

Stereocontrolled 1,3-Phosphatyloxy and 1,3-Halogen Migration Relay toward Highly Functionalized 1,3-Dienes

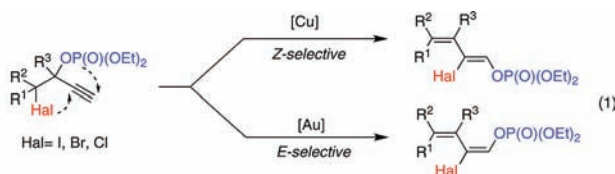
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S Supporting Information

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-phosphatyloxy group migration followed by 1,3-shifts of bromine and chlorine as well as the unprecedented 1,3-migration of iodine. The reaction is stereodivergent: (*Z*)-1,3-dienes are formed in the presence of a copper catalyst, whereas gold-catalyzed reactions exhibit inverted stereoselectivity, producing the corresponding *E* products.

Processes involving 1,*n*-halogen migrations are powerful tools for obtaining valuable functionalized synthons for organic chemistry.^{1–6} Among known methods are the base-mediated 1,2-migration of halogen atoms to the anionic center (the 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-precedented.⁷ However, double migration reactions employing two functionalizable groups are exceedingly rare.⁸ Herein we report a double 1,3-phosphatyloxy and 1,3-halogen migration relay leading toward highly functionalized 1,3-dienes. This cascade transformation features stereodivergent formation of (*Z*)- and (*E*)-dienes and 1,3-shifts of bromine and chlorine atoms as well as the unprecedented 1,3-migration of iodine (eq 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^{7c} (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 functionalized 1,3-dienes **A** (eq 3).

To this end, the isomerization of α -bromo propargylic phosphate **1a** was examined under a variety of conditions (Table 1).⁹ 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 and 3).

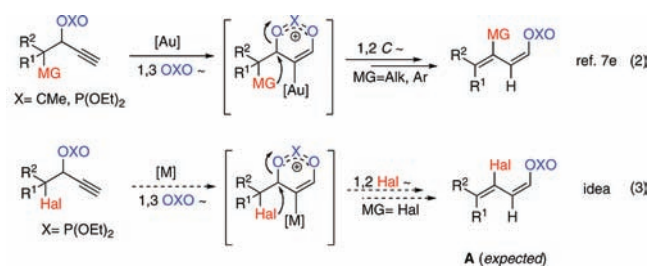


Table 1. Optimization of the Reaction Conditions

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 analysis. ^bIsolated yields. ^cL = 2-pyridinecarboxylate. ^dYield was not determined.

Similarly, silver and platinum catalysts provided no reaction as well (entries 4 and 5). However, the use of gold(I) and gold(III) halides *unexpectedly* produced a mixture of the stereoisomeric 1,3-dienes **2a** and **3a**, the products of a double 1,3-/1,3-migration sequence (entries 6–8), with no 1,3-diene **A** observed. The use of Ph₃PAuCl as the 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: use of [CuOTf]₂·PhH as the catalyst (entry 11) provided the 1,3-/1,3-migration product **2a** with excellent *Z* selectivity! Gratifyingly, performing the reaction at a higher

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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).

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

Table 2. Cu-Catalyzed Synthesis of (*Z*)-Dienes

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

^aThe major stereoisomer is shown. ^bIsolated yields. ^c*Z*:*E* = 19:1. ^d*Z*:*E* = 9:1.

tandem transformation to produce dienes **2a–c** efficiently (entries 1–3). Chlorine-containing compound **1b** gave a better yield of the isomerization product than did its bromine-bearing analogue **1a**. Propargylic phosphate **1d** possessing a cyclic substituent was also effectively converted into the corresponding exocyclic diene **2d** in both good yield and stereoselectivity. Likewise, heterocyclic compound **1e** also provided 1,3-diene **2e** solely as the *Z* isomer in good yield. To our delight, cyclic-ketone-derived substrates **1f–j** provided the corresponding products in moderate to excellent yields. Notably, these substrates possessing a hydrogen atom adjacent to a halogen provided 1,3-dienes **2f–j**, the products of exclusive migration of the halogen atom rather than the hydrogen atom. Isomerization of substrates **1f** and **1g** containing five-membered rings gave the

diene products **2f** and **2g** as the sole stereoisomers in excellent yields (entries 6 and 7). Similarly, substrates **1h–j** bearing six-membered rings 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-phosphatyloxy/1,3-halogen double migration reaction leading to (*E*)-1,3-diene products (Table 3). Several halogenated

Table 3. Au-Catalyzed Synthesis of (*E*)-Dienes

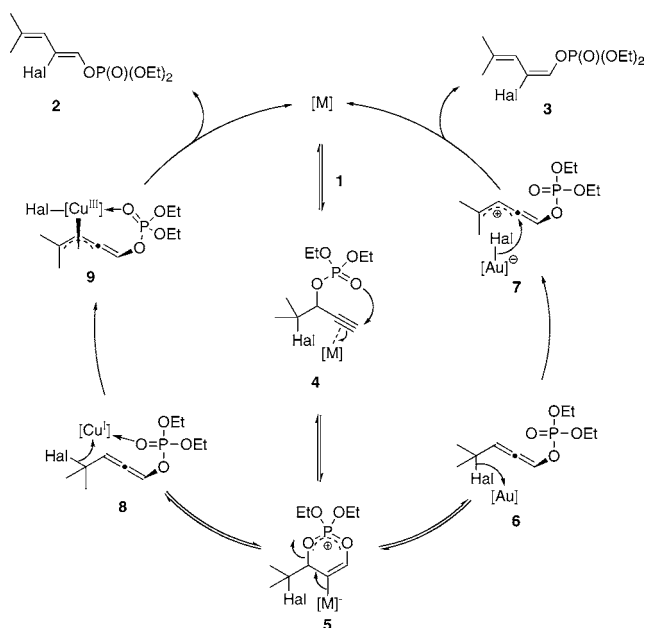
entry	substrate	product ^a	yield, % ^b	(<i>E</i> : <i>Z</i> ratio) ^c
1	1a	3a	95	(9:1)
2	1b	3b	89	(6:1)
3	1c	3c	97	(8:1)
4	1m	3m	98	(13:1)
5	1n	3n	91	(9:1)
6	1d	3d	90	(19:1)
7	1j	3j	89	(1.5:1)

^aThe major stereoisomer is shown. ^bIsolated yields. ^cDetermined by ¹H NMR analysis.

propargylic phosphates bearing acyclic substituents were converted into the corresponding (*E*)-dienes in excellent yields with good to excellent selectivities (entries 1–4). Likewise, exocyclic (*E*)-dienes **3d** and **3n** could also be efficiently obtained via this transformation. Finally, cyclohexyl-containing substrate **1j** underwent this cascade transformation with exclusive 1,3-migration of the iodine atom to produce the corresponding (*E*)-1,3-diene **3j** in high yield, albeit with a lower level of stereocontrol.

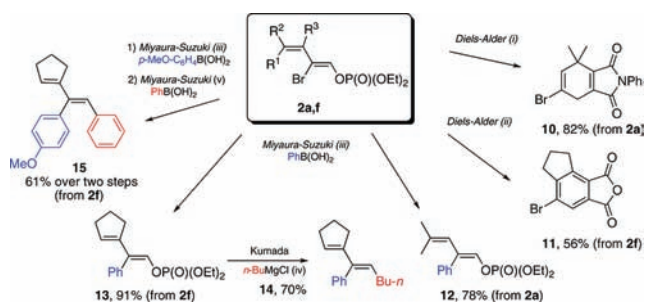
We propose the following plausible mechanism for these cascade transformations (Scheme 1). First, coordination of the metal to the π system of the alkyne **4** enables 1,3-migration of the phosphatyloxy group to produce cyclic intermediate **5**, which upon elimination of the metal produces allenyl phosphate **6** or **8**.^{7d–g} In the case of the Au catalyst, π -allylation **7**¹¹ is produced upon halogen abstraction from **6**. Subsequent delivery of a halide from the 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

Scheme 1. Proposed Mechanism for the Double Phosphatyloxy/Halogen Migration Relay



takes place (8). Halogen abstraction by copper produces phosphate-coordinated π -allyl complex **9**.¹² In this way, subsequent delivery of the halogen is directed by the phosphate group and occurs syn to it, producing the corresponding isomeric *Z* product **2**.¹³

Next, the synthetic utility of the 1,3-dienes obtained via the Cu-catalyzed isomerization reaction was examined (Scheme 2).

Scheme 2. Selected Transformations of (*Z*)-1,3-Dienes **2^{a,f}**

^aConditions: (i) *N*-Phenylmaleimide (1.5 equiv), anisole, 150 °C, 12 h. (ii) Bromomaleic anhydride (1.5 equiv), anisole, 150 °C, 12 h. (iii) Pd₂(dba)₃ (4 mol %), XPhos (8 mol %), ArB(OH)₂ (2.0 equiv), K₃PO₄ (3.0 equiv), toluene, 80 °C, 15 h. (iv) Fe(acac)₃ (6 mol %), TMEDA (2.0 equiv), *n*-BuMgCl (1.5 equiv), THF, 0 °C. (v) Ni(cod)₂ (5 mol %), PCy₃·HBF₄ (10 mol %), PhB(OH)₂ (2.0 equiv), K₃PO₄ (3.0 equiv), THF, 75 °C. Abbreviations: dba, *trans,trans*-dibenzylideneacetone; XPhos, 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl; acac, acetylacetonate; TMEDA, *N,N,N,N*-tetramethylethylenediamine; cod, 1,5-cyclooctadiene.

Thus, the Diels–Alder reactions of **2a** with *N*-phenylmaleimide and **2f** with bromomaleic anhydride⁷⁰ efficiently produced cycloadduct **10** and pentasubstituted benzene derivative **11**, respectively. Furthermore, the Miyaura–Suzuki cross-coupling reactions¹⁴ of dienes **2a** and **2f** with phenylboronic acid proceeded well, giving phenylated 1,3-dienes **12** and **13** in yields of 78 and 91%, respectively. Notably, the phosphatyloxy terminus of (*Z*)-diene **2f** could also be functionalized after the

Miyaura–Suzuki cross-coupling reaction of the vinyl bromide moiety. Thus, the diene **13** underwent the Kumada cross-coupling reaction of the phosphatyloxy moiety in the presence of an iron catalyst¹⁵ to give diene **14**. Finally, a sequential Miyaura–Suzuki reaction on the 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 and 1,3-halogen migration relay. Depending on the 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 exclusively in the presence of a copper catalyst, whereas the use of a gold catalyst afforded predominantly (*E*)-dienes. Notably, these transformations feature an unprecedented 1,3-migration of iodine atoms. Finally, the synthetic utility of the obtained 1,3-dienes was demonstrated in efficient Diels–Alder and cross-coupling reactions.

■ ASSOCIATED CONTENT

S 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>.

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Notes

The authors declare no competing financial interest.

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