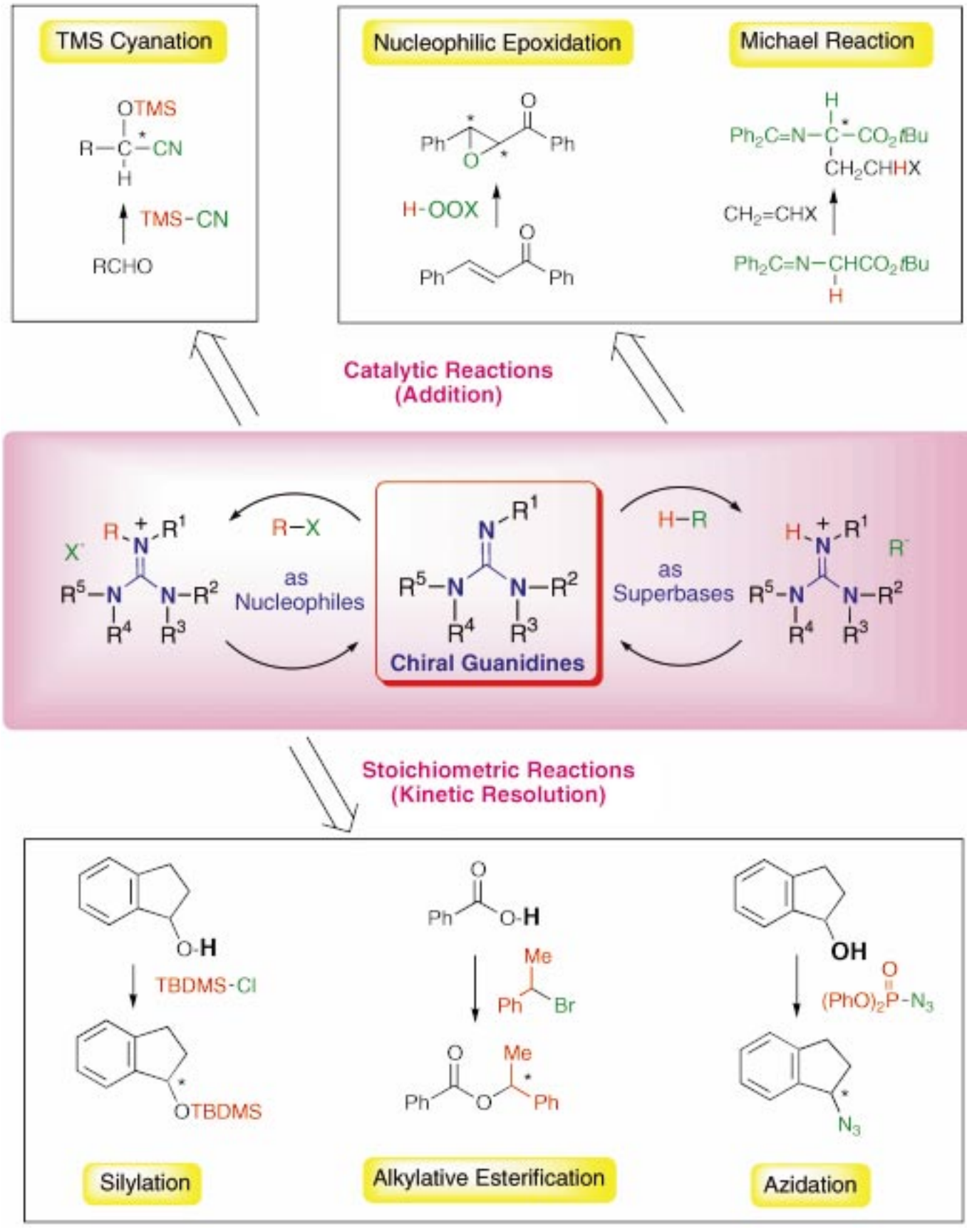
Guanidine-Assisted Asymmetric Syntheses



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Modified Guanidines as Chiral Auxiliaries

Tsutomu Ishikawa*[a] and Toshio Isobe[b]

Abstract: Investigations on modified guanidines, prepared by newly developed methods, as potential chiral auxiliaries led to reasonable asymmetric induction not only in catalytic but also in stoichiometric asymmetric syntheses. These guanidine-mediated reactions may contribute to the development of green chemistry because of their possible application as re-cyclable (economically favored) and easily functionalizable (widely applicable) auxiliaries.

Keywords: asymmetric catalysis · asymmetric synthesis · chiral auxiliaries · guanidines · kinetic resolution

Introduction

Asymmetric synthesis is a very important and powerful method for new generation of stereogenic centers. Optically active amines are widely used as the key ligands[1] of chiral auxiliaries or as the basic skeletons of phase-transfer catalysts.[2] They are also used as chiral bases in some cases after modification to metal amides with strong basicity;[3] however, to our knowledge, their successful application as organic bases themselves without modification is limited to a few conjugate additions[4] due to their low basicity in spite of the advantages of not only easy handling (without requiring strict reaction conditions such as air protection in many cases of metal-mediated reactions) but also simple handling (just mixing).

Guanidines **1** can be classified as organic bases such as amines **2** and amidines **3**, in which **1** are regarded the strongest bases[5] due to resonance stabilizability of their conjugated acids.[6] The presence of three nitrogen atoms in the guanidine compounds may lead to wide and easy molecular modification, as it is theoretically possible to introduce five chiral centers at the nitrogen atoms (Figure 1). Thus, it can be anticipated that modified guanidines play important roles as chiral bases (or auxiliaries) in asymmetric synthesis.

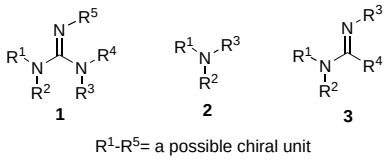

Figure 1. Different guanidines **1**, amines **2**, and amidines **3**.

Some applications of guanidines to asymmetric synthesis as chiral bases can be found in the literature;[7] however, not only difficult manipulation as a result of their strong basicity but also lack of simple and general synthetic methods hampered the use of guanidines in asymmetric synthesis. We have reported the availability of 2-chloro-1,3-dimethylimidazolinium chloride (DMC)[8] (**4**) as a replacement for the dehydrating agent dicyclohexylcarbodiimide. In the course of these studies we observed that DMC derivatives are easily converted into the corresponding cyclic guanidine derivatives **5** by treatment with appropriate primary amine functionalities (Figure 2). These facts stimulated us to develop guanidine chemistry mainly focusing on their role as chiral auxiliaries in asymmetric synthesis.

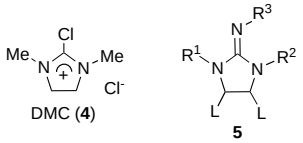

Figure 2. DMC (**4**) and a basic skeleton of modified guanidines **5**.

Discussion

Preparation of modified guanidines: We recently established a new and practical synthesis of nine types of modified guanidines by four different methods dependent upon the key reactions used.[9] The first method involves the reaction of DMC derivatives with amines[9a] (Scheme 1). Thus, 1,3-disubstituted 2-iminoimidazolidines **8** with or without 4,5-

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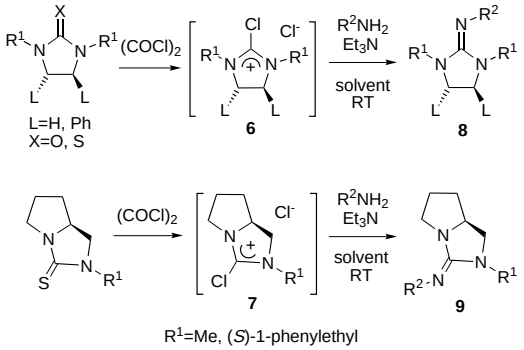
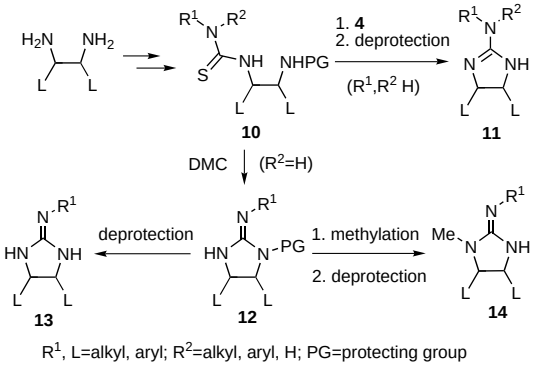


Scheme 1. Preparation of guanidines **8** and **9** from DMC derivatives.

diphenyl groups and bicyclic guanidines **9** were prepared from DMC derivatives **6** and **7**, respectively, by treatment with primary amines.

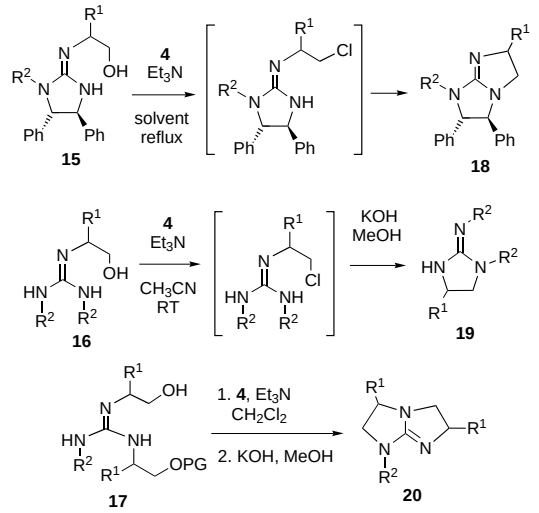
The second method involves DMC-induced cyclization of protected thiourea intermediates derived from the corresponding ethylenediamines as a key reaction[9b] (Scheme 2). Thus, 2-aminoimidazolines **11** were prepared from trisubstituted thioureas **10** (R^1,$R^2 \neq$H), whereas 1,3-unsubstituted **13** and 1-methyl-2-iminoimidazolidines **14** were synthesized from disubstituted thioureas **10** (R^2 = H) through protected imidazolidine derivaitves **12**.



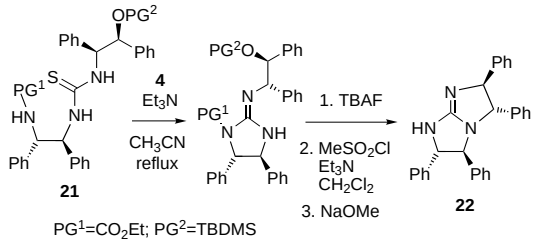
Scheme 2. Preparation of guanidines **11**, **13**, and **14** by DMC-induced cyclization of thiourea.

The third method constitutes an alternative DMC-induced cyclization of guanidines with a hydroxyethyl function at the nitrogen atom through substitution of the hydroxy group by a chlorine atom[9c] (Scheme 3). Thus, 3,7,8-trisubstituted 1,4,6-triazabicyclooctene systems **18** were prepared from 2-(2-hydroxyethylimino)imidazolidines **15**. Reaction of linear-type guanidines **16** with DMC followed by base treatment afforded 1,4-disubstitued 2-iminoimidazolidines **19**. Another type of 1,4,6-triazabicyclooctenes **20** was also prepared from guanidines **17** containing two 2-hydroxyethyl substituents by double DMC-induced cyclization.

Finally, a C_2-symmetrical bicyclic guanidine[10] **22**, (2*S*,3*S*,7*S*,8*S*)-2,3,7,8-tetraphenyl-1,4,6-triazabicyclooctene, was provided using thiourea **21** by DMC-induced cyclization followed by intramolecular S_N2 reaction of the monocyclic guanidine as shown in Scheme 4.



Scheme 3. Preparation of guanidines **18**, **19**, and **20** by DMC-induced cyclization of guanidines with a hydroxyethyl group.



Scheme 4. Preparation of guanidine **22** by DMC-induced cyclization followed by S_N2 cyclization.

Roles as chiral auxiliaries: The concept of modified guanidines as chiral auxiliaries in asymmetric synthesis is quite simple as illustrated in Scheme 5, in which guanidines **5** could be converted to reactive, but resonance-stabilized, guanidinium salts **23** by quarternization with a reagent (A-B). The key intermediate **23** may react with activated unsaturated substrates (C = D), such as in a Michael reaction, trimethylsilyl (TMS) cyanation, or nucleophilic epoxidation, to give addition products **24**, in which **5** should act as catalyst (route A in Scheme 5).

On the other hand, the guanidinium salts **23** could be used for kinetic resolution of racemic secondary (*sec*) alcohols (E-OH), in which **23** act as either an electrophile or a nucleophile, such as in silylation or in azidation, to give hydrogen-substituted products (EO-A) **25** (route B in Scheme 5) or OH-substituted products (E-B) **26** (route C in Scheme 5), respectively. In the former reactions protonated guandidines (**5**·HB) may be produced, whereas in the latter cases alternative ones (**5**·HOA) could be formed. Furthermore, racemic *sec*-alkyl halides may also be resolved by electrophilic displacement of **23** with acidic compounds such as carboxylic acids according to route B in Scheme 5 when alkyl halides are used for the guanidinium salt formation as A-B. In these substitution reactions guanidines **5** are needed in stoichiometric amount.

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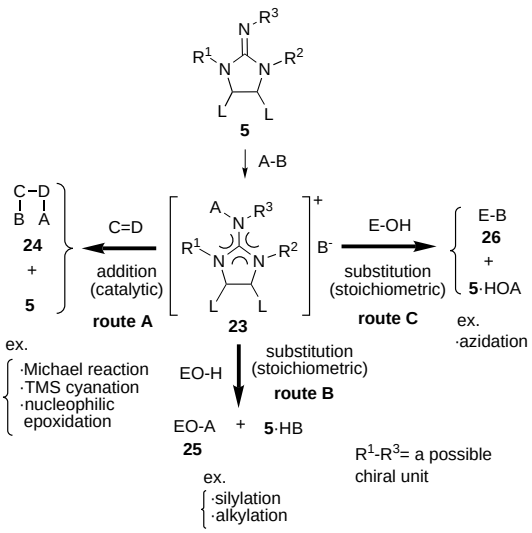
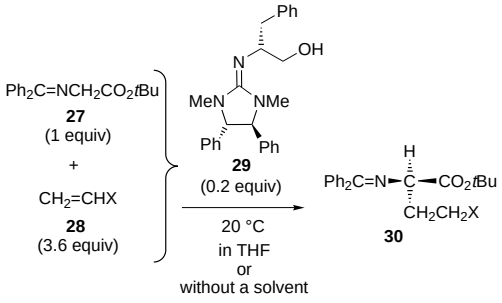


Scheme 5. Concept of modified guanidines **5** as chiral auxiliaries in asymmetric synthesis. ex.: example.

Application to catalytic reactions

Michael reactions: According to our concept as shown in route A in Scheme 5 we first tried the guanidine-catalyzed Michael reaction between diphenyliminoglycinate **27** and reactive vinyl compounds **28** leading to an amino acid synthesis[11] (see Scheme in Table 1). After preliminary examinations using a catalytic amount (20 mol%) of several guanidines, (4*S*,5*S*)-1,3-dimethyl-4,5-diphenyl-2-[(*R*)-1-hydroxymethyl-2-phenylethylimino]imidazolidine (**29**), belonging to the monocyclic guanidine **8** [L = Ph, R^1 = Me, R^2 = (*R*)-$CH(CH_2OH)CH_2Ph$] (see Scheme 1), was found to be the most effective catalyst in this Michael reaction.[12] Especially when using ethyl acrylate (**28a**) as a Michael acceptor, an excess amount of the (*R*)-adduct **30a** was quantitatively obtained with 97% *ee* when the reaction was carried out without a solvent (entry 4); however, a less effective reaction (79% *ee* in 15% yield) was observed in a THF solution (entry 1). Interestingly, replacement of **28a** to methyl vinyl ketone (**28b**) led to opposite results (entries 2 and 5). Thus, higher asymmetric induction (96% *ee*) was obtained in the THF solution even with longer reaction time (90% yield after six days). In general, remarkable rate-acceleration was observed in reactions without any solvents (entries 4–6). We have proposed a possible transition state[13] for these guanidine-participated Michael reactions giving excess (*R*)-adducts as shown in Figure 3.

Table 1. Guanidine-catalyzed Michael reaction of the diphenyliminoglycinate **27**.



Entry	THF	**28** (X)	*t*	Yield[a] [%]	**30** *ee* [%]	Conf.[b]
1	+	**a**: CO_2Et	7 d	15	79	*R*
2	+	**b**: COMe	6 d	90	96	(*R*)
3	+	**c**: CN	5 d	NR[c]	–	–
4	–	**a**: CO_2Et	3 d	85 (100)	97	*R*
5	–	**b**: COMe	15 h	90 (100)	80	(*R*)
6	–	**c**: CN	5 d	79 (100)	55	(*R*)

[a] Isolated, non-optimized yields. Values in parentheses show product yield estimates determined from ^1H NMR spectra. [b] Configuration of an excess enantiomer. Parentheses indicate the expected absolute configuration. [c] NR: No reaction.

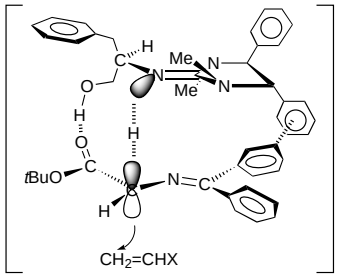
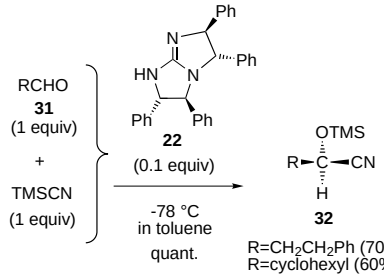


Figure 3. Proposed transition state for the Michael reaction of **27** with **28** catalyzed by **29**.

The modified guanidine **29** was also found to catalyze another Michael reaction[14] between dibenzyl malonate and cyclopentenone, in which an excess of the (*R*)-adduct was obtained in 38% yield with 43% *ee* when the reaction was carried out in chloroform under reflux for twelve days[15] (data not shown).

TMS cyanation: It has been reported that the reaction of carbonyl compounds with TMSCN is catalyzed by amines[16] to afford addition products. Application of modified guanidines to this TMS cyanation reaction using aldehydic compounds indicates that a C_2-symmetrical bicyclic guanidine **22** (see Scheme 4) was found to be the most effective catalyst[17] (Scheme 6). Thus, treatment of **31** with TMSCN in toluene at

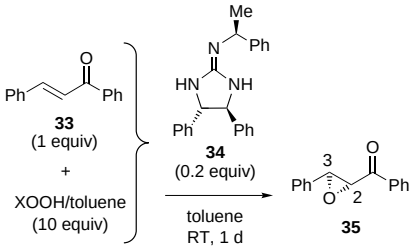


Scheme 6. Guanidine-catalyzed TMS cyanation of aliphatic aldehydes **31**.

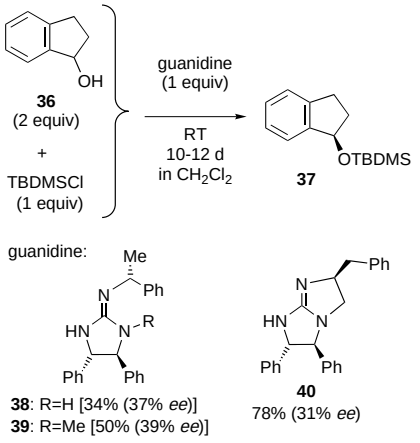
−78 °C in the presence of 10 mol% of **22** resulted in the quantitative formation of an excess of the (*R*)-adduct **32** with good enantioselectivity; however, the use of ketone instead of an aldehyde caused both lower chemical yield and *ee* (data not shown).

Nucleophilic epoxidation: Effective asymmetric epoxidation was observed when chalcone **33** was treated with a combination of DBU and urea hydroperoxide in the presence of poly-L-leucine (Julia – Colonna condition).[18] In our experiments for guanidine-catalyzed epoxidation with a hydroperoxide, (4*S*,5*S*)-4,5-diphenyl-2-[(*S*)-1-phenylethylimino]imidazolidine (**34**), belonging to the monocyclic guanidine **13** [L = (*S*)-Ph, R^1 = (*S*)-CH(Me)Ph] (see Scheme 2), was found to be an effective catalyst[19] (Table 2). Thus, treatment of **33** with *tert*-butylhydroperoxide in toluene in the presence of 20 mol % of **34** at room temperature for one day gave a (2*R*,3*S*)-epoxide **35** in 34 % yield with 49 % *ee*. As expected, higher asymmetric induction was observed when a more bulky cumene hydroperoxide was used as the oxidant at room temperature. The reaction under reflux caused rate acceleration, but lower selectivity.

Table 2. Guanidine-catalyzed epoxidation of chalcone **33** with hydroperoxides.



XOOH (X)	*T*	**35** Yield [%]	*ee* [%]
*t*Bu	RT	34	49
$PhC(Me)_2$	RT	52	64
	reflux	82	53



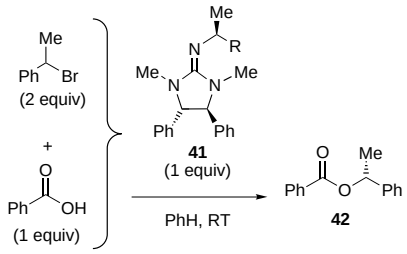
Scheme 7. Guanidine-mediated silylation of (±)-1-indanol **36**.

Application to stoichiometric reactions (kinetic resolutions): Although racemic compounds could be theoretically resolved by several methods, successful kinetic resolution with chemical means is limited to only esterification of *sec*-alcohols,[20] as far as we know. We tried kinetic resolutions of *sec*-alcohols by silylation[21] and *sec*-alkyl halides by alkylative esterification[22] according to our concept shown in route B in Scheme 5, in which key guanidinium salts **23** could be used as an electrophile.

In addition, we examined an alternative kinetic resolution of *sec*-alcohols by azidation[23] according to our concept shown in route C in Scheme 5, in which **23** could be used as a nucleophile.

Silylation: In the reaction[21] using cyclic alcohols such as (±)-1-indanol (**36**) and *tert*-butyldimethylsilyl chloride (TBDMSCl) moderate kinetic resolution (31 – 39 % *ee*) was observed in the silylated product **37** when the diastereomer **38** of a 1,3-unsubstituted guanidine used in epoxidation (see Table 2) and its 1-methyl derivative **39**, belonging to the monocyclic guanidine **14** [L = (*S*)-Ph, R^1 = (*R*)–CH(Me)Ph] (see Scheme 2), or (3*S*,7*S*,8*S*)-3-benzyl-7,8-diphenyl-1,4,6-triazabicyclo[3.3.0]oct-4-ene (**40**), belonging to the bicyclic guanidine **18** [R^1 = (*S*)-CH_2Ph, R^2 = H] (see Scheme 3), were used as auxiliaries (Scheme 7). The use of a more bulky triisopropylsilyl chloride as a silylating agent effected on increase of the *ee* up to ≈70 % (data not shown).

Alkylative esterification: In the alkylative esterification[22] using (±)-1-phenylethyl bromide and benzoic acid in benzene (4*S*,5*S*)-1,3-dimethyl-4,5-diphenylimidazolidine (**41a**) with a 2-[(*S*)-1-phenylethylimino] function, belonging to the monocyclic guanidine **8** [L = Ph, R^1 = Me, R^2 = (*S*)-CH(Me)Ph] (see Scheme 1), afforded an (*R*)-excess ester **42** in 96 % yield with 15 % *ee* (Scheme 8). The results could not be improved even by replacement of a phenyl group in the 2-phenylethyl residue with a more bulky 1-naphthyl group as in **41b**.



Scheme 8. Guanidine-mediated kinetic resolution of (±)-1-phenylethyl bromide by alkylative esterification with benzoic acid.

Azidation: Treatment of **36** with diphenylphosphoryl azide (DPPA) in dichloromethane at room temperature for six days in the presence of a C_2-symmetric bicyclic guanidine **22** or a related (3*S*,7*S*,8*S*)-3,7,8-triphenyl-1,4,6-triazabicyclo[3.3.0]oct-4-ene (**43**), belonging to the bicyclic guanidine **18** [R^1 = (*S*)-Ph, R^2 = H] (see Scheme 3), gave an (*R*)-excess 1-azidoindan (**44**) in ca 60 % yield with about 30 % *ee*[23] (Scheme 9).

Conclusion

In summary, experiments with our concept of modified guanidines as potential chiral auxiliaries led to reasonable asymmetric induction in both catalytic and stoichiometric

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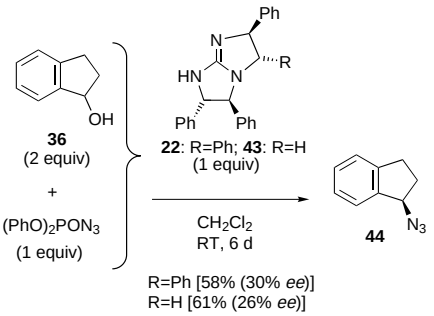

Scheme 9. Guanidine-mediated azidation of (±)-1-indanol **36**.

asymmetric syntheses. The effectivity is found to be greatly dependent upon the structural characteristics of the modified guanidines used. It is noteworthy that excellent selectivity (>96% *ee*) was observed in Michael reaction of a prochiral glycine derivative with vinyl compounds either with or without a solvent under simple and mild conditions. Furthermore, silylation, alkylative esterification, and azidation examined here are nominated as the first successful examples of kinetic resolutions using these reactions, albeit with moderate effectivity.

The modified guanidines used can be easily recovered in reuseable form from the reaction mixture by chromatographic separation. Therefore, although the separation method should be modified to non-chromatographic technique, these guanidine-mediated asymmetric syntheses could contribute to development of green chemistry,[24] because of their possible roles as reuseable (economically favored) and easily functionalizable (widely applicable) auxiliaries. Approaches to the mechanistic rationale, kinetics, and optimization of these guanidine-mediated asymmetric synthesis are at present under study in our laboratory.

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[13] The referee suggested the possible formation of an ion pair between an enolate and a guanidinium ion by substraction of an acidic hydrogen of **27** with **29** and an alternative transition state dependent upon the ion pair, in which two hydrogen-bond donating centers (OH and NH^+) in the resulting guanidinium ion could form hydrogen bonds to the partially negative oxygens of the enolate and a Michael substrate **28**. The transition state suggested is attractive with respect to the energy level, however, it is difficult to explain the (*R*) enantioselectivity in the adduct **30**. Thus, we propose a fixed complex of **27** and **29** formed through non-bond interactions shown in Figure 3 as a more possible transition state, even with higher energy level. Approaches to rationale for the transition state using spectroscopic means are currently under investigation. We thank the referee for useful comments on the transition state.

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