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Synthesis of conjugated enynes by assembly of three components, ketones, chloromethyl *p*-tolyl sulfoxide, and acetylenes, with the magnesium carbenoid 1,2-CC insertion as the key reaction

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ABSTRACT

The reaction of 1-chlorovinyl *p*-tolyl sulfoxides, which were derived from ketones and chloromethyl *p*-tolyl sulfoxide, with lithium acetylides gave adducts in moderate to good yields. Treatment of the adducts with Grignard reagents resulted in the formation of magnesium carbenoids by the sulfoxide-magnesium exchange reaction. 1,2-Carbon–carbon insertion (1,2-CC insertion) reaction of the generated magnesium carbenoids took place to afford conjugated enynes in good to high yields. This procedure provides a good method for the synthesis of multi-substituted conjugated enynes.

1. Introduction

Conjugated enynes have been receiving considerable attention in organic, synthetic organic, and bio-organic chemistry. The famous enediyne antibiotics,[1] such as calicheamicine[2] and dynemicin[3], have conjugated enyne moiety as the essential structure for their biological activities. Conjugated enynes are also very important compounds in synthetic organic chemistry.[4]

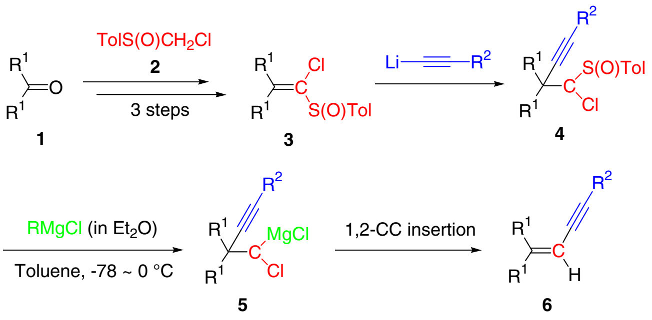
The synthesis of conjugated enynes has received special attention in these days and some methods have already been published. For example, the cross-coupling of vinyl halides with terminal acetylenes in the presence of Pd(0) or Pd(II)/Cu is known to be Sonogashira coupling.[5] Rhodium- or palladium-catalyzed hydroalkynylation of alkynes with terminal and internal alkynes,[6] and dimerization of terminal alkynes with rare-earth metal alkyl complexes[7] are the methods for the synthesis of conjugated enynes from two acetylenes. Some other methods for the synthesis of conjugated enynes have been reported.[8]

We are also interested in the synthesis of conjugated enynes and have published their synthesis based on the reaction of magnesium alkylidene carbenoids with lithium acetylides.[9] In continuation of our interest in the synthesis of conjugated enynes by our original chemistry, the chemistry of magnesium carbenoids, here, we report a new method for the synthesis of conjugated enynes by assembly of three components, ketones, chloromethyl *p*-tolyl sulfoxide, and acetylenes with the magnesium carbenoid 1,2-CC insertion as the key reaction, as shown in Scheme 1.

Thus, 1-chlorovinyl *p*-tolyl sulfoxides **3** were synthesized from ketones **1** and chloromethyl *p*-tolyl sulfoxide **2** in three steps in high overall yields.[10] Treatment of **3** with lithium acetylides resulted in the formation of adducts **4**. Finally, adducts **4** were treated with Grignard reagents to afford magnesium carbenoids **5**, from which 1,2-CC insertion reaction took place to give conjugated enynes **6** in good to high yields.

2. Results and discussion

Representative example is reported in Scheme 2. 1-Chlorovinyl *p*-tolyl sulfoxide **7**, derived from cyclohexane-1,4-dione monoeth-



Scheme 1.

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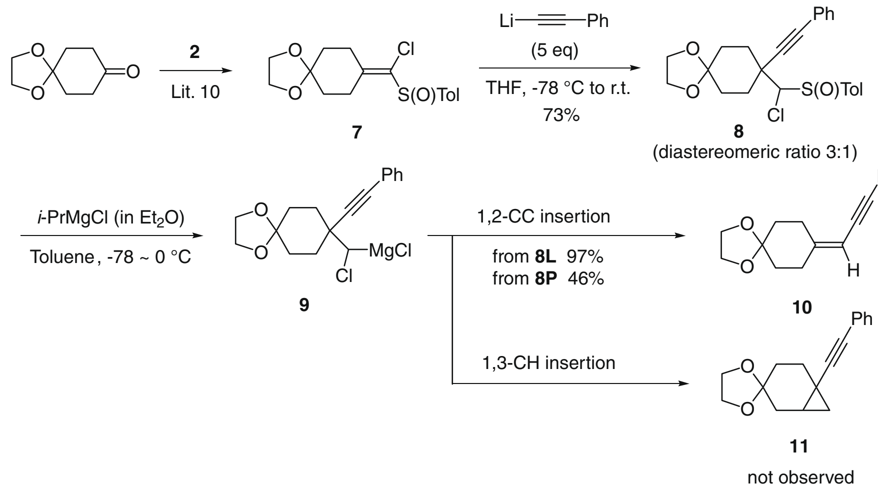
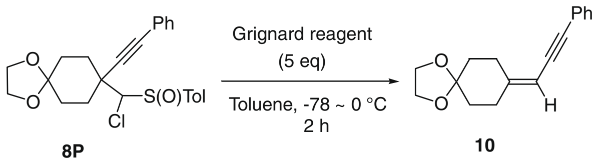


Scheme 2.

ylene ketal and chloromethyl *p*-tolyl sulfoxide **2**,[10] was treated with lithium acetylide (derived from phenylacetylene with *n*-BuLi) to give adduct **8** in 73% yield as easily separable mixture of two diastereomers (less polar adduct **8L** and more polar adduct **8P** on silica gel TLC; with the ratio of 3:1, respectively). Treatment of a toluene solution of the main diastereomer **8L** with 5 equiv of *i*-PrMgCl (in ether) at −78 °C resulted in the formation of magnesium carbenoid **9**. The reaction mixture was slowly allowed to warm to 0 °C to give a very clean reaction mixture in which we observed a single product. At first, based on our experiences, we anticipated that bicyclo[4.1.0]heptane **11** was the product by the 1,3-CH insertion reaction of magnesium carbenoid **9**.[11] However, very interestingly, the product was confirmed to be conjugated enyne **10** (97% yield) and no bicyclo[4.1.0]heptane **11** was obtained. The same reaction of the minor diastereomer **8P** gave the same conjugated enyne **10**; however, the yield was moderate (46%). Significant difference about the yields of **10** from diastereomers **8P** and **8L** was observed; however, the real reason is not clear at present.

As we recognized that this reaction is unprecedented and would become quite an interesting way for preparing conjugated enynes, at first, increasing the yield of **10** from the minor diastereomer **8P** was investigated and the results are summarized in Scheme 3. As shown in the table in Scheme 3, cyclopentylmagnesium chloride (*c*-PentMgCl) was found to be the best Grignard reagent investigated and 71% yield of **10** was obtained.

Next, conditions for the addition reaction of **7** with lithium phenylacetylide were investigated and the results are summarized in Table 1. The conditions in entry 1 are the aforementioned ones. The addition reaction can be started at −30 °C and a somewhat better yield was obtained (entry 2). Starting the reaction at 0 °C gave a diminished yield (entry 3). Using LDA instead of *n*-BuLi gave a much better yield of **8** (entry 4).[12] Toluene and diethyl ether were proved to be unsuitable solvents in this reaction (entries 6 and 7). We decided to use the conditions in entry 4 in this study.



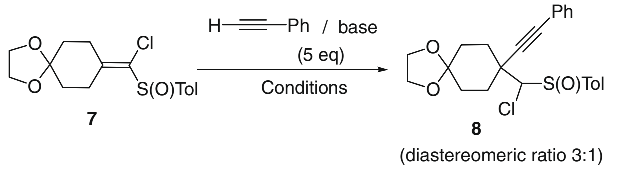
Grignard reagent (in Et_2O)	**10** / Yield / %
i-PrMgCl	46
EtMgCl	40
PhMgCl	51
c-PentMgCl	71

Scheme 3. The yield for the reaction of **8P** with Grignard reagents.

By using the above-mentioned conditions, generality of this procedure was investigated and the results are summarized in Table 2. Thus, 1-chlorovinyl *p*-tolyl sulfoxides **3** derived from cyclohexanone, cyclododecanone, cyclopentadecanone, and 4-heptanone were used as the representative examples of the starting material, and phenylacetylene was used as the representative example of the acetylene. The addition reaction of 1-chlorovinyl *p*-tolyl sulfoxides derived from large-membered cyclic ketones and an acyclic ketone was not completed and about 30% yield of adducts **12b–d** were obtained (entries 3–8). In these cases, a significant amount of the staring materials was recovered and the yields calculated based on the consumed starting material were not too bad.

Treatment of adducts **12a–d** with Grignard reagents was conducted in the same way as described above. The reaction of **12a**,

Table 1
Addition reaction of lithium acetylide derived from phenylacetylene to 1-chlorovinyl *p*-tolyl sulfoxide **7** to afford adduct **8**

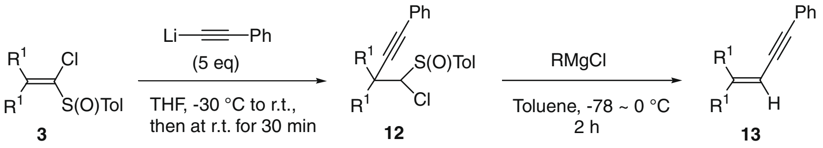


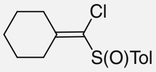
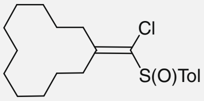
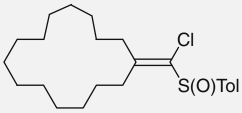
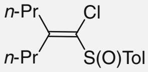
Entry	Conditions				**8**
	Temp (°C)	Time (h)	Solvent	Base	Yield (%)
1	−78–rt	3	THF	*n*-BuLi	73
2	−30–rt	2	THF	*n*-BuLi	75
3	0–rt	1	THF	*n*-BuLi	60
4	−30–rt	2	THF	LDA	80
5	−30–rt	2	THF	LHMDS	48
6	−30–rt	2	Toluene	LDA	20[a]
7	−30–rt	2	Et_2O	LDA	19[b]

[a] Starting material **7** was recovered in 69% yield.
[b] Starting material **7** was recovered in 64% yield.

Table 2

Addition reaction of 1-chlorovinyl *p*-tolyl sulfoxides **3** with lithium acetylide generated from phenylacetylene with LDA and the reaction of adducts **12** with Grignard reagents to give conjugated enynes **13**



Entry	3	12 Yield (%) (diastereomeric ratio)[a]	RMgCl	13 Yield (%)
1		**12a** 73 (2:1)	*i*-PrMgCl	98 (from **12aL**)
2			*c*-PentMgCl	42 (from **12aP**)
3		**12b** 36 (3:2)[b]	*i*-PrMgCl	93 (from **12bL**)
4			*c*-PentMgCl	96 (from **12bP**)
5		**12c** 33 (3:2)[c]	*i*-PrMgCl	91 (from **12cL**)
6			*c*-PentMgCl	99 (from **12cP**)
7		**12d** 29 (9:2)[d,e]	*i*-PrMgCl	98 (from **12dL**)
8			*c*-PentMgCl	99 (from **12dP**)

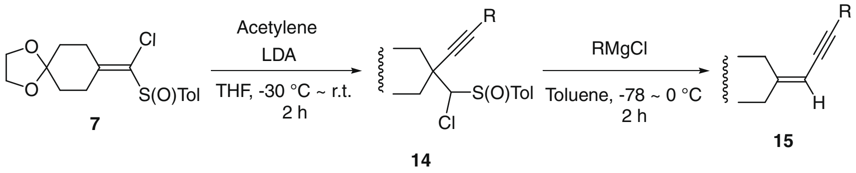
[a] The ratio for less polar product (L) and more polar product (P) on silica gel TLC.
[b] Starting material was recovered in 27% yield.
[c] Starting material was recovered in 42% yield.
[d] Starting material was recovered in 59% yield.
[e] The reaction mixture was slowly allowed to warm from −30 °C to room temperature for 2 h, then stirred at room temperature for 2 h.

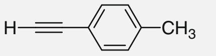
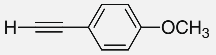
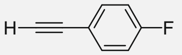
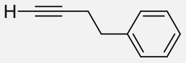
which has medium-sized cyclic carbon chain, showed significant difference with respect to the two diastereomers again (entries 1 and 2). Quite interestingly, in the reaction with adducts bearing a large-membered cyclic carbon chain (**12b**, **c**) or acyclic carbon chain (**12d**), both the diastereomers gave almost quantitative yields of conjugated enynes **13** (entries 3–8). Generality of this procedure was verified from the results shown in Table 2.

Next, scope and limitation of the acetylenes were studied and the results are summarized in Table 3. As shown in Table 3, addition reaction of lithium acetylides derived from arylacetylenes and silylacetylenes with 1-chlorovinyl *p*-tolyl sulfoxide **7** proceeded smoothly to afford moderate to good yields of adducts **14a–d** (entries 1–8). However, interestingly, the addition reaction of lithium acetylide derived from an alkylacetylene, 4-phenyl-1-

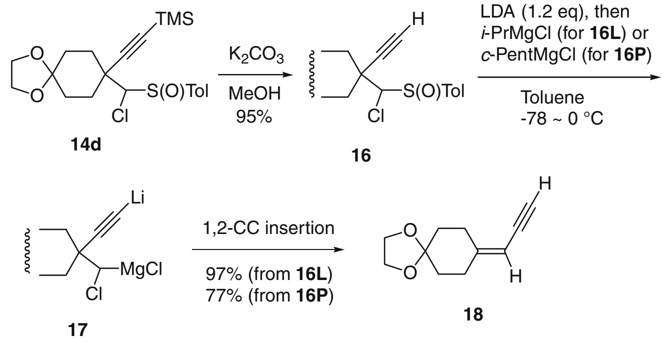
Table 3

Addition reaction of 1-chlorovinyl *p*-tolyl sulfoxides **7** with lithium acetylide generated from arylacetylenes with LDA and reaction of the adducts with Grignard reagents to give conjugated enynes **15**



Entry	Acetylene	14 Yield (%) (diastereomeric ratio)[a]	RMgCl	15 Yield (%)
1		**14a** 69[b] (2:1)	*i*-PrMgCl	**15a** 93 (from **14aL**)
2			*c*-PentMgCl	**15a** 54 (from **14aP**)
3		**14b** 55[c] (2:1)	*i*-PrMgCl	**15b** 93 (from **14bL**)
4			*c*-PentMgCl	**15b** 80 (from **14bP**)
5		**14c** 66 (2:1)	*i*-PrMgCl	**15c** 95 (from **14cL**)
6			*c*-PentMgCl	**15c** 56 (from **14cP**)
7	$H-C\equiv C-Si(CH_3)_3$	**14d** 77 (5:2)	*i*-PrMgCl	**15d** 99 (from **14dL**)
8			*c*-PentMgCl	**15d** 52 (from **14dP**)
9		—[d]		

[a] The ratio for less polar product (L) and more polar product (P) on silica gel TLC.
[b] The reaction mixture was slowly allowed to warm from −30 °C to room temperature for 2 h and then stirred for 30 min at the temperature.
[c] Starting material was recovered in 15% yield.
[d] No addition reaction was observed.



Scheme 4.

butyne, did not proceed at all (entry 9). Generation of the magnesium carbenoids was conducted with *i*-PrMgCl or *c*-PentMgCl, and similar results, less polar adducts gave almost quantitative yields of conjugated enynes **15** and more polar adducts gave lower yields, were observed (compare the results in Table 3 with those shown in Scheme 2 and Table 2, entries 1 and 2).

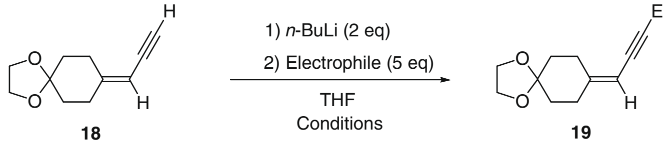
The conjugated enyne without a substituent on the acetylenic carbon was synthesized from **14d** as shown in Scheme 4. Thus, the trimethylsilyl group of **14d** was cleaved with potassium carbonate to give terminal acetylene **16** in almost quantitative yield. Acetylene **16** was treated with 1.2 equiv of LDA followed by a Grignard reagent to afford conjugated enyne **18** through magnesium carbenoid **17** in good to high overall yields.

As mentioned above, lithium acetylide derived from alkylacetylene did not give adduct **4** (see Table 3, entry 9). This result implies that we could not synthesize conjugated enynes bearing an alkyl group on the acetylenic carbon by the presented method. However, they can be obtained by the alkylation of the aforementioned conjugated enyne **18**. The results for the treatment of **18** with *n*-BuLi followed by electrophiles including iodoalkanes are summarized in Table 4.

Thus, as shown in Table 4, conjugated enyne **18** was treated with 2 equiv of *n*-BuLi followed by iodomethane (5 equiv) in THF at 0 °C and the reaction mixture was stirred at 0 °C for 30 min to give conjugated enyne bearing a methyl group on the acetylenic carbon **19a** in 69% yield (entry 1). The alkylation with iodoethane and 1-iodohexane required somewhat forcing conditions and an additive (HMPA); however, the desired conjugated enynes having ethyl (**19b**) or *n*-hexyl group (**19c**) were obtained in moderate to good yields (entries 2 and 3).[13] Benzoyl chloride and ethyl chloroformate gave the desired products **19d** and **19e**, respectively, in up to 64% yield (entries 4 and 5). Benzaldehyde reacted with the lithium acetylide to give adduct **19f** in 65% yield (entry 6). Even iodine reacted to give iodoacetylene **19g** in good yield (entry 7).

Table 4

Treatment of conjugated enyne **18** with *n*-BuLi followed by electrophiles to afford conjugated enynes **19**



Entry	Electrophile	E	Additive	Conditions		19	
				Time	Temp (°C)		Yield (%)
1	CH_3I	CH_3	non	30 min	0	**19a**	69
2	CH_3CH_2I	CH_3CH_2	HMPA (6 equiv)	o.n.	rt	**19b**	52
3	$CH_3(CH_2)_5I$	$CH_3(CH_2)_5$	HMPA (6 equiv)	o.n.	rt	**19c**	82
4	PhCOCl	PhCO	non	30 min	0	**19d**	64
5	$ClCOOC_2H_5$	$COOC_2H_5$	non	30 min	0	**19e**	57
6	PhCHO	PhCH(OH)	non	30 min	0	**19f**	65
7	I_2	I	non	30 min	0	**19g**	79

In conclusion, we have found that the magnesium carbenoids bearing an acetylenic group on the β-position gave conjugated enynes via 1,2-CC insertion reaction in good to high yields. Both conjugated enynes bearing an aromatic group and an alkyl group on the acetylenic carbon can be obtained by the presented procedure. The chemistry presented here is unprecedented and should contribute to the synthesis of conjugated enynes.

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12. *Addition of lithium phenylacetylide to* **7** *and the synthesis of conjugated enyne* **10**: Phenylacetylene (0.055 mL; 0.5 mmol) was added to a solution of LDA (0.5 mmol) in 1 mL of dry THF in a flame-dried flask under argon atmosphere dropwise at 0 °C with stirring. The reaction mixture was stirred for 10 min at 0 °C and cooled to −30 °C. A solution of **7** (33 mg; 0.1 mmol) in 1 mL of THF was added to the solution and the reaction mixture was slowly allowed to warm to room temperature for 2 h. The reaction was quenched with satd aq NH_4Cl and the whole mixture was extracted three times with $CHCl_3$. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The product was purified by flash column chromatography (hexane/AcOEt) to give **8L** (25.7 mg; 60%) as colorless crystals and **8P** (8.5 mg; 20%) as colorless oil. **8L**: mp 137.5–138 °C (hexane/AcOEt); IR (KBr) 2957, 2884, 1152, 1110, 1087 (SO), 1054 (SO), 809, 758, 693 cm^{-1}; ^1H NMR δ 1.75–1.93 (3H, m), 2.07–2.25 (5H, m), 2.41 (3H, s), 3.92–4.02 (4H, m), 4.40 (1H, s), 7.29–7.37 (5H, m), 7.46–7.55 (4H, m). Anal. Calcd for $C_{24}H_{25}ClO_3S$: C, 67.20; H, 5.87; Cl, 8.26; S, 7.48. Found: C, 67.06; H, 6.02; Cl, 8.14; S, 7.39. **8P**: IR (neat) 2954, 2883, 2232, 1164, 1107, 1083 (SO), 1052 (SO), 809, 757, 692 cm^{-1}; ^1H NMR δ 1.70–1.90 (3H, m), 1.94–2.25 (4H, m), 2.40 (3H, s), 2.72–2.80 (1H, m), 3.90–4.02 (4H, m), 4.40 (1H, s), 7.27–7.34 (5H, m), 7.44–7.48 (2H, m), 7.70–7.75 (2H, m). MS *m*/*z* (%) 428 (M^+, 2), 289 (38), 253 (100), 167 (61), 139 (33), 99 (40). Calcd for $C_{24}H_{25}ClO_3S$: *M*, 428.1213. Found: *m*/*z* 428.1219. To a flame-dried flask under argon atmosphere was added dry toluene (3 mL) followed by *i*-PrMgCl (2.0 M solution in diethyl ether; 0.195 mL, 0.39 mmol) at −78 °C. A solution of **8L** (33.6 mg; 0.078 mmol) in toluene (1 mL) was added dropwise to the solution

of the Grignard reagent with stirring and the reaction mixture was slowly allowed to warm to 0 °C for 2 h. The reaction was quenched with satd aq NH_4Cl and the whole mixture was extracted three times with $CHCl_3$. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The product was purified by flash column chromatography (hexane/AcOEt) to give **10** (19.2 mg; 97%) as colorless oil. IR (neat) 2951, 2882, 2197, 1120, 1087, 1034, 906, 756, 690 cm^{-1}; ^1H NMR δ 1.72–1.79 (4H, m), 2.36–2.42 (2H, m), 2.63–2.68 (2H, m), 3.97–4.00 (4H, m), 5.50 (1H, s), 7.27–7.32 (3H, m), 7.41–7.44 (2H, m). MS *m*/*z* (%) 254 (M^+, 100), 209 (20), 192 (20), 167 (57), 153 (20), 115 (19). Calcd for $C_{17}H_{18}O_2$: *M*, 254.1307. Found: *m*/*z* 254.1303.

13. *Synthesis of conjugated enyne bearing hexyl group **19c** from* **18**. A solution of **18** (20.6 mg; 0.12 mmol) in 1 mL of THF and HMPA (0.12 ml; 0.72 mmol) was added to a solution of *n*-BuLi (1.57 M solution in hexane, 0.15 mL; 0.24 mmol) in 1.3 mL of dry THF in a flame-dried flask under argon atmosphere at 0 °C and the reaction mixture was stirred for 10 min to generate lithium acetylide. Iodohexane (0.09 mL; 0.6 mmol) was added to the reaction mixture dropwise with stirring and the whole mixture was stirred at room temperature overnight. The reaction was quenched with satd aq NH_4Cl and the whole mixture was extracted three times with $CHCl_3$. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The product was purified by flash column chromatography (hexane/AcOEt) to give **19c** (25.7 mg; 82%) as light yellow oil. IR (neat) 2931, 2858, 1120, 1083, 1035, 908, 684 cm^{-1}; ^1H NMR δ 0.89 (3H, t, *J* = 6.8 Hz), 1.24–1.59 (8H, m), 1.66–1.78 (4H, m), 2.27–2.36 (4H, m), 2.50–2.58 (2H, m), 3.97 (4H, s), 5.26 (1H, s). MS *m*/*z* (%) 262 (M^+, 100), 233 (14), 191 (12), 147 (13), 119 (14), 105 (19), 91 (24), 80 (14). Calcd for $C_{17}H_{26}O_2$: *M*, 262.1933. Found: *m*/*z* 262.1941.