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Application of dehydroabietic acid in palladium-catalysed enyne cycloisomerisation

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Abstract. Dehydroabietic acid (DAA) promotes palladium(0)-catalysed cyclisations of arene-tethered 1,7-enynols and 1,m-enynoates (m = 6,7) to give fused carbocyclic dienes. 6,6,6,5-tetracyclic lactones are accessible by one-pot cycloisomerisation / Diels-Alder reaction / lactonisation from 1,7-enynols. Furthermore, asymmetric counteranion-directed catalysis was developed, which afforded an indene derivative with an all-carbon quaternary stereogenic center.

Keywords: enynol; dehydroabietic acid; Diels-Alder reaction-lactonisation; asymmetric counteranion directed catalysis; cycloisomerisation, palladium

Introduction

Fused carbocyclic lactones have attracted much attention from synthetic chemists owing to their structural diversity, and the existence of these motifs in a variety of natural products and pharmaceuticals (Figure 1).[1] In this regard, the cascade Diels-Alder reaction / lactonisation is among the most powerful routes to access such products.[2]

A cycloisomerisation / Diels-Alder reaction / lactonisation cascade of enynes equipped with allylic alcohols[3a] would offer an attractive, atom-economical means to convert simple building blocks into this type of complex polycycle.[3b] Although palladium-catalysed aliphatic enyne cycloisomerisation has undergone extensive studies since the first Alder-ene reaction,[3] there are few reports on the cyclisation of arene-tethered 1,7-enynols,[4] presumably because the propargylic alcohol can undergo acid-catalysed [1,3]-shift (the Meyer-Schuster/Rupe rearrangement),[5a,5b] or can eliminate under palladium catalysis.[5c]

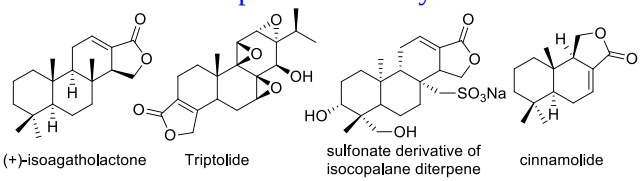


Figure 1. Representative examples of fused polycyclic lactones.

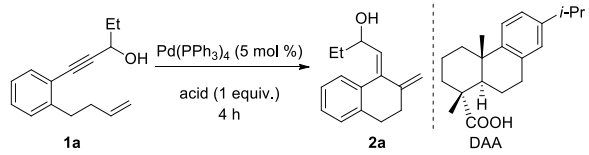
Herein, we report that dehydroabietic acid (DAA) promotes the palladium-catalysed cyclisation of arene-tethered 1,7-enynols and 1,m-enynoates (m = 6, 7), and avoids these side-reactions to deliver polycyclic diene products suitable for further chemistry, including Diels-Alder cycloaddition / lactonisation.

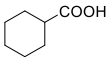
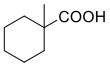
Results and Discussion

Initial investigations into palladium-catalysed cyclisation of **1a** (Table 1) revealed that no cycloisomerisation occurred in absence of an electron-rich phosphine ligand (Pd_2dba_3 / AcOH, entry 1); however, productive cyclisation to **2a** was observed using $Pd(PPh_3)_4$ as pre-catalyst in combination with HOAc, albeit in poor yield (entry 2). Replacing HOAc by a stronger acid (trifluoroacetic acid) led to no reaction (entry 3), whilst **2a** was delivered in a moderate yield using formic acid, with **1a** consumed completely (entry 4). In contrast, the cycloisomerisation did not take place in the absence of acid, nor with catalytic amounts of acid (entries 5 and 6), thus disfavoring a possible pathway through a palladacyclopentene intermediate, and indicating that a stoichiometric amount of acid is crucial to initiate

the hydropalladation of alkynyols in the cycloisomerisation. We hypothesised that sterically unhindered Brønsted acids could react with the hydroxyl group prior to coordination of Pd to the enyne, thus promoting Meyer-Schuster rearrangement, and potentially facilitating acid-catalysed elimination of water from dienol **2a**.[6] By considering the pK_a of a selection of alternative acid additives, including primary, secondary and tertiary acids (entries 8 to 14), we were pleased to observe that **1a** was converted into **2a** in excellent yield in toluene at 80 °C (93%, entry 14), using a bulky acid with a relatively high p*K*a: dehydroabietic acid (pK_a = 7.9).[7]

Table 1. Optimisation of enynol cyclisation conditions.[a]



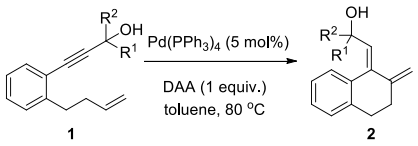
entry	acid	solvent	T (°C)	yield[b]
1[c]	HOAc	toluene	80	N.R.[d]
2	HOAc	THF	50	23
3	CF_3COOH	THF	50	N.R.[d]
4	HCOOH	THF	50	60
5	none	THF	50	N.R.[d]
6	DAA[e]	THF	50	trace
7	DAA	THF	50	59 (95)[f]
8	HOAc	toluene	80	64
9	HCOOH	toluene	80	77
10	PivOH	toluene	80	88
11	PhCOOH	toluene	80	83
12		toluene	80	87
13		toluene	80	87
14	DAA	toluene	80	93
15	DAA	toluene	100	46
16	DAA	toluene	120	66
17[g]	DAA	toluene	80	81

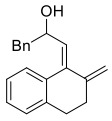
[a] Reaction conditions, unless otherwise specified: **1a** (0.17 mmol), $Pd(PPh_3)_4$ (9.8 mg, 5 mol %), acid (0.17 mmol), solvent (4 mL), N_2, specified heating temperature, 4 h; [b] isolated yield; [c] $Pd_2(dba)_3$ (2.5 mol %); [d] N.R. = no reaction; [e] 5 mol %; [f] based on recovered starting material; [g] $Pd(PPh_3)_4$ (4.9 mg, 2.5 mol %).

The scope of the cyclisation was then investigated under the optimised conditions (Table 2). For substrates **1** bearing secondary (**1a-1d**) and tertiary propargylic alcohols (**1e-1g**), the corresponding benzocyclic dienols **2** were obtained in good yields, regardless of additional steric hindrance at the propargylic carbon (**1f**, **1g**) or at the homopropargylic position (**1b-1d**); however, it was notable that substrates with β-tertiary or quaternary substituents (**1h**, **1i**) did not afford product. The terminal alkyne **1j**, lacking a propargylic alcohol, also underwent cycloisomerisation, however the corresponding diene **2j** was not detected: instead, the product of Diels-Alder dimerization (**2j'**) was observed.[8]

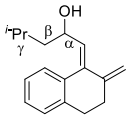
The configuration of the newly-formed alkene was confirmed by X-ray crystal structure of **2d**, which revealed that the alkene had formed as the *Z* stereoisomer (Figure 2).[9]

Table 2. Scope of the reaction with respect to 1,7-enynols.[a]

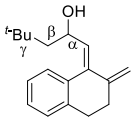




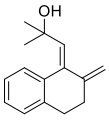
2b, R^1 = Bn 80%



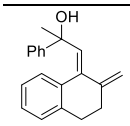
2c, R^1 = CH_2-*i*-Pr 81%



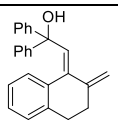
2d, R^1 = CH_2-*t*-Bu 86%



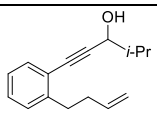
2e, $R^1 = R^2$ = Me 95%



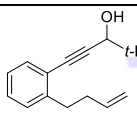
2f, R^1 = Ph, R^2 = Me, 85%



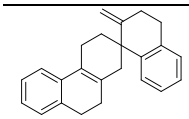
2g, $R^1 = R^2$ = Ph 76%



1h, R^1 = *i*-Pr, N.R.



1i, R^1 = *t*-Bu, N.R.



2j',[b] 94%,[c] 84%,[d] 33%[e]

[a] **1** (1 equiv.), $Pd(PPh_3)_4$ (5 mol%), DAA (1 equiv.), toluene (0.04 M), N_2, 80 °C, 4 h; Yields are for the isolated product; [b] diene was not isolated, instead cyclodimerization of diene was observed; [c] $Pd(PPh_3)_4$ (2.5 mol%), DAA (1 equiv.); [d] $Pd(PPh_3)_4$-DAA (1:1, 2.5 mol%); [e] $Pd(PPh_3)_4$ (2.5 mol %).

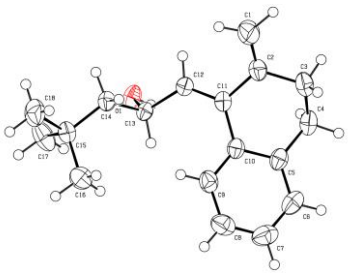
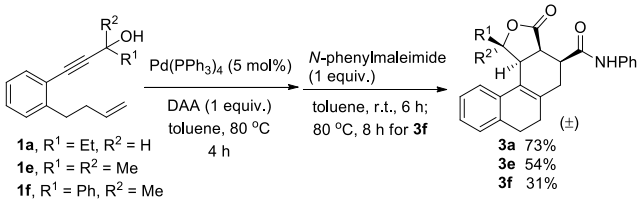


Figure 2. Crystal structure of **2d**

The benzocyclic dienols **2** were prone to decompose slowly[10] upon standing overnight in $CDCl_3$ or d_6-acetone; partial decomposition was also observed upon silica gel chromatography. To avoid this, as well as to demonstrate the utility of the products **2**, we applied a one-pot stepwise cycloisomerisation / Diels-Alder reaction / lactonisation protocol (Scheme 1), which afforded satisfying overall yields of **3** for the secondary and tertiary propargylic alcohols **1a** and **1e** respectively. The sense of diastereoinduction in the Diels-Alder reaction was determined by X-ray crystallographic analysis of analogue **3f** (Figure 3).[9]

To further explore the utility of DAA for cycloisomerisations of benzene-tethered enynes, we next attempted DAA-promoted cyclisation of 1,7-enynoates. We were pleased to observe a high yielding cyclisation at an optimised loading of 2.5 mol% of Pd(0)/DAA (80%, Table 3, Entry 1). A range of substrates proved effective, including



Scheme 1. One-pot cycloisomerised Diels-Alder reaction-lactonisation of **1**.

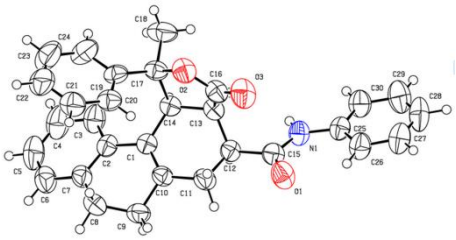
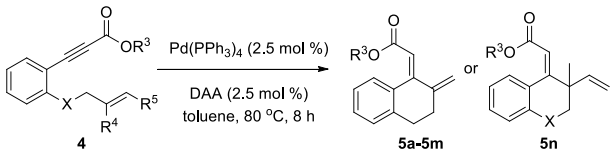


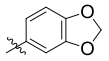
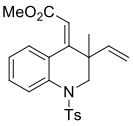
Figure 3. Crystal structure of **3f**

primary, secondary, and tertiary aliphatic alkynoates (entries 1-8). In addition, electron-rich or sterically demanding groups at the *ortho*-, *meta*-, or *para*-position of aryl esters were also tolerated in their transformations into benzocyclic dienoates **5** (entries 9-13). Cyclisation of **4n**, bearing a trisubstituted alkene,[3d,4a] was also performed with catalytic DAA / $Pd(PPh_3)_4$, which although requiring additional heating afforded **5n**, featuring a quaternary carbon center (entry 14), in respectable yield (51%).[11]

Table 3. Scope of the reaction with 1,7-enynoates.[a]



For entry 1-13, X = C, $R^4 = R^5 = H$;
entry 14, X = NTs, $R^4 = R^5 = Me$

entry	R^3, product	yield	entry	R^3, product	yield
1	Me, **5a**	65%[b] 80% 83%[c] 81%[d]	8	*t*-Bu, **5h**	67%
2	Et, **5b**	76%	9	Ph, **5i**	78%
3	*n*-Bu, **5c**	59%	10	Mes, **5j**	52%
4	*i*-Pentyl, **5d**	56%	11	anisole, **5k**	86%
5	Cy, **5e**	77%	12	*o*-OMe-C_6H_4, **5l**	73%
6	Cp, **5f**	81%	13	 **5m**	65%
7	*i*-Pr, **5g**	66%	14	 **5n**	51%[e]

[a] Unless specified, all entries were conducted with $Pd(PPh_3)_4$-DAA (1:1, 2.5 mol%); [b] $Pd(PPh_3)_4$-DAA (1:1, 1 mol%); [c] $Pd(PPh_3)_4$-DAA (1:1, 5 mol%); [d] $Pd(PPh_3)_4$-DAA (1:1, 10 mol%); [e] 100 °C, 36 h.

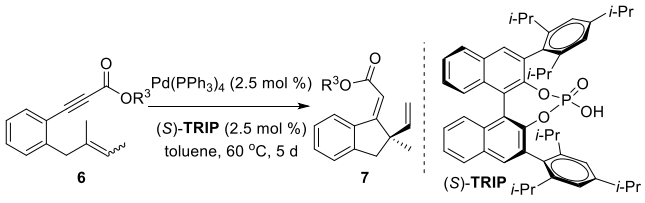
Asymmetric counteranion-directed catalysis (ACDC)[12] has recently emerged as an exciting new concept for asymmetric induction in reactions that are sensitive to both the steric and electronic nature of the reactants. High levels of stereocontrol are often thought to be achieved through weak binding of the chiral anion to the 'naked' catalyst through non-covalent electrostatic interactions.

In the field of cycloisomerization, the only examples of the asymmetric construction of quaternary carbon centers in palladium-catalysed enyne cycloisomerisation reported to date are the pioneering study by Mikami,[3d,4a] which specifically focused on the use of chiral bidentate phosphanes; in

general, asymmetric enyne cycloisomerization has proven difficult to realise.[13] Mikami found that to achieve enantioselective cyclisations furnishing quaternary stereocenters *via* intramolecular Heck coupling in congested environments, higher temperatures and polar solvents were required. However, such conditions pose a challenge to the as yet unrealised ACDC approach, as strong ion-pairing interactions are likely to be favored only in non-polar solvents.[12d] Accordingly, cyclisations carried out in polar solvents or under heating seem destined to suffer in terms of stereoselectivity due to ion dissociation.

We probed the applicability of ACDC strategy to Pd(0)-catalysed 1,6-enyne cycloisomerisation *via in situ* generation of ion-paired $[H–Pd(II)]^+ \cdot$phosphate from (*S*)-TRIP and $[H\text{-}Pd(II)]^+ \cdot DAA^-$.[14] We were delighted to find that the sterically demanding **7** was furnished in good yields and moderate *ee* upon heating to 60 °C (Table 4, entries 1 and 2). The yield was improved by increasing the reaction temperature, but with a consequent loss of enantioselectivity (entries 4 and 5). Generation of ion paired $[H–Pd(II)]^+ \cdot$carboxylate from natural (+)-DAA led only to low *ee*s (entries 3 and 6).

Table 4. ACDC to construct quaternary stereogenic carbon.[a]



entry	R^3	yield (%)[b]	ee (%)[c]
1	Me, **7a**	83	66
2	Cp, **7c**	56	66
3[d]	Cp, **7c**	93	-7
4[e]	Cp, **7c**	92	8
5[e]	Cy, **7d**	87	10
6[d]	Cy, **7d**	80	-15

[a] **6** (1 equiv.), $Pd(PPh_3)_4$ (2.5 mol %), (*S*)-TRIP (2.5 mol %), toluene (0.04 M), N_2, 60 °C, 5 days; [b] Yields are for the isolated product; [c] Determined by chiral HPLC; [d] **6** (1 equiv.), $Pd(PPh_3)_4$ (2.5 mol %), DAA (2.5 mol %), toluene (0.04 M), N_2, 80 °C, 24 h; [e] 100 °C, 24 h.

Conclusion

In summary, we have found that palladium-catalysed cycloisomerisations, initiated or promoted by dehydroabietic acid, convert a wide range of 1,7-enynols and enynoates to benzocyclic dienes. In spite of the moderate instability of these dienols, one-pot cycloisomerisation / Diels-Alder cycloaddition / lactonisation offers a straightforward route into tetracyclic lactones with high efficiency. We also achieved the first example of ACDC in palladium-catalayded cycloiomerisation, where moderate enantioselectivities were observed. Further investigations to explore and optimise this reactivity are ongoing.

Experimental Section

General procedure of stoichiometric dehydroabietic acid (DAA)-mediated 1,7-enynol cycloisomerisation

Toluene (3 mL) was injected under nitrogen into a Schlenk tube containing $Pd(PPh_3)_4$ (10 mg, 0.0085 mmol, 5 mol %) and dehydroabietic acid (51 mg, 0.17 mmol, 1 equiv.), and this suspension was stirred at room temperature for 20 min. The 1,7-enynol substrate (0.17 mmol, 1 equiv.) in toluene (1 mL) solution was added, and the tube was sealed with a screw cap. The mixture was stirred at 80 °C for 4-8 hours (monitored by TLC). The reaction mixture was washed with brine, and extracted with ethyl acetate. The organic phases were concentrated, and the residue was purified by column chromatography to afford **2**.

General procedure of one-pot cycloisomerisation / Diels-Alder reaction / lactonisation of 1

Toluene (3 mL) was injected under nitrogen into a Schlenk tube containing $Pd(PPh_3)_4$ (9 mg, 0.008 mmol, 5 mol %) and dehydroabietic acid (48 mg, 0.16 mmol, 1 equiv.), and this suspension was stirred at room temperature for 20 min. The 1,7-enynol substrate (0.16 mmol, 1 equiv.) in toluene (1 mL) solution was added, and the tube was sealed with a screw cap. The mixture was stirred at 80 °C for 4-8 hours until full consumption of the starting material **1**, monitored by TLC. Then *N*-phenylmaleimide (0.16 mmol, 1 equiv.) was added in one-portion under nitrogen purge and the reaction was stirred at room temperature for 6 hours, until full consumption of the starting material by TLC. The reaction mixture was washed with brine and extracted with ethyl acetate three times. The combined organic layer was dried by $MgSO_4$, filtered, and was concentrated *in vacuo*, and the residue was purified by column chromatography to afford **3**.

General procedure of dehydroabietic acid (DAA)-catalysed enynoate cycloisomerisation

Toluene (3 mL) was injected under nitrogen into a Schlenk tube containing $Pd(PPh_3)_4$ (5 mg, 0.004 mmol, 2.5 mol %) and dehydroabietic acid (1.3 mg, 0.004 mmol, 2.5 mol %), and this suspension was stirred at room temperature for 20 min. The enynoate **4** (0.17 mmol, 1 equiv.) in toluene (1 mL) solution was added, and the tube was sealed with a screw cap. The mixture was stirred at 80 °C for 8 hours as monitored by TLC. The reaction mixture was washed with brine and extracted with ethyl acetate. The combined organic layers were evaporated in *vacuo* and the residue was purified by column chromatography to afford corresponding cyclisation product.

Supporting Information

General experimental procedures, spectral data, NMR spectra for all compounds, and the X-ray crystal structures of **2d** and **3f** are provided in the Supporting Information.

Acknowledgements

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FULL PAPER

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