A diastereoselective carbocyclisation of allene-hydrazones through the intramolecular allylic transfer reaction†

Sang-Hoon Kim, Seung-Ju Oh, Yurim Kim and Chan-Mo Yu*

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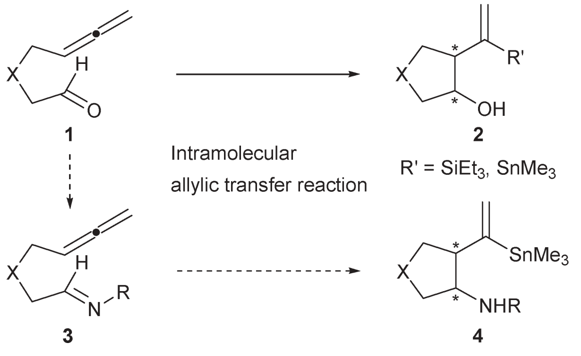
A diastereoselective synthesis of cyclic hydrazines was achieved from a carbocyclisation of allene-hydrazones by the Pd-catalyzed distannylation of an allene moiety, followed by the transmetallation of allylic stannane intermediates with $TiCl_4$.

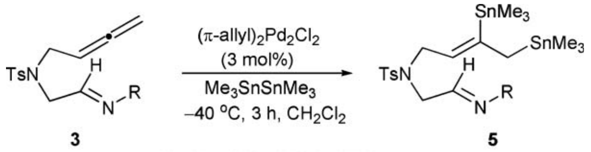
Among the variety of synthetic methods for the construction of cyclic compounds, reactions involving the use of transition metals offer some of the most attractive methodologies, since reactions can directly construct complicated molecules from relatively simple starting materials.[1] As a consequence, many advances in cyclisations mediated by transition metals have been made through a variety of synthetic strategies.[2] In this regard, allenes have proved to be useful substrates for a variety of transition metal catalytic reactions, particularly for cyclisations in the construction of carbo- and heterocycles.[3] For example, the transition metal-catalysed cyclisation of an allene-aldehyde has emerged as a highly convergent method for the stereoselective synthesis of cyclic alkenols. Many advances relating to this methodology have been reported.[4]

Recently, we disclosed our discoveries of cyclisation methods for the synthesis of **2** from allene-carbonyl functionalities **1** by using transition metals, as shown in Scheme 1,[5] as part of an allylic transfer strategy using allenes as substrates or intermediates.[6] The characteristic features of this protocol, in terms of the chemical efficiency of the three component coupling process and the structural features of the products, have encouraged us to carry out further investigations to introduce other functionalities, which would expand the scope and utility of this reaction. As a consequence, we became interested in the practical and convenient synthesis of **4** by the three-component assembly of allene-imine **3** with a stannyl group through an intramolecular allylic transfer reaction, as illustrated in Scheme 1. There have been a variety of reports regarding nucleophilic addition reactions to imines to produce amines in the literature.[7] However, the lack of data concerning cyclisations between imines and unsaturated bonds involving the use of transition metal catalysts or reagents surprised us,[8] in view of the expected similarity of such systems to the well-defined cycloisomerisation reactions with aldehydes.[9] Recently, Grigg and co-workers reported an intramolecular allylic transfer reaction of allene-sulfinimines with aryl iodides involving the use of Pd/In.[10] We wish to report our discovery of a remarkable substrate effect by the introduction of the hydrazone functionality for the conversion of **3** to **4**, which allows the reaction process to complete in good yield and with excellent diastereoselectivity.



Scheme 1 Our general synthetic route.

With this issue in mind, several allene-imine, -oxime and -hydrazones were prepared, as shown in eqn. (1). Initial attempts to cyclize **3** with $Me_3SnSnMe_3$ in the presence of $(\pi\text{-allyl})_2Pd_2Cl_2$ (3 mol%) at −40 °C for 3 h in CH_2Cl_2 (similar conditions to those mainly employed for the carbocyclisation of allene-aldehydes[5a]) indicated that the conversion to the corresponding lactam **4** could not be realized, mainly due to a lack of reactivity for the cyclisation. Reactions always produced the distannylated **5** with good conversions in all cases.[11]

 (1)

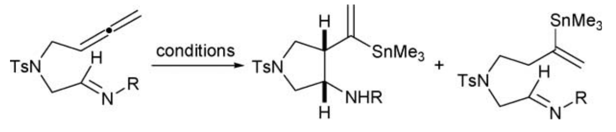
R = Bn, OMe, NPhth, NHBz

We subsequently speculated that the utilization of an additional Lewis acid might be needed to enhance reactivity. However, the introduction of various Lewis acids to the allene-imine and -oxime turned out to be unpromising. Fortunately, we found that allene-hydrazones could be converted to **4** under Lewis acidic conditions. As a starting point, allene-hydrazones **6a** and **9a** (Table 1) were selected as model substrates. Attempted cyclisation reactions of **6a** and **9a** indicated that their conversion to the corresponding **7a** and **10a** could not be satisfied with many Lewis acids, including $Sn(OTf)_2$, $AlMe_3$, $Al(NTf_2)_3$ and Me_3SiOTf, under various reaction conditions. We could not observe any notable effect of Lewis acids on the promotion of the cyclization process. Fortunately, we found that $BF_3{\cdot}OEt_2$ could be an effective Lewis acid for this purpose. Initial experiments on the distannylation of **6a** under the same conditions as those described in eqn. (1), followed by intramolecular allylic transfer with $BF_3{\cdot}OEt_2$

BK-21 School of Chemical Materials Science and Department of Chemistry, Sungkyunkwan University, Suwon 440-746, Korea. E-mail: cmyu@chem.skku.ac.kr; Fax: +82 31 290 7075; Tel: +82 31 290 7067

† Electronic supplementary information (ESI) available: Experimental procedures, characterization data and NMR spectra for all products. See DOI: 10.1039/b712856h

Table 1 Selected preliminary investigations



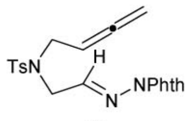
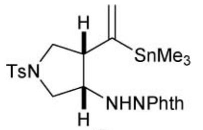
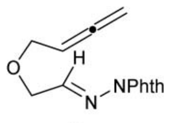
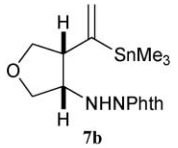
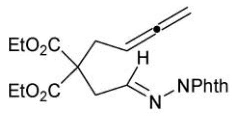
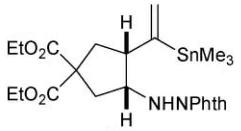
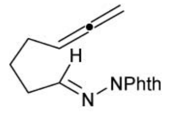
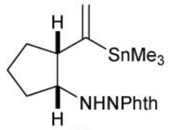
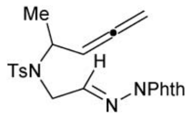
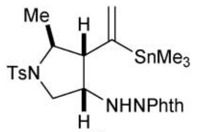
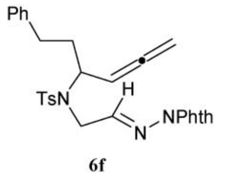
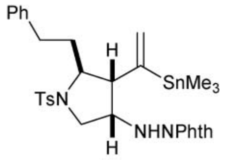
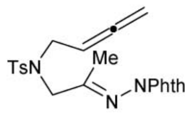
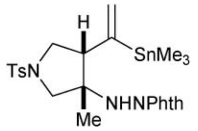
6a R = NPhth **7a** **8a**
9a R = NHBz **10a** **11a**

conditions: i) (π-allyl)$_2$Pd$_2$Cl$_2$ (3 mol%), Me$_3$SnSnMe$_3$, −40 °C, 3 h, CH$_2$Cl$_2$
ii) Lewis acid, −78 °C, t/h

Entry	6/9	Lewis acid[a]	*t*/h	*cis* : *trans*[b]	Ratio[b,c]	Yield (%)[d]
1	**6a**	BF$_3$·OEt$_2$	12	78 : 22	>95 : 5	33
2	**9a**	BF$_3$·OEt$_2$	12	71 : 29	>95 : 5	23
3	**6a**	SnCl$_4$	10	**7** only	80 : 20	54
4	**9a**	SnCl$_4$	10	**10** only	34 : 66	24
5	**6a**	TiCl$_4$	2	**7** only	>98 : 2	83
6	**9a**	TiCl$_4$	2	>95 : 5	37 : 63	27
7	**6a**	Ti(O*i*Pr)$_2$Cl$_2$	10	**7** only	71 : 29	41
8	**9a**	Ti(O*i*Pr)$_2$Cl$_2$	10	**10** only	35 : 65	22
9	**6a**	TiBr$_4$	5	**7** only	92 : 8	67
10	**9a**	TiBr$_4$	5	**10** only	29 : 71	23

[a] 1.1 equivalents. [b] *cis* : *trans* ratios (**7** : **10**) were determined by ^{1}H NMR spectroscopy of the crude products. [c] Ratios of **7** : **8** or **10** : **11**. [d] Isolated yields of **7** or **10** after chromatography.

Table 2 Intramolecular allylic transfer reactions of **6**

Entry	Allene-hydrazone (**6**)	Product (**7**)	Yield (%)[a]
1	 **6a**	 **7a**	83
2	 **6b**	 **7b**	61
3	 **6c**	 **7c**	68
4	 **6d**	 **7d**	63
5	 **6e**	 **7e**	75
6	 **6f**	 **7f**	77
7	 **6g**	 **7g**	67

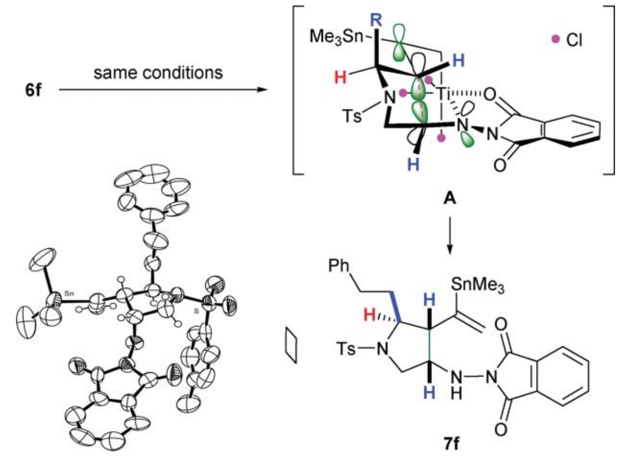
[a] In reference to the isolated product.

(1.1 equiv.) at −78 °C for 12 h in CH$_2$Cl$_2$, afforded encouraging but marginal results. Although **7a** and **10a** were produced during the reactions, moderate diastereoselectivities (**7a**, dr = 78 : 22; **10a**, dr = 71 : 29) and low chemical yields (**7a**, 33%; **10a**, 23%) remained problems to be solved. After surveying numerous conditions with a variety of Lewis acids, we were delighted to find that TiCl$_4$ was a suitable Lewis acid in terms of diastereoselectivity and chemical conversion, as shown in Table 1.

During the orienting experiments, several key findings emerged as follows: (1) the use of TiCl$_4$ proved to be most effective Lewis acid for the intramolecular allylic transfer; (2) 1.1 equivalents of TiCl$_4$ were required for the optimal conditions in terms of chemical yields and reaction rates; (3) reactions performed at −78 °C in CH$_2$Cl$_2$ resulted in the best chemical yields in comparison with other solvents, such as toluene and CH$_3$CH$_2$CN; (4) the phthaloylhydrazone **6a** proved to be a more suitable substrate than the benzoylhydrazone **9a** for this transformation; (5) the reaction also produced destannylated products **8a** or **11a**, along with unidentified base line impurities, especially for **9a**. Under optimal conditions, the reaction was conducted by the dropwise addition of a mixture of **6a** (1 equiv.) and Me$_3$SnSnMe$_3$ (1.1 equiv.) in CH$_2$Cl$_2$ for 20 min to a solution of (π-allyl)$_2$Pd$_2$Cl$_2$ (3 mol%) at −40 °C in CH$_2$Cl$_2$. After 3 h at −40 °C, the reaction mixture was cooled to −78 °C. To this solution, pre-cooled TiCl$_4$ (1.1 equiv.) at −78 °C in CH$_2$Cl$_2$ was added in one portion using a cannula. After 2 h at −78 °C, the reaction was quenched by the addition of saturated aqueous NaHCO$_3$, and then worked up and chromatographed on silica gel to afford **7a** in 83% yield in a diastereomerically pure form.

With the notion that this approach might lead to a general and efficient method for the synthesis of **7**, we set out to determine the scope for producing various structurally related products. Indeed, the method was successful with **6b–f**, yielding the cyclic products **7b–f**, respectively, as single diastereomers in moderate to high yields, as can be seen in Table 2. Relative stereomerical relationships for **7a** and **7g** were proved by NOE experiments, and also by the X-ray crystallographic analysis of **7f** (the ORTEP drawing of *ent*-**7f** with 50% probability thermal ellipsoids is shown in Scheme 2‡). We also observed that the internal chirality transfer of substituted **1d** and **1e** turned out to be excellent. It is worthy of note that the reaction produced none or only trace amounts of the destannylated products (less than 2%), except for **6b** (9% isolated; Table 2, entry 2), according to the ^{1}H NMR spectra of the crude products. Unfortunately, the extension of this method to the synthesis of 6-membered rings turned out to be unpromising.

Although the exact mechanistic aspects of this transformation have not been rigorously elucidated, Scheme 2 could illustrate a possible stereochemical route for the remote stereocontrol and diastereoselectivity of the products. From a mechanistic perspective, the two major functions that determine the



Scheme 2 A plausible stereochemical route, and the ORTEP structure of **7f**.

stereoselectivity are immediately discernable in the reaction process: transmetallation and chelation effects. After the distannylation of an allene functionality, the allylic stannane moiety must be transmetallated by $TiCl_4$ to the allylic titanium reagent,[12] and then subsequently undergo an intramolecular addition of the latter to the hydrazone. We reasoned that if model **A**, assembled from the allylic titanium species, was an intermediate on the reaction pathway, then it might be possible to describe the remote stereocontrol by the existing R-group, as well as the *cis*-selectivity during the cyclisation. The products obtained can be accounted-for by the intervention of the pseudopericyclic stereochemical model **A**, with minimal steric interactions and optimal orbital interactions that lead to the major reaction pathway illustrated in Scheme 2. The enhanced reactivity offered by the phthaloylhydrazone functionality, compared to the others, could be explained by assuming that the tight chelation to the allylic titanium by the phthaloylhydrazone group in a hexacoordinate array could result in the extent of LUMO energy decreasing as well as HOMO energy increasing, similar to the Lewis base-catalyzed carbonyl addition.[13]

In summary, this Communication describes a carbocyclisation of allene-hydrazones **6** to **7** through the intramolecular allylic transfer reaction, which promises to become synthetically useful. This transformation involves the distannylation of an allene by a palladium catalyst, the transmetallation of the allylstannyl moiety to a titanium species and subsequently the intramolecular allylic transfer reaction with the hydrazone. Further studies, including synthetic applications and the extension of this method to enantiomeric pathways, are in progress.

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Notes and references

‡ *Crystal data for* **7f**: $C_{32}H_{37}N_3O_4SSn$, $M = 678.40$, orthorhombic, space group *Pbca*, $a = 21.858(5)$, $b = 12.108(3)$, $c = 24.590(4)$ Å, $V = 6508(2)$ Å^3, $Z = 8$, $D_{\text{calc}} = 1.385$ Mg m^{-3}, $\mu_{\text{Mo-K}\alpha} = 0.888$ mm^{-1}, $T = 293(2)$ K. 5734 reflections were collected and used in the refinement. w$R2/R1 = 0.1749/0.0916$ ($I > 2\sigma$) and 0.2509/0.2761 (all data). CCDC 656121. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b712856h

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