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A Ring-Closing Yne-Carbonyl Metathesis of Ynamides

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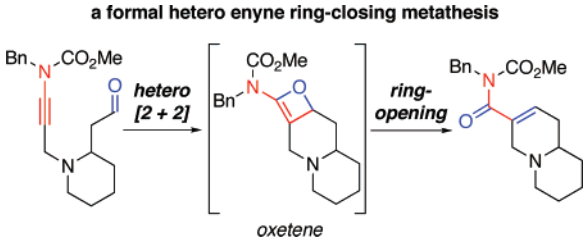
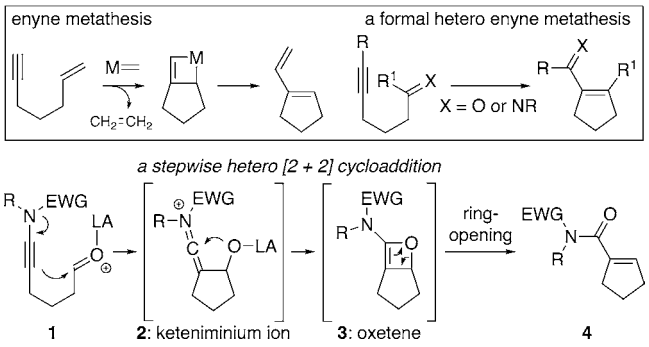
ABSTRACT



An acid-catalyzed ring-closing ynamide-carbonyl metathesis is described here. This hetero RCM methodology is applicable to the construction of carbocycles as well as heterocycles such as chromenes, quinolizidines, indolizidines, and pyrrolizidines.

Ring-closing metathesis (RCM) is widely recognized as one of the most powerful tools in organic synthesis.[1] Considerable investigation has taken place in the areas of alkene-alkyne (or enyne) ring-closing metathesis, and many inventive works appear in the literature.[2−4] However, less common are those metatheses where one of the reacting partners is a carbonyl-containing functional group; such transformations are formal hetero enyne metatheses (Scheme 1).[5] Most recently, Krische reported an elegant account describing a catalytic intramolecular metathesis with acetylenic ketones and aldehydes.[6] Our interest in developing useful synthetic methodologies

Scheme 1. Formal Hetero Enyne RCM



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(1) For reviews on RCM, see: (a) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18. (b) Schrock, R. R.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4592. (c) Walters, M. A. *Prog. Heterocycl. Chem.* **2003**, *15*, 1. (c) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127. (d) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199. (e) McReynolds, M. D.; Dougherty, J. M.; Hanson, P. R. *Chem. Rev.* **2004**, *104*, 2239. (f) Wallace, D. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 1912.

(2) For reviews on enyne metathesis, see: (a) Diver, S. T.; Giessert, A. J. *Chem. Rev.* **2004**, *104*, 1317. (b) Mori, M. *J. Mol. Catal. A* **2004**, *213*, 73. (c) Poulsen, C. S.; Maden, R. *Synthesis* **2003**, 1. (d) Mori, M. In *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, 2003. (e) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012.

(3) For some recent examples of enyne metathesis, see: (a) Hansen, E. C.; Lee, D. *J. Am. Chem. Soc.* **2004**, *126*, 15074. (b) Castarlenas, R.; Eckert, M.; Dixneuf, P. H. *Angew. Chem., Int. Ed.* **2005**, *44*, 2576. (c) Galan, B. R.; Giessert, A. J.; Keister, J. B.; Diver, S. T. *J. Am. Chem. Soc.* **2005**, *127*, 5762. (d) Kim, M.; Lee, D. *Org. Lett.* **2005**, *7*, 1865.

(4) For enyne metathesis using heteroatom-substituted alkynes, see: (a) Saito, N.; Sato, Y.; Mori, M. *Org. Lett.* **2002**, *4*, 803. (b) Huang, J.; Xiong, H.; Hsung, R. P.; Rameshkumar. C.; Mulder, J. A.; Grebe, T. P. *Org. Lett.* **2002**, *4*, 2417. (c) Schramm, M. P.; Reddy, D. S.; Kozmin, S. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4274. (d) Timmer, M. S. M.; Ovaa, H.; Filippov, D. V.; Van der Marel, G. A.; Van Boom, J. H. *Tetrahedron Lett.* **2001**, *42*, 8231. (e) Clark, J. S.; Hamelin, O. *Angew Chem., Int. Ed.* **2000**, *39*, 372.

(5) For leading examples, see: (a) Curini, M.; Epifano, F.; Maltese, F.; Rosati, O. *Synlett* **2003**, 552. (b) Viswanathan, G. S.; Li, C.-J. *Tetrahedron Lett.* **2002**, *43*, 1613. (c) Wempe, M. F.; Grunwell, J. R. *Tetrahedron Lett.* **2000**, *41*, 6709. (d) Balog, A.; Geib, S. J.; Curran, D. P. *J. Org. Chem.* **1995**, *60*, 345. For some earlier studies, see: (e) Harding, C. E.; Hanack, M. *Tetrahedron Lett.* **1971**, *12*, 1253. (f) Balf, R. J.; Rao, B.; Weiler, L. *Can. J. Chem.* **1971**, *49*, 3135.

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using ynamides[7−10] led us to explore the possibility of ring-closing ynamide-carbonyl metathesis possibly promoted by a Lewis acid (**1** → **4**), which is not known.[11] Mechanistically, this reaction would proceed through ring opening of an amide-substituted oxetene intermediate **3** formed through a stepwise hetero [2 + 2] cycloaddition pathway.[12,13] We communicate here our preliminary success in ring-closing yne-carbonyl metathesis employing ynamides.

To achieve such a hetero ring-closing metathesis, we commenced our work by screening a range of Lewis acids as summarized in Table 1. Specifically, oxazolidinone,

Table 1. Screening of Lewis Acids and Catalysts

entry	aldehyde[a]	Lewis acid	mol %	time [h]	temp [°C]	product	yield [%][b]
1		BF_3-OEt_2	5	0.5	rt		51
2		BF_3-OEt_2	10	0.5	rt		74
3		BF_3-OEt_2	25	0.5	rt		82
4		BF_3-OEt_2	50	0.5	rt		74
5		BF_3-OEt_2	75	0.5	rt		71
6		BF_3-OEt_2	100	0.5	rt		74
7		$InCl_3$	25	20	- 78 °C to rt		7
8	**5**	$Mg(OTf)_2$	25	5	rt	**6**	85
9		$Sn(OTf)_2$	25	5	rt		92
10		$Ti(O\text{-}iPr)_3Cl$	25	20	- 78 °C to rt		nd[c]
11		$TiCl_4$	25	20	- 78 °C to rt		nd
12		$Zn(OTf)_2$	25	5	rt		81
13		BF_3-OEt_2	25	0.5	rt		51
14		$Mg(OTf)_2$	25	5	rt		45
15		$Sn(OTf)_2$	25	5	rt		42
16		$Sn(OTf)_2$	25	5	rt		43
17	**7**	$Zn(OTf)_2$	25	5	rt	**8**	56
18		BF_3-OEt_2	25	20	- 78 °C to rt		46
19		$Mg(OTf)_2$	25	5	rt		14
20		$Zn(OTf)_2$	25	5	rt		48
21		$Sn(OTf)_2$	25	5	rt		48
22	**9**	$In(OTf)_3$	25	20	rt	**10**	4

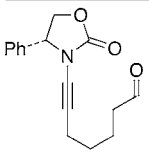
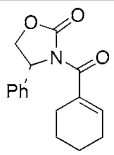
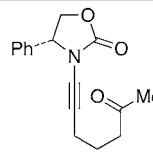
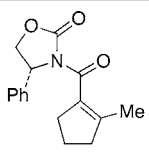
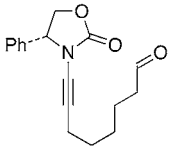
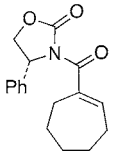
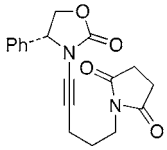
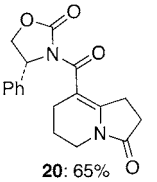
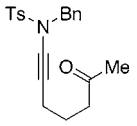
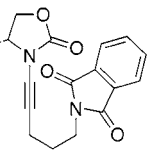
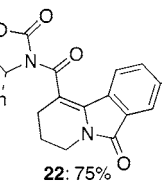
[a] All reactions were carried out in CH_2Cl_2 at a concentration of 0.01 M. [b] Isolated yields. [c] nd: not determined.

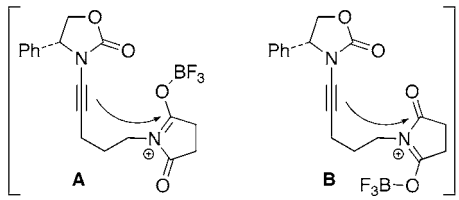
camphor lactam, and sulfonamide based ynamides **5**, **7**, and **9** were used, as they represent three major classes of ynamides. Entries 1−6 establish that BF_3-OEt_2 is an excellent catalyst with a loading of 25 mol % (entry 3), giving the highest yield of the oxazolidinone-based metathesis product **6**.[14] However, other Lewis acids also worked comparably well at room temperature (entries 8, 9, and 12).

In general, metal triflate catalyzed reactions appear to be slower than those catalyzed by BF_3-OEt_2 and required reaction times of 5 h or greater. The exceptions are $InCl_3$ (entry 7), $TiCl_4$, and $Ti(O\text{-}iPr)_3Cl$ (entries 10 and 11),[15] which failed to give the desired product. Hetero-RCM of less stable ynamides such as **7** (*aza*-camphor substituted) and **9** (sulfonyl substituted) were also feasible, although yields of the corresponding metathesis products were lower than those of **5**. We attribute these lower yields to the relative stability of ynamides **7** and **9**.

The generality of this hetero RCM is shown in Table 2. Specifically, six- and seven-membered rings are also acces-

Table 2. Scope of theYne-Carbonyl Ring-Closing Metathesis

substrate[a]	product[b]	substrate[a]	product[b]
			
11: 25 mol %[c]	**12:** 75%	**17:** 25 mol %	**18:** 88%
			
13: 25 mol %	**14:** 35%	**19:** 125 mol %[e]	**20:** 65%
			
15: 25 mol %[d]	**16:** 33%	**21:** 125 mol %[e]	**22:** 75%



[a] All reactions were carried out with BF_3-OEt_2 in CH_2Cl_2 at a concentration of 0.01 M. [b] Isolated yields. [c] Entries for substrates **11**, **13**, **19**, and **21** were done at room temperature. [d] Reaction temperature for **15** and **17** went from − 78 °C to room temperature. [e] 1.25 equiv of BF_3-OEt_2 was used at room temperature with a concentration of 0.04 M.

sible via this method (**11** → **12** and **13** → **14**), though the seven-membered ring was formed in lower yield. In addition, ynamides **15** and **17** also underwent the hetero ring-closing

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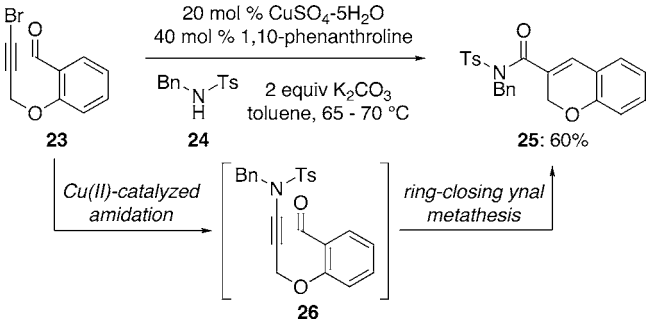
metathesis with ketones to give methyl cyclopentenes **16** and **18** in 33% and 89% yields, respectively.

Intriguingly, ynamides **19** and **21** tethered with imides also underwent hetero RCM to give indolizidine motifs **20** and **22**, respectively, in good yields. In these cases, however, 1.25 equiv of BF_3-OEt_2 had to be used and triflate salts were entirely ineffective. These two reactions suggest that the initial 1,2-addition of ynamides could likely proceed through either the *N*-acyl imidinium intermediate **A** (most likely) or **B** (Table 2) obtained via BF_3-OEt_2 activation of one of the two imide carbonyl groups.[16]

Another interesting example of this ynamide-carbonyl RCM is given in Scheme 2. During the synthesis of ynamide

Scheme 2. Tandem Amidation−Metathesis



26 under our amidation conditions,[10b] we discovered that the ynal ring-closing metathesis had occurred concomitantly to give chromene **25** with an overall yield of 60%, constituting a tandem amidation−metathesis.

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(10) For the synthesis of ynamides, see: (a) Frederick, M. O.; Mulder, J. A.; Tracey, M. R.; Hsung, R. P.; Huang, J.; Kurtz, K. C. M.; Shen, L.; Douglas, C. J. *J. Am. Chem. Soc.* **2003**, *125*, 2368. (b) Zhang, Y.; Hsung R. P.; Tracey, M. R.; Kurtz, K. C. M.; Vera, E. L. *Org. Lett.* **2004**, *6*, 1151. Also see: (c) Dunetz, J. R.; Danheiser, R. L. *Org. Lett.* **2003**, *5*, 4011. (d) Couty, S.; Barbazanges, M.; Meyer, C.; Cossy, J. *Synlett* **2005**, 906. (e) Wei, L.-L.; Mulder, J. A.; Xiong, H.; Zificsak, C. A.; Douglas, C. J.; Hsung, R. P. *Tetrahedron* **2001**, *57*, 459.

(11) For a preliminary disclosure of this work, see: Kurtz, K. C. M.; Hsung, R. P.; Zhang, Y. 229th ACS National Meeting, San Diego, CA, March, 2005; Abstract ORGN-620.

(12) (a) Fuks, R.; Viehe, H. G. *Chem. Ber.* **1970**, *103*, 564. (b) Hsung, R. P.; Zificsak, C. A.; Wei, L.-L.; Douglas, C. J.; Xiong, H.; Mulder, J. A. *Org. Lett.* **1999**, *1*, 1237.

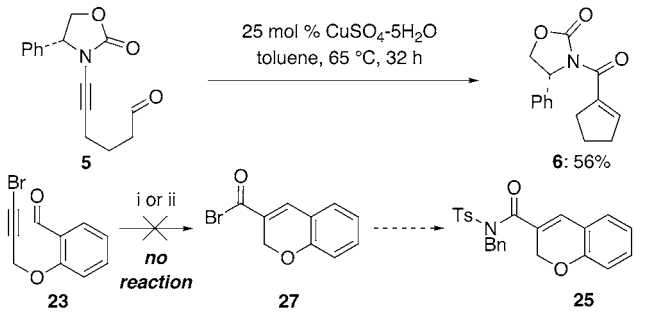
(13) (a) Mori, S.; Shindo, M. *Org. Lett.* **2004**, *6*, 3945. (b) Shindo, M.; Sato, Y.; Yoshikawa, T.; Koretsune, R.; Shishido, K. *J. Org. Chem.* **2004**, *69*, 3912. (c) Shindo, M.; Matsumoto, K.; Mori, S.; Shishido, K. *J. Am. Chem. Soc.* **2002**, *124*, 6840. (d) For a review, see: Shindo, M. *Synthesis* **2003**, 2275.

(14) Procedures and characterizations for all new compounds can be found in Supporting Information.

(15) In some of these cases, trace amounts of the α-chloroenamide were observed.

(16) For some examples of related additions to imide carbonyls, see: (a) Lee, J.; Ha, J. D.; Cha, J. K. *J. Am. Chem. Soc.* **1997**, *119*, 8127. Also see recently: (b) Dvornikovs, V.; Hoye, T. R. 229th ACS National Meeting, San Diego, CA, March, 2005; Abstract ORGN-665.

Scheme 3. $CuSO_4$·$5H_2O$-Catalyzed Metathesis

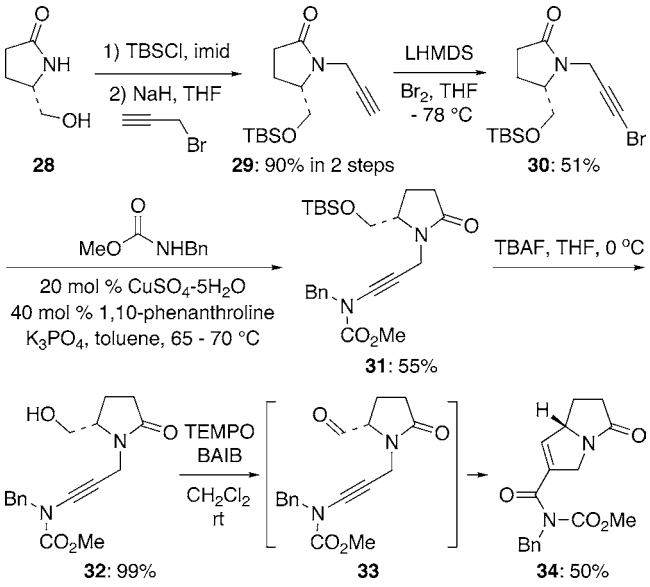


i) 20 mol % $CuSO_4$-$5H_2O$, toluene, 65-70 °C, 40 h. **ii)** 20 mol % $CuSO_4$-$5H_2O$ and 40 mol % 1,10-phenanthroline, toluene, 65-70 °C, 40 h.

To clarify that this is likely a tandem amidation−metathesis and not tandem metathesis−amidation, we carried out two control studies. As shown in Scheme 3, hetero RCM of ynamide **5** could be achieved using 25 mol % of $CuSO_4$·$5H_2O$, although heating at 65 °C was necessary to drive the reaction to completion over 32 h, leading to **6** in 56%. On the other hand, hetero RCM of alkynyl bromide **23** did not occur while heating with 20 mol % of $CuSO_4$·$5H_2O$ or 40 mol % of 1,10-phenanthroline in addition to $CuSO_4$·$5H_2O$ at 65 °C.[17] This effectively rules out acyl bromide **27** as an intermediate leading to chromene **25**. Because we were intrigued with potential reactivities of alkynyl halides[17] such as **23**, we further attempted the ring-closing metathesis by employing 10 mol % of $AgBF_4$ at 90 °C in $(CH_2Cl)_2$ for 14 h, conditions described in Krische's report.[6] However, we only observed a trace amount of the potential hetero RCM product.

Having established the feasibility of an ynamide-carbonyl ring-closing metathesis, we were able to successfully apply this hetero RCM to the synthesis of an optically enriched

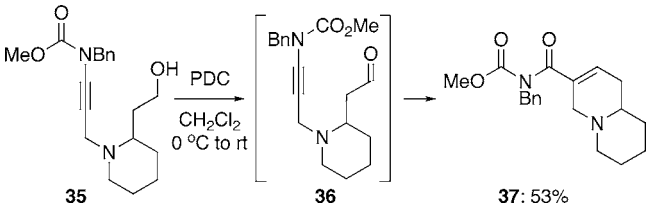
Scheme 4. An Approach to Pyrrolizidine Alkaloids



pyrrolizidine motif. As shown in Scheme 4, starting from (*S*)-5-hydroxymethyl-pyrrolidin-2-one **28**, TBS protection and propargylation of the amide nitrogen gave **29** in good yield over 2 steps. Bromination was carried out with LHMDS and bromine, and subsequent Cu(II)-catalyzed cross-coupling[10b] yielded ynamide **31**. Removal of the TBS protecting group in **31** was followed by oxidation using TEMPO and BAIB (bisacetoxy-iodobenzene).[18] However, under the these oxidative conditions, hetero RCM occurred in situ to give pyrrolizidinone **34** in 50% yield.

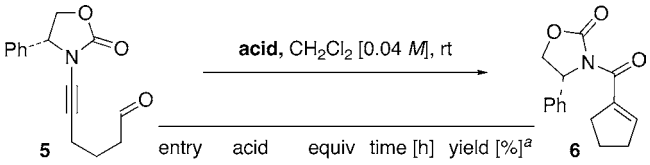
While this success provides a rather facile approach toward pyrrolizidine alkaloids, we were intrigued by this tandem oxidation−metathesis, especially after finding that PDC oxidation of ynamide **35** also led to quinolizidine **37** in 53% overall yield via the same tandem oxidation−metathesis process (Scheme 5).

Scheme 5. Tandem Oxidation−Metathesis



We suspected that HOAc or a related Brønsted acidic species[19] was promoting the hetero RCM during the oxidation of **32** or **35**. As shown in Scheme 6, when in excess, HOAc could promote the RCM of ynamide **5**, although the reaction is much slower than using BF_3-OEt_2 (entry 1 versus entries 2−4). A stronger Brønsted acid such as PNBSA[9d,f] (*p*-nitrobenzenesulfonic acid) was an improvement, albeit still inferior to BF_3-OEt_2 in terms of the required loading and reaction time (entries 5 and 6). It turned out that $HNTf_2$ was again a "magic" Brønsted acid[9a,20,21] with an efficiency comparable to that of BF_3-OEt_2. By using 25 mol %, the

Scheme 6. Comparison with Brønsted Acids



entry	acid	equiv	time [h]	yield [%][a]
1	BF_3-OEt_2	0.25	0.25	74
2	HOAc[b]	0.25	15	trace
3	HOAc[b]	1.25	30	40[c]
4	HOAc[b]	3.25	48	37[d]
5	PNBSA[e]	0.25	15	trace
6	PNBSA	1.25	0.5	73
7	$HNTf_2$	0.25	0.25	64

[a] Isolated yields. [b]Entries 2−4 represent the same continuous reaction in which HOAc was added successively. [c]Conversion of **5**. [d]Isolated yield at 50% conversion. [e]PNBSA = *p*-nitrobenzenesulfonic acid.

RCM product **6** was isolated in 64% yield after only 15 min at room temperature (entry 7). However, overall none of these reactions was as clean as those promoted by BF_3-OEt_2. Nevertheless, the feasibility of using Brønsted acids to promote this hetero ring-closing metathesis provides another useful dimension to this methodology, especially when the RCM occurs in a tandem manner.

In summary, an acid-catalyzed ring-closing ynamide-carbonyl metathesis has been developed. This method is applicable to the construction of carbo- as well as oxygen- and nitrogen-containing heterocycles.

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Supporting Information Available: Experimental and ^{1}H NMR spectral and characterizations for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) For a recent account on methods using alkynyl halides, see: Yoo, W.-J.; Allen, A.; Villeneuve, K.; Tam, W. *Org. Lett.* **2005**, *7*, ASAP.

(18) De Mico, A.; Margarita, R.; Parlanti, L.; Vescovi, A.; Piancatelli, G. *J. Org.* Chem. **1997**, *62*, 6974.

(19) Actually, ynamide **5** (neat) slowly underwent hetero RCM upon standing in the refrigerator, and over a period of 4.5 months, it gave a mixture of **5** and the metathesis product **6** in 2.7:1 ratio.

(20) For some examples of Brønsted acid catalysis, see: (a) Sun, J.; Kozmin, S. A.; *J. Am. Chem. Soc.* **2005**, *127*, 13512. (b) Williams, A. L.; Johnston, J. N. *J. Am. Chem. Soc.* **2004**, *126*, 1612. (c) Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2004**, *126*, 10204. (d) Cossy, J.; Lutz, F.; Alauze, V.; Meyer, C. *Synlett* **2002**, 45. (e) Ishihara, K.; Hiraiwa, Y.; Yamamoto, H. *Synlett* **2001**, 1851.

(21) For a study on the acidity of $HNTf_2$, see: Thomazeau, C.; Olivier-Bourbigou, H.; Magna, L.; Luts, S.; Gilbert, B. *J. Am. Chem. Soc.* **2003**, *125*, 5264.