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Synthesis of Enantiopure Tertiary Skipped Diynes via One-Pot Desymmetrizing TMS-Cleavage

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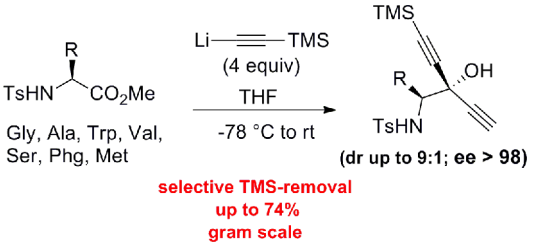
ABSTRACT



Enantiopure tetrasubstituted skipped diynes were readily synthesized from N-protected amino esters upon addition of lithium TMS-acetylide which was found to be desymmetrizing through one-pot selective TMS-cleavage. The deprotection of the TMS group was realized through a one-pot silicon atom attack by the liberated methoxide, which was diastereoselective due to a conformational favorable chelate.

Skipped diynes are 1,4-diyn-1,5-diyl units where an sp^3 carbon separates the two triple bounds.[1,2] They are valuable synthons for the construction of carbon-rich structures and precursors of 1,4-*cis*,*cis*-dienes present in many bioactive compounds.[3] Tertiary chiral diynes are important building blocks that could be used in a broad array of reactivities and transformed into more complex compounds.[4] Diederich has proven the utility of 1,4-diynes as precursors of chiral oligomers,[5] two- and three-dimensional alleno-acetylenic chiral macrocycles.[6] Chauvin and co-workers have described the synthesis of carbo-benzene from 1,4-dialkynylbutatrienes.[7] Another elegant application is the enantioselective synthesis of cyclopentenones via rhodium-catalyzed desymmetrization of 4-diynals reported by Fu.[8]

Recently, skipped diynes were also used in metal-catalyzed intramolecular cyclization to reach heterocycles[9] such as pyrrolines.[10]

Very recently, our group has been involved in the development of a cascade rearrangement of enediynes.[11] In continuation of these investigations, we were interested

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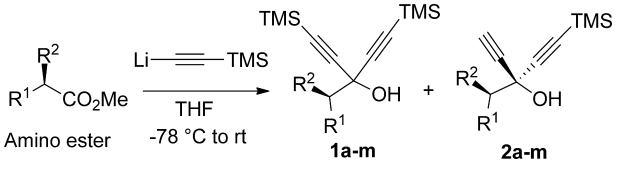
in getting access to pyrrolidines from skipped diynes via the copper-carbenoid[12] mediated allenoate formation followed by an intramolecular aminocyclization according to a methodology developed by Tan.[13] During attempts to reach the substrates, an unprecedented phenomenon was evidenced. Results are detailed hereafter.

Scheme 1. Addition of TMS-Acetylene on Amino Esters Leading to **1** or **2**



As an initial target, we started with the synthesis of the diyne **1a** in a classical way (Scheme 1 and entry 1, Table 1). In the first attempt, to 4 equiv of trimethylsilylacetylene and *n*-BuLi in THF at −78 °C was added Ts-glycine ethyl ester. Unexpectedly, it was observed that, by warming the reaction to rt, the product **2a** was obtained in 37% yield together with only 27% of the expected product **1a**. A desymmetrization of diyne **2a** by a selective deprotection of the TMS group was induced by warming the reaction. This result encouraged us to study further the desymmetrization process because this class of compounds is offering a large potential of applications after their postfunctionalization.

Interestingly, when Ts-alanine methyl ester (Ts-Ala-OMe) was submitted to similar experimental conditions, the monoprotected diyne **2b** was isolated as the major product in 71% yield. More interestingly, the diastereoselective cleavage of one trimethylsilyl group led to a diastereomeric ratio (dr) of 5:1.[14] Furthermore, despite the use of an excess of *n*-BuLi, no racemization occurred when an enantiopure amino ester was used; the enantiomeric excess of the tetrasubstituted diyne was higher than 98% (entry 3, Table 1). The procedure was realized in gram scale (2.6 g of substrate).[15] It is also important to mention that the dr of **2b** is constant during the reaction time.

In order to further explore the system, we envisaged different experiments. The addition of 3 equiv of lithium acetylide to the amino ester afforded 33% of the desired product **2b** and 14% of **1b** (entry 4). 22% of the free diyne (double deprotection) was also isolated which was also enantiopure. When the reaction was conducted with TMS-acetylide generated with MeLi (entry 5), only a small difference in yield was observed as compared to *n*-BuLi conditions. Suppressing the amide hydrogen by replacing it with a methyl group, i.e. Ts-Me-Ala-OMe (entry 6, Table 1), only furnished **1c** in 61% isolated yield, and TMS-cleavage did not occur. This result suggests that the amide anion is presumably involved in a chelated species.

Table 1. Addition of TMS-Acetylene on Amino Esters (AE) Leading to **1** or **2**

entry	AE[a]	*t* (h)		**1** (%)[b]	**2** (%)[b]	dr[c]
1	Gly[d]	4	**a**	27.5	37	–
2	Ala	4	**b**	nd[e]	71	5:1
3	(*S*)-Ala	4	**b**	nd	70 (ee >98)	5:1
4	Ala	4[f]	**b**	14	33	–
5	Ala	4[g]	**b**	8	58	5:1
6	Ala	4[h]	**c**	61	–	–
7	Ala	4[i]	**d**	19	55	6:1
8	Phg	5	**e**	nd	74	9:1
9	Met	5	**f**	nd	69	4:1
10	Lactate	4[j]	**g**	82	–	–
11	pGlu	24[k]	**h**	82	–	–
12	Pro	4	**i**	83	–	–
13	(*S*)-Trp	4	**j**	nd	65 (ee >99)	4:1
14	Ser	4	**k**	nd	50	4:1
15	Val	5	**l**	34	38	2:1
16	*β*-Ala	4	**m**	57	–	–

[a] (±)-N-Ts methyl amino ester elsewhere mentioned. [b] Isolated yield. [c] Diastereomeric ratio determined by ^{1}H NMR of the crude mixture. [d] Ts-Gly-OEt was used. [e] Not determined, yield <5%. [f] 3 equiv of acetylide were used. [g] MeLi was used instead of *n*-BuLi. [h] Ts-Me-Ala was used instead of (±)-Ts-Ala. [i] Ac-Ala was used instead of Ts-Ala. [j] (±)-Methyl lactate was used instead of Ts-Ala. [k] (±)-Methyl pyrroglutamate was used.

At this stage of the investigation, rationalizing the mechanism of the TMS-removal is not obvious.[16] Cleavage with butyl lithium has never been reported, but MeLi-induced deprotection is known to be possible.[17] When the reaction was performed at −78 °C, the expected diyne **1b** was the sole product which confirms that **1b** is the intermediate in the formation of **2b**. In order to elucidate the role of *n*-BuLi in the desymmetrization, we subjected diyne **1b** to a reaction with 1, 2, or 3 equiv of *n*-BuLi at room temperature (Scheme 2). After 4 h, only 15% of **2b** were formed and **1b** was recovered. We can then conclude that *n*-BuLi alone is not implicated in the cleavage of the TMS group.

A second mechanism is possible: Another nucleophile which is present in the medium (namely MeO^- generated from the alanine methyl ester) could be responsible for the silicon atom attack. To validate this hypothesis, the diyne **1b** was subjected to the reaction with lithium methoxide (4 equiv) in THF to reproduce nearly the same conditions as the one-pot desymmetrization process (Scheme 2). After 4 h, the diyne **1b** was completely consumed and **2b** was formed in 46% yield. The diyne **2b**

(12) For an example of furylcyclobutene synthesis from diazoacetates and diynes, see: Barluenga, J.; Riesgo, L.; López, L. A.; Rubio, E.; Tomás, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 7569–7572.

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(14) For asymetric synthesis of diynes from optically active propargyl ketone, see: Convertino, V.; Manini, P.; Schweizer, W. B.; Diederich, F. *Org. Biomol. Chem.* **2006**, *4*, 1206–1208.

(15) When a preliminary generated Ts-Ala-OMe amide anion was added to 3 equiv of lithium acetylide, the same yield was observed.

(16) For the deprotection of the TMS group, see: (a) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 4th ed.; Wiley and Sons: New York, 2000. (c) For review, see: Crouch, R. D. *Tetrahedron* **2004**, *60*, 5833. (d) For a selective TMS acetylene group cleavage in the presence of alkyl silyl ethers, see: Yeom, C.-E.; Kim, M. J.; Choi, W. B.; Kim, M. *Synlett* **2008**, 565–568.

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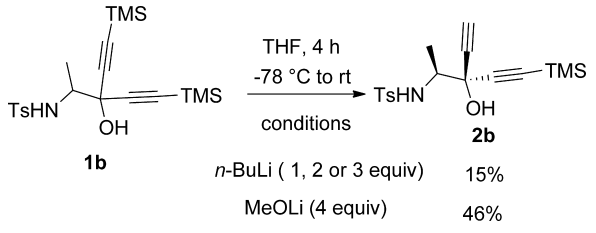
had a diastereomeric ratio identical to that observed above. Additionally, 29% of free diyne (removal of the two TMS) were also isolated. In light of these observations, we can postulate that a chelated lithium methoxide, formed during the addition of the acetylide to the amino ester, is most probably responsible for the TMS-cleavage. Moreover, when the addition of lithium acetylide was carried out on Ts-Ala-O-*t*-Bu instead of Ts-Ala-OMe, the ratio of **2b:1b** was only 1:4. This result confirms the chelation hypothesis in that the bulky alkoxide (*t*-BuO$^-$) would be less effective in the attack of the TMS group.

Scheme 2. Role of *n*-BuLi and MeOLi in the TMS-Removal



The reaction scope of different amino esters has been then studied in the presence of 4 equiv of lithium acetylide. Replacing the sulfonyl group by an acetyl one resulted in slowing down the reaction rate. The yield of **2d** was 55% and 19% for **1d**, but almost the same diastereoselectivity was observed (entry 7, Table1).

N-Ts-phenylglycine methyl ester (Ts-Phg-OMe, entry 8) gave similar results to those obtained with the alanine analogue with the formation of **2e** in 74% isolated yield and 9:1 dr. A methionine-derived substrate was also tested under the same conditions, and **2f** was isolated in 69% with dr of 4:1 (entry 9). To better understand the mechanism, we compared the reactivity of alanine and a lactate derivative. It is interesting to mention that with the latter we observed only the formation of **1g** in 82% isolated yield and no trace of **2g** was detected (entry 10, Table 1). This behavior indicates that the nitrogen atom is probably playing a major role in the selective cleavage of the TMS group. Lithium ligation by an amide anion should be involved in the process as stated above.

When methyl pyrroglutamate was used as the substrate (entry 11), diyne **1h** was formed in 82% yield. Reaction of proline methyl ester showed the same behavior; i.e., no TMS-cleavage occurred (entry 12). In the case of cyclic substrates, the lack of flexibility or a constrained bicyclic transition state would prevent the cleavage of the trimethylsilyl group.

The methodology was also applied to a tryptophan derivative with free nitrogen at the indole moiety at gram scale (3 g of substrate). Interestingly, the product **2i** was isolated in 65% yield with a 4:1 diastereomeric ratio and high ee (> 99.5%, entry 13). An unprotected serine analogue gave also the same reactivity with lithium acetylide, and the desymmetrized compound **2k** was obtained in satisfactory yield (50%) with a dr of 4:1 (entry 14).

An analogy could be made between the chelation of MeOLi with compound **1** and TMEDA-BuLi chelation. A monomer- or dimer-based pathway could be involved.[18] The pro-(*S*) attack of the chelated methoxide on the silicon atom would be diastereoselective giving rise to (*S*,*S*)-**2**. This process is probably sequential (with preliminary methoxide dissociation) and not concerted because of a nonfavored constrained transition state of the attack. The pro-(*R*) attack would be disfavored by the tosyl group; this face is hindered as illustrated by the simplified Chem-3D model of the monomer (Figure 1).[19] Therefore, the sulfonyl group could play a role in driving the MeOLi nucleophile toward the pro-(*S*) trimethylsilylethynyl substituent. Another possible explanation would be the formation of a chiral trans-dimer or any analogue (Scheme 3). This dimer is C_2-symmetric and could be predominant in the medium,[20] by way of favoring the formation of the major (*S*,*S*)-diastereomer. The suggested relative stereochemistry was confirmed by an NOE sequence after derivatization of **2** (*vide infra*).

A more complex tetramer aggregate could also be hypothesized since these complexes have already been discussed.[21]

These hypotheses are coherent; the reaction of Ts-Val-OMe showed low diastereoselectivity because of a bulky isopropyl group which does not allow differentiation of the two faces in the TMS deprotection. This was also confirmed by a longer reaction time in the formation of **2l** as compared to **2b** (entry 15, Table 1).

The mechanism involving a five-membered chelate would be preferred since the use of a β-alanine ester substrate (entry 16, Table 1) did not afford deprotection of the TMS group, and only compound **1m** was isolated. This is again in agreement with the proposed chelate.

In order to demonstrate the relative stereochemistry, we coupled diynes **2** to ethyl diazoacetate in the presence of a catalytic amount of copper(I) iodide[22] to prepare the pyrrolidine motif (Scheme 4).[23]

When the diyne **2b** was reacted with ethyl diazoacetate in the presence of 5 mol % of CuI in acetonitrile, the desired pyrrolidine **6** was obtained in 42% yield as a single diastereoisomer with an ee > 99%. Attempts to demonstrate the relative stereochemistry of pyrrolidines **6** by an NOE sequence were unsuccessful. We therefore

(18) (a) Chadwick, S. T.; Rennels, R. A.; Rutherford, J. L.; Collum, D. B. *J. Am. Chem. Soc.* **2000**, *122*, 8640–8647. (b) Qu, B.; Collum, D. B. *J. Am. Chem. Soc.* **2005**, *127*, 10820–10821. (c) For a computational study of lithium methoxide mixed aggregates, see: Pratt, L. M.; Kwon, O.; Ho, T. C.; Nguyen, N. V. *Tetrahedron* **2008**, *64*, 5314–5321.

(19) (a) For a lithium dianion, see: Gruver, J. M.; West, S. P.; Collum, D. B.; Sarpong, R. *J. Am. Chem. Soc.* **2010**, *132*, 13212–13213. (b) For aminoalkoxide lithium aggregates, see: Khartabil, H. K.; Gros, P. C.; Fort, Y.; Ruiz-López, M. F. *J. Am. Chem. Soc.* **2010**, *132*, 2410–2416. (c) For a review, see: Gros, P.; Fort, Y. *Eur. J. Org. Chem.* **2002**, 3375–3383.

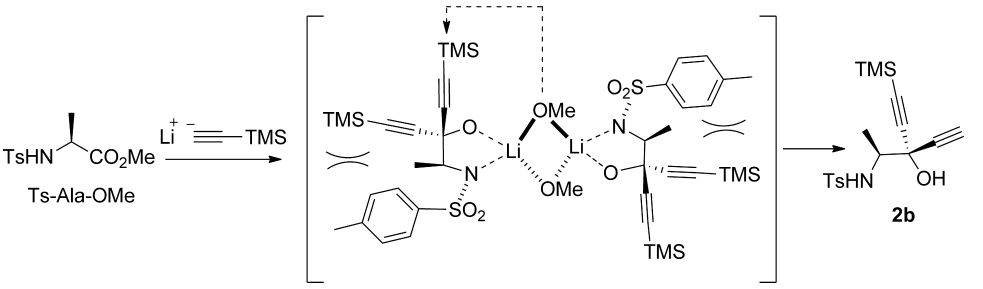
(20) For an example of C_2-symmetric Li-dimer, see: Martin, A.; Kocks, B. M.; Spek, A. L.; Van Koten, G. *J. Organomet. Chem.* **2001**, *624*, 271–286.

(21) Jones, A. C.; Sanders, A. W.; Bevan, M. J.; Reich, H. J. *J. Am. Chem. Soc.* **2007**, *129*, 3492–3493 and references cited therein.

(22) Suarez, A.; Fu, G. C. *Angew. Chem., Int. Ed.* **2004**, *43*, 3580–3582.

(23) For details, see Supporting Information.

Scheme 3. Tentative Rationale for the Observed Diastereoselective TMS-Removal: Methoxide Attack after Its Dissociation[a]



[a] THF and Li^+ have been removed for clarity.

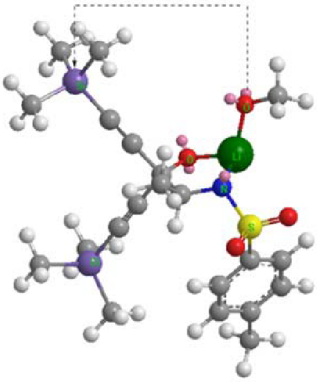
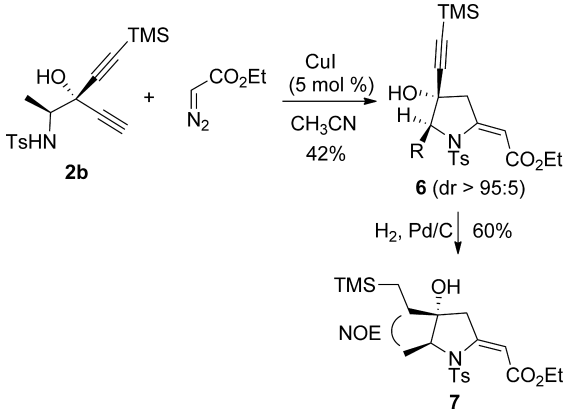


Figure 1. Chem-3D model of the monomer chelate intermediate: methoxide attack after its dissociation.

Scheme 4. NOE Demonstration of the Relative Stereochemistry



hydrogenated the alkyne moiety. The saturated derivative which revealed a clear correlation between the methylene hydrogens and the methyl group of **7** confirmed the speculated relative stereochemistry and therefore (*S*,*S*)-configurations.[24]

In summary, unexpected desymmetrizing deprotection of a TMS group occurred upon addition of TMS-acetylide on amino esters, leading to enantiopure tetrasubstituted diynes. The latter were obtained in good diastereoselectivities and excellent ee's. They represent an interesting class of compounds which offer great potential in post-functionalization. A preliminary sequence to access chiral pyrrolidines has already been realized, and designing more complex molecules is planned as well as theoretical calculations and will be reported in the future.

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Supporting Information Available. Experimental procedures and full characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(24) (*S*,*S*)-Pyrrolidine derived from **2e** was similarly assigned.

The authors declare no competing financial interest.