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Diastereoselective, Titanium-Mediated Cyclization of ω-Vinyl Tethered Imides

Soumava Santra, Nikolai Masalov, Oleg L. Epstein, and Jin Kun Cha*

*Department of Chemistry, Wayne State University, 5101 Cass Ave,
Detroit, Michigan 48202*

jcha@chem.wayne.edu

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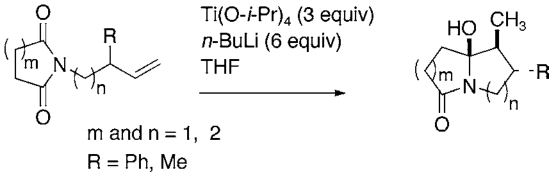
ABSTRACT



Diastereoselective reductive coupling reactions of ω-vinyl tethered cyclic imides are achieved by a preexisting stereocenter at an allylic position. Particularly noteworthy is the effective use of a 1:2 mixture of Ti(O-*i*-Pr)$_4$ and *n*-BuLi to afford the *N*-acylhemiaminal products in good yields.

The titanium-mediated cyclization of ω-vinyl tethered imides, which was built on the Kulinkovich cyclopropanation of esters,[1] has been developed into a general method for preparing pyrrolizidine, indolizidine, and related alkaloids.[2,3] To broaden the synthetic utility of this cyclization, we examined the regio- and stereocontrol of the titanium-mediated coupling reactions of cyclic imides equipped with α-substitutents on the ring: cyclization was found to take place with complete regiocontrol away from α-substituents, but with little diastereoselectivity.[2e] We report herein diastereoselective reductive coupling reactions of ω-vinyl tethered succinimides and glutarimides containing a preexisting stereocenter at an allylic position. As enantiomerically pure starting materials are readily available, this approach lends itself to an enantioselective synthesis of nitrogen-containing heterocycles.

Besides developing the diastereoselective, titanium-mediated cyclization of suitably substituted imides, another objective was to improve the reaction yields: the cyclization reactions of ω-vinyl tethered imides often proceed in respectable, but modest yields under typical reaction conditions involving slow addition of Grignard reagents.[2,3] Toward this end, we first explored the use of a 1:2 mixture of titanium isopropoxide and *n*-butyllithium, which Eisch had reported by adaptation of the well-known Negishi reagent (the Negishi zirconocene equivalent).[4,5] Application of Eisch's protocol to imide **1** afforded the *N*-acylhemiaminal **2** in up to 93% yield, when excess amounts (3 and 6 equiv, respectively) of Ti(O-*i*-Pr)$_4$ and *n*-BuLi were employed (Scheme 1). During subsequent studies to reliably reproduce high (82−93%) yields under Eisch's conditions,[5] carefully controlled reaction conditions were identified: among several key reaction variables, the "aging" of the Eisch reagent, "Ti(O-*i*-Pr)$_2$", was found to exert a critical influence on reaction yields.[6] Stirring the Eisch reagent at room temperature for 15 min

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[1] For reviews, see: (a) Kulinkovich, O. G.; de Meijere, A. *Chem. Rev.* **2000**, *100*, 2789. (b) Sato, F.; Urabe, H.; Okamoto, S. *Chem. Rev.* **2000**, *100*, 2835.

[2] (a) Lee, J.; Ha, J. D.; Cha, J. K. *J. Am. Chem. Soc.* **1997**, *119*, 8127. (b) Kim, S.-H.; Kim, S.-I.; Lai, S.; Cha, J. K. *J. Org. Chem.* **1999**, *64*, 6771. (c) Sung, M. J.; Lee, C.-W.; Cha, J. K. *Synlett* **1999**, 561. (d) Kim, S.-H.; Cha, J. K. *Synthesis* **2000**, 2113. (e) Kim, S.-H.; Park, Y.; Choo, H.; Cha, J. K. *Tetrahedron Lett.* **2002**, *43*, 6657.

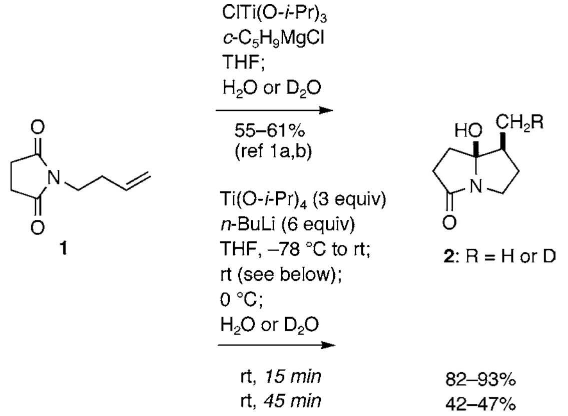
[3] (a) Ollero, L.; Mentink, G.; Rutjes, F. P. J. T.; Speckamp, W. N.; Hiemstra, H. *Org. Lett.* **1999**, *1*, 1331. (b) Cao, B.; Xiao, D.; Joullié, M. M. *Org. Lett.* **1999**, *1*, 1799.

[4] (a) Negishi, E.; Holmes, S. J.; Tour, J. M.; Miller, J. A.; Cederbaum, F. E.; Swanson, D. R.; Takahashi, T. *J. Am. Chem. Soc.* **1989**, *111*, 3336. (b) For a recent review, see: Negishi, E. *Dalton Trans.* **2005**, 827.

[5] (a) Eisch, J. J. *J. Organomet. Chem.* **2001**, *617*, 148. (b) Eisch, J. J.; Gitua, J. N.; Otieno, P. O.; Shi, X. *J. Organomet. Chem.* **2001**, *624*, 229. (c) Eisch, J. J.; Gitua, J. N. *Eur. J. Inorg. Chem.* **2002**, 3091. (d) Eisch, J. J.; Gitua, J. N. *Organometallics* **2003**, *22*, 24. (e) Eisch, J. J.; Adeosun, A. A.; Gitua, J. N. *Eur. J. Org. Chem.* **2003**, 4721.

10.1021/ol0525157 CCC: $30.25

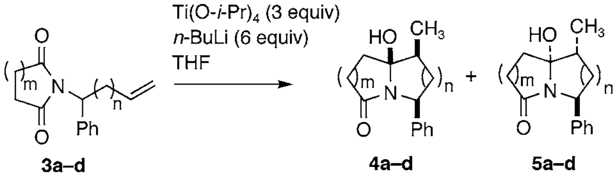
Scheme 1



proved to be suitable in several runs. When the reagent became aged (i.e., longer than 45 min), a significant decrease in yields was observed. This finding suggests limited stability or possibly an inhomogeneous nature of active species generated.[7,8] Without pre-warming a 1:2 mixture of Ti(O-*i*-Pr)$_4$ and *n*-BuLi to room temperature prior to addition of **1**, compound **2** was isolated in only poor (<10%) yield from a complex reaction mixture. In light of excellent yields available under carefully controlled conditions, we utilized the Eisch reagent in subsequent studies.

Imides **3a−d** were first chosen to evaluate possible utilization of $A^{(1,3)}$ strain in controlling the stereochemical outcome.[9a] The cyclization reactions proceeded cleanly in good yields, but the apparent lack of diastereoselectivity was disappointing (Scheme 2). The stereochemical assignment of **4a−d** and **5a−d** rested on difference NOE measurements and was confirmed by X-ray analysis of **4c**, **5a**, and **5d**.[9b,c] It is interesting to note that Hart achieved diastereoselective *N*-acyliminium ion cyclization of a related derivative by minimization of $A^{(1,3)}$ strain.[10]

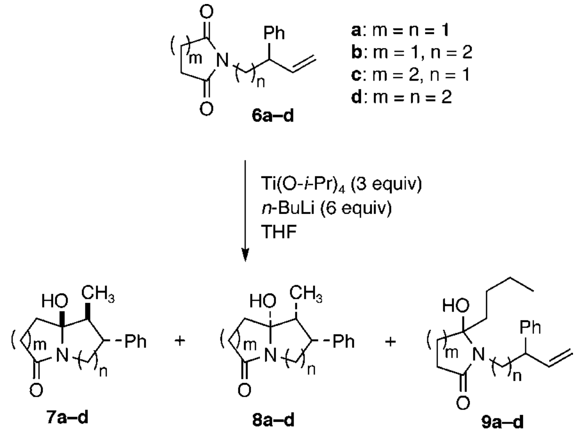
Scheme 2



a: m = n = 1	**a**: 3 : 1	(87%)
b: m = 1, n = 2	**b**: 1 : 1	(83%)
c: m = 2, n = 1	**c**: 2 : 1	(77%)
d: m = n = 2	**d**: 1 : 3	(53%)

The stereodirecting effect of an allylic substituent was next examined with imides **6a−d** (Scheme 3).[9,11] In all examples, the titanium-mediated reductive cyclization reactions proceeded with good to excellent diastereoselectivity to give **7a−d** as the major products. Yields (45−65%) were lower than the cyclization of cognate **3a−d** (53−87%) presumably due to the presence of the allylic substituent.[12] Also isolated were small amounts of side products **9a−d**, which were

Scheme 3



a: m = n = 1
b: m = 1, n = 2
c: m = 2, n = 1
d: m = n = 2

	7 : 8	yield	9
a:	9 : 1	(65%)	2–5%
b:	21 : 1	(60%)	4–7%
c:	12 : 1	(67%)	3–6%
d:	12 : 1	(45%)	8–10%

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[6] **Typical procedure: reductive coupling of *N*-3-butenylsuccinimide (1):** To a solution of titanium(IV) isopropoxide (0.45 mL, 1.5 mmol) in 4 mL of anhydrous THF, which had been cooled to −78 °C, was added dropwise a 1.6 M solution of *n*-BuLi in hexane (1.9 mL, 3 mmol) under a gentle stream of argon. (The flask was placed between an argon inlet and a bubbler.) After the resulting clear solution had been stirred at the same temperature for 15−20 min, the bath was removed and the reaction mixture was allowed to warm to room temperature during 10−15 min. The mixture was stirred at room temperature for 15 min. The dark homogeneous solution was cooled to 0 °C (ice bath), and a solution of **1** (77 mg, 0.5 mmol) in anhydrous THF (1 mL) was then added dropwise. The resulting deep red reaction mixture was stirred at 0 °C for 20 min, quenched by slow addition of 0.5 mL of water (the suspension became dark blue), exposed to air, and stirred until it became white (15−30 min). Ethyl acetate (5 mL) and anhydrous $MgSO_4$ (1−2 g) were added to the reaction mixture and the resulting slurry was stirred for an additional 15 min. After filtration, solids were washed thoroughly with EtOAc−MeOH (9:1) and the combined organic filtrates were concentrated under reduced pressure. The residue was purified by column chromatography on silica gel, using EtOAc as eluent to afford 70 mg (90%) of **2**.

[7] Some time ago we examined the intra- and intermolecular cyclopropanation reactions of carboxylic esters by means of a 1:2 mixture of Ti(O-*i*-Pr)$_4$ and *n*-BuLi, but the cyclopropanol products were obtained only in lower than 15−20% yields: Lee, J.; Masalov, N.; Cha, J. K. Unpublished results.

[8] (a) Matiushenkov, E. A.; Sokolov, N. A.; Kulinkovich, O. G. *Synlett* **2004**, 77. (b) Churykau, D. H.; Zinovich, V. G.; Kulinkovich, O. G. *Synlett* **2004**, 1949. (c) Thorn, M. G.; Hill, J. E.; Waratuke, S. A.; Johnson, E. S.; Fanwick, P. E.; Rothwell, I. P. *J. Am. Chem. Soc.* **1997**, *119*, 8630. See also: (d) Handa, Y.; Inanaga, J. *Tetrahedron Lett.* **1987**, *28*, 5717. (e) Nugent, W. A.; RajanBabu, T. V. *J. Am. Chem. Soc.* **1988**, *110*, 8561. (f) Gansäuer, A.; Bluhm, H.; Pierobon, M. *J. Am. Chem. Soc.* **1998**, *120*, 12849. (g) Enemærke, R. J.; Larsen, J.; Skrydstrup, T.; Daasbjerg, K. *J. Am. Chem. Soc.* **2004**, *126*, 7853.

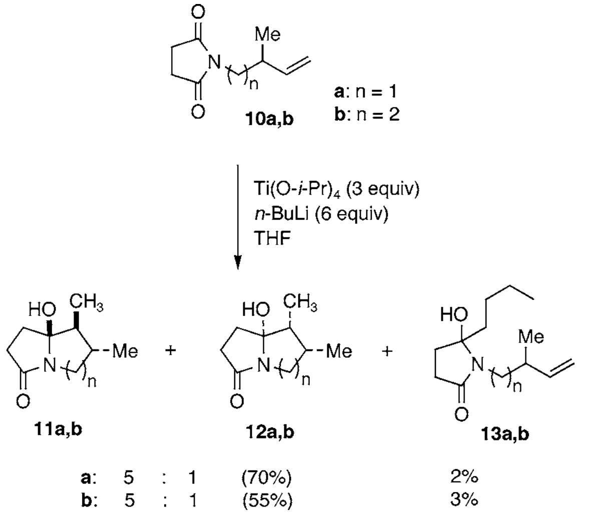
[9] (a) Imides were prepared in excellent yields by the Mitsunobu reaction of the respective imides with 3-butenols or 4-pentenols. (b) We thank Dr. Mary Jane Heeg for single-crystal X-ray analyses. The X-ray data have been deposited with the Cambridge Structural Database: please refer to CSD Nos. 236917 (**5a**), 239451 (**4c**), 249692 (**7b**), 253361 (**5d**), and 253717 (**7d**). (c) Santra, S. M.S. Thesis, Wayne State University, December 2004.

[10] Hart, D. J. *J. Am. Chem. Soc.* **1980**, *102*, 397.

[11] Cf.: Quan, L. G.; Kim, S.-H.; Lee, J. C.; Cha, J. K. *Angew. Chem., Int. Ed.* **2002**, *41*, 2160.

[12] Cf.: Lee, J.; Kang, C. H.; Kim, H.; Cha, J. K. *J. Am. Chem. Soc.* **1996**, *118*, 291.

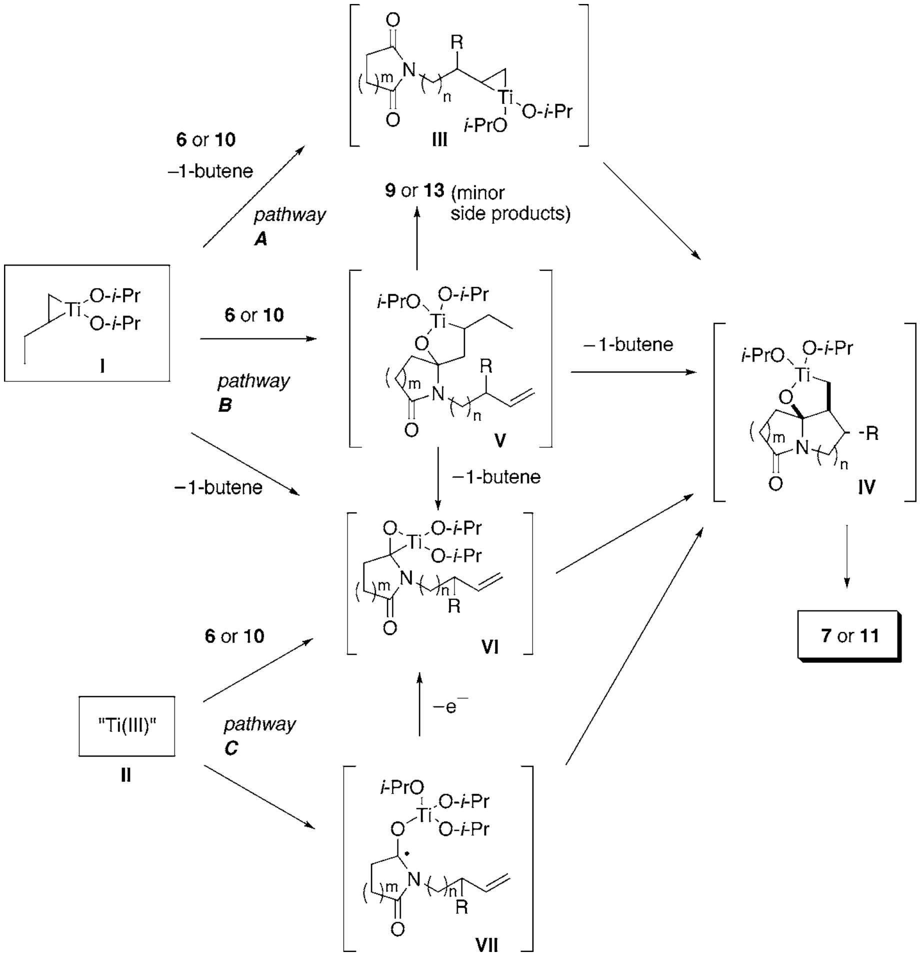
Scheme 4



indicative of the intermediacy of (η^2-butene)Ti(O-i-Pr)$_2$.[1,13] The stereochemistry of **7a−d** and **8a−d** was tentatively assigned on the basis of difference NOE measurements, and the structures of **7b** and **7d** were unequivocally established by X-ray analysis.[9b,c] Similarly, comparable results were obtained with imides **10a**,**b** bearing a methyl group at the allylic position (Scheme 4). Lower diastereoselectivity observed for **10a**,**b** compared to **6a−d** suggests that the stereochemical course of cyclization is largely controlled by steric effects (Me vs Ph).

As noted above, the exact structure of the Eisch reagent is unclear at the present time, and elucidation of its precise structure must await further studies. The observation that this reagent is ineffective in the Kulinkovich cyclopropanation of esters,[7] yet efficacious in the reductive cyclization of ω-vinyl tethered imides also raises an intriguing question regarding the reaction mechanism (Scheme 5). The intermediate **I**, which is presumed to be formed under Eisch conditions, could undergo ligand exchange with starting imides **6** and **10** to set off *pathway* A (**III** → **IV** → **7** or **11**) by analogy to the widely accepted mechanism for the Kulinkovich cyclopropanation of esters.[1] The requisite formation of **IV** is supported by deuterium labeling experiment (i.e., hydrolysis with D$_2$O), as well as oxidation with molecular oxygen.[2] Alternatively, *pathway* B entails initial conversion of **I** to **V** to afford **7** and **11** via either **VI** or **IV**, although the transformation **V** → **VI** is unprecedented. The isolation of the byproducts **9** and **13** (in very small amounts)

Scheme 5



is in accord with the intermediacy of **V**. Direct formation of **VI** from **I** also might be plausible, but would not lead to formation of **9** and **13**. Especially when R is bulky (vs R = H), *pathway* B could compete with *pathway* A. Additionally, the prerequisite of more than a stoichiometric amount of the Eisch reagent for high yields might be attributed to the inefficient formation of the Eisch reagent and/or its lability; another intriguing possibility is the involvement of a Ti(III) species **II**,[8,14] which is expected to reduce an imide carbonyl group to generate **VII** (*pathway* C). The second reduction is necessary in both **VII** → **VI** → **IV** and **VII** → **IV**. Further studies will be directed to shed light on the reaction pathway(s), as well as synthetic applications.

In summary, the diastereoselective, low-valent titanium-mediated cyclization reactions of ω-vinyl tethered cyclic imides directed by a preexisting stereocenter at an allylic position have been developed so as to broaden the utility of this approach in the syntheses of nitrogen heterocycles. Also noteworthy is the effective use of a 1:2 mixture of Ti(O-*i*-Pr)$_4$ and *n*-BuLi by adaptation of Eisch's method to achieve the cyclization in good yields.

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Supporting Information Available: Experimental details and spectroscopic data for key intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) In some cases very small amounts (≤3%) of simple reduction products of imides, presumably by the action of a titanium hydride, were also observed by GC/MS.

(14) The greenish color of the Eisch reagent prior to addition of an imide indicates the presence of a Ti(III) species.