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Designed Bifunctional Phosphine Ligand-Enabled Gold-Catalyzed Isomerizations of Ynamides and Allenamides: Stereoselective and Regioselective Formation of 1-Amido-1,3-dienes

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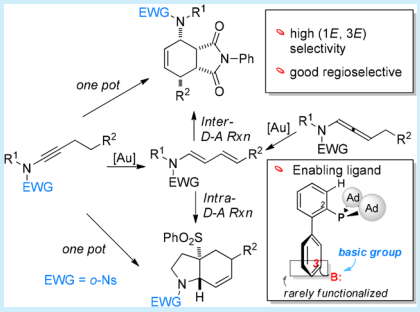
Supporting Information

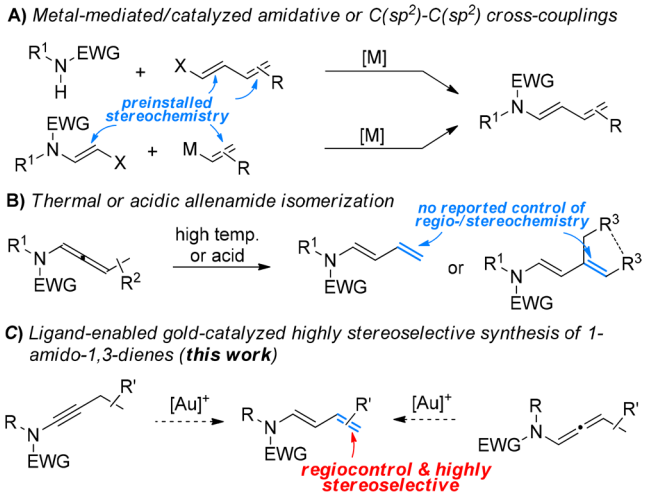
ABSTRACT: By using designed biphenyl-2-ylphosphines functionalized with a remote basic groups as ligands, *N*-alkynyl-*o*-nosylamides are directly converted to (1*E*,3*E*)-1-amido-1,3-dienes with excellent diastereoselectivities under gold catalysis. With allenamides as substrates, the gold-catalyzed isomerizations are high yielding and applicable to a broad substrate scope including various nitrogen protecting groups and exhibit unprecedented (3*E*)-selectivities for the distal C−C double bond and good regioselectivities. Combining this gold catalysis with one-pot Diels−Alder reactions leads to rapid assembly of valuable bicyclic compounds.



1-Amido-1,3-diene is an attractive *N*-delivering structural motif owing to its general stability over its amino counterparts, and synthetic intermediates featuring it could participate in inter- or intramolecular Diels−Alder reactions en route to valuable *N*-containing cyclic structures. This synthetic potential, however, has been seldom reported, likely due to their limited access in synthetically desirable stereoselective and regioselective manners. In contrast, the related 1-amidofurans are frequently employed in total synthesis.[1] The reported synthetic methods include the following: (a) the thermal rearrangements of propargylic trichloroacetimidates to form (1*Z*)-1-amido-1,3-dienes,[2] which is less desirable for the D−A reaction, and upon Et_3N treatment affords a mixture of (1*E*) and (1*Z*) isomers (e.g., 85/15); (b) metal-mediated/-catalyzed amidative[3] or $C(sp^2)-C(sp^2)$[4] cross-couplings, which, however, suffers from the need for halodiene substrates of preinstalled regio- and stereochemistry in the former and the need for controlling stereochemistry of both reacting partners in the latter (Scheme 1A); (c) allenamide isomerization under excessive heating (e.g., 135 °C[5]) or in the presence of an acid catalyst (Scheme 1B), which is limited in scope to products that avoid regio- or stereochemical issues at the distal C−C double bond.[5,6]

Recently we[7] reported gold-catalyzed isomerizations of arylalkynes and certain types of aliphatic alkynes into dienes[8] via the intermediacy of allenes. The chemistry is enabled by designed biphenyl-2-ylphosphine ligands[7,9] featuring a basic 3′-amino group. We envision that 1-amido-1,3-dienes could be prepared via our alkyne isomerization chemistry directly from ynamides or from the intermediary allenamides (Scheme 1C). Moreover, our gold-specific ligands might enable unprecedented control of the stereo- and regiochemical outcomes.

Scheme 1. Formations of 1-Amido-1,3-dienes and Our Design on Gold-Catalyzed Isomerization



Herein, we disclose the results including the combination of gold catalysis with a one-pot Diels−Alder reaction to construct valuable *N*-containing bicyclic structures.

Our initial reaction discovery and conditions optimization were conducted with the ynamide **1a-Ns(*o*)** (eq 1; for details, please see Supporting Information (SI)). Under the optimal conditions, i.e., **L1**AuCl (5 mol %), NaBARF (20 mol %), DCE, 3 Å MS, 60 °C, and 36 h, the desired 1-amido-1,3-diene

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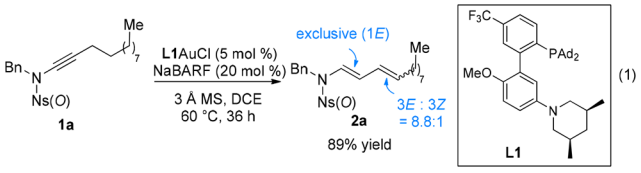
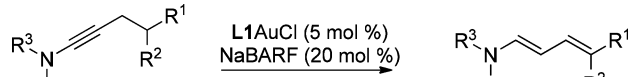
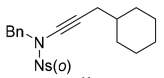
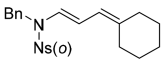
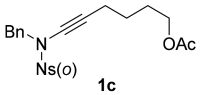
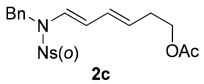
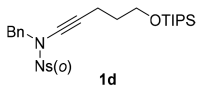
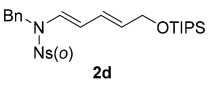
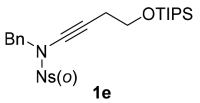
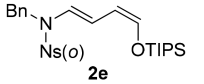
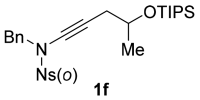
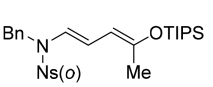
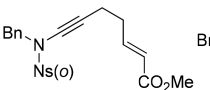
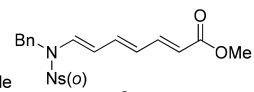
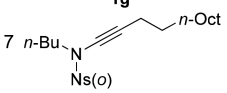
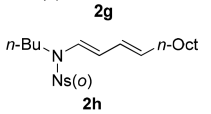


2a-Ns(o) was formed in 89% isolated yield and exhibits exclusive (1*E*) geometry and a synthetically valuable 8.8:1 (3*E*)-selectivity at the distal C−C double bond. Notably, ynamides have been extensively studied in gold catalysis[10] and invariably exhibit pronounced polarization upon interaction with electrophilic species (e.g., LAu^+) in the form of ketenimium-type intermediates, which is opposite to what occurs in our chemistry. Remarkably the conventional gold ligands, e.g., Ph_3P, IPr, JohnPhos, are completely incapable of promoting this amidodiene formation.

The reaction scope was then studied under the optimal conditions. As shown in Table 1, **1b** with a cyclohexylmethyl group at the alkyne end reacted smoothly to afford 1-amido-1,3-diene **2b** in 93% yield. The effect of having a functional group close to the triple C−C bond was then probed. Compared to **1a-Ns(*o*)**, substrates possessing a 6-OAc group and a 5-OTIPS group were less reactive, and the catalyses required longer reaction times and higher catalyst loadings to afford the corresponding dienes in 78% and 71% yield, respectively (entries 2 and 3). Intriguingly, the reaction of **1e** possessing a 4-OTIPS exhibited good reactivity, and the amidodiene **2e** was formed with mostly (*Z*)-configuration on the distal C−C double bond (entry 4). However, ynamide **1f** derived from the related secondary alcohol afforded the amidodiene **2f** with mostly (3*E*)-configuration in 83% yield (entry 5). The ynamide **1g** with a tethered electron-deficient olefin was also successfully isomerized into the corresponding *ω*-amidotrienoate product **2g**, albeit with a 10 mol % catalyst loading and in a moderate yield (entry 6). Finally, the *N*-alkyl substrate **1h** participated well in the reaction, affording **2h** in 81% yield (entry 7). It remains to be pointed out that these reactions display excellent (1*E*)-selectivity and the (1*Z*)-isomers were not observed.

Table 1. Scope of Ynamide Isomerization[a]



entry	1	2	condi-tions	yield[b] (3E/3Z)
1	 **1b**	 **2b**	60 °C 36 h	93 (-)
2[c]	 **1c**	 **2c**	60 °C 48 h	78 (9.2/1)
3[c]	 **1d**	 **2d**	60 °C 48 h	71 (12.5/1)
4	 **1e**	 **2e**	60 °C 36 h	80 (1/9)
5	 **1f**	 **2f**	60 °C 36 h	83 (6.9/1)
6[d]	 **1g**	 **2g**	60 °C 72 h	48 (>12/1)
7	 **1h**	 **2h**	80 °C 48 h	81 (8.3/1)

[a]Reactions were carried out with **L1**AuCl (5 mol %), NaBARF (20 mol %), 3 Å MS in DCE (0.05 M) for 36 h. [b]Isolated yield. [c]**L1**AuCl (7.5 mol %), NaBARF (30 mol %) were used. [d]**L1**AuCl (10 mol %), NaBARF (30 mol %) were used.

The ynamide isomerization, however, does not work with substrates possessing additional substitution at the propargylic position [e.g., *N*-benzyl-*N*-(cyclohexylethynyl)-2-nitrobenzenesulfonamide] and is limited to *o*-nosylamides. We surmised that the culprit must be the first proton shuttling in the gold catalysis, i.e., the isomerization of the ynamide into an allenamide intermediate.[7] As such, allenamides, also available via Cu catalysis,[11] would permit a broadened reaction scope if employed as substrates. To this end, a range of allenamides were subjected to the gold catalysis (Table 2). To our delight, *N*-tosylallenamide **3a** reacted efficiently in the presence of only 0.5 mol % **L1**AuCl and 2.0 mol % NaBARF at ambient temperature and in 2 h, affording the terminal 1-amido-1,3-diene **4a** with exclusive (1*E*)-geometry and in 96% yield. Similarly, **3b** with the distal allene end fully substituted underwent highly efficient transformation under mild conditions (entry 2). The reaction of **3c** featuring an *n*-propyl at the allene distal end was again high yielding, and most notably the 1-amido-1,3-diene product **4c** exhibits excellent (3*E*)-selectivity (>50:1) in addition to the exclusive (1*E*)-geometry (entry 3). In contrast, the treatment of **3c** with CSA[5] led to a nearly equal mixture of (3*E*)- and (3*Z*)-products and a lower yield, highlighting the extraordinary utility of the designed ligand. In addition, with JohnPhos as the gold ligand, only trace **4c** (<5%) was formed under the same conditions (i.e., rt, 2 h) and an 11% yield was produced at 40 °C for 12 h (68% conversion), again highlighting the enabling nature of our designed bifunctional ligand. Variation of the amide moiety to include benzamide (entry 4), oxazolidinone (entry 5), and lactam (entry 6) were inconsequential, and the gold catalyses uniformly exhibit >90% yields and exceptional (3*E*)-selectivities, in contrast to the poor or no geometric selectivities with the distal alkene in CSA-catalyzed counterparts.

Allenamide **3g** with two different substituents at its distal allene terminus poses an additional and significant challenge to the intended isomerization, i.e. regioselectivity. As shown in entry 7, with **L1** as the ligand, the reaction remained highly efficient and (3*E*)-selective in the case of **4g**, but the ratio of the regioisomers **4g** and **4g′** was only 1.5/1, favoring the former. With CSA as the catalyst, both the regio- and diastereoselectivity were poor, despite the methylene product **4g′** is slightly favored. Recently we reported that by positioning the remote aniline nitrogen in **L1** further away from the pendent phenyl ring in the form of more basic tertiary amines, the isomerization of propargylic esters can be realized with controlled regioselectivity.[9b] When one of the ligands, i.e., **L2**,

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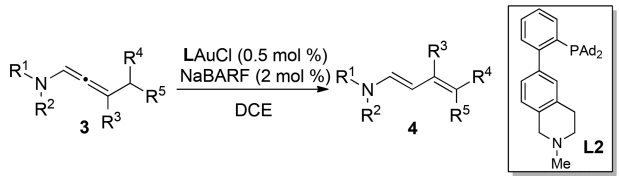
Table 2. Scope of Allenylamide Isomerization[a]



entry	ligand	3	4	temp., time yield[d] (3*E*/3*Z*)	*with acid* yield[b,c] (3*E*/3*Z*)
1	L1	3a	4a	rt, 2 h 96% (-)	-
2	L1	3b	4b	40 °C, 12 h 94% (>50/1)	-
3	L1	3c	4c	rt, 2 h 93% (>50/1)	80% (1.1/1)
4	L1	3d	4d	40 °C, 24 h 93% (>50/1)	84% (1/1)
5	L1	3e	4e	rt, 2 h 91% (>50/1)	75% (1.2/1)
6	L1	3f	4f	rt, 2 h 92% (>50/1)	80% (1/1)
7	L1	3g	4g / 4g'	rt, 12 h 92%[c,e] **4g/4g'** = 1.5/1 (**4g**,3*E*/3*Z*: >20/1)	95% **4g/4g'** = 0.6/1 (**4g**,3*E*/3*Z* = 1.2/1)
8	L2	3g	4g	40 °C, 8 h 91%[e] **4g/4g'**: >20/1	-
9	L2	3h	4h / 4h'	40 °C, 2 h 85%[f] **4h/4h'** = 7/1 (**4h**, 3*E*/3*Z*: >20/1)	96% **4h/4h'** = 0.8/1 (**4h**,3*E*/3*Z* = 1.2/1)
10	L1	3i	4i / 4i'	rt, 2 h 92%[e] **4i'/4i**: >50/1	77% **4i** 4% **4i'**

[a]Reactions were carried out with LAuCl (0.5 mol %), NaBARF (2.0 mol %) in DCE (0.10 M). [b]Reactions were carried out with 10% CSA, 3 Å MS in DCM (0.10 M) at rt for 20 min. [c]NMR yield was reported using triisopropylbenzene as internal reference. [d]Isolated yield. [e]LAuCl (2.5 mol %), NaBARF (10 mol %) were used. [f]LAuCl (7.5 mol %), NaBARF (20 mol %) were used.

was employed, much to our delight, the isomerization is highly regioselective, affording **4g** with a trisubstituted distal C−C double bond with exclusive (3*E*)-geometry in an excellent yield (entry 8). With the *n*-octyl in **3g** replaced by a $TBSOCH_2$ group in **3h**, **L2** is again a more effective ligand, resulting in the formation of (1*E*,3*E*)-**4h** with good regioselectivity and again excellent geometric selectivity (entry 9); in contrast, both the regioselectivity and geometric selectivity were again poor in the Brønsted acid catalysis. Finally, when the allenamide **3i** was subjected to our gold catalysis, the **L1**Au^+-catalyzed reaction led to regioselective deprotonation at the smaller methyl group and hence afforded the kinetic product **4i'** in 92% yield (entry 10). In contrast, the acid-catalyzed transformation yielded mostly the thermodynamic product **4i**, in which the deprotonation occurs at the much bigger isopropyl group. This result demonstrates the sensitivity of our design ligand to steric hindrance en route to hard-to-achieve regioselectivity.

The observed regio- and stereoselectivities in these gold catalyses can be readily rationalized by invoking the essential role of the ligand remote basic group. For details, see the SI.

We anticipated that the synthesis of 1-amido-1,3-dienes from the gold catalyzed ynamide isomerizations could be rendered in tandem with Diels−Alder reactions in one pot, therefore enabling rapid assembly of versatile cyclic structures. We first examined intramolecular D−A reactions. As shown in Table 3,

Table 3. Scope of Ynamide Isomerization−Cycloaddition Domino Reaction[a]

entry	substrate	product	yield (%)[c]
1	1i	5a	51
2	1j	5b	54
3	1k	5c-1 : 5c-2 (1.2 : 1)	64
4[b]	1a +	5d	78

[a]Reactions were carried out with **L1**AuCl (10 mol %), NaBARF (30 mol %), 3 Å molecular sieves in DCE (0.05 M) at 80 °C for 48 h, and then treated with BHT in mesitylene at 180 °C for 12 h. [b]**L1**AuCl (5 mol %), NaBARF (20 mol %), 3 Å molecular sieves in DCE (0.05 M) at 60 °C for 36 h, and then 100 °C for 12 h. [c]Isolated yield.

ynamides **1i** and **1j** featuring *α,β*-unsaturated sulfones tethered at the nitrogen atom indeed underwent this tandem process to afford the hexahydroindole **5a** and the octahydroquinoline **5b** with exquisite relative stereochemistry in synthetically useful yields (entries 1 and 2). The Diels−Alder reactions were performed at 180 °C and displays excellent *endo* selectivity. With a maleate properly installed at the alkyne end, **1k** smoothly underwent the tandem process to deliver the bicyclic lactone **5c** as a mixture of diastereomeric isomers in a moderate 64% combined yield (entry 3). In the case of an intermolecular Diels−Alder reaction, we heated **1a** in the presence of *N*-phenylmaleimide in DCE at 60 °C for 36 h and then raised the

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temperature to 100 °C for 12 h. The *endo*-cycloadduct **5d** was isolated in 78% yield (entry 4).

In summary, by using a remotely base-functionalized biphenyl-2-ylphosphine as a ligand, we demonstrated for the first time that *N*-alkynyl-*o*-nosylamides can be converted directly to synthetically versatile (1*E*,3*E*)-1-amido-1,3-dienes with good geometric selectivities under gold catalysis. With allenamides as substrates, the gold-catalyzed isomerizations have excellent yields and exhibit a broad substrate scope including various nitrogen protecting groups; moreover, in contrast to the generally poor regio- and stereoselectivities under Brønsted acid catalysis, the reaction affords excellent (3*E*)-selectivities for the distal C−C double bond and good regioselectivities. For both approaches, typical gold ligands are either incompetent or substantially less effective, confirming the unique capacity of the designed ligands and the essential role of the remoted basic group. Considering the ease of substrate synthesis, these ligand-enabled isomerizations provide facile and stereoselective approaches to versatile (1*E*,3*E*)-1-amido-1,3-dienes, the synthetic potential of which is demonstrated in one-pot Diels−Alder reactions, which offer rapid access to valuable bicyclic compounds.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02624.

Experimental procedures and compound characterization and spectra (PDF)

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Notes

The authors declare no competing financial interest.

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