Soft Propargylic Deprotonation: Designed Ligand Enables Au-Catalyzed Isomerization of Alkynes to 1,3-Dienes

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Supporting Information

ABSTRACT: By functionalizing the privileged biphenyl-2-ylphosphine with a basic amino group at the rarely explored α position, the derived gold(I) complex possesses orthogonally positioned “push” and “pull” forces, which enable for the first time soft propargylic deprotonation and permit the bridging of a difference of ∼30 pKₐ units (in DMSO) between a propargylic hydrogen and a protonated tertiary aniline. The application of this design led to efficient isomerization of alkynes into versatile 1,3-dienes with synthetically useful scope under mild reaction conditions.

1,3-Diene is an important structural motif found in many natural products and can be prepared via isomerization of a C−C triple bond. Among the known methods, only the isomerizations of ynone to diene products, facilitated by transition-metal catalysts, such as Ru, Ir, and Pd and organocatalytic phosphine, are of significant synthetic utility, as the isomerization of internal aliphatic and aryl alkynes in the presence of Rh or Pd catalysts resulted in consistently low diastereoselectivities (dr ≤5).

Soft enolization of carbonyl compounds by using a combination of a Lewis acid and a mild base is a versatile strategy in carbonyl chemistry that circumvents the use of strong bases such as Et₃N and PhNMe₂ and focused our effort on designing new gold ligands with an optimally positioned basic site. The gold complex with such a ligand, as shown in Figure 1C would offer the best chance to succeed as (a) the “push” and the “pull” forces are orthogonal and (b) the rigid ligand framework and the intramolecular nature can minimize the entropy cost during the reaction.

Received: April 23, 2014
Published: June 9, 2014

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half of the pendant phenyl ring (i.e., the 3′, 4′, and 5′ positions),
perhaps owing to the square planar structures of Pd(II)
complexes. The only exceptions are a 3′-sulfone derived from
SPhos and a 4′-sulfonate from XPhos for the purpose of
increasing catalyst aqueous solubility.13 On the other hand, these
ligands have found extensive utility in homogeneous gold
catalysis,14 although Au(I) complexes typically assume a
distinctively different linear structure. To this end, there exist
effort yet largely unexplored opportunities15 for the develop-
ment of novel gold catalysis based on new biphenyl-2-
phosphines ligands specifically tailored to accommodate the
linear Au(I) complexes. Our simple structural modeling revealed,
as shown in Figure 1D, that with bulkier groups on phosphorus
governing the P−Au−alkyne centroid axis parallel to the pendant
phenyl ring the C−C triple bond would lie roughly at the same
level as the line defined by C3′ and C5′, suggesting that functionalization of these positions and C4′ would offer unique and
potentially novel reactivities to gold chemistry.15

With the task of soft propargylic deprotonation in hand, we
reasoned that a basic amino group in the form of an aniline
substituted at C3′, C4′, or C5′ would likely present an orthogonal
“push” force and importantly be in close proximity to the
propargylic hydrogens, thereby facilitating the targeted prop-
argylic deprotonation (Figure 1D).

To establish the validity of the above ligand design, we
prepared a range of new biphenyl-2-ylphosphines containing
basic amino groups at the bottom half of the pendant phenyl ring
via two sequential cross-coupling reactions (for details, see SI).
Some selected examples are shown in Figure 1E. Much to our
delight, treating 1-phenyl-1-hexyne (1a) with the gold complex
L1AuCl (5%) derived from the di(adamantyl-1-yl)phosphine
containing a 3′-NMe2, i.e., L1, and the chloride scavenger
NaBARF (10%) in PhCF3 at 60 °C for 8 h resulted the formation of
(1E,3E)-hexa-1,3-dienylbenzene (2a), albeit in only 3% yield
(Table 1, entry 1). Just as we suspected, the location of the basic
site of the ligand turned out to be crucial as no 2a was detected
when the Me2N group was moved to the C4′ position as in the
ligand L2 (entry 2). Our subsequent ligand optimization was
focused on increasing the basicity of the aniline nitrogen and the
acidity of the gold center. As such, the resulting gold complex
should be more capable of promoting deprotonation of the
propargylic hydrogen and hence increasing the reaction yield.

Indeed, with a more basic piperidine ring in the ligand L3, the
yield 2a was improved to 19% (entry 3). Moreover, by installing
an electron-donating methoxy group para to the N-heterocycle,
the yield increased to 35% (entry 4). At this stage, we probed the
importance of restricting the rotation of P−C2 bond by the bulky
phosphorus substituents and hence the swinging of the P−Au−
alkyne centroid axis. When both adamantyl groups on the
phosphorus of L4 were replaced with sterically less demanding
cyclohexyl (e.g., L5), the reaction became much less efficient
(entry 5), suggesting that conformational rigidity is crucial for
efficient deprotonation. To further improve this reaction, the
acidity of the gold center was increased by using the ligand L6,
where its phosphorus center was less σ-donating due to the
substitution of an electron-withdrawing para CF3 group. Indeed,
a much improved, respectful 77% yield was achieved with this
ligand after 8 h reaction (84% conversion). Finally, the best
results, 90% yield of 2a with 4% of 1a remained unreacted,
were achieved with the optimal ligand L7, which differs from L6 by
possessing two cis-methyl groups at the 3,5-positions of the
piperidine ring (entry 7). This improvement is attributed to the
more basic nature of the cis-3,5-dimethylpiperidin-1-yl than the
unsubstituted piperidin-1-yl. To confirm the identity of this optimal
catalyst, [L7Au+]2+ BARF2−, we first ascertained the structure of the precatalyst, L7AuCl, by X-
ray diffraction studies (Figure 2A), and then attempted to synthesize it by mixing

![Figure 2. Ortep drawings with 50% ellipsoid probability: (A) L7AuCl and (B) [(L7Au)2]2+
BARF2− with the counteranions and the solvent molecule (i.e., DCE) omitted for clarity.](image-url)

**Table 1. Ligand Optimization and Conditions Study of Gold-Catalyzed Isomerization of Alkynes to Diene**

| Entry | L     | Yield (conv.) | Entry | L     | Yield (conv.) |
|-------|-------|---------------|-------|-------|---------------|
| 1     | L1    | 3% (9%)       | 6     | L6    | 77% (84%)     |
| 2     | L2    | 0% (6%)       | 7     | L7    | 90% (90%)     |
| 3     | L3    | 19% (23%)     | 8     | L8    | 54% (55%)     |
| 4     | L4    | 35% (40%)     | 9     | L9    | ~1% (<4%)     |
| 5     | L5    | 4% (8%)       | 10    | L10   | 92%           |

Reactions were performed in a,α,α-trifluorotoluene at 60 °C for 8 h in vials. 2H NMR yield using diethyl phthalate as the internal reference. 3Dimeric complex, [(L7Au)2]2+ BARF2− (2.5 mol %), was used as the catalyst. 4L7AuCl (6 mol %)/AgX (5 mol %) [X = NTF2, SbF6, BF4, OTf, and PF6] was used as the catalyst. 52 mol % of L7AuCl used; reaction time: 12 h. 6Isolated yield, δr = 49.1.
double bonds in the major products are in (E)-configurations, while the C−C double bonds distal to the benzene ring in the minor products possess (Z)-geometry; it appears that the selectivity for the most stable all (E)-products increases as the aromatic substituents move away from the alkyne. A thiophen-3-yl terminated alkyne (i.e., 1h) also underwent the gold-catalyzed isomerization without incident (entry 7).

The gold catalysis can also tolerate ethereal moieties in close proximity to the C−C triple bond. For example, the phenyl alkyne 1i containing a γ-benzyloxy group reacted efficiently to afford the allylic benzyl ether 2i in 88% yield (entry 8). Of more significance is the formation of the synthetically versatile dienyl benzene (i.e., 1j) upon subjecting (4-(benzyloxy)but-1-yn-1-yl)benzene (i.e., 1j) to the reaction conditions (entry 9). The relatively low isolation yield was due to its labile nature. When N-phenylmaleimide, a dienophile, was added to the initial reaction mixture, it did not impede the gold catalysis and, moreover, reacted with in situ generated 2j smoothly to deliver the Diels–Alder adduct 3 in a respectful 62% yield (eq 1).

Some polyene natural products1 feature multiple conjugated C−C double bonds with further conjugated carbonyl groups. To illustrate the synthetic potential of this gold catalysis, we subjected the ethyl ynoneate 1k to the optimized reaction conditions. Gratifyingly, the anticipated trienoate 2k was isolated in 73% yield (entry 10). An even better yield was obtained with the alkenyl ester substrate (entry 11). The methyl ketone analogue 1m, however, resulted in a much lower yet serviceable yield (entry 12).

We propose a mechanism in Scheme 1 using 1a as the substrate: in line with our initial design, the coordination of 1a to L7AuCl, as shown in the structure A, would enable propargylic deprotonation even with such a weak base (pKₐ in DMSO ~4). The resulting allenylgold intermediate B could undergo ipso-protodeauration to deliver the gold allene complex C. It is notable that the aniline nitrogen acts as a proton shuttle in these two steps, and there must be some conformational flexibility along the C−P bond in order to enable the proton relocation. If the allene substituents could stabilize a developing carbocation, it is conceivable that an equilibrium between C and a gold-substituted allylic cation (i.e., D) would be established. The latter structure would again position a C−H bond α to the allyl cation moiety near the aniline nitrogen. A consequential intramolecular deprotonation would then afford the dienylgold complex E, which is consistent with the observed yield. If allene 2p, formed in 30% yield along with 7% of remaining 1p, 11% yield of the hydration product methyl ketone, and 52% yield of the alkyne migration product 4 (eq 2). Attempts to improve the allene formation were unsuccessful due to the reversible nature of the isomerization.

Table 2. Reaction Scope

| Entry | Alkyne (1) | Diene (2) | Yld (%) (dr), T (h) |
|-------|------------|------------|---------------------|
| 1b    | R = p-OMe | 2b (R = p-OMe) | 68% (49:1), 17h |
| 2c    | R = p-CF₃ | 2c (R = p-CF₃) | 87% (>50:1), 41h |
| 3d    | R = m-CO₂Et | 2d (R = m-CO₂Et) | 92% (20:1), 24h |
| 4e    | R = m- Me₂(CH)₂ | 2e (R = m- Me₂(CH)₂) | 88% (33:1), 24h |
| 5f    | R = o-Br  | 2f (R = o-Br) | 97% (16:1), 12h |
| 6g    | R = o-I   | 2g (R = o-I) | 95% (8:3:1), 24h |
| 7h    |           |            | 77% (24:1), 12h |
| 8i    |           |            | 88% (>99:1), 12h |
| 8j    |           |            | 53% (11:1), 22h |
| 10k   |           |            | 73% (12:1), 48h |
| 11l   |           |            | 82% (9:6:1), 48h |
| 12m   |           |            | 46% (>8:1), 48h |
| 13n   |           |            | 80% (N/A), 12h |
| 14o   |           |            | 84% (N/A), 12h |

 Reaction conditions: L7AuCl (2 mol %) and NaBARF (10 mol %) in α,α,α-trifluorotoluene, 60 °C. Isolated yield. Minor isomer has a newly formed (Z)-π bond. L7AuCl (5 mol %). DCM as solvent and reaction temperature was 40 °C.

Scheme 1. Proposed Reaction Mechanism
which could undergo internal ipso-proton deauration to afford the
diene product 2a and regenerate the catalyst. In these latter
transformations, the aniline again serves as a proton shuttle. The
observed high E-selectivity can be rationalized by that the
intermediate D adopts the most stable conformation (as shown),
and its transformation to the diene product is very facile. Hence,
the net result of this gold catalysis would be two sequential
aniline-assisted proton shuttling. It is important to point out that
the previously reported isomerizations using transition-metal
catalysts likely proceed via a characteristically different
mechanism, where a metal hydride serves as the intermediate
and sequential migratory insertion and β-hydride elimination is
the recurring theme.

The proposed mechanism indicates that allene can be formed
upon the first proton migration and metal decomplexation. This
is consistent with the observed formation of 2pf (see eq 2).
However, in the other cases, allene intermediates were mostly
not detectable. This phenomenon can be attributed to the faster
nature of the second proton migration due to the enhanced
stability of allyl cations of type D bestowed by conjugating
substituents (Table 1 and Table 2 except entry 13) or additional
substituents (Table 2, entry 13) and its rapid subsequent
transformations. In the case of 1pf, the corresponding allyl cation
derived from the allene 2pf′ would have only one alkyl substituent
and is apparently not stabilized enough to enable the second
proton migration. To offer additional support for the
intermediacy of allene, we subjected the terminal alkyn 1qf
to the optimal reaction conditions (eq 3).

As expected, the diene isomers, with the kinetic product as the
major, were formed in similar ratios. Moreover, in accordance to
our reasoning, the reaction of 7 completed in 45 min at 40 °C,
which was much shorter than 6 h needed for the complete
consumption of 1qf. Our further deuterium labeling studies (see SI)
is consistent with the proposed proton migration.

In summary, by functionalizing the privileged biphenyl-2-
ynylphosphine with a basic amino group at the rarely explored 3′
position, the derived gold(I) complex possesses orthogonally
positioned “push” and “pull” forces, which enables for the first
time soft propargylic deprotonation and permits the bridging of a
difference of >26 \( pK_a \) units (in DMSO) between a propargylic
hydrogen and a protonated tertiary aniline. The application of
this design led to efficient isomerization of alkynes into versatile
1,3-dienes with synthetically useful scope under mild reaction
conditions. The work constitutes a dramatic deviation from the
classic soft deprotonation of carbonyl compounds and reveals
new opportunities to access organometallic species such as B
and E via deprotonative process under exceptionally mild conditions.

**ACKNOWLEDGMENTS**

We are grateful for the generous financial support by NIH (R01
GM084254) and NSF (CHE-1301343).

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**ASSOCIATED CONTENT**

+ Supporting Information

Experimental details, compound characterization, and spectra. 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.