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Palladium Catalyzed Regioselective Elimination-Hydrocarbonylation of Propargylic Alcohols

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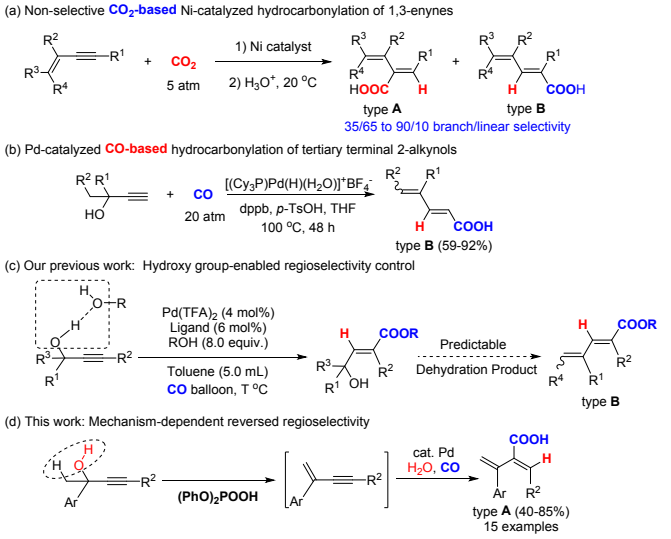
A straightforward approach to substituted 1,3-alkadien-2-yl carboxylic acids starting from readily available propargylic alcohols was developed. Based on mechanistic studies, the reaction was found to proceed via regioselective hydrocarbonylation of the C-C triple bonds of the in situ formed 1,3-enyne intermediates providing 1,3-alkadien-2-yl carboxylic acids with a very high selectivity.

1,3-Dienes are important building blocks in organic synthesis and material sciences due to their wide existence in natural products and their utility in Diels-Alder reactions.[1] In particular, 1,3-alkadienes with an electron-deficient carboxylic acid or ester group in different location have received much attention.[2,3] The syntheses of **B**-type 2,4-alkadienoic acids have been well-established.[2] In contrast, **A**-type 1,3-alkadien-2-yl carboxylic acids were usually prepared via Wittig reaction of aldehydes,[3a] carbonylation of 2,3-dien-1-ols,[3b] and addition-elimination of 3-(methoxycarbonyl)-1,2-allen-4-ols[3c]. In addition, Ni-catalyzed CO_2-based hydrocarboxylation of 1,3-enynes affords a isomeric mixture of these two types of products (Scheme 1a).[4] On the other hand, propargylic alcohols are readily available chemicals and the corresponding carbonylation reactions may afford 2-hydroxylacrylic acids, dicarbonylation products, lactones, and 2,3-allenoic acids.[5,6] Of particular interest, Alper and coworkers disclosed that the carbonylation of terminal alkynols leads to the selective formation of 2,4-alkadienoic acids (Scheme 1b).[7] We recently reported a hydroxy group-enabled linear-selective hydroesterification reaction of alkynes, affording 3-hydroxy-2(*E*)-alkenoates (Scheme 1c).[5g] Here we present an unexpected elimination-hydrocarbonylation of propargylic alcohols with a reversed regioselectivity-a highly selective atom-economic approach to afford **A**-type 1,3-alkadien-2-yl carboxylic acids from readily available tertiary 2-alkynylic alcohols under 1 atm of CO (Scheme 1d).



Scheme 1. Approaches to A- and B-types of 1,3-alkadienyl carboxylic acids or esters

During our investigation on carbonylation of 2-phenyloct-3-yn-2-ol **1a** to afford 2,3-allenote,[8] 1,3-enyne **2a** was found to be a byproduct. In the absence of methanol, when we increased the amount of $(PhO)_2POOH$ to 0.5 equiv., no enyne **2a** was left and (*E*)-1,3-dien-2-yl carboxylic acid (*E*)-**3a** with a branched selectivity and 2,4-alkadienoic acid (*E*)-**4a**[6] with a linear selectivity was obtained in 66% and 5% yields, respectively (Table 1, entry 1). The regioselectivity is reversed as compared to what is shown in Scheme 1d.[7] When PPh_3 was applied, 18% yield of (*E*)-**3a** and 5% yield of (*E*)-**4a** were detected, together with 9% yield of dehydration product 1,3-enyne **2a** (Table 1, entry 2). When DPPM was used, 58% yield of enyne **2a** was detected and only 3% yield of the product (*E*)-**3a** was generated (Table 1, entry 3). In contrast, DPPB offered 39% yield of (*E*)-**3a**,

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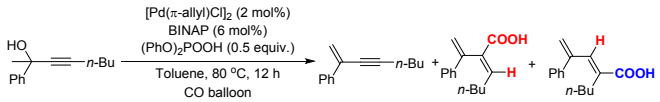
10% yield of (*E*)-**4a**, and 15% yield of 1,3-enyne **2a** (Table 1, entry 4). Commercially available bisphosphine ligands such as DPEphos, DPPF, and BIPHEP were then tested, demonstrating that BINAP is the optimal ligand (Table 1, entries 5-7). Then different palladium precursors such as $PdCl_2$, $Pd(PPh_3)Cl_2$, $Pd(dppf)Cl_2$, $Pd(TFA)_2$, $Pd(acac)_2$, and $Pd(PPh_3)_4$ were screened, however, they all gave inferior results (Table 1, entries 8-13).

Table 1. Optimization of reaction conditions[a]



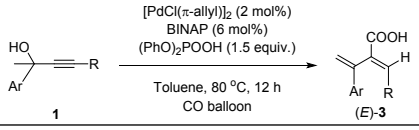
Entry	Changes from the conditions shown in the equation	NMR yield (%) [b]			Recovery of **1a** (%) [b]
		2a	**3a**	**4a**	
1	none	0	66	5	3
2[c]	PPh_3as the ligand	9	18	5	7
3	DPPM as the ligand	58	3	0	0
4	DPPB as the ligand	15	39	10	5
5	DPEphos as the ligand	5	25	0	22
6	DPPF as the ligand	0	43	12	9
7	BIPHEP as the ligand	5	50	10	5
8[d]	$PdCl_2$ as the precursor	21	32	1	2
9[d]	$Pd(PPh_3)_2Cl_2$ as the precursor	34	21	1	0
10[d]	$Pd(dppf)Cl_2$ as the precursor	59	4	0	0
11[d]	$Pd(TFA)_2$ as the precursor	0	64	7	3
12[d]	$Pd(acac)_2$ as the precursor	0	51	0	6
13[d]	$Pd(PPh_3)_4$ as the precursor	0	20	0	6
14	1.0 equiv. $(PhO)_2POOH$	0	81	1	1
15[e]	1.0 equiv. $(PhO)_2POOH$	0	79	1	1
16[e]	1.5 equiv. $(PhO)_2POOH$	0	84	0	0
17[e]	2.0 equiv. $(PhO)_2POOH$	0	83	0	0
18[e,f]	1.5 equiv. $(PhO)_2POOH$	0	46	0	0
19[e,g]	1.5 equiv. $(PhO)_2POOH$	0	48	0	0

[a] Reaction conditions: **1a** (0.5 mmol), [(π-allyl)PdCl]$_2$ (2 mol%), ligand (6 mol%), and $(PhO)_2POOH$ (0.5 equiv.) in toluene (2.5 mL) at 80 °C under 1 atm of CO unless otherwise noted. [b] Determined by ^1H NMR analysis of the crude product using dibromomethane as the internal standard. [c] PPh_3 (12 mol%) was used. [d] [Pd] (4 mol%) was used. [e] The reaction was conducted on 1.0 mmol scale. [f] The reaction was conducted under 5 atm of CO. [g] The reaction was conducted under 10 atm of CO.

When the loading of $(PhO)_2POOH$ was improved to 1.0 equivalent, the yield of the branched product (*E*)-**3a** was improved dramatically with an excellent regioselectivity (Table 1, entry 14). The reaction was then carried out on 1 mmol scale with no obvious decline in yield (Table 1, entry 15). We further increased the loading of $(PhO)_2POOH$ to 1.5 equivalent and found that the branched product (*E*)-**3a** was formed exclusively with an increased yield of 84% (Table 1, entry 16). When the loading of $(PhO)_2POOH$ was increased to 2.0 equivalent, no further improvement was observed (Table 1, entry 17). The influence of CO pressure was then examined and similar low yield was achieved under 5 or 10 atm of CO (Table 1, entry 18, 19). Thus, reaction conditions of entry 16 in Table 1 were chosen as the optimal conditions.

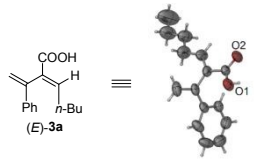
With the optimized reaction conditions in hand, the substrate scope was then evaluated (Table 2). When aryl (Ar) is phenyl group, R may be 1-alkyl, 4-chlorobutyl, 2-phenylethyl, isopropyl, aryl, and hydrogen (Table 2, entries 1-8). This aryl group may be substituted with halogen, methyl, and methoxy at the meta/para position (Table 2, entries 10-14). 2-Naphthyl was also tolerated (Table 2, entry 15). The configuration of the C=C bond in (*E*)-**3a** was further established by X-ray diffraction study (Scheme 2).[9]

Table 2. Scope studies[a]



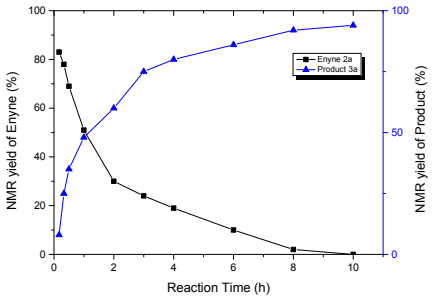
Entry	Ar	R	Product	Yield of **3**(%) [b]
1	Ph	*n*-Bu	**3a**	82
2	Ph	-$(CH_2)_4$Cl	**3b**	85
3	Ph	-$(CH_2)_2$Ph	**3c**	76
4[c]	Ph	*i*-Pr	**3d**	80
5	Ph	H	**3e**	47
6[d]	Ph	Ph	**3f**	58
7[e]	Ph	3-MeC_6H_4	**3g**	40
8[f]	Ph	4-ClC_6H_4	**3h**	48
9[g]	4-ClC_6H_4	Ph	**3i**	51
10	4-ClC_6H_4	*n*-Bu	**3j**	69
11	4-MeC_6H_4	*n*-Bu	**3k**	40
12	4-BrC_6H_4	*n*-C_6H_{13}	**3l**	73
13	3-MeC_6H_4	*n*-C_6H_{13}	**3m**	74
14	3-$MeOC_6H_4$	*n*-C_6H_{13}	**3n**	76
15	2-Naphthyl	*n*-C_6H_{13}	**3o**	75

[a] Reaction conditions: **1** (1.0 mmol), [(π-allyl)PdCl]$_2$ (2 mol%), BINAP (6 mol%), and $(PhO)_2POOH$ (1.5 equiv.) in toluene (5.0 mL) at 80 °C under 1 atm of CO unless otherwise noted. [b] Isolated yield. [c] The reaction was carried out for 30 h; 10% enyne was detected. [d] The reaction was carried out for 42 h. [e] 29% enyne was detected. [f] 14% enyne was detected. [g] The reaction was carried out for 24 h.



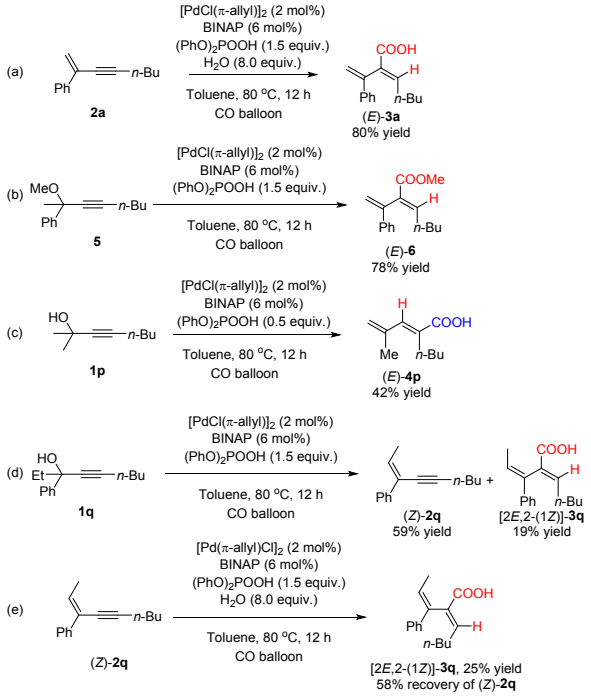
Scheme 2. The ORTEP representation of (*E*)-**3a**

To shed light on the mechanism, the reaction was monitored using substrate **1a** (See supporting information for the details). It illustrated that enyne **2a** emerged at the very beginning of the process and then it was slowly transformed to the hydrocarbonylation product (*E*)-**3a** (Scheme 3).



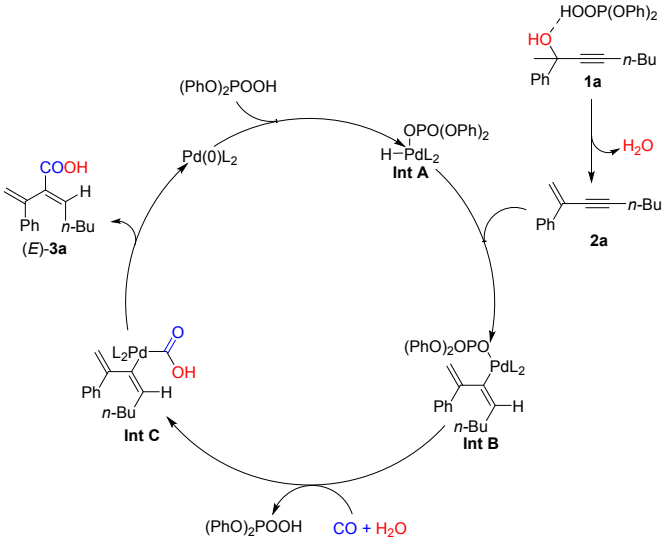
Scheme 3. Reaction profile by monitoring of **2a** and (*E*)-**3a**

A couple of control experiments were also conducted to provide further insights into the mechanism (Scheme 4): (1) when 1,3-enyne **2a** was prepared and subjected to the optimized conditions, product (*E*)-**3a** was generated with a similar yield, further proving that **2a** is the intermediate (Scheme 4a); (2) when 2-phenyloct-3-yn-2-yl methyl ether **5** was applied, the corresponding dienoate (*E*)-**6** was also formed in high yield (Scheme 4b). (3) Interestingly, when 2-methyloct-3-yn-2-ol **1p** was used, **B**-type linear product (*E*)-**4p** was formed instead (Scheme 4c), disclosing that the regioselectivity is substrate dependent; (4) When 3-phenylnon-4-yn-3-ol **1q** was applied, 59% yield of (*Z*)-3-phenyl-2-nonen-4-yne (*Z*)-**2q**[10] and 19% yield of hydrocarbonylation product [2*E*,2-(1*Z*)]-**3q** was isolated(Scheme 4d); (5) Direct application of (*Z*)-**2q** also led to the formation of [2*E*,2-(1*Z*)]-**3q** in 25% yield, indicating that the steric effect at C=C bond side has an influence on the reaction yield but it will not affect the regioselectivity (Scheme 4e).



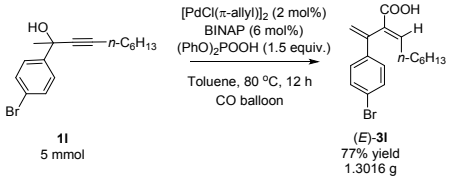
Scheme 4. Control experiments

Based on the above results, a plausible mechanism for the formation of **3a** is proposed (Scheme 5): Oxidative addition of phosphoric acid with Pd(0) gives rise to Pd-H species **Int A**.[11] The loading of phosphoric acid assisted the dehydration of **1a** to form 1,3-enyne **2a**. Subsequent insertion of C-C triple bond in **2a** to the Pd-H bond in intermediate **Int A** would give intermediate **Int B**. The aryl group may account for the observed regioselectivity. Then CO insertion in the presence of water would afford intermediate **Int C**. Reductive elimination would yield product (*E*)-**3a** and regenerate Pd(0) to complete the catalytic cycle.



Scheme 5. Proposed mechanism

The reaction of 2-(4-bromophenyl)dec-3-yn-2-ol **1l** was then conducted on 5 mmol scale, providing the corresponding branched product (*E*)-**3l** in 1.3016 g without obvious decline in yield (Scheme 6).



Scheme 6. Gram scale reaction

To illustrate the usefulness of this product, several transformations were conducted (Scheme 7): (1) When (*E*)-**3l** was firstly transformed to ester, it could react with(3-nitrophenyl)boronic acid to give the Suzuki coupling product (*E*)-**7** in 80% yield;[12] (2) When treated with DIBAL-H, the corresponding alcohol (*E*)-**8** was obtained in 60% yield; (3) Aldehyde (*E*)-**9** can also be obtained in 58% yield after (*E*)-**3l** was transformed into the Weinreb amide,[13] followed by reduction with $LiAlH_4$.

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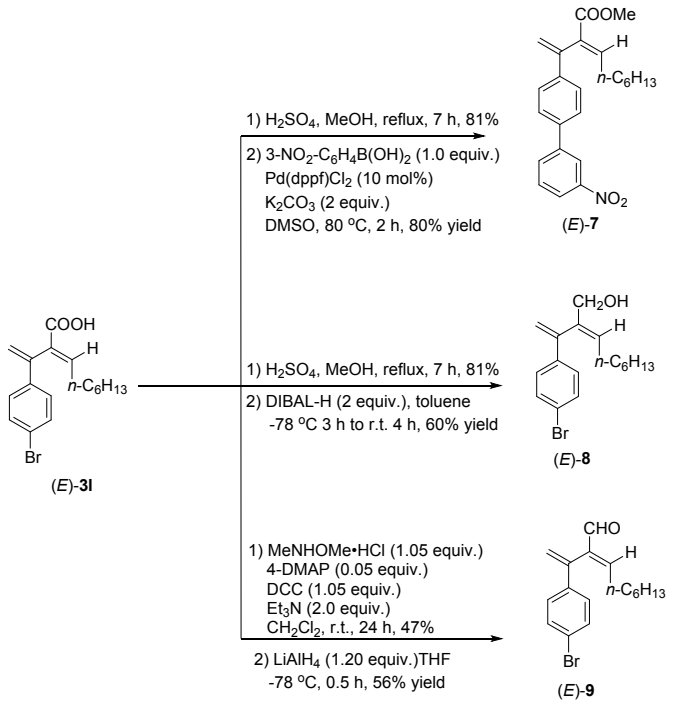

Scheme 7. Synthetic applications of 1,3-alkadien-2-yl carboxylic acids

In conclusion, a palladium-catalyzed efficient synthesis of 1,3-alkadien-2-yl carboxylic acids through regioselective hydrocarbonylation of the in situ generated conjugated 1,3-enynes from readily available propargylic alcohols in the presence of CO was established. $(PhO)_2POOH$ was found to be the key additive for two steps in this transformation. Synthetic potential leading to other useful building blocks was also demonstrated. Further studies in this area are being conducted in our laboratory.

ACKNOWLEDGMENTS

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Conflicts of interest

There are no conflicts to declare.

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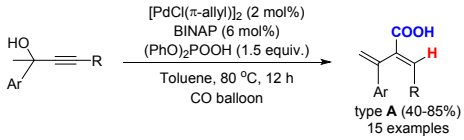

Substituted 2-aryl-1,3-alkadien-2-yl carboxylic acids were formed from readily available propargylic alcohols via a dehydration-carboxylation process.