Stereoselective synthesis of cycloalkylamines from unsaturated imines by (η^2-propene)Ti(OPr^i)$_2$-promoted bicyclization

Yuan Gao, Kousuke Harada and Fumie Sato*

Department of Biomolecular Engineering, Tokyo Institute of Technology, 4259 Nagatsuta-cho, Midori-ku, Yokohama, Kanagawa 226, Japan

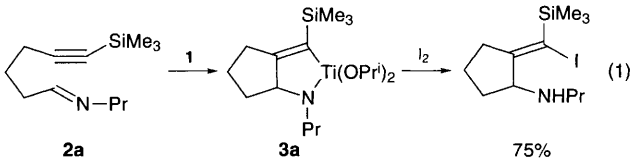
Treatment of unsaturated imines and hydrazones with (η^2-propene)Ti(OPr^i)$_2$ induces bicyclization in excellent yields, providing an efficient preparation of cycloalkylamines, including optically active ones.

Conversion of dienes, enynes and diynes into the corresponding metallacycles followed by their conversion into bicyclic or monocyclic organic compounds has been widely accepted as synthetically useful methodology.[1] Metal-induced bicyclization reactions of substrates which contain both carbon–carbon multiple bonds and unsaturated carbon–heteroatom linkages have also attracted much interest. These reactions include (η^5-C_5H_5)$_2$Ti(PMe$_3$)$_2$-induced bicyclization of unsaturated carbonyl compounds[2] and imines,† (η^5-C_5H_5)$_2$ZrBu$_2$-promoted intramolecular cocyclization of unsaturated hydrazones and aromatic aldimines,[3] and $WCl_2(PMePh_2)_2$-mediated intramolecular coupling of enones.[4]

We have recently reported that the reaction of Ti(OPr^i)$_4$ with 2 equiv. of Pr^{i}MgCl affords (η^2-propene)Ti(OPr^i)$_2$ **1**, a synthetically versatile Ti^{II}-equivalent,[5] and also the compound **1** mediated the bicyclization of dienes, enynes and diynes to furnish the corresponding titanabicycles.[5d] We also found that treatment of **1** with alkynes quantitatively afforded titanium–alkyne complexes which in turn reacted with carbonyl compounds[5b] and imines[5e] to furnish the corresponding addition products in excellent yields. We have now found that the bicyclization of unsaturated imines **2** is readily promoted by **1**, Scheme 1, thus providing an efficient synthetic preparation of cycloalkylamines, including optically active ones.

A series of unsaturated imines **2a–d** were subjected to bicyclization in the presence of **1** to afford the corresponding cycloalkylamines **4a–d** in excellent yields after hydrolysis followed by chromatographic purification (Table 1).‡ The bicyclization of unsaturated hydrazone **2e** proceeded similarly (entry 5).

The results summarized in Table 1 clearly demonstrate the synthetic generality and operational simplicity of this annulation method. Thus, both olefinic and acetylenic imines and hydrazones gave the cyclized products in good to excellent yields. The iodinolysis of the reaction product of **2a** and **1** shown in eqn. (1) not only indicates the formation of the

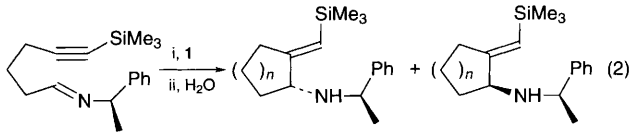


2a **3a** 75% (1)

titanacycle in the present reaction but also the synthetic usefulness of the reaction.

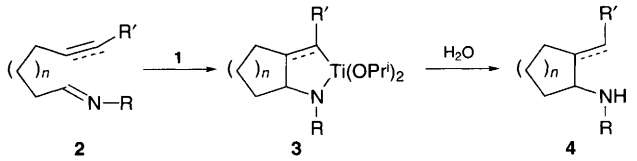
The present bicyclization reaction is highly practical because the starting materials, Ti(OPr^i)$_4$ and Pr^{i}MgCl, are inexpensive and available in bulk in comparison with (η-$^5C_5H_5$)$_2$Ti(PMe$_3$)$_2$ and (η^5-C_5H_5)$_2$ZrBu$_2$ which, as mentioned above, have been used previously for this type of reaction. We therefore directed our efforts to utilize chiral imines in enantioselective bicyclization as it might provide an efficient and practical route to chiral cycloalkylamines.

Chiral imines **2f** and **2g** were synthesized from the corresponding unsaturated aldehydes and (*R*)-(+)-1-phenylethylamine, and then treated with compound **1**. As shown in eqn. (2),



2f $n = 1$ (94% yield) (*R*)-**4f** 91 : 9 (*S*)-**4f**
g $n = 2$ (92% yield) (*R*)-**4g** 68 : 32 (*S*)-**4g**

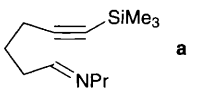
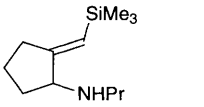
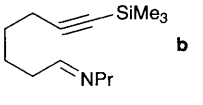
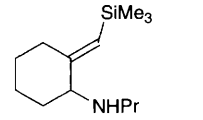
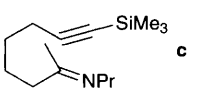
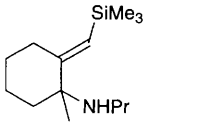
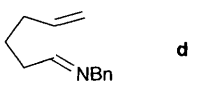
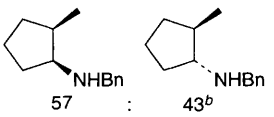
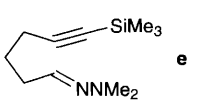
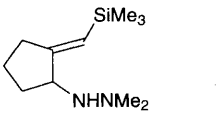
the degree of chiral induction (determined by ^{1}H NMR analysis) was high for **2f** and moderate for **2g**. The absolute configuration of the newly created asymmetric carbons in the major



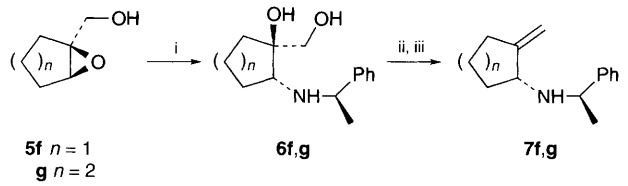
2 **3** **4**

Scheme 1

Table 1 Conversion of the unsaturated imines to cycloalkylamines[a]

Entry	Unsaturated imine 2		Product 4	Isolated yield(%)
1		a		80
2		b		91
3		c		68
4		d	 57 : 43[b]	78
5		e		92

[a] The reaction was carried out in Et_2O at −78–−30 °C over 2 h with **2** : Ti(OPr^i)$_4$: Pr^{i}MgCl = 0.8 : 1 : 2. [b] Determined by ^{1}H NMR.



Scheme 2 *Reagents and conditions*: i, (*R*)-(+)-1-phenylethylamine/$Ti(OPr^i)_4$, room temp.; ii, $NaIO_4$; iii, $CH_2I_2/Zn/TiCl_4$

diastereoisomers of both **4f** and **4g** was determined to be *R* by comparing their protodesilylated products **7** with authentic samples synthesized according to the procedure shown in Scheme 2. Thus **7f** and **7g** were synthesized from the corresponding optically active epoxy alcohols **5**§ by regioselective epoxide ring opening,[7] oxidative cleavage of the resultant diols **6** to ketones and then a carbonyl methylenation reaction.[8] The ^1H and ^{13}C NMR spectra of **7f** and **7g** were coincident with those of the corresponding **7** obtained from the major isomers of **4f** and **4g** after protodesilylation.[9]

Footnotes

† One example of $(\eta^5\text{-}C_5H_5)_2Ti(PMe_3)_2$-induced bicyclization of an olefinic imine was recently reported.[2c]

‡ *Typical experimental procedure*: To a stirred solution of $Ti(OPr^i)_4$ (0.498 g, 1.75 mmol) and unsaturated imine **2a** (0.293 g, 1.40 mmol) in ether (9 ml) was added a 1.02 mol dm^{-3} ethereal solution of Pr^iMgCl (3.43 ml, 3.50 mmol) at −78 °C. The resulting yellow homogeneous mixture was gradually warmed to −30 °C over 2 h and then quenched with water (1.5 ml), allowed to warm to room temp. and then filtered through a short pad of Celite. The filtrate was dried over $MgSO_4$ and concentrated *in vacuo* to give an oil. Purification by flash chromatography on silica gel afforded (*E*)-1-propylamino-2-trimethylsilylmethylenecyclopentane **4a** (0.237 g, 80% yield).

§ The epoxides **5f** and **5g** were obtained in >93% e.e. from 1-cyclopentenylmethanol and 1-cyclohexenylmethanol, respectively, by asymmetric epoxidation.[6]

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