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Copper-Free Synthesis of Skipped Diynes via Cross-Coupling Reactions of Alkynylalanes with Propargylic Electrophiles

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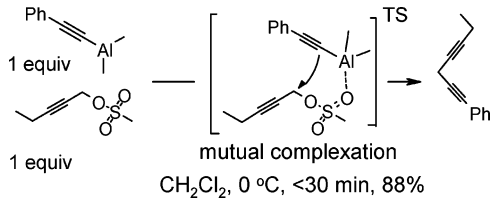
ABSTRACT



Alkynylalanes provide a new, copper-free route to skipped diynes when combined with propargylic electrophiles bearing an aluminum-complexing leaving group. The reaction is mild, efficient, and, *in contrast to copper-mediated methods*, highly regioselective.

Extensive research attention has rendered traditionally copper-mediated $C_{sp}-C_{sp}$[1] and $C_{sp}-C_{sp^2}$[2] cross-coupling reactions into copper-free[3] and, recently, even into entirely transition-metal-free procedures.[4]

Less focus has been placed on $C_{sp}-C_{sp^3}$ cross-coupling reactions,[5] and typically these methods still rely on generation of a copper-acetylide which reacts with an electrophilic halide or sulfonates.[6]

Our interest lies in methylene-bridged 1,4-diynes (commonly referred to as skipped diynes) which are valuable intermediates and target molecules for natural product synthesis,[7] as well as attractive synthons for construction of novel organic molecules[8] and coordination complexes.[9] The principle approaches to such skipped diynes involve cross-coupling copper-acetylides with propargylic electrophiles.[10] The requisite acetylenic copper species is usually generated in situ using stoichiometric amounts of copper(I) in the presence of a weak base such as potassium carbonate. Alternatively, catalytic quantities of copper(I) suffice when preformed magnesium-acetylides are employed as coupling partners.[8,11]

Although widely employed, this copper-mediated cross-coupling approach to 1,4-diynes can suffer from a number of limitations. First, the yield of the desired coupled product **1** can be reduced due to competitive formation of regioiso-

(1) (a) Glaser, C. *Ber.* **1869**, *2*, 422. (b) Eglinton, G.; Galbraith, A. R. *Chem. Ind.* **1956**, 737. (c) Hay, A. S. *J. Org. Chem.* **1960**, *25*, 1275. (d) Chodkeiwicz, W.; Cadiot, P. *C. R. Soc. Fr.* **1955**, *241*, 1055.

(2) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467.

(3) (a) Negishi, E.; Anastasia, L. *Chem. Rev.* **2003**, *103*, 1979. (b) For copper-free Sonogashira coupling, see: Soheili, A.; Albaneze-Walker, J.; Murry, J. A.; Dormer, P. G.; Hughes, D. L. *Org. Lett.* **2003**, *5*, 4191.

(4) (a) Jan, J.; Wang, L. *Synth. Commun.* **2005**, *35*, 2333. (b) Leadbeater, N. E.; Marco, M.; Tominack, B. J. *Org. Lett.* **2003**, *5*, 3919.

(5) It should be noted that in particular advances have been made in the use of tris(alkynyl)indiums with benzyl bromide catalyzed by $Cl_2Pd(dppf)$ (Perez, J.; Perez-Sestelo, L.; Sarandeses, A. *J. Am. Chem. Soc.* **2001**, *123*, 4155.) and in the use of alkynylboron dichlorides with benzyl, benzylallyl, and benzylpropargyl secondary alcohols (Kabalka, G. W.; Yao, M.-L.; Borella, S. *Org. Lett.* **2006**, *8*, 879.).

(6) For a general review, see: Normant, J. F. *Synthesis* **1972**, 63.

(7) (a) Durand, S.; Parrain, J.-L.; Santelli, M. *J. Chem. Soc., Perkin Trans. 1* **2000**, 253. (b) Tedeschi, C.; Saccavini, C.; Maurette, L.; Soleilhavoup, M.; Chauvin, R. *J. Organomet. Chem.* **2003**, *670*, 151.

(8) Such as pericyclynes: Maurette, L.; Godard, C.; Frau, S.; Lepetit, C.; Soleilhavoup, M.; Chauvin, R. *Chem.−Eur. J.* **2001**, *7*, 1165.

(9) Cobalt complexes and ruthenium complexes have been described: (a) Guo, R.; Green, J. R. *Chem. Commun.* **1999**, 2503. (b) Cabeza, J. A.; Grepioni, F.; Moreno, M.; Riera, V. *Organometallics* **2000**, *19*, 5424.

(10) For these types of couplings and a few copper-free references, see ref 7 and references cited therein.

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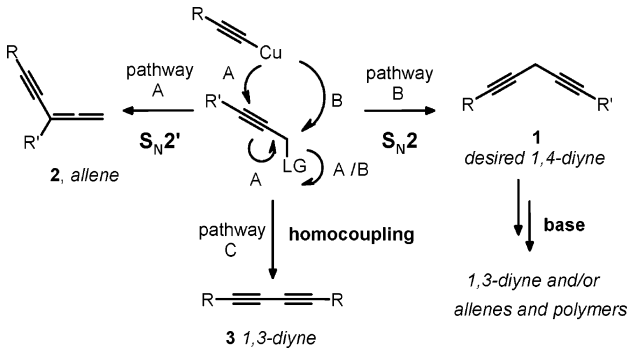
meric alkynylallenes **2** which result from an undesired nucleophilic attack by the acetylenic copper species at the triple bond (S_N2') rather than at the sp^3 carbon of the electrophile (pathways A and B, respectively, in Scheme 1).

Scheme 1. Competitive Reactions Involved in the Formation of 1,4-Skipped Diynes **1**

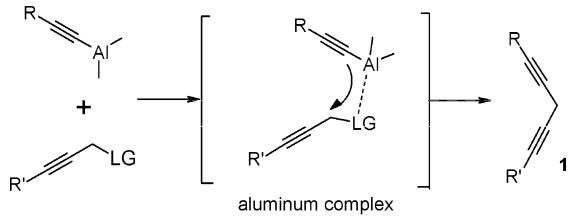


In turn, these allenic products are prone to polymerization. Second, undesired isomerization of the 1,4-diyne **1** to the corresponding allenes and eventually the 1,3-isomer is possible even under the weakly basic conditions, thus lowering the yield and complicating the isolation of the skipped diynes.[12] Finally, the acetylenic copper species can be prone to oxidative homocoupling (pathway C, Scheme 1).[13]

During the course of our work devoted to alternative approaches to skipped 1,4-diynes which address the aforementioned limitations of copper(I)-mediated couplings, we have recently reported a method obviating the use of base which employs a bimetallic silicon−copper system.[14] Herein, we present the first use of alkynylalanes for the preparation of methylene-bridged 1,4-diynes via their cross-coupling with a selection of propargylic electrophiles. This novel $C_{sp}-C_{sp^3}$ bond-forming reaction relies on the sole use of a monometallic aluminum-alkynyl species and thereby circumvents the ubiquitous need for copper in such cross-coupling reactions.

The origin of this work rests on the expectation that if an alkynylalane is generated in the presence of a propargylic electrophile capable of complexing with the Lewis acid aluminum species a coupling reaction could ensue and lead to the formation of a skipped diyne. The successful transfer of the alkynyl residue would rely in part on weakening the $C_{sp}-$aluminum σ bond, as well as the propargylic $C_{sp^3}-$leaving group bond, as a consequence of the proposed complexation shown in Scheme 2.

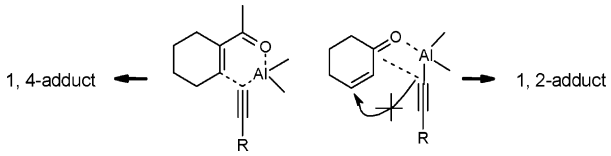
Scheme 2. 1,4-Diynes via Mutual Activation of Alkynylalanes and Propargylic Electrophiles



LG : Leaving group containing residues capable of complexing to the alane

In analogy, Hooz et al.[15] also invoke such aluminum complexes to explain the different regioselective outcomes of alkynylalane additions to α,β-unsaturated endo- and exocyclic ketones as shown in Scheme 3.

Scheme 3. Regioselectivity of the Addition of Alkynylalane to α,β-Unsaturated Ketones



The alkynylalane adds to give the 1,4-Michael addition product in acyclic systems, but in conformationally restricted systems such as cyclohexenylethanone and cyclohexenone, only the α,β-unsaturated ketone which is able to adopt a cisoid conformation in the transition state complex leads to a 1,4-Michael adduct.[16]

A differentiation should be made between these types of mutual complexation couplings and those between alanes and allylic,[17] benzylic,[18] and tertiary[19] electrophiles considered to proceed by a cationic S_N1 mechanism which, through a lack of stabilization (as well as a lack of regioisomers),[20] would be implausible here.

For the preparation of our base-sensitive diynes (vide supra), it was preferable to avoid the use of strongly basic transmetalation methods (alkynyl-alkali metal−Al exchange) commonly applied for the generation of the requisite alkynylalane species[21] (pathway A in Scheme 4).

(11) (a) Brandsma, L. *Synthesis of Acetylenes, Allenes and Cumulenes*; Elsevier: Amsterdam, 2003 and references therein. (b) Jeffery, T.; Guenot, S.; Linstrumelle, G. *Tetrahedron Lett.* **1992**, *33*, 5757. (c) Hansen, T. V.; Stenstrom, Y. *Tetrahedron: Asymmetry* **2001**, *12*, 1407. (d) Spinella, A.; Caruso, T.; Martino, M.; Sessa, C. *Synlett* **2001**, 1971. (e) For an exception: Padmanabhan, S.; Nicholas, K. M. *Tetrahedron Lett.* **1983**, *24*, 2239.

(12) (a) Mel'nikova, V. I.; Pivnitskii, K. K. *Zh. Neorg. Khim.* **1990**, *26*, 78. (b) Mathai, I. M.; Taniguchi, H.; Miller, S. I. *J. Am. Chem. Soc.* **1967**, *89*, 115. (c) Hungerford, N. L.; Kitching, W. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1839.

(13) (a) Trost, B. M.; Fleming, I. *Comprehensive Organic Synthesis*; Pergamon: Oxford, 1991; Vol. 5, p 1543. (b) Bohlmann, F.; Schoenowsky, H.; Inhoffen, E.; Grau, G. *Chem. Ber.* **1964**, *97*, 794.

(14) Montel, F.; Beaudegnies, R.; Kessabi, J.; Martin, B.; Muller, E.; Wendeborn, S.; Jung, P. M. J. *Org. Lett.* **2006**, *8*, 1905.

(15) Hooz, J.; Layton, R. B. *J. Am. Chem. Soc.* **1971**, *93*, 7320.

(16) This limitation can be overcome indirectly by employing a nickel catalyst: (a) Schwartz, J.; Carr, D. B.; Hansen, R. T.; Dayrit., F. M. *J. Org. Chem.* **1980**, *45*, 3053. (b) Kwak., Y.-S.; Corey, E. J. *Org. Lett.* **2004**, *6*, 3385.

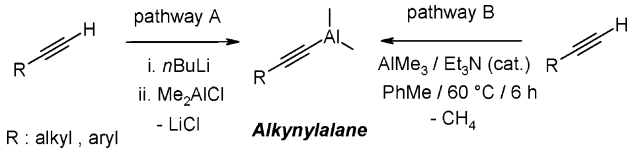
(17) (a) Trost, B. M.; Ghadiri, M. R. *J. Am. Chem. Soc.* **1986**, *108*, 1098. (b) Gallina, C. *Tetrahedron Lett.* **1985**, *26*, 519.

(18) Miller, D. B. *J. Org. Chem.* **1966**, *31*, 908.

(19) Negishi, E.; Baba, S. *J. Am. Chem. Soc.* **1975**, *97*, 7385.

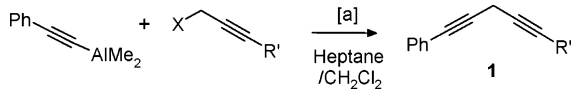
(20) Flemming, S.; Kabbara, J.; Nickisch, K.; Westermann, J.; Mohr, J. *Synlett* **1995**, 183.

Scheme 4. Approaches to Alkynylalanes



We therefore opted for a salt-free method recently reported by Micouin[22] which involves treating terminal alkynes with trimethylaluminum in the presence of only catalytic amounts of triethylamine (pathway B, Scheme 4). For our purposes, the alkynylalane of phenyl acetylene was prepared according to Micouin's conditions[22] and employed as a model substrate for coupling with numerous propargyl electrophiles. The coupling procedure is straightforward and simply involves dropwise addition of the phenylethynylalane to the electrophile in dichloromethane at 0 °C or at room temperature.[23] The outcomes of these reactions are reported in Table 1. Our first attempt at generating the 1,4-diyne using pent-2-ynyl acetate as a coupling partner led to an undesired double 1,2-addition to the carbonyl group of the ester function (entry 1, Table 1).

Table 1. Cross-Coupling Reaction of Phenylethynylalane with Propargylic Electrophiles: The Effect of the Leaving Group[a]



entry	equiv of alane	X	R′	temp (°C)	time (h)	yield of **1**[b] (%)
1	2	OAc	Et	rt	–	–[c]
2	2	OAc	H	rt	–	–[d]
3	2	OCOOMe	Et	rt	12	15
4	2	$OPO(OEt)_2$	Et	0−rt	8	79
5	2	$OPO(OPh)_2$	Et	rt	10	85
6	2	$OPO(Ph)_2$	Et	rt	8	80
7	2	OSO_2Me	Et	0	2	92
8	1	OSO_2Me	H	0	0.5	88
9	2	OSO_2pTol	Et	0	1	96
10	2	OSO_2pTol	H	0	2	85
11	2	Cl	Et	rt	–	–[d]
12	2	I	Et	rt	15	–[d]
13	2	OMe	H	rt	–	–[d]
14	2	OCH_2OMe	Et	rt	–	–[d]

[a] Reaction conditions:[23] $PhC{\equiv}CAlMe_2$ in (CH_2Cl_2)/heptane (1 M) was added to the electrophile in CH_2Cl_2, and the reaction was followed by GC. [b] Isolated yields. [c] Major isolated component is a result of a double addition to the carbonyl of the acetate providing $PhC{\equiv}CC(OH)(CH_3)C{\equiv}CPh$. [d] Recovery of phenylacetylene after a hydrolytic quench and slow degradation of the propargylic electrophile.

On the basis of this result, we rationalized that a more suitable electrophilic coupling partner could be that which possesses a group with the ability to complex the alkynylaluminum species but which would be less subject to undesirable nucleophilic attack. One such candidate is propargyl carbonate which upon reaction with phenylethynylalane led to the desired skipped diyne product in 15% yield (entry 3),[24,25] encouraging our further investigation.

Our attention was drawn toward the incorporation of non-carbonyl-based propargylic functionalities, such as phosphates and phosphinates, known for their inertness toward nucleophilic attack at the phosphorus−oxygen double bond. Initially, coupling of the easily prepared propargyl diethylphosphate with 2 equiv of phenylethynylalane led to a clean reaction according to GC and ^1H NMR analysis of the crude material. Our desired skipped diyne **1** had been generated for the first time not only in high isolated yield (79%, entry 4) but also free from the regioisomeric alkynylallene. Attempts to carry out the reaction of propargyl phosphates with just 1 equiv of the alkynylalane resulted in absolutely no consumption of the electrophile even in the presence of different Lewis acids ($ZnCl_2$, ZnI_2, $Al(OiPr)_3$, $Al(OiBu)_3$). In addition, the cross-coupling reactions of the corresponding readily available diphenylphosphate and diphenylphosphinate with phenylethynylalane were similarly regioselective and equally effective (entries 5 and 6, respectively).

An added improvement for the preparation of methylene-bridged diynes such as **1** came from the observation that inexpensive propargylic methyl- and tolyl-sulfonates were even better partners in this novel alkynylalane-mediated cross-coupling because they led to the highest yields of the skipped diyne (cf. entries 7−10 vs entries 4−6). Advantageously, just stoichiometric amounts of alkynylalane were required when the mesylate was used as the coupling partner (entry 8). Furthermore, the propargylic sulfonates—whether derived from terminal or internal acetylenes—were found to be as reactive at lower temperatures (−30 °C for the mesylate and 0 °C for the tosylate) as they were at room temperature.

Particularly noteworthy is the high yield of the regioselective reaction between the terminal propargylic sulfonates and the alkynylalane (entries 8 and 10) because literature precedent,[26] as well as our own experiences,[27] has shown that S_N2' attack predominates on terminal propargylic electrophiles when the nucleophilic coupling partner is an alkynyl-copper (presumably resulting in allene formation and subsequent polymerization).

Of consideration is that electrophiles which possess a chloride, iodide, methoxy, or methoxymethyl substituent at the propargylic position did not cross-couple with the alkynylalane under these conditions. Upon extended reaction times, only inseparable mixtures were generated in each

(21) (a) Shinoda, M.; Iseki, K.; Oguri, T.; Hayasi, Y.; Yamada, S.; Shibasaki, M. *Tetrahedron Lett.* **1986**, *27*, 87. (b) Fried, J.; Sih, J. C. *Tetrahedron Lett.* **1973**, *14*, 3899. (c) Fried, J.; Lin, C.; Ford, S. H. *Tetrahedron Lett.* **1969**, *10*, 1379. (d) Ben-Efraim, D. A.; Sondheimer, F. *Tetrahedron* **1969**, *25*, 2823.

(22) (a) Feuvrie, C.; Blanchet, J.; Bonin, M.; Micouin, L. *Org. Lett.* **2004**, *6*, 2333. (b) Wang, B.; Bonin, M.; Micouin, L. *Org. Lett.* **2004**, *6*, 3481.

(23) See Supporting Information for experimental procedure.

(24) The corresponding *N*,*N*-dimethyl carbamate behaved similarly according to GC analysis.

(25) The GC and NMR of this product are identical to those of the coupling product prepared by traditional copper chemistry (see ref 23).

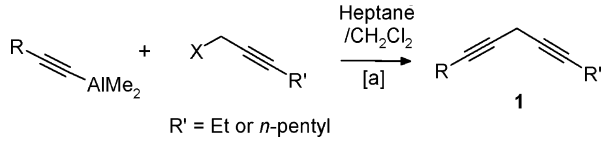
(26) Lapitskaya, M. A.; Vasiljeva, L. L.; Pivnitsky, K. K. *Synthesis* **1993**, 65.

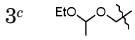
(27) Kessabi, J.; Beaudegnies, R.; Jung, P. M. J.; Martin, B.; Montel, F.; Wendeborn, S., unpublished results.

instance from which only phenyl acetylene was identifiable (entries 11−14), thereby supporting the argument in favor of the important complexing roles played by the ester, sulfonyl, and phosphonyl/phosphinyl groups in the cross-couplings which were successful (entries 3−10). This may be rationalized by invoking the formation of a favorable six-membered aluminum-coordinated transition state.[28]

The preparation of dialkyl-substituted methylene-bridged diynes was also shown to be possible using this alkynylalane-mediated cross-coupling as shown in Table 2. First, the use of propargyl phosphate as the electrophilic coupling partner provided dodeca-3,6-diyne (entry 1) regioselectively, albeit in low yield (23%). In contrast, the coupling of the corresponding mesylate (entry 2) was significantly higher yielding (77%) and advantageously could be carried out at temperatures much lower than that required for the phosphate (0 vs 90 °C). Moreover, the mesylate necessitated a significantly shorter reaction time compared to the phosphate (1 vs 73 h) and only required the use of stoichiometric amounts of the alane which is consistent with what was previously observed (cf. Table 1, entry 8).

Table 2. Cross-Coupling Reactions of Functionalized Alkynylalanes with Propargylic Phosphates and Mesylates[a]



entry	R	alane (equiv)	X	temp (°C)	time (h)	yield of **1**[b] (%)
1[c]	*n*-pentyl	2	$OPO(OEt)_2$	0−90	73	23
2[c]	*n*-pentyl	1	OSO_2Me	0−23	1	77
3[c]		2	OSO_2Me	−35−rt	4	49
4[c]		2	OSO_2Me	−35−rt	4	55
5[d]	$Cl(CH_2)_6$	1	OSO_2Me	0−23	7	73

[a] The alane was added to the mesylate in toluene.[23] [b] Isolated yields. [c] R′ = ethyl. [d] R′ = *n*-pentyl.

A useful extension of this methodology would be its application for the preparation of functionalized diynes which are amenable to further transformations. To this end, the propargyl alcohol derived ethoxyethyl ether and *tert*-butyldiphenylsilyl ether were selected as precursors to representative functionalized alkynylalanes (entries 3 and 4, respectively). Although Micouin's conditions for alkynylalane preparation failed to provide the requisite nucleophilic coupling partners in these instances, they were attainable on treatment with *n*BuLi and transmetalation with $AlMe_2Cl$ at −35 °C. Their subsequent cross-couplings with the mesylate derived from pent-2-yn-1-ol were regioselective and afforded the desired acetal and silyloxy functionalized diynes in moderate yields (49 and 55%, respectively, Table 2 (R′ = Et)). In addition, the chloroalkyl-substituted diyne was successfully prepared as shown in entry 5 via the intermediacy of 1-chloro-oct-7-ynylalane, highlighting the chemoselective nature of the substitution at the mesylate center rather than at the chloride during the cross-coupling.

In summary, a novel, copper-free, and regioselective synthesis of methylene-bridged skipped diynes has been developed which relies on cross-coupling alkynylalanes with phosphinate-, phosphate-, or sulfonate-based propargylic electrophiles capable of mutual complexation with the nucleophile. The method is efficient and mild and advantageously does not lead to detrimental isomerization of the base-sensitive skipped diyne because only catalytic amounts of triethylamine are required for initial preparation of the alkynylalane.

Supporting Information Available: General experimental data and characterization data for compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(28) The need for 2 equiv of alkynylalane when employing propargyl phosphates and phosphinates suggests that the reaction is proceeding via an alternative mechanism, essentially involving Lewis acid activation prior to coordination and transfer brought on by the second equivalent of alkynylalane.