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Titanium(IV) Chloride-Mediated Carbocyclization of 1,6-Enynes: Selective Synthesis of 3-Azabicyclo[3.1.0]hexanes and Functionalized Allenes by Controlling the Reaction Temperature

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Keywords: Cyclization / Carbocycles / Carbocyclization / Enynes / Allenes / Titanium

1,6-Enynes can be transformed into 3-azabicyclo[3.1.0]hexanes and functionalized allenes in moderate to good yields along with moderate to high diastereoselectivities by controlling the reaction temperature in the presence of titanium(IV) chloride. A plausible mechanism is proposed.

Introduction

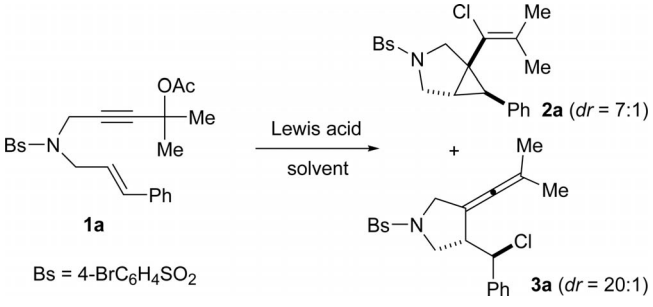
Carbocyclization of 1,6-enynes is a powerful method in organic synthesis to access five or six-membered rings and has drawn increasing attention. One of the most interesting aspects in this field is the construction of nitrogen-containing heterocyclic compounds which are important structural motifs found in many natural and pharmaceutical materials. Although a variety of transition metals, such as gold,[1] platinum,[2] palladium,[3] ruthenium,[4] rhodium,[5] iridium,[6] and mercury,[7] have been examined for their catalytic abilities in this reaction, finding new types of cyclization of enyne derivatives is still highly desirable due to the synthetic diversity of these reactions.[6a]

$TiCl_4$ has been widely used in many carbon–carbon bond-forming reactions,[8] to the best of our knowledge, no investigation of cyclization of enynes has been carried out using $TiCl_4$ as a promoter. Thus far, $TiCl_4$-catalyzed or mediated carbon–carbon bond forming reactions with alkynes include the additions of propargylsilanes or silylacetylenes to carbonyl compounds;[9] unactivated alkynes to aldehydes,[8a,8b] expoxides,[8f,8g] and α-aryl-substituted carbonyl compounds.[8h] Only one notable example is the $TiCl_4$–Et_3N-mediated intramolecular carbocyclization of active methine compounds with unactivated alkyne groups.[10] Herein, we wish to report a novel carbocyclization of 1,6-enynes in which easily available and inexpensive metal halides can serve as effective mediates to achieve the selective synthesis of 3-azabicyclo[3.1.0]hexanes and functionalized allenes by controlling the reaction temperature. These 3-azabicyclo[3.1.0]hexanes are core structures of a variety of biologically active natural products[11] and the examples of direct transformation of enynes into allenes accompanied with ring formation are rare.[12]

Results and Discussion

Initially, we tested the carbocyclization of enyne **1a** using various Lewis acids such as $BiCl_3$, $TiCl_4$, BCl_3 and $TiBr_4$ (see the Supporting Information for the details). We found that only $TiCl_4$ gave good results, affording **2a** in 73% yield within 20 min at room temperature (25 °C) (Table 1, entry 4). Further optimization of the reaction conditions re-

Table 1. Optimization of the reaction conditions.[a]



Entry	Lewis acid [equiv.]	Solvent	T [°C]	t [min]	Yield [%][b] **2a**	**3a**
1	$TiCl_4$ (1.40)	toluene	r.t.	20	39	–
2	$TiCl_4$ (1.40)	CH_2Cl_2	r.t.	20	42	–
3	$TiCl_4$ (1.40)	$ClCH_2CH_2Cl$	r.t.	20	69	–
4	$TiCl_4$ (1.70)	$ClCH_2CH_2Cl$	r.t.	20	73	–
5	$TiCl_4$ (2.00)	$ClCH_2CH_2Cl$	r.t.	20	67	–
6	$TiCl_4$ (1.70)	$ClCH_2CH_2Cl$	–15	30	13	52
7	$TiCl_4$ (1.05)	$ClCH_2CH_2Cl$	–20	120	–	67
8	$TiCl_4$ (1.70)	$ClCH_2CH_2Cl$	–20	30	–	69

[a] [substrate] = 0.10 M. [b] Isolated yield.

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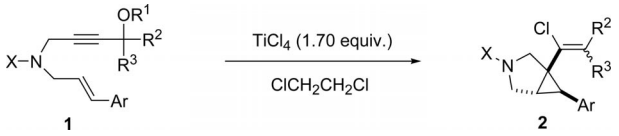
Table 2. $TiCl_4$-mediated synthesis of 3-azabicyclo[3.1.0]hexanes **2** from 1,6-enynes **1**.[a]



Entry	**1**	X	Ar	R^1	R^2/R^3	*T* [°C]	Yield [%][b]	*dr*[c] (*anti*/*syn*)
1	**1b**	Ts	Ph	Ac	Me/Me	room temp.	**2b**, 65	8:1
2	**1c**	Ts	Ph	Ac	Et/Et	room temp.	**2c**, 72	6:1
3	**1d**	Ts	Ph	Ac	*i*Pr/*i*Pr	reflux	**2d**, –	–
4	**1e**	Ts	Ph	Ac	*n*Bu/*n*Bu	room temp.	**2e**, 58	9:1
5	**1f**	Ts	Ph	Ac	$–CH_2(CH_2)_2CH_2–$	room temp.	**2f**, 70	47:1
6	**1g**	Ts	Ph	Ac	$–CH_2(CH_2)_3CH_2–$	room temp.	**2g**, 77	22:1
7	**1g**	Ts	Ph	Ac	$–CH_2(CH_2)_3CH_2–$	–20	**2g**, 54	36:1
8	**1h**	Bs	Ph	Ac	$–CH_2(CH_2)_3CH_2–$	–20	**2h**, 61	11:1
9	**1h**	Bs	Ph	Ac	$–CH_2(CH_2)_3CH_2–$	–30	**2h**, 55	15:1
10	**1i**	Ts	Ph	Piv	Me/Me	room temp.	**2b**, 58	8:1
11	**1j**	Ts	Ph	Ac	*n*Pr/H	room temp.	**2j**, –	–
12	**1k**	Ts	Ph	Ac	Me/*n*Pr	room temp.	**2k**, 58	7:1
13	**1l**	Bs	Ph	Piv	$–CH_2(CH_2)_3CH_2–$	–30	**2h**, 76	22:1
14	**1q**	Ts	$pMeC_6H_4$	Ac	Et/Et	room temp.	**2q**, –[d]	–
15	**1r**	Ts	$pClC_6H_4$	Ac	Me/Me	room temp.	**2r**, 61	4:1

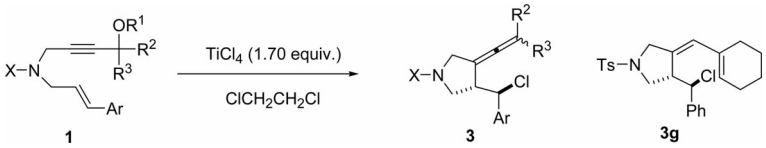
[a] [substrate] = 0.10 M. [b] Isolated yield. [c] Determined by ^1H NMR spectroscopic data. [d] **2q** could not be isolated in pure form.

vealed that decreasing the reaction temperature to –5 °C, allene **3a** was formed along with **2a** although it could not be separated from **2a** by silica gel column chromatography (Table 1, entry 6). However, it was found that **3a** could be obtained as the sole product in 69% yield at –20 °C after 30 min in the presence of 1.70 equiv. $TiCl_4$ (Table 1, entry 8). The configuration of *anti*-**2a** has been unequivocally assigned by X-ray diffraction and its X-ray crystal data are presented in the Supporting Information.[13]

With these optimized conditions in hand, we next investigated the tolerance of $TiCl_4$-mediated carbocyclization with various enynes **1b**–**1r** to construct the corresponding 3-azabicyclo[3.1.0]hexanes and the results are outlined in Table 2. As depicted in Table 2, all of the reactions proceeded smoothly to give the desired products **2b**, **2c** and **2e** in moderate yields at room temperature (25 °C) when R^2 and R^3 were methyl, ethyl or *n*-butyl group (Table 2, entries 1, 2 and 4). However, no formation of **2d** was observed even under reflux presumably due to the isopropyl group's steric hindrance (Table 2, entry 3). As for the cycloalkyl-substituted enynes **1f**–**1h**, products **2f**–**2h** were obtained in 54–77% yields along with excellent diastereoselectivities and it was found that these products could be given in better diastereoselectivities at lower temperature (Table 2, entries 6–9). For various propargylic esters **1i** and **1l** in which R^1 is a pivalyl group, the corresponding products **2b** and **2h** were obtained in 55% yield and 76% yield, respectively (Table 2, entries 10 and 13). Moreover, substrate **1j** in which R^3 was a hydrogen atom gave no reaction (Table 2, entry 11). Substrate **1k** with the different substitutions of R^2 and R^3 also gave the corresponding product **2k** in reasonable yield with moderate diastereoselectivity (7:1 mixture of major and minor diastereomers) (Table 2, entry 12). In the case of substrate **1q** having a methyl group on the benzene ring, the corresponding product **2q** could not be obtained as pure form (Table 2, entry 14). In contrast, substrate **1r** with a chlorine atom on the benzene ring gave the desired product **2r** in 61% yield (Table 2, entry 15).

To obtain allene derivatives **3**, the reaction should be conducted at lower temperature (–20 or –30 °C) and the results are shown in Table 3. For various alkyl groups substituted **1b**–**1e** as well as **1m** and **1n**, the corresponding allene derivatives **3b**–**3e**, **3m** and **3n** could be obtained in 60–85% yields along with excellent diastereoselectivities (8:1 to 26:1) at –20 °C (Table 3, entries 1–5, 11 and 12). In the case of substrate **1d**, product **3d** was obtained in 60% yield with moderate diastereoselectivity (4:1) even at room temperature without the formation of **2d**, perhaps due to the steric bulkiness of two isopropyl groups (Table 3, entry 4). As for substrate **1f** with a cyclopentyl group, **2f** was formed rather than the allene derivative **3f** (Table 3, entry 6). In the case of substrate **1g** with a cyclohexyl group, the product (*E*)-3-[chloro(phenyl)methyl]-4-(cyclohexenylmethylene)-1-tosylpyrrolidine (**3g**) was obtained in 68% yield without the formation of the corresponding allene derivative (Table 3, entry 7). For pivalate ester **1i**, the reaction also proceeded smoothly to give the corresponding allene derivative **3b** in 53% yield (Table 3, entry 8). Substrate **1j** in which R^3 was a hydrogen atom gave no reaction under the standard conditions (Table 3, entry 9). Substrate **1k** bearing different substitutions of R^2 and R^3 can be transformed to the corresponding product **3k** as isomeric mixtures (Table 3, entry 10). Notably, substrate **1o** having two cyclohexyl groups reacted efficiently in the presence of $TiCl_4$, giving the desired product **3o** in 91% yield (Table 3, entry 13). Substrates **1p** and **1q** having a methyl group and a chlorine atom on the benzene rings gave the corresponding products **3p** and **3q** in 88% yield and 50% yield along with moderate to excellent diastereoselectivities (4:1 and 12:1) (Table 3, entries 14 and 15). The *anti*-configuration of the major isomer

Table 3. $TiCl_4$-mediated synthesis of allenes **3** from 1,6-enynes **1**.[a]



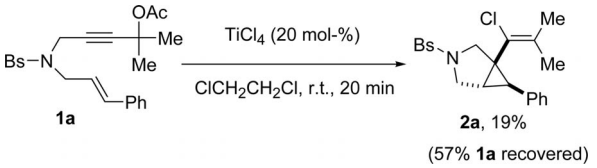
1 3 3g

Entry	1	X	Ar	R^1	R^2/R^3	*T* [°C]	Yield [%][b]	*dr*[c] (*anti*/*syn*)
1	**1b**	Ts	Ph	Ac	Me/Me	–20	**3b**, 62	12:1
2	**1c**	Ts	Ph	Ac	Et/Et	–20	**3c**, 80	8:1
3	**1d**	Ts	Ph	Ac	*i*Pr/*i*Pr	–20	**3d**, 69	11:1
4	**1d**	Ts	Ph	Ac	*i*Pr/*i*Pr	room temp.	**3d**, 60	4:1
5	**1e**	Ts	Ph	Ac	*n*Bu/*n*Bu	–20	**3e**, 75	26:1
6	**1f**	Ts	Ph	Ac	$–CH_2(CH_2)_2CH_2–$	–30	**3f**,–[d]	–
7	**1g**	Ts	Ph	Ac	$–CH_2(CH_2)_3CH_2–$	–30	**3g**, 68[e]	>99:1
8	**1i**	Ts	Ph	Piv	Me/Me	–20	**3b**, 53	6:1
9	**1j**	Ts	Ph	Ac	*n*Pr/H	–20	**3j**, –	–
10	**1k**	Ts	Ph	Ac	Me/*n*Pr	–20	**3k**, 61[f]	–
11	**1m**	Bs	Ph	Ac	Et/Et	–20	**3m**, 85	18:1
12	**1n**	Ts	Ph	Ac	*i*Bu/*i*Bu	–20	**3n**, 64	13:1
13	**1o**	Ts	Ph	Ac	Cy/Cy	–20	**3o**, 91	14:1
14	**1p**	Ts	$pClC_6H_4$	Ac	Et/Et	–20	**3p**, 88	12:1
15	**1q**	Ts	$pMeC_6H_4$	Ac	Et/Et	–25	**3q**, 50[g]	4:1

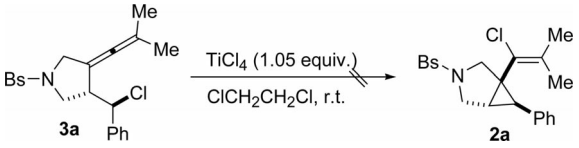
[a] [substrate] = 0.10 M. [b] Isolated yield. [c] Determined by ^1H NMR spectroscopic data. [d] See Table 2, entry 5. [e] The product is (*E*)-3-[chloro(phenyl)methyl]-4-(cyclohexenylmethylene)-1-tosylpyrrolidine. [f] The product's ^1H NMR spectrum is complex. [g] The reaction was carried out in CH_2Cl_2.

of **3p** has been unequivocally assigned by X-ray diffraction and its X-ray crystal data are presented in the Supporting Information.[13]

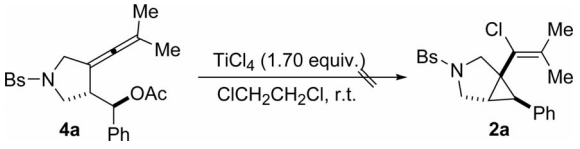
To gain more mechanistic insight into the carbocyclization of **1** into **2** and **3**, the control experiments have been performed using catalytic amount of $TiCl_4$ (20 mol-%) as the promoter and it was found that **2a** could be obtained in 19% yield along with recovery of **1a** in 57% yield [Equa-



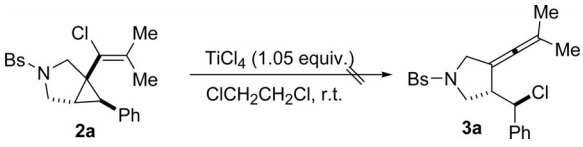
(1)



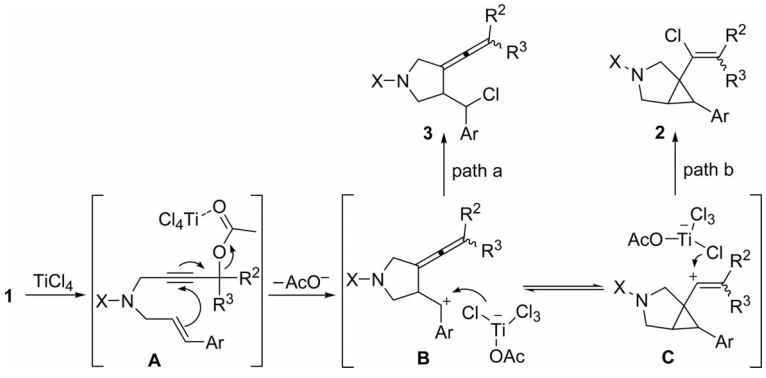
(3)



(2)



(4)



Scheme 1. Plausible $TiCl_4$-mediated carbocyclization mechanism.

tion (1)]. Compound **4a** which is derived from 1,5-acyloxy migration remained unchanged in the presence of $TiCl_4$ [Equation (2)].[12a] Moreover, compound **3a** could not be isomerized to **2a** upon treatment with 1.05 equiv. $TiCl_4$ at room temperature [Equation (3)].[14] Treatment of compound **2a** with $TiCl_4$ (1.05 equiv.) could also not afford allene **3a** under the standard conditions [Equation (4)].

Based on above studies, we proposed a mechanism for the $TiCl_4$-mediated carbocyclization in Scheme 1.[15] Coordination of the ester group to $TiCl_4$ gives intermediate **A**. The nucleophilic intramolecular addition of the pendant olefin to the alkyne along with acyloxy group leaving affords carbocation **B**, which contains a vinylidene moiety.[12a] At low temperature, the chloride ion from the metal is transferred to incipient benzylic carbocation to produce chlorinated allene **3** (path a).[16] Due to the stability of the benzylic cation, the intermediate **B** could be isomerized to vinyl cation **C** at elevated temperature, which then undergoes chloride ion transfer from the metal to generate the chlorinated 3-azabicyclo[3.1.0]hexane **2** (path b). Steric hindrance effect occurs at intermediate **C** when R^2/R^3 are sterically bulky substituents.

Conclusions

In conclusion, we have reported a novel $TiCl_4$-mediated carbocyclization of 1,6-enynes containing propargylic ester moiety. By controlling the reaction temperature, 3-azabicyclo[3.1.0]hexanes and functionalized allenes could be synthesized respectively in moderate to good yields along with moderate to high diastereoselectivities. Further investigation on the mechanism of $TiCl_4$-mediated carbocyclization and the extension of this procedure to other carbon-carbon bond forming reactions are in progress.

Experimental Section

General Procedure for the Preparation of 2 or 3: A solution of $TiCl_4$ (1.0 M in 1,2-dichloroethane, 1.70 equiv.) was added dropwise to a solution of **1** (0.20 mmol, 1.00 equiv.) in anhydrous 1,2-dichloroethane (1.6 mL) under Ar at room temperature (25 °C) or at –20 °C. The resulting reaction mixture was stirred for over 2 min and the reaction was monitored by TLC. When all the starting material consumed, the mixture was quenched by addition of saturated aqueous $NaHCO_3$ solution (5.0 mL). After filtration, the filtrate was extracted with dichloromethane (5.0 mL × 2) and dried with anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by flash silica gel chromatography to give compound **2** or **3** (eluent: ethyl acetate/petroleum ether, 1:10, products **2** and **3** have the same R_f value, some unidentified byproducts could not be separated in pure form by silica gel column chromatography).

Supporting Information (see footnote on the first page of this article): Experimental procedures, compound characterization data and X-ray crystal data of *anti*-**2a** and *anti*-**3p**.

Acknowledgments

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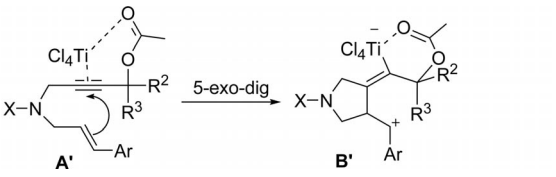
[13] CCDC-779201 (for *anti*-**2a**) and -201478 (for *anti*-**3p**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[14] For the control experiments related to $BiCl_3$ and the plausible mechanism of $BiCl_3$-mediated carbocyclization of **1**, see the Supporting Information.

[15] An alternative mechanism that includes the formation of vinyltitanium intermediate **B′** is also possible. For selected examples of vinyltitanium, see: a) B. J. Hewitt, A. K. Holliday, R. J. Puddephatt, *J. Chem. Soc., Dalton Trans.* **1973**, 801–804; b) R. B. Grossman, S. L. Buchwald, *J. Org. Chem.* **1992**, *57*, 5803–5805; c) A. Kasatkin, S. Okamoto, F. Sato, *Tetrahedron Lett.* **1995**, *36*, 6075–6078; d) K. Suzuki, H. Urabe, F. Sato, *J. Am. Chem. Soc.* **1996**, *118*, 8729–8730; e) H. Urabe, K. Suzuki, F. Sato, *J. Am. Chem. Soc.* **1997**, *119*, 10014–10027; f) S. J. Sturla, N. M. Kablaoui, S. L. Buchwald, *J. Am. Chem. Soc.* **1999**, *121*, 1976–1977.



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