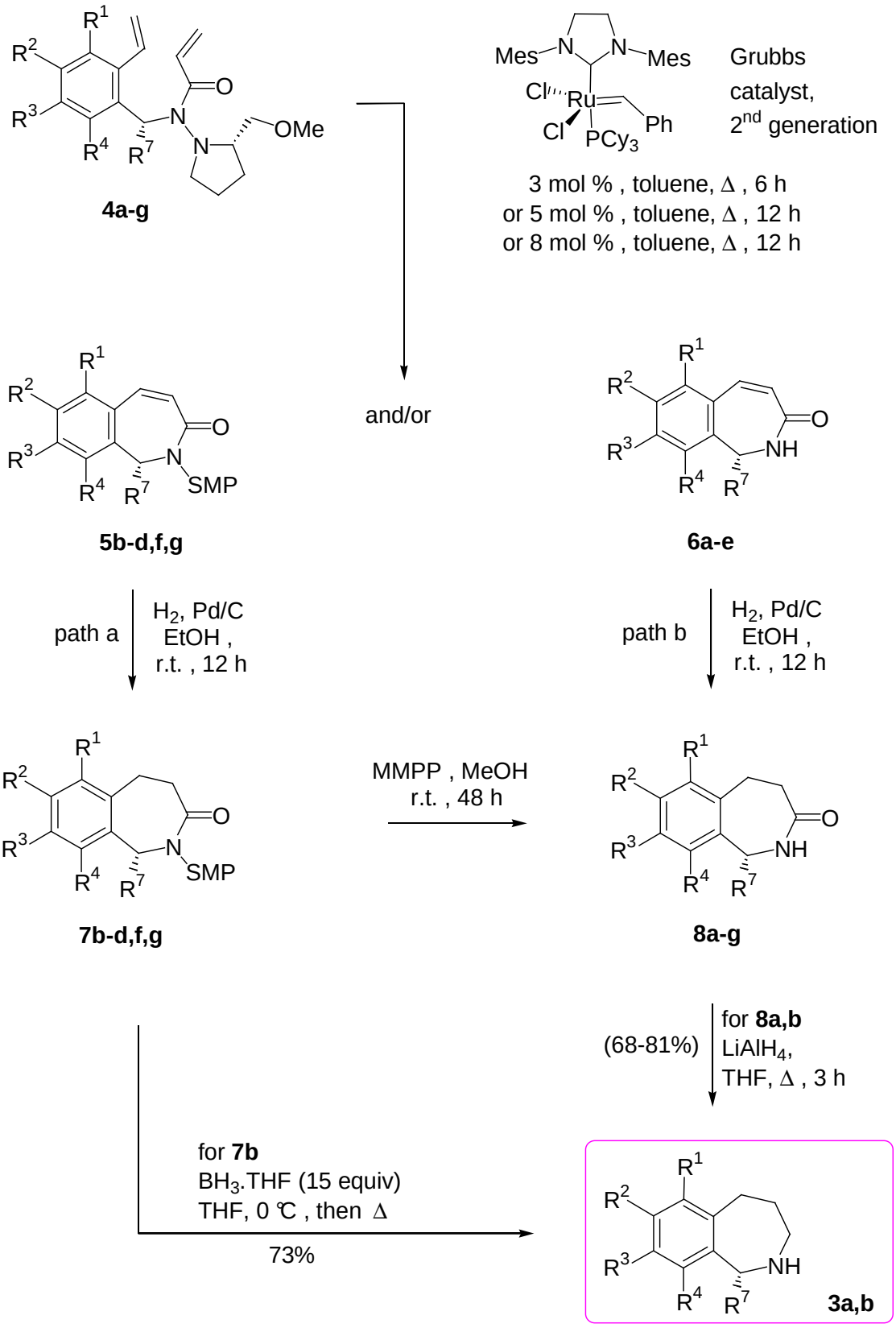
Asymmetric Synthesis of 1-Alkyl-Tetrahydro-Benzo[*c*]azepines (3).

1. Synthesis of the Styrenic Enehydrazides (4a-g)



Scheme 5.

2. Synthesis of 1-Alkyl-Tetrahydro-Benzo[c]azepines via RCM



Scheme 6.

Noteworthy the expected diastereopure dihydrobenzazepinones (**5b-d,f,g**) were obtained along with the NH free (*R*)-dihydrobenzazepinones (**6a-e**) released from the chiral appendage, probably due to the N-N bond cleavage catalyzed by the efficient ruthenium catalyst (Scheme 6, Table 3). However the formation of compounds **5** and **6** was not detrimental to the outcome of the synthetic process liable to give access to the targeted titled compounds **3** (Scheme 6, paths a & b).

Table 3. Compounds **3-8** Prepared

R^1	R^2	R^3	R^4	R^7	**4a-g**	**5** and/or **6**		**8** from **6**	**8** from **5** *via* **7**	**3**
								(Yield %)		
H	OMe	OMe	OMe	$CH_3(CH_2)_3$	**4a** (56)	-	50[a]	**8a** (90)	-	**3a** (68)
H	H	H	H	Me	**4b** (69)	72	-	-	**8b** (74)	**3b** (81)
					4b	38	41[a]	**8b** (90)	-	**3b** (73)
H	H	H	H	$CH_3(CH_2)_3$	**4c** (47)	43	48[a]	**8c** (92)	**8c** (56)	-
H	H	H	H	$CH_3(CH_2)_5$	**4d** (41)	11	42[a]	**8d** (95)	**8d** (52)	-
H	OCH_2O		H	$CH_3(CH_2)_3$	**4e** (57)	-	48[a]	**8e** (90)	-	-
H	OCH_2O		H	Me	**4f** (66)	41	-	-	**8f** (64)	-
H	OMe	OMe	H	Me	**4g** (48)	54	-	-	**8g** (50)	-

[a] After extended reaction time (12 h).

Conclusion

We have developed flexible and efficient routes for the stereoselective synthesis of an array of constitutionally diverse 1-alkyl, 3- or 4-aryl or alkyl-tetrahydrobenzo[*c*]azepines. The key steps are the highly diastereoselective metallation/alkylation and nucleophilic 1,2-addition applied to SAMP-hydrazones combined with RCM or cyclomethylenation reactions.

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