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Au-Catalyzed Synthesis of (1*Z*,3*E*)-2-Pivaloxy-1,3-Dienes from Propargylic Pivalates

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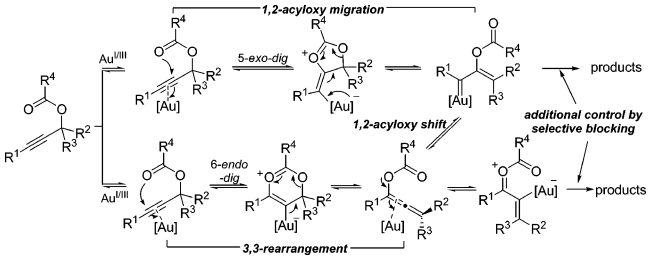
Propargylic carboxylates are versatile substrates in Au catalysis[1] and have been transformed into various synthetically valuable products via two routes: 3,3-rearrangement[2] and 1,2-acyloxy migration[3] (Scheme 1[4]). These two competing routes differ in the initial carbonyl group cyclization to the Au-activated C−C triple bond in either the 5-*exo*-*dig* or 6-*endo*-*dig* mode. The selectivity between these two cyclization modes is largely influenced by the sterics and electronics of the substituents at either end of the propargyl moiety.[5] For example, propargylic esters with terminal[3] or electron-deficient C−C triple bonds[6] normally undergo 1,2-acyloxy migration, while those with electronically unbiased internal C−C triple bonds prefer 3,3-rearrangement.[2] Examples of the opposite selectivities are limited.[3b,c,e] Herein, we report that propargylic esters with electronically unbiased internal alkynes undergo 1,2-acyloxy migration selectively; moreover, synthetically highly useful (1*Z*,3*E*)-2-pivaloxy-1,3-dienes[7] are readily formed with excellent stereoselectivity and can participate efficiently in one-pot inter-/intramolecular Diels−Alder reactions.

We envision that the reversible nature[4] of the 3,3-rearrangement and 1,2-acyloxy migration offers additional selectivity controls (Scheme 1). Thus, with a proper combination of reaction conditions and Au catalysts, a reaction route otherwise disfavored by substitution patterns can be productive if no facile downstream transformation is available to the other route. In this context, we surmise propargylic esters with electronically unbiased internal alkynes (i.e., **1** in Scheme 2) can also undergo 1,2-acyloxy migration, forming alkenyl Au carbenoid **A**. If there is a H α to the gold carbenoid moiety in **A**, subsequent irreversible carbene 1,2-C−H insertion will offer a viable exit from the equilibrium, resulting in the formation of 2-acyloxy-1,3-dienes. The key for the success of this design is that all possible reactions stemmed from the favored 3,3-rearrangement are blocked or minimized.

We set out to discover reaction conditions suitable for the intended 1,3-diene synthesis using oct-3-yn-2-yl acetate (i.e., **2a**, Table 1). In our previous studies, this simple propargylic acetate was shown to selectively undergo 3,3-rearrangements, yielding enone **4** in the presence of H_2O and a cationic Au(I) complex (entry 1)[2b] or α-ethylidene-β-diketone **5a** using dichloro(pyridine-2-carboxylato)Au(III) as catalyst (entry 2).[2c] To our delight, when $IPrAuNTf_2$[8] was used as catalyst and a solution of **2a** in 1,2-dichloroethane (DCE) was heated to 80 °C, the desired acetoxydiene (i.e., **3a**) was indeed formed in 45% yield along with substantial amount of enone **4** and diketone **5a** (entry 3). Other gold catalysts (e.g., entry 4) or $PtCl_2$ (entry 5) gave either poor results or no reaction. While the enone formation could be minimized under anhydrous conditions, we reason that the diketone formation can be avoided by manipulating the migrating acyl group.[2c] Indeed, by simply increasing the steric size of the acyl group, the amount of diketone **5** largely decreased and diene **3** was formed in increasing efficiency (entries 3, 6−8). When

Scheme 1. Au-Catalyzed Reactions of Propargylic Esters



Scheme 2. Design on Au-Catalyzed Formation of 2-Acyloxy-1,3-dienes

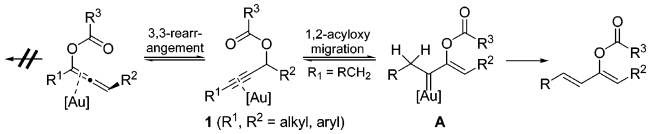
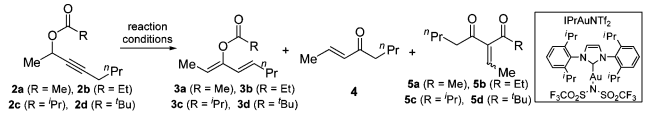


Table 1. Discovering Reaction Conditions for 1,3-Diene Formation



Ent.[a]	**2**	Catalyst	Reaction conditions	Rxn. time	Yield[b] (%) **3**	**4**	**5**
1		$Au(PPh_3)NTf_2$ (2 mol %)	2-butanone/H_2O (160/1), rt	16 h	0	95	0
2		$LAuCl_2$ (1 mol %)[c]	toluene, 80°C	3.5 h	0	0	>99
3	**2a**	$IPrAuNTf_2$ (5 mol %)	anhydr. DCE, 80°C	9 h	45	15	20
4		$IMesAuNTf_2$ (5 mol %)[d]	anhydr. DCE, 80°C	12 h	5	35	31
5		$PtCl_2$	toluene, 80°C	12 h	no reaction		
6	**2b**	$IPrAuNTf_2$ (5 mol %)	anhydr. DCE, 80°C	9 h	31	9	32
7	**2c**	$IPrAuNTf_2$ (5 mol %)	anhydr. DCE, 80°C	9 h	64	13	6
8	**2d**	$IPrAuNTf_2$ (5 mol %)	anhydr. DCE, 80°C	9 h	76	9	0
9		$IPrAuNTf_2$ (5 mol %)	anhydr. DCE, 80°C, 4Å MS	9h	34[e]	0	0
10		**$IPrAuNTf_2$ (5 mol %)**	**anhydr. DCE, 80°C**	**9 h**	**86**[f]	**8**	**0**

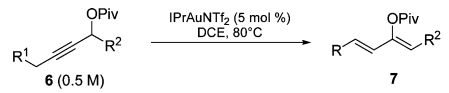
[a] The substrate concentration was 0.05 M for entries 1 and 2, 0.2 M for entries 3−9, and 0.5 M for entry 10. [b] NMR yield using diethyl phthalate as internal reference. [c] L = pyridine-2-carboxylato. [d] IMes = bis(2,4,6-trimethylphenyl)imidazol-2-ylidene. [e] 17% of **2d** left. [f] Isolated yield.

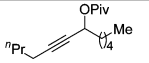
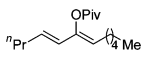
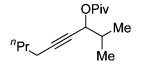
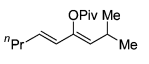
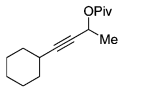
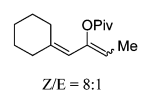
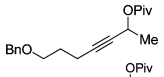
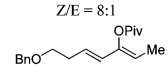
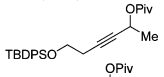
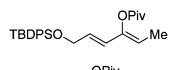
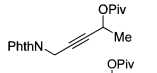
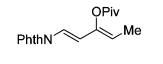
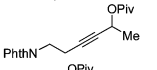
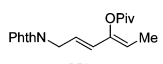
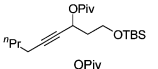
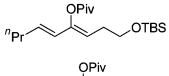
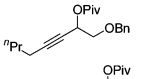
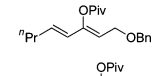
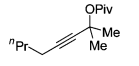
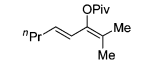
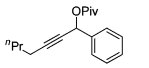
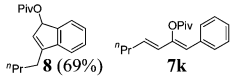
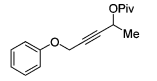
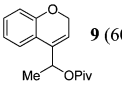
pivalate **2d** was used, no diketone **5d** was detected, and diene **3d** was formed in 76% yield (entry 8). Attempts to eliminate enone formation were largely unsuccessful. When 4 Å MS was added, enone **4** indeed did not form but other side reactions set in (entry 9). Finally, using a higher substrate concentration (0.5 M) and small sealed vials as reaction vessels, the yield of **3d** was improved to 86% (entry 10). A notable feature of this chemistry is that 2-carboxy-1,3-diene **3** was formed as the (1*Z*,3*E*)-isomer only.

The scope of this chemistry was shown in Table 2. Pivalate **6** derived from linear or branched aliphatic aldehydes underwent smooth reactions, yielding pivaloxydiene **7** in good yields (entries 1 and 2) and in excellent stereoselectivities. Of note, pivalate **6** derived from pivalaldehyde (i.e., R^2 = ^{t}Bu) was a very sluggish

10.1021/ja800001h CCC: $40.75

Table 2. Scope Study

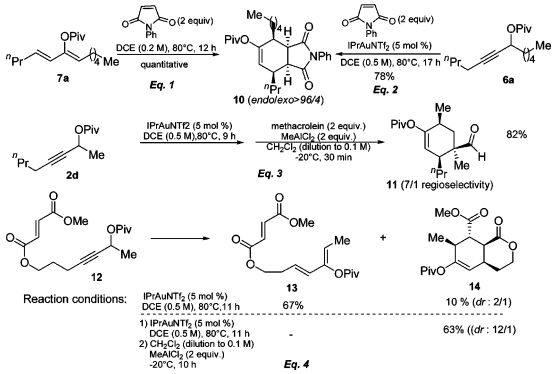


Entry	6		7[a]		Time	Yld.of 7[b]
1		**6a**		**7a**	8 h	85%
2		**6b**		**7b**	10 h	75%
3		**6c**	 Z/E = 8:1	**7c**	10 h	80%
4		**6d**		**7d**	10 h	67%
5		**6e**		**7e**	22 h	71%
6		**6f**		**7f**	9 h	52%
7		**6g**		**7g**	10 h	80%
8		**6h**		**7h**	11 h	67%
9		**6i**		**7i**	10 h	36%[c]
10		**6j**		**7j**	7 h	36%[d]
11		**6k**	 **8** (69%) **7k**		10 h	11%
12		**6l**	 **9** (60%)		3 h	-

[a] Only the (1*Z*,3*E*) isomer was observed except in entry 3. [b] Isolated yield. [c] 30% of enone was isolated. [d] 20% of enyne and 20% of enone were formed.

substrate and only 10% conversion was observed after 10 h. A cyclohexyl ring on the alkyne terminus was allowed, and terminally disubstituted diene **7c** was isolated in 80% yield although in this case the enolic double bond exhibited eroded *Z*-selectivity (entry 3). This reaction also tolerated various protected hydroxyl groups at different positions of the substrate (entries 4, 5, 8, and 9), allowing facile access to pivaloxydienes with variously located oxygen functionalities. Although the yield of **7i** (entry 9) was low, its alternative synthesis via enolate acylation is likely problematic due to potentially facile elimination. To our delight, a phthalimide group was allowed, thus offering protected amino groups in the diene products (i.e., **7f** and **7g**). Of note is product **7f**, where the phthalimide group is directly attached to the diene. This reaction did not work well with propargylic esters derived from ketones (e.g., entry 10), and a major side reaction was the elimination to form enynes. When a phenyl group is located in close proximity to the propargylic moiety (e.g., entries 11 and 12), known processes[2e,9] compete effectively, thus limiting, to a certain extent, the reaction scope.

The dienes formed via this method are excellent substrates for the Diels−Alder reaction. For example, heating **7a** with *N*-phenylmaleimide in DCE at 80 °C for 12 h gave cycloadduct **10** in quantitative yield (eq 1). Moreover, *N*-phenylmaleimide did not affect the Au catalysis, and heating a mixture of pivalate **6a** and *N*-phenylmaleimide in the presence of $IPrAuNTf_2$ for 17 h led to 78% isolated yield of **10** (eq 2). Treatment of the reaction mixture of **2d** after Au catalysis with methacrolein (2 equiv) and $MeAlCl_2$ (2 equiv) at −20 °C also led to an efficient Diels−Alder reaction (eq 3). To our delight, a dienophile unit (i.e., fumarate) was allowed in substrate **12** (eq 4), and a one-pot, sequential Au-catalyzed diene formation and $MeAlCl_2$-catalyzed intramolecular Diels−Alder reaction was realized, offering rapid access to complex bicyclic lactone **14** in 63% yield (eq 4). Of note, residual Au complexes did not affect these Diels−Alder reactions.



In summary, propargylic pivalates with electronically unbiased internal alkynes were selectively transformed into (1*Z*,3*E*)-2-pivaloxy-1,3-dienes containing various functionalities. The unusual selectivity of 1,2-acyloxy migration over the structurally preferred 3,3-rearrangement was realized. This reaction is highly stereoselective and can offer a rapid access to dienes for one-pot intra-/intermolecular Diels−Alder reactions either under thermal conditions or with Lewis acid catalysis.

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Supporting Information Available: Experimental procedures, compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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