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Concise and Stereoselective Synthesis of Enamides and Dienamides by a Titanium-Mediated Coupling Method

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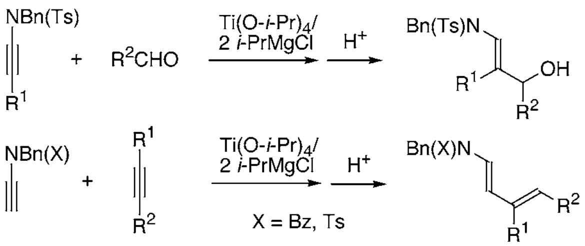
ABSTRACT



Ynamide–titanium alkoxide complexes underwent hydrolysis or addition to aldehydes and ketones to give single, stereodefined di- or trisubstituted enamides in good yields. Alternatively, coupling of a variety of alkyne–titanium alkoxide complexes with terminal ynamides generated amino-substituted titanacyclopentadienes, hydrolysis or aldehyde addition of which afforded stereodefined dienamides.

There are many dependable methods for the stereoselective preparation of enol derivatives such as enol silyl ethers, acetates, and ethers with various substitution patterns (Figure 1, **A**),[1] which serve for the efficient construction of complex molecular architecture typically via aldol reaction, Diels−Alder reaction, transition metal-catalyzed coupling reaction, and so on.[1] However, stereoselective access to their nitrogen analogues, that is, substituted enamine derivatives (Figure 1, **B**), has so far been much less explored,[2] even though they are versatile starting materials similar to the aforementioned enol derivatives. Herein we report a convenient method for preparing enamides and dienamides, a useful and easy-to-handle class of enamine derivatives, via titanium(II)-mediated regio- and stereoselective coupling of ynamides with carbonyl compounds or other acetylenes.

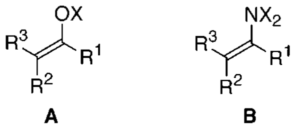


Figure 1.

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(1) General: Trost, B. M., Fleming, I., Eds. *Comprehensive Organic Synthesis*; Pergamon Press: Oxford, 1991; Vols. 1−7. Enol silyl ethers: Fleming I.; Barbero, A.; Walter, D. *Chem. Rev.* **1997**, *97*, 2063−2192. Pawlenko, S. In *Houben-Weyl Methods of Organic Chemistry*, 4th ed.; Kropf, H., Schaumann, E., Eds.; Thieme: Stuttgart, 1993; Vol. E15/1, pp 404−462. Weber, W. P. *Silicon Reagents for Organic Synthesis*; Springer-Verlag: Berlin, 1983; pp 206−272. Colvin, E. W. *Silicon in Organic Synthesis*; Butterworth: London, 1981; pp 198−287. Enol esters: Frauenrath, H. In *Houben-Weyl Methods of Organic Chemistry*, 4th ed.; Kropf, H., Schaumann, E., Eds.; Thieme: Stuttgart, 1993; Vol. E15/1, pp 1−117. Enol ethers: Frauenrath, H. In *Houben-Weyl Methods of Organic Chemistry*, 4th ed.; Kropf, H., Schaumann, E., Eds.; Thieme: Stuttgart, 1993; Vol. E15/1, pp 140−349.

(2) For review on enamines, see: Whitesell, J. K. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 6, pp 705−719. Rademacher, P. In *Houben-Weyl Methods of Organic Chemistry*, 4th ed.; Kropf, H., Schaumann, E., Eds.; Thieme: Stuttgart, 1993; Vol. E15/1, pp 598−717.

10.1021/ol027209x CCC: $25.00

Scheme 1. Preparation of Trisubstituted Enamide

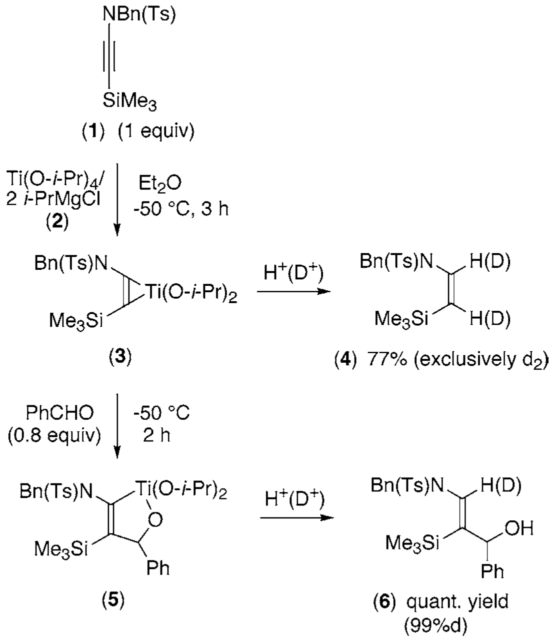
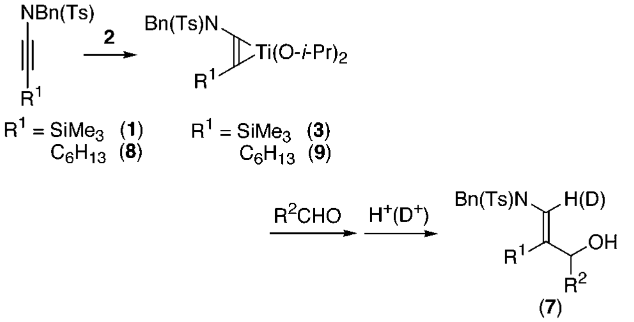


Table 1. Preparation of Various Trisubstituted Enamides According to Scheme 1



entry	R^1 of **1**/**8**	R^2CHO	workup	yield (%)[a]	D (%)
1	$SiMe_3$	PhCHO	$H^+(D^+)$	quant	99
2	C_6H_{13}			93	97
3	$SiMe_3$	$C_8H_{17}CHO$	$H^+(D^+)$	91	99
4	C_6H_{13}			quant	99
5	$SiMe_3$	*i*-PrCHO	H^+	94	
6	C_6H_{13}			71	
7	$SiMe_3$	$H_{11}C_5$–CH=CH–CHO	H^+	87	
8	C_6H_{13}			54	

[a] Isolated yield. Isomeric products were not formed.

(Sulfonylamino)acetylene **1** (Bn = benzyl), readily prepared by a literature method,[3] was treated with an economical titanium(II) alkoxide reagent, Ti(O-*i*-Pr)$_4$/2 *i*-PrMgCl (**2**),[4] to generate ynamide–titanium complex **3**, the formation of which was confirmed by hydrolysis and deuteriolysis to give the corresponding (*Z*)-enamides **4** and **4**-d_2 with high deuterium content (Scheme 1). Actually, to the best of our knowledge, this is the first example of the generation of an (amino-substituted acetylene)-group 4 metal complex,[5,6] and the fact that it hydrolyzes itself enables the facile preparation of (*Z*)-enamide **4** with excellent isomeric purity.[7] However, a more important observation is that the coupling of **3** with a carbonyl compound proceeded in a highly regio- and stereoselective manner to give a single, stereodefined trisubstituted enamide **6**,[8,9] the structure of which was unambiguously established by NOE experiments of ^{1}H NMR spectroscopy.[10] In addition, deuteriolysis confirmed the presence of the most likely intermediate, oxatitanacycle **5**, which may enable further synthetic transformations based on the remaining carbon–titanium bond.[4,11]

Other results are summarized in Table 1. Acetylene–titanium complex **9** was successfully generated from nonsilylated ynamide **8** as well (even entries). Both silylated and nonsilylated ynamide–titanium complexes **3** and **9**, respectively, always reacted with a variety of aldehydes at

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(3) Witulski, B.; Stengel, T. *Angew. Chem., Int. Ed.* **1998**, *37*, 489–492. Murch, P.; Williamson, B. L.; Stang, P. J. *Synthesis* **1994**, 1255–1256. Witulski, B.; Gössmann, M. *Chem. Commun.* **1999**, 1879–1880. For reviews, see: Himbert, G. In *Houben-Weyl Methods of Organic Chemistry*, 4th ed.; Kropf, H., Schaumann, E., Eds.; Thieme: Stuttgart, 1993; Vol. E15/3, pp 3267–3443. Collard-Motte, J.; Janousek, Z. *Top. Curr. Chem.* **1986**, *130*, 89–131.

(4) Sato, F.; Urabe, H.; Okamoto, S. *Chem. Rev.* **2000**, *100*, 2835–2886. Kulinkovich, O. G.; de Meijere, A. *Chem. Rev.* **2000**, *100*, 2789–2834. Eisch, J. J. *J. Organomet. Chem.* **2001**, *617–618*, 148–157. Sato, F.; Okamoto, S. *Adv. Synth. Catal.* **2001**, *343*, 759–784. Sato, F.; Urabe, H. In *Titanium and Zirconium in Organic Synthesis*; Marek, I., Ed.; Wiley-VCH: Weinheim, Germany, 2002; pp 319–354.

(5) For reviews on acetylene–metal complexes, see the following. Ti and Zr: ref 4. Buchwald, S. L.; Nielsen, R. B. *Chem. Rev.* **1988**, *88*, 1047–1058. Negishi, E.; Takahashi, T. *Acc. Chem. Res.* **1994**, *27*, 124–130. Ohff, A.; Pulst, S.; Lefeber, C.; Peulecke, N.; Arndt, P.; Burlakov, V. V.; Rosenthal, U. *Synlett* **1996**, 111–118. Negishi, E.; Takahashi, T. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 755–769. Nb and Ta: Kataoka, Y.; Miyai, J.; Oshima, K.; Takai, K.; Utimoto, K. *J. Org. Chem.* **1992**, *57*, 1973–1981. Hartung, J. B., Jr.; Pedersen, S. F. *J. Am. Chem. Soc.* **1989**, *111*, 5468–5469. Strickler, J. R.; Bruck, M. A.; Wexler, P. A.; Wigley, D. E. *Organometallics* **1990**, *9*, 266–273.

(6) Quite recently, generation and reactions of acetylenic phosphonate–zirconocene complexes were reported: Quntar, A. A. A.; Srebnik, M. *Org. Lett.* **2001**, *3*, 1379–1381. Quntar, A. A. A.; Srebnik, M. *J. Org. Chem.* **2001**, *66*, 6650–6653. Quntar, A. A. A.; Melman, A.; Srebnik, M. *Synlett* **2002**, 61–64.

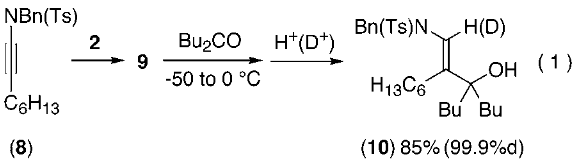
(7) For recent reports on the preparation of (*E*)- or (*Z*)-disubstituted enamides, see: Trost, B. M.; Surivet, J.-P. *Angew. Chem., Int. Ed.* **2001**, *40*, 1468–1471. Fürstner, A.; Brehm, C.; Cancho-Grande, Y. *Org. Lett.* **2001**, *3*, 3955–3957. Krompiec, S.; Pigulla, M.; Szczepankiewicz, W.; Bieg, T.; Kuznik, N.; Leszczynska-Sejda, K.; Kubicki, M.; Borowiak, T. *Tetrahedron Lett.* **2001**, *42*, 7095–7098. Miniere, S.; Cintrat, J.-C. *Synthesis* **2001**, 705–707. Snider, B. B.; Song, F. *Org. Lett.* **2000**, *2*, 407–408. Witulski, B.; Buschmann, N.; Bergsträsser, U. *Tetrahedron* **2000**, *56*, 8473–8480. Alonso, D. A.; Alonso, E.; Nájera, C.; Yus, M. *Synlett* **1997**, 491–492. Kondo, T.; Tanaka, A.; Kotachi, S.; Watanabe, Y. *J. Chem. Soc., Chem. Commun.* **1995**, 413–414. Ogawa, T.; Kiji, T.; Hayami, K.; Suzuki, H. *Chem. Lett.* **1991**, 1443–1446. Hudrlik, P. F.; Hudrlik, A. M.; Rona, R. J.; Misra, R. N.; Withers, G. P. *J. Am. Chem. Soc.* **1977**, *99*, 1993–1996.

(8) Stereoselective preparation of trisubstituted enamides of type **7**, *which have two different β-alkyl (and -silyl) substituents*, appears to be quite difficult. On the contrary, trisubstituted enamides having the same two β-substituents have been reported. Meuzelaar, G. J.; van Vliet, M. C. A.; Neeleman, E.; Maat, L.; Sheldon, R. A. *Liebigs Ann./Recl* **1997**, 1159–1163. Murai, T.; Kasai, Y.; Ishihara, H.; Kato, S. *J. Org. Chem.* **1992**, *57*, 5542–5545. Shono, T.; Matsumura, Y.; Tsubata, K.; Sugihara, Y.; Yamane, S.; Kanazawa, T.; Aoki, T. *J. Am. Chem. Soc.* **1982**, *104*, 6697–6703. Stille, J. K.; Becker, Y. *J. Org. Chem.* **1980**, *45*, 2139–2145.

(9) For the preparation of cyclic enamides from ynamides, see: Witulski, B.; Gössmann, M. *Synlett* **2000**, 1793–1797. Rainier, J. D.; Imbriglio, J. E. *J. Org. Chem.* **2000**, *65*, 7272–7276.

(10) See Supporting Information.

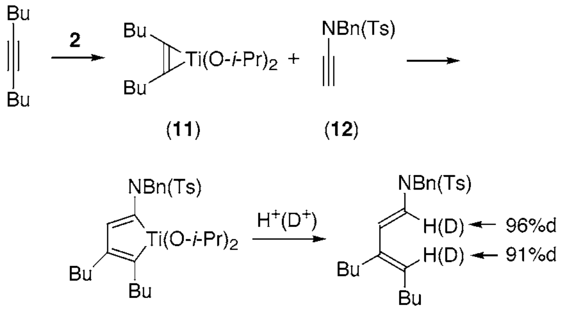
the β-position to the amino group to give virtually single trisubstituted enamides **7**, which are otherwise difficult to obtain.[8] Acetylene complex **9** was found to react with a ketone in the same way but at a higher reaction temperature to give **10** as shown in eq 1.



(**8**) (**10**) 85% (99.9%d)

Stereoselective construction of aminodienes is a critical step in the preparation of nitrogen-functionalized cyclic systems via a concerted process such as the Diels–Alder reaction.[12] Known acetylene–titanium complex **11** generated from 5-decyne and **2**[4,13] was found to undergo regio- and stereoselective coupling reaction with terminal ynamide **12** at −50 °C to give single dienamide **14** after hydrolytic workup (Scheme 2).[14,15] Its structure was verified by the coupling constants and NOE study of ^1H NMR spectroscopy.[10] In place of the simple hydrolysis, deuteriolysis gave bis-deuterated dienamide **14**-d_2, confirming the presence of titanacyclopentadiene **13** as the intermediate.

Scheme 2. Preparation of Dienamide

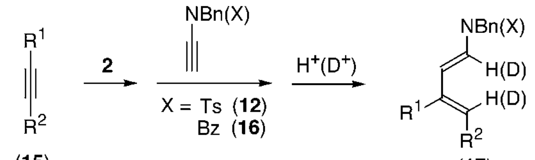


(**11**) (**12**)

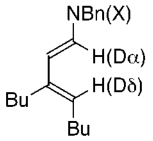
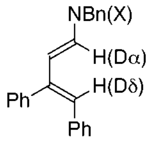
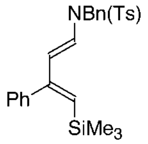
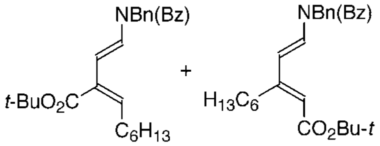
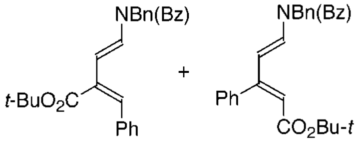
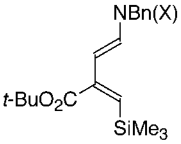
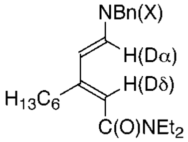
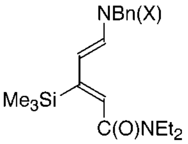
(**13**) (**14**) 73%

Table 2 shows the generality of this reaction. With **15** as the first acetylene, dialkylacetylene (entries 1 and 2), diphenylacetylene (entries 3 and 4), silylacetylene (entry 5), and acetylenic esters (entries 6–9) and amides (entries 10–

Table 2. Preparation of Various Dienamides According to Scheme 2



(**15**) (**17**)

entry	acetylene **15**	X in **12/16/17**	workup	dienamide(s) **17**[a]	yield (%)[b] [%d or ratio]
1	$Bu-C\equiv C-Bu$	Ts	$H^+(D^+)$		73 [Dα, 96%d; Dδ, 91%d]
2		Bz	H^+		51
3	$Ph-C\equiv C-Ph$	Ts	$H^+(D^+)$		92 [Dα, 96%d; Dδ, 97%d]
4		Bz	H^+		84
5	$Ph-C\equiv C-SiMe_3$	Ts	H^+		90
6	$CO_2Bu\text{-}t-C\equiv C-C_6H_{13}$	Bz	H^+		45 + 32
7	$CO_2Bu\text{-}t-C\equiv C-Ph$	Bz	H^+		90 [55:45]
8	$CO_2Bu\text{-}t-C\equiv C-SiMe_3$	Ts	H^+		91
9		Bz	H^+		56
10	$C_6H_{13}-C\equiv C-C(O)NEt_2$	Ts	$H^+(D^+)$		84 [Dα, 96%d; Dδ, 97%d]
11		Bz	$H^+(D^+)$		85 [Dα, 98%d; Dδ, 97%d]
12	$SiMe_3-C\equiv C-C(O)NEt_2$	Ts	H^+		87
13		Bz	H^+		93

[a] Unless otherwise stated, isomeric products were not observed. The stereochemistry was unambiguously determined in several representative entries (see ref 10). [b] Isolated yield.

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(11) For synthetic application of organotitanium compounds, see: Reetz, M. T. *Organotitanium Reagents in Organic Synthesis*; Springer-Verlag: Berlin, 1986. Ferreri, C.; Palumbo, G.; Caputo, R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 1, pp 139–172. Reetz, M. T. In *Organometallics in Synthesis*; Schlosser, M., Ed.; Wiley: Chichester, UK, 1994; pp 195–282.

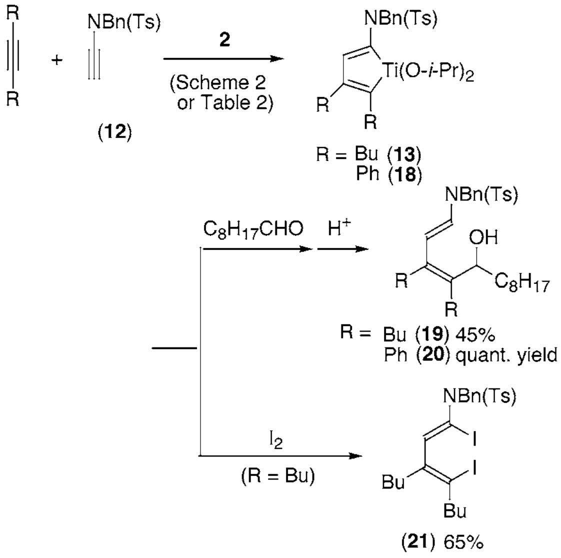
(12) Fringuelli, F.; Taticchi, A. *Dienes in the Diels–Alder Reaction*; Wiley: New York, 1990.

(13) Harada, K.; Urabe, H.; Sato, F. *Tetrahedron Lett.* **1995**, *36*, 3203–3206

(14) For reported preparation of 1-amino-1,3-butadiene derivatives, see: Overman, L. E.; Clizbe, L. A. *J. Am. Chem. Soc.* **1976**, *98*, 2352–2354 and 8295. Overman, L. E.; Taylor, G. F.; Petty, C. B.; Jessup, P. J. *J. Org. Chem.* **1978**, *43*, 2164–2167. Yli-Kauhaluoma, J. T.; Ashley, J. A.; Lo, C.-H.; Tucker, L.; Wolfe, M. M.; Janda, K. D. *J. Am. Chem. Soc.* **1995**, *117*, 7041–7047. Kozmin, S. A.; Rawal, V. H. *J. Am. Chem. Soc.* **1997**, *119*, 7165–7166. Huang, Y.; Iwama, T.; Rawal, V. H. *Org. Lett.* **2002**, *4*, 1163–1166 and references therein.

(15) For our previous effort to make nonfunctionalized or electron-deficient dienes, see: Hamada, T.; Suzuki, D.; Urabe, H.; Sato, F. *J. Am. Chem. Soc.* **1999**, *121*, 7342–7344.

Scheme 3. Synthetic Utility of Titanacycles



13) participated in the coupling reaction. On the other hand, both (sulfonylamino)- and (benzoylamino)acetylenes **12** and **16**[3] (Bz = benzoyl) could be used as the second acetylene to give a variety of dienamides **17** in good to excellent yields. Although alkyl- and phenylpropiolates in entries 6 and 7 unfortunately yielded a mixture of regioisomeric dienes, other reactions afforded the products as a single regio- as well as stereoisomer. In addition, the utility of intermediate titanacycles **13** and **18** was exemplified by further side-chain extension through the regio- and stereoselective aldehyde addition to furnish **19** and **20** or by iodinolysis of **13** to give diiodide **21** (Scheme 3).[10]

In conclusion, substituted enamide derivatives were conveniently prepared by the titanium(II)-mediated coupling reactions of ynamides, where excellent regio- and stereoselectivities were newly disclosed. Further synthetic application of the products obtained herein is now in progress.

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Supporting Information Available: Experimental procedures and physical properties of products. This material is available free of charge via the Internet at http://pubs.acs.org.

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