Published in final edited form as:

J Am Chem Soc. 2012 April 25; 134(16): 6928–6931. doi:10.1021/ja301243t.

Stereocontrolled 1,3-Phosphatylxy and 1,3-Halogen Migration Relay Toward Highly Functionalized 1,3-Dienes

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Abstract

A double migratory cascade reaction of α -halogen-substituted propargylic phosphates to produce highly functionalized 1,3-dienes has been developed. This transformation features 1,3-phosphatylxy group migration followed by 1,3-shifts of bromine and chlorine, as well as unprecedented 1,3-migration of iodine atom. The reaction is stereodivergent; (*Z*)-1,3-dienes are formed in the presence of copper catalyst, whereas gold-catalyzed reactions invert the stereoselectivity producing the corresponding *E* products.

Processes involving 1,*n*-halogen migrations are a powerful tool for obtaining valuable functionalized synthons for organic chemistry.^{1–6} Among known methods are base-mediated 1,2-migration of halogen atoms to the anionic center, namely halogen dance reaction,¹ migrations via halonium-,² allyl cation-,³ and α -halo metal carbene⁴ intermediates, halogen shifts during radical processes,⁵ and metal-mediated alkyne-vinylidene isomerizations.⁶ Furthermore, various migrations of a range of other functionalizable groups are well preceded.⁷ However, double migration reactions employing two functionalizable groups are exceedingly rare.⁸ Herein we wish to report a double 1,3-phosphatylxy and 1,3-halogen migration relay toward highly functionalized 1,3-dienes. This cascade transformation features a stereodivergent formation of *Z*- and *E*-dienes, 1,3-shifts of bromine and chlorine atoms, as well as unprecedented 1,3-iodine migration (eq 1).

(1)

We have previously shown that propargylic esters and phosphates can undergo a facile double 1,3/1,2-migratory cascade to produce (*E*)-1,3-dienes^{7e} (eq 2). We hypothesized that it should be possible to expand the scope of the migrating group to halogen (MG = Hal), thus aiming at the synthesis of difunctionalized 1,3-dienes **A** (eq 3).

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ASSOCIATED CONTENT

Supporting Information. Detailed experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

To this end, the isomerization of α -bromo propargylic phosphate **1a**⁹ was examined under a variety of conditions (Table 1). We found **1a** to be unaffected by the original catalytic system (entry 1). Likewise, employing gold (I) complexes with alternative counterions such as SbF₆ or BF₄ did not provide product formation at all (entries 2, 3). Similarly, silver and platinum catalysts provided no reaction as well (entries 4, 5). However, employment of gold(I) and gold(III) halides *unexpectedly* produced a mixture of stereoisomeric 1,3-dienes **2a** and **3a**, the products of double 1,3/1,3-migration sequence (entries 6–8), with no 1,3-diene **A** observed. Employment of Ph₃PAuCl catalyst resulted in good *E*-stereoselectivity of the reaction and moderate yield (entry 9). Use of a more electron deficient phosphine ligand led to *E*-diene **3a** in an excellent yield and good stereoselectivity (entry 10). Further catalyst screening led to another surprising observation: the [CuOTf]₂•PhH catalyst provided the 1,3/1,3-migration product **2a** with *excellent Z*-selectivity (entry 11)! Gratifyingly, performing the reaction at a higher temperature resulted in the efficient and exclusive formation of *Z*-1,3-diene **2a** (entry 12). In addition, a control experiment indicated that no product formation occurred in the absence of a catalyst (entry 13).

(2)

(3)

Inspired by these observations, we first investigated the scope of the Cu-catalyzed *Z*-selective reaction under the optimized conditions (Table 2). Acyclic compounds **1a–c** underwent this tandem transformation to efficiently produce dienes **2a–c** (entries 1–3). Chlorine-containing compound **1b** gave a better yield of the isomerization product compared to its bromine-bearing analog **1a**. Propargylic phosphate possessing cyclic substituent **1d** was also effectively converted into the exocyclic diene **2d** in both good yield and stereoselectivity. Likewise, heterocyclic compound **1e** also provided 1,3-diene **2e** as a sole *Z*-isomer in a good yield. To our delight, cyclic ketone-derived substrates **1f–j** provided the corresponding products in moderate to excellent yields. Notably, these substrates possessing hydrogen atom adjacent to a halogen provided 1,3-diene **2f–j**, the products of the exclusive halogen over hydrogen atom migration. Isomerization of five-membered ring-containing substrates **1f–g** gave diene products **2f–g** as sole stereoisomers in excellent yields (entries 6–7). Similarly, substrates **1h–j** bearing six-membered ring furnished the desired products in good yields.¹⁰ Remarkably, compound **1j** underwent a 1,3-iodine migration in this tandem transformation to produce the *Z*-diene **2j** as a single stereoisomer in moderate yield (entry 10). *To the best of our knowledge, this is the first example of 1,3-migration of iodine.*

Next, we investigated the Au-catalyzed cascade 1,3-phosphatylxy/1,3-halogen double migration reaction leading to *E*-1,3-diene products (Table 3). Several halogenated propargylic phosphates bearing acyclic substituents were converted into the corresponding *E*-dienes in excellent yields and with good to excellent selectivities (entries 1–4). Likewise, exocyclic *E*-dienes **3d,n** could also be efficiently obtained via this transformation. Finally, cyclohexyl-containing substrate **1j** underwent this cascade transformation with exclusive

1,3-migration of iodine atom to produce the corresponding 1,3-diene **3j** in high yield, albeit with a lower level of stereocontrol.

We propose the following plausible mechanism for these cascade transformations (Scheme 1). First, coordination of the metal to the π -system of the alkyne **4** renders a 1,3-migration of phosphatyloxy group to produce the cyclic intermediate **5**, which upon elimination of the metal produces allenyl phosphate **6** or **8**.^{7d-g} In the case of Au catalyst, π -allyl cation **7**¹¹ is produced upon a halogen abstraction from **6**. A subsequent delivery of a halide from gold halide species to **7** occurs *anti* to the phosphate group giving the *E*-diene **3**. Alternatively, in the case of copper catalysis, additional coordination of the metal to the phosphate group of allene takes place (**8**). The halogen abstraction by copper produces phosphate-coordinated π -allyl complex **9**.¹² In this way, a subsequent delivery of the halogen is directed by the phosphate group and occurs *syn* to it to produce the corresponding isomeric *Z*-product **2**.¹³

Next, synthetic utility of 1,3-dienes obtained in the Cu-catalyzed isomerization reactions was examined (Scheme 2). Thus, Diels-Alder reaction of **2a** with *N*-phenylmaleimide and **2f** with bromomaleic anhydride^{7o} efficiently produced cycloadduct **10** and pen-tasubstituted benzene derivative **11**, respectively. Furthermore, Miyaura-Suzuki cross-coupling reaction¹⁴ of dienes **2a,f** with phenylboronic acid proceeded well to give phenylated 1,3-dienes **12** and **13** in 78% and 91% yields, respectively. Notably, the phosphatyloxy terminus of *Z* diene **2f** could also be functionalized after the Miyaura-Suzuki cross-coupling reaction of a vinyl bromide moiety. Thus, the diene **13** underwent Kumada cross-coupling reaction on the phosphatyloxy moiety in the presence of iron catalyst¹⁵ to give diene **14**. Finally, a sequential Miyaura-Suzuki reaction on vinyl bromide¹⁴ and phosphate¹⁶ groups of diene **2f** furnished highly functionalized diene **15** in good overall yield (Scheme 2).

In summary, a stereocontrolled isomerization of α -halo-substituted propargylic phosphates into valuable highly functionalized 1,3-dienes has been developed. This methodology features a double 1,3-phosphatyloxy/1,3-halogen migration relay. Depending on a choice of catalyst, synthesis of either *Z*- or *E*-1,3-dienes could be achieved selectively in typically high yields. Thus, *Z*-dienes could be obtained with the exclusive stereoselectivity in the presence of copper catalyst, whereas the employment of gold catalyst afforded predominantly *E*-dienes. Notably, these transformations feature unprecedented 1,3-migration of iodine atom. Finally, the synthetic utility of obtained 1,3-dienes was demonstrated in efficient Diels-Alder and cross-coupling reactions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank the National Institute of Health (GM-64444) for financial support of this work.

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Scheme 1.
Proposed mechanism for double phosphatylxy-Halogen migration relay

Scheme 2.

Selected Transformations of (*Z*)-1,3-dienes **2**⁹

(i) *N*-Phenylmaleimide (1.5 equiv), anisole, 150 °C, 12h. (ii) bromomaleic anhydride (1.5 equiv), anisole, 150 °C, 12h. (iii) $\text{Pd}_2(\text{dba})_3$ (4 mol%), XPhos (8 mol%), ArB(OH)_2 (2.0 equiv), K_3PO_4 (3.0 equiv), toluene, 80 °C, 15h (iv) $\text{Fe}(\text{acac})_3$ (6 mol%), TMEDA (2.0 equiv), $n\text{-BuMgCl}$ (1.5 equiv), THF, 0 °C. (v) $\text{Ni}(\text{cod})_2$ (5 mol%), $\text{PCy}_3 \cdot \text{HBF}_4$ (10 mol%), PhB(OH)_2 (2.0 equiv), K_3PO_4 (3.0 equiv), THF, 75 °C. dba = *trans, trans*-dibenzylideneacetone, XPhos = 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl, acac = acetylacetonato, TMEDA = *N,N,N,N*-tetramethylethylenediamine, cod = 1,5-cyclooctadiene.

Table 1

Optimization of the reaction conditions

entry	catalyst (mol%)	solvent	T (°C)	2a : 3a ^a	yield, % ^b
1	Ph ₃ PAuOTf (5)	DCE	rt	-	0
2	Ph ₃ PAuSbF ₆ (5)	DCE	rt	-	0
3	Ph ₃ PAuBF ₄ (5)	DCE	rt	-	0
4	AgOTf (10)	DCE	50	-	0
5	PtCl ₂ (5)	DCM	40	-	0
6	AuI (5)	PhH	50	1 : 6	ND ^d
7	AuCl ₃ (5)	PhH	40	1 : 1.5	ND ^d
8	LAuCl ₂ ^c (5)	DCE	80	1 : 2	ND ^d
9	Ph ₃ PAuCl (5)	DCE	80	1 : 9	65
10	(<i>p</i> -F ₃ CC ₆ H ₄) ₃ PAuCl (5)	PhMe	100	1 : 9	96
11	[CuOTf] ₂ •PhH (10)	DCE	50	24 : 1	50
12	[CuOTf] ₂ •PhH (10)	DCE	80	100 : 0	85
13	None	PhMe	0	-	0

^aDetermined by ¹H NMR.^bIsolated yield.^cL = 2-pyridinecarboxylato.^dYield was not determined.

Table 2

Cu-Catalyzed Synthesis of *Z*-Dienes

$ \begin{array}{c} \text{R}^2 \quad \text{R}^3 \quad \text{OP(O)(OEt)}_2 \\ \quad \quad \\ \text{R}^1 - \text{C} - \text{C} \equiv \text{C} \\ \\ \text{Hal} \end{array} \xrightarrow[0.05 \text{ M in DCE, } 80^\circ \text{C}]{[\text{CuOTf}]_2 \cdot \text{PhH (10 mol \%)}} \begin{array}{c} \text{R}^2 \quad \text{R}^3 \\ \quad \\ \text{R}^1 - \text{C} = \text{C} \\ \quad \\ \text{Hal} \quad \text{OP(O)(OEt)}_2 \end{array} $			
entry	substrate	product ^a	yield, % ^b
1	1a	2a	86
2	1b	2b	95
3	1c	2c	69 ^c
4	1d	2d	75 ^d
5	1e	2e	77
6	1f	2f	91
7	1g	2g	95
8	1h	2h	79
9	1i	2i	86
10	1j	2j	64

^aMajor stereoisomer shown.^bIsolated yield.^c*Z*:*E* = 19:1.^d*Z*:*E* = 9:1

Au-Catalyzed Synthesis of *E*-Dienes

Au-Catalyzed Synthesis of *E*-Dienes

Au-Catalyzed Synthesis of *E*-Dienes

Au-Catalyzed Synthesis of *E*-Dienes

Au-Catalyzed Synthesis of *E*-Dienes