Modified guanidines as chiral superbases: the first example of asymmetric silylation of secondary alcohols

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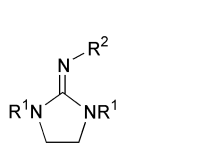
Modified guanidines could effectively mediate asymmetric silylation of secondary alcohols as recyclable bases under simple and mild conditions.

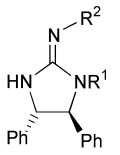
Due to their strongly basic character,[1] guanidines can be characterized as superbases[2] and, although chiral guanidines are expected to have potential as asymmetric reagents, their limited use[3] in asymmetric synthesis as chiral auxiliaries is due mainly to the lack of simple preparation methods. We have explored the possibility of modified guanidines as recyclable chiral superbases in organic synthesis under simple and mild conditions and recently reported their application to an asymmetric alkylative esterification of benzoic acid.[4] Kinetic resolution of racemic secondary alcohols is used for the selective preparation of one enantiomer. Enzymes such as esterases have been widely utilized for this purpose,[5] whereas non-enzymatic methods have been succeeded only in acylation.[6] In this communication we present the first example of asymmetric silylation of secondary alcohols mediated by chiral guanidines.

Reactions of indan-1-ol (**1**) with TBDMS (TBDMSCl) or TIPS chlorides (TIPSCl) were chosen as representatives for kinetic silylation of secondary alcohols because of the unsuccessful separation of each enantiomer of the silylated products by chiral HPLC when other acyclic alcohols or silylating agents were used in preliminary experiments.[7] Three different types of monocyclic guanidines [unsubstituted type **I**;[8a] 4-substituted type **II**;[8b,9] (4*S*,5*S*)-4,5-diphenylsubstituted type **III**[8c,9] and bicyclic guanidines **IV**[8b,9] (Fig. 1) were examined for their ability as catalysts in the silylation reaction. Thus, racemic **1** (2 equiv.) was first treated with TBDMSCl (1 equiv.) in DCM at rt in the presence of a chiral guanidine (1 equiv.) for several days to give, as expected, a silylated product **2** with recovery of the starting compound **1** (Table 1).



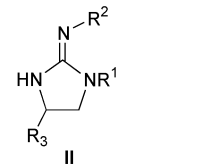
I

a: R^1=Me R^2=(*R*)-CH(Me)Ph
b: R^1=R^2=(*S*)-CH(Me)Ph



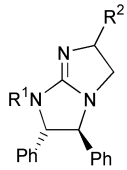
III

a: R^1=H, R^2=Et
b: R^1=H, R^2=CH_2Ph
c: R^1=H, R^2=(*S*)-CH(Me)Ph
d: R^1=H, R^2=(*R*)-CH(Me)Ph
e: R^1=Me, R^2=(*R*)-CH(Me)Ph



II

a: R^1=R^2=$CHMe_2$ R^3=(*R*)-Ph
b: R^1=R^2=(*S*)-CH(Me)Ph R^3=(*S*)-CH_2Ph
c: R^1=R^2=(*S*)-CH(Me)Ph R^3=(*R*)-CH_2Ph
d: R^1=R^2=(*S*)-CH(Me)Ph R^3=(*R*)-Ph



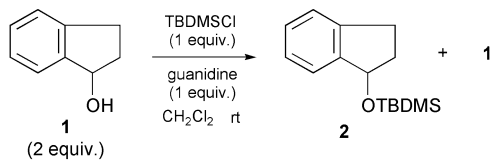
IV

a: R^1=H R^2=(*S*)-CH_2Ph
b: R^1=Me R^2=(*S*)-CH_2Ph
c: R^1=H R^2=(*R*)-Ph
d: R^1=H R^2=(*S*)-Ph

Fig. 1

Simple guanidines **I** were not effective for asymmetric induction (runs 1 and 2). However, moderate ee was observed in the cases of 4-substituted guanidines **II** (runs 3–6), in which the stereogenic center of the silylated product **2** was found to be controlled by the stereochemistry of the imidazolidine ring (C4). Thus, **IIb** with an (*S*)-configuration produced an (*R*)-excess product (run 4), whereas a diastereomeric **IIc** gave an (*S*)-excess product (run 5). Reasonable ee's was obtained when 4,5-diphenylguanidines **III** were used. It was found that the chiral center of the substituent on the external nitrogen atom played an important role in effective asymmetric induction. Thus, (*R*)-phenylethyl-substituted guanidines **IIId** and **IIIe** gave an (*R*)-excess **2** with 37% ee (run 10) and 39% ee (run 11), respectively, whereas a lower ee (6%) was observed in the case of **IIIc** with an (*S*)-phenylethyl-substituent (run 9). The formation of an (*R*)-excess product in each case indicated that the stereochemistry of **2** was controlled by the ring chiral centres of guanidines.

Table 1 Trials for kinetic silylation of **1** with TBDMSCl in the presence of chiral guanidines



			2[a]		
Run	Guanidine	Time/d	Yield[b] (%)	Ee[c] (%)	Conf.[d]
1	**Ia**	14	82	0	—
2	**Ib**	7	38	0	—
3	**IIa**	3	70	19	*S*
4	**IIb**	6	31	6	*R*
5	**IIc**	9	66	14	*S*
6	**IId**	16	61	13	*S*
7	**IIIa**	8	47	14	*R*
8	**IIIb**	6	67	16	*R*
9	**IIIc**	12	34	6	*R*
10	**IIId**	11	34	37	*R*
11	**IIIe**	9	50	39	*R*
12[e]	**IVa**	10	78	31	*R*
13	**IVb**	9	53	7	*R*
14	**IVc**	7	86	0	—
15	**IVd**	6	32	27	*R*

[a] Authentic (*S*)-**2** was prepared from (*S*)-**1** by a conventional method. [b] The starting **1** was quantitatively recovered. [c] The ee was estimated by chiral HPLC (CHIRALCEL OD, 0.5 ml min^{-1} with hexane). The peak detection was done by UV (254 nm). The retention times of (*R*)- and (*S*)-**2** were 9.67 and 11.61 min, respectively. [d] Absolute configuration of the excess enantiomer. [e] An (*S*)-excess **1** (18% ee) was quantitatively recovered. The guanidine **IVa** was completely recovered in a re-useable form.

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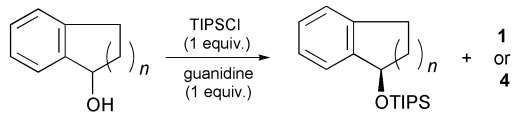
Table 2 Asymmetric silylation of **1** or **4** with TlPSCl in the presence of either guanidine **IIId** or **IVd**



				3 or **5**[a]	
Run	**1** or **4**	Guanidine	Temp.	Yield[b] (%)	Ee (%)
1	**1**	**IIId**	rt	**3**: 36	59[c]
2	**1**	**IIId**	reflux	**3**: 48	59[c]
3	**1**	**IVa**	rt	**3**: 79	58[c]
4	**4**	**IVa**	rt	**5**: 15[d]	70[e]

[a] Authentic (*S*)-**3** and -**5** were prepared from (*S*)-**1** and -**4**, respectively, by conventional methods. [b] The starting **1** was quantitatively recovered. [c] The (*R*)-excess enantiomer was obtained. The ee was estimated by chiral HPLC (CHIRALCEL OD-H, 0.5 ml min^{-1} with hexane). The peak detection was done by UV (254 nm). The retention times of (*R*)- and (*S*)-**3** were 7.75 and 9.29 min, respectively. [d] Side products were detected on TLC during the reaction. [e] The ee was estimated by chiral HPLC (CHIRALCEL OD-H, 0.2 ml min^{-1} hexane). The peak detection was done by UV (254 nm). The retention times of (*R*)- and (*S*)-**5** were 19.82 and 20.68 min, respectively.

With bicyclic guanidines **IV**, equally asymmetric induction was observed when **IVa** was used (run 12). Introduction of a methyl group onto the ring nitrogen did not affect asymmetric induction in the cases of monocyclic guanidines as mentioned above (see runs 10 and 11). However, marked reduction of ee was observed in the reaction using the *N*-methylguanidine **IVb** (run 13). Furthermore, a match–mismatch relationship was observed in reactions using diastereomeric **IVc** and **IVd** similarly to reactions using monocyclic guanidines **IIIc** and **IIId**. Thus, **IVd** with a (2*S*,3*S*,7*S*)-configuration was a more effective base (run 15: 27% ee) than **IVc** (run 14: no ee).

Theoretically, indan-1-ol (**1**) should be obtained as an (*S*)-enantiomer-rich alcohol in these silylation reactions and the guanidine used could be recovered in a re-useable form. Isolation of both **1** and **IVa** in run 12 resulted in their expected and quantitative recovery as an (*S*)-excess alcohol (18% ee) and as a re-useable guanidine, respectively. In addition, we tried the asymmetric silylation in the presence of **IIId** in various solvents such as MeCN, toluene, trifluoromethylbenzene, and THF; however, no improvement of ee was observed in each case.

From the above experiments using TBDMSCl as a silylating agent, **IIId**, **IIIe** or **IVa** among the guanidines examined were suggested to be promising chiral bases for asymmetric silylation. Next, reactions with a more bulky TIPSCl in the presence of either **IIId** or **IVa** were attempted under the same conditions[10] described in Table 1 (Table 2). Reactions of **1** with TIPSCl at rt similarly proceeded to afford an (*R*)-excess **3** in 59% ee with **IIId** (run 1) and 58% ee with **IVa** (run 3), respectively. Interestingly, no loss of ee was observed even in the reaction under heating (run 2), indicating that this silylation would be tolerant to the reaction temperature.[11] Application of the guanidine-mediated silylation using **IVa** to 1,2,3,4-tetrahydro-1-naphthol (**4**) in place of **1** gave a silylated product **5** with high stereoselection (70% ee), albeit the chemical conversion[12] was low (run 4).

In conclusion, we have found that guanidines could effectively mediate asymmetric silylation of secondary alcohols as recyclable bases under simple and mild conditions. Although the ee obtained and reaction rates are not neccessarily perfect, it is noteworthy that these results offer not only the first example of chemical asymmetric silylation of secondary alcohols, but also experimental evidence for a possible ion-pair complex[13] between a silylating agent and a base. Formation of a silylguanidinium salt has been partially suggested by inspection of the ^{1}H NMR spectrum of an equimolar mixture of the guanidine **IIId** and TBDMSCl. Approaches to the mechanistic rationale, kinetics, and optimization of the reaction are at present under study in our laboratory.

Notes and references

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7 TBDMS, TIPS, and TBDPS derivatives of 1-phenylethyl alcohol and TIPS derivatives of 1-phenylpropyl and 2-phenylcyclohexyl alcohols were examined.

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9 It is known that substituted guanidines can exist in tautomerization of amino and imino forms depending upon the substitution patterns (see, K. Tanatani, K. Yamaguchi, I. Azumaya, R. Fukotomi, K. Shudo and H. Kagechika, *J. Am. Chem. Soc.*, 1998, **120**, 6433). One tautomer is arbitrarily described as a structure of guanidines with at least one NH function in Fig. 1.

10 We also tried catalytic silylation reactions in the coexistence of Et_3N. The reaction proceeded smoothly (57% conversion after 43 h), but no asymmetric induction was observed.

11 On the other hand, the reaction of **1** with TBDMSCl using **IVa** at −20 °C for 20 days afforded **2** in 16% yield with 33% ee, resulting in no improvement of asymmetric induction.

12 The low yield of **5** probably was caused by considerable production of side-products, whereas only the silylation reaction was observed in the use of **1** as a substrate.

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