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Article

α- and β-Functionalized Ketones from 1,3-Dienes and Aldehydes: Control of Regio- and Enantioselectivity in Hydroacylation of 1,3-Dienes

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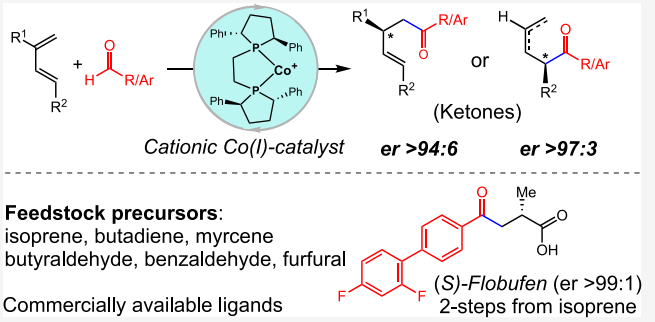
ABSTRACT: Ketones are among the most widely used intermediates in organic synthesis, and their synthesis from inexpensive feedstocks could be quite impactful. Regio- and enantioselective hydroacylation reactions of dienes provide facile entry into useful ketone-bearing chiral motifs with an additional latent functionality (alkene) suitable for further elaboration. Three classes of dienes, 2- or 4-monosubstituted and 2,4-disubstituted 1,3-dienes, undergo cobalt(I)-catalyzed regio- and enantioselective hydroacylation, giving products with high enantiomeric ratios (er). These reactions are highly dependent on the ligands, and we have identified the most useful ligands and reaction conditions for each class of dienes. 2-Substituted and 2,4-disubstituted dienes predominantly undergo 1,2-addition, whereas 4-substituted terminal dienes give highly enantioselective 4,1- or 4,3-hydroacylation depending on the aldehyde, aliphatic aldehydes giving 4,1-addition and aromatic aldehydes giving 4,3-addition. Included among the substrates are feedstock dienes, isoprene (US$1.4/kg) and myrcene (US$129/kg), and several common aldehydes. We propose an oxidative dimerization mechanism that involves a Co(I)/Co(III) redox cycle that appears to be initiated by a cationic Co(I) intermediate. Studies of reactions using isolated neutral and cationic Co(I) complexes confirm the critical role of the cationic intermediates in these reactions. Enantioselective 1,2-hydroacylation of 2-trimethylsiloxy-1,3-diene reveals a hitherto undisclosed route to chiral siloxy-protected aldols. Finally, facile syntheses of the anti-inflammatory drug (*S*)-Flobufen (2 steps, 92% yield, >99:1 er) and the food additive (*S*)-Dihydrotagetone (1 step, 83% yield; 96:4 er) from isoprene illustrate the power of this method for the preparation of commercially relevant compounds.



INTRODUCTION

Acyclic 1,3-dienes and aldehydes are among the most readily available precursors for organic synthesis, many of them marketed in bulk as feedstock materials for chemical industry.[1] Regio- and enantioselective union of easily accessible 1,3-dienes and aldehydes (industrially produced by alkene hydroformylation) is a reaction whose full potential has not yet been realized and, like other similar reactions of dienes, can provide valuable building blocks adorned with latent functionalities for further synthetic elaboration.[2−8] Unlike reactions of simple alkenes, reactions of prochiral dienes present additional challenges, since a multitude of primary products can be formed, even for the simplest of these compounds, such as a monosubstituted (*E*)-1,3-diene (Figure 1A, **1**, $R^1 = R^2 = R^3 = H$; R^4 = alkyl). Thus, in a generic hydrofunctionalization reaction, possibility exists for the formation of 1,2/2,1-, 1,4/4,1-, and 3,4/4,3-adducts (regioselectivity defined by the number of the carbons of the diene to which are attached the X and H, respectively), in addition to geometrical isomers of the residual double bonds in some of the products, even if an enantioselective reaction can be accomplished. Additional substituents on the diene, use of difunctionalization reagents,[3,8] and multicomponent additions further exacerbate the situation. Among the reactions of 1,3-dienes, there are examples of highly selective C−C bond-forming reactions, even though enantioselective variations are still rare. These include 3,4-additions of activated nucleophiles such as involved in hydrocyanation,[9] hydroalkynylation,[10] hydroalkylation,[11−15] hydroarylation,[16−19] 2,1- or 4,1-reductive coupling,[20−24] and hydrovinylation reactions.[25−30] In addition, several highly selective multicomponent additions involving 1,3-dienes have also been reported.[31−36]

Conspicuously absent among these reports on diene functionalizations are the uses of regio- and enantioselective hydroacylation, a versatile and potentially important C−C

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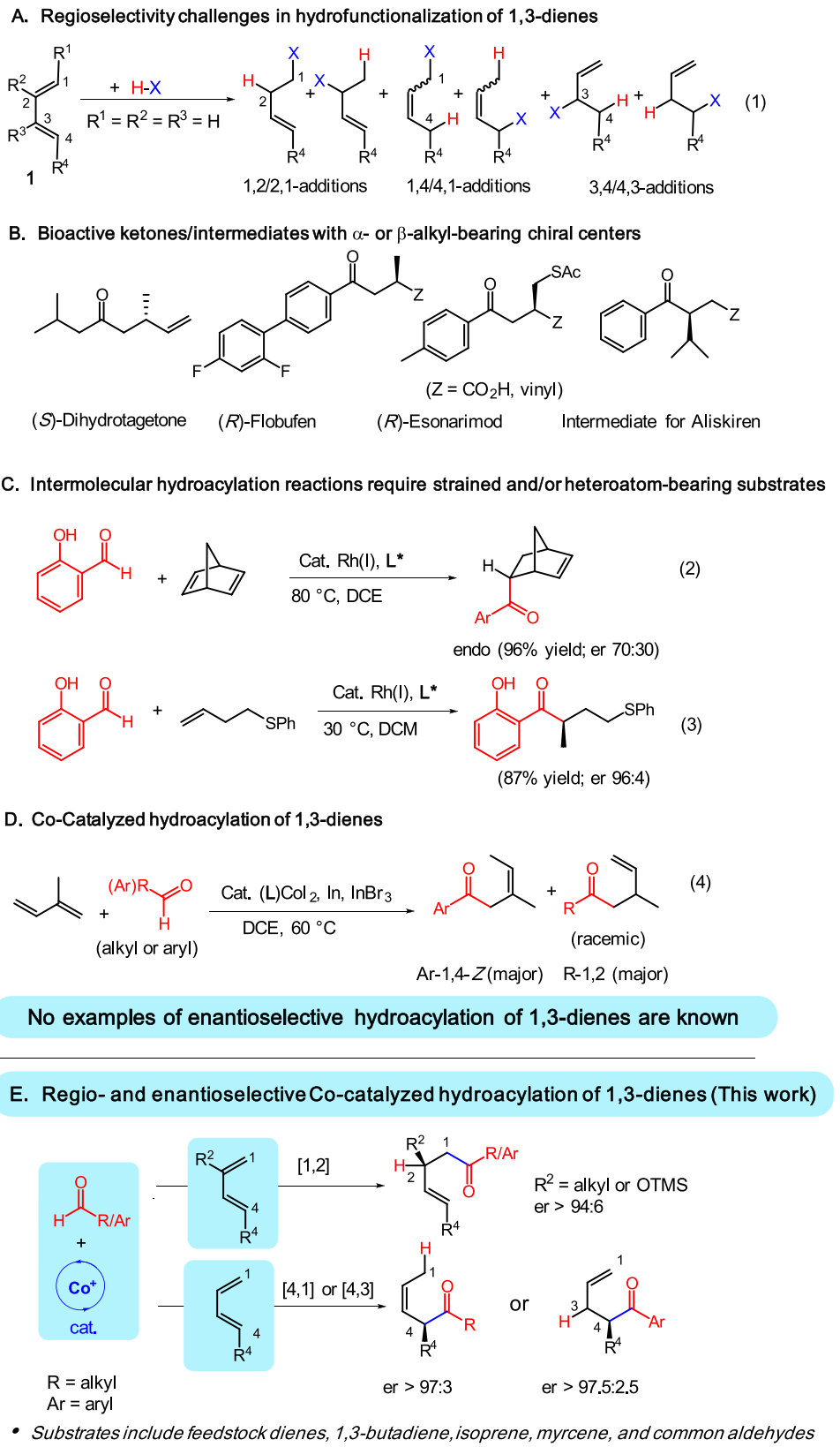

Figure 1. (A) Hydrofunctionalization of 1,3-dienes can lead to multiple chiral and achiral products. (B) Examples of medicinally relevant ketones with α- or β-alkyl-bearing stereogenic centers. The alkene residue in the hydroacylation products can serve as a latent functionality for further elaboration of the primary products. (C) Enantioselective *intermolecular* hydroacylations of alkenes are carried out with expensive Rh catalysts and are limited to strained alkenes and/or aldehydes carrying heteroatoms capable of secondary coordination. (D) Lone reported example of Co-catalyzed hydroacylation of 1,3-dienes (see text). (E) Judicious choice of ligands and activators enables highly selective hydroacylation of broad classes of 1,3-dienes at room temperature (this work).

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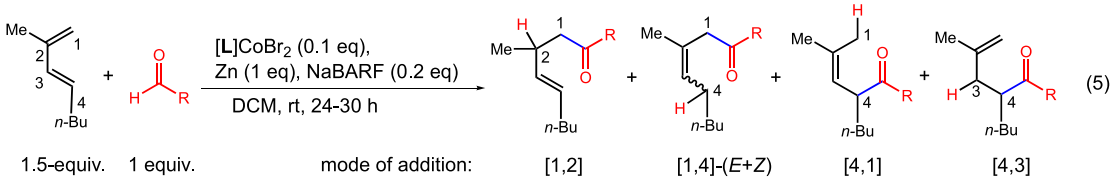
Table 1. Hydroacylation of (*E*)-2-Methyl-1,3-octadiene: Optimization of Solvents and Activators[a]



(5)

entry	aldehyde, ligand	activator	solvent, conv.(%)	regioselectivity (%)			
	***n*-Heptanal**			**1,2**	**1,4-[*E*+*Z*]**	**4,1**	**4,3**
1	dcype	NaBARF	DCM/100	87	8	1	2
2	dcype	NaBARF	ether/30	95	5	0	0
3	dcype	NaBARF	toluene/<5	nd	nd	nd	nd
4	dcype	NaBARF	EtOAc/<5	nd	nd	nd	nd
	***i*-Butyraldehyde**						
5	dcype	NaBARF	DCM/100	89	8	3	0
6	dcype	$InBr_3$	DCM/100	3	-	-	-
7	dcype	$AgSbF_6$	DCM/80	21	3	-	-
8	(*S*,*S*)-Ph-BPE	NaBARF	DCM/100	94	3	2	1
9[b]	(*S*,*S*)-Ph-BPE	$ZnBr_2$	DCM/100	-	-	-	-
10[b]	(*S*,*S*)-Ph-BPE	$InBr_3$	DCM/100	-	-	-	-
11[b]	(*S*,*S*)-Ph-BPE	$AgSbF_6$	DCM/100	-	-	-	-

[a]See eq 5 and Supporting Information, pp S11 and S16, for details of the procedures. [b]No hydroacylation products. Only low yields of hetero-Diels–Alder and oligomerization products of the diene were observed.

bond-forming reaction known for the synthesis of ketones from aldehydes and alkenes (Figure 1C,D).[37−39] Ketones with α- and β-alkyl-bearing chiral centers are ubiquitous motifs in many medicinally important natural products, especially among polyketides exemplified by erythromycin, rapamycin, and spongistatin and their analogs.[40,41] They are also versatile intermediates for synthesis of numerous pharmaceutical and other fine chemicals, examples of which are shown in Figure 1B. Examples of enantioselective *intramolecular* hydroacylation reactions for the synthesis of ketones have been reported, even though developments in arguably the more broadly applicable *intermolecular* reactions have lagged behind. Most successful of these *intermolecular* reactions have been limited to the use of rhodium (US$55,000−65,000/mol) as the catalytic metal and involve substrates that are characterized by increased reactivity due to strain (eq 2, Figure 1C),[42−44] or those carrying additional chelating groups to circumvent side reactions such as decarbonylations (eq 3, Figure 1C).[45−50] A lone example of a non-enantioselective hydroacylation of 1,3-dienes catalyzed by cobalt was reported by Dong in 2014 (Figure 1D).[51] Even though the scope of the reaction with respect to the precursors was not fully explored, this seminal study provided useful hints on the mechanism (oxidative heterodimerization) and viable ligands (electron-rich) for this reaction. From our initial studies, it appears that the published protocol for diene hydroacylation (CoI_2/In/$InBr_3$/DCE/60 °C)[51] may not be suitable for enantioselective versions of several dienes, especially for the more substituted ones that are sensitive to Lewis acids (see later, Table 1 and Table S1 in the Supporting Information). Yet another noteworthy example in the context of cobalt catalysis is Brookhart's Cp*Co(I)(vinylsilane)$_2$-catalyzed hydroacylation of vinylsilane.[52,53] In addition, a 1,6-enyne cycloisomerization terminating with a hydroacylation has been reported,[54] and an enantioselective version of this reaction[55] uses the catalyst system similar to what we first reported in 2017.[30] No examples of enantioselective hydroacylation of 1,3-dienes have been reported to date.[56] In this paper we disclose the first examples of highly regio- and enantioselective hydroacylations of variously substituted 1,3-dienes that can be accomplished at room temperature using readily accessible cationic Co(I) complexes. Additionally, the role of these cationic complexes in these reactions will be clarified. The regioselectivity in the reactions of terminally substituted 1,3-dienes is exquisitely controlled by the nature of the aldehyde (aromatic vs aliphatic). A highly enantioselective hydroacylation of 2-trimethylsiloxy-1,3-diene opens a new route to nearly enantiopure silyl-protected aldols (Figure 1E, R^2 = OTMS, R^4 = H). Applications for short enantioselective syntheses of the flavoring agent (*S*)-Dihydrotagetone[57] (er: 96:4) and anti-inflammatory 3-aroyl-2-methylpropionic acid (*R*)-Flobufen[58] (er: >99:1) from isoprene are also disclosed.

RESULTS AND DISCUSSION

Optimization Studies. For our initial studies (eq 5, Table 1), we chose an especially challenging substrate, (*E*)-2-methyl-1,3-octadiene, a 2,4-disubstituted diene, and two prototypical aliphatic aldehydes, *n*-heptanal and isobutyraldehyde, which together represent a large set of precursors that would considerably expand the scope of the intermolecular hydroacylation. The choice of methyl-substituted diene was inspired

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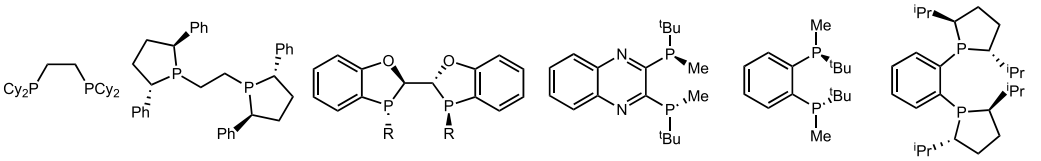
Table 2. Hydroacylation of (*E*)-2-Methyl-1,3-octadiene with Isobutyraldehyde: Selected Ligand Effects[a]

entry	ligand[b]	% conv.[c] (yield)	regiosel. adduct (%) [c]				er [c] (1,2)
			1,2	1,4-[*E*+*Z*]	4,1	4,3	
1	dcype	100 (96)	89	8	3	0	–
2	(*S*,*S*)-BDPP	50	39	50	8	3	89:11
3	*t*-Bu-BIBOP	100 (78)	80	20	0	0	97:3
4[d]	Ph-BIBOP	100	0	0	0	0	–
5	(*R*,*R*)-QuinoxP*	87	46	54	0	0	90:10
6	(*S*,*S*)-BenzP*	100 (82)	77	22	0	1	83.5:16.5
7	(*R*,*R*)-*i*-Pr-DUPHOS	100 (66)	83	8	3	5	86.5:13.5
8[d]	(*S*,*S*)-Et-DUPHOS	100	0	0	0	0	–
9	(S,*S*)-Ph-BPE	95 (75)	94	3	2	1	97:3
10[d]	(*R*,*R*)-Et-BPE	100	0	0	0	0	–



dcype (*S*,*S*)-Ph-BPE *t*-Bu-BIBOP Ph-BIBOP (*R*,*R*)-QuinoxP* (*S*,*S*)-BenzP* (*R*,*R*)-[*i*]Pr-DUPHOS

[a]For a more complete table (including ratio of *E*:*Z* isomer for [1,4]-adduct), see Supporting Information, Table S2; for procedure, see eq 5 in Table 1; and for experimental details, see Supporting Information, p S11. [b]For chart showing the structures of the ligands, see Supporting Information, p S20. [c]Conversion, regioselectivities, and enantioselectivities were determined by GC. nd = not determined. See experimental part in the Supporting Information, pp S24, S34, S45, and S65, for absolute configuration of the products. [d]Complete conversion of diene, and no low-molecular-weight (hydroacylation) products were detected.

by the frequency of methyl-bearing chiral centers, which are ubiquitous in propionate-derived natural products[40,41,59] that could be targeted via the products of the hydroacylation reactions. In the intermolecular context, hydroacylation reactions of aliphatic aldehydes are less developed in scope and sometimes involve the use of excess of the diene and/or elevated temperatures.[51,53] The test substrates were subjected to the reaction conditions established[30] for the efficient generation of cationic Co(I) species, following all products (eq 5, Tables 1 and 2) formed in the reaction by GC and GCMS.

Initial experiments quickly confirmed that, like the other [(**L**)Co(I)]$^+$-catalyzed reactions we had reported,[30,60,61] there were strong solvent, counterion, and ligand effects in these reactions (Table 1).[62] While toluene and other hydrocarbons lead to a sluggish reaction, oxygenated solvents such as THF, ether, and ethyl acetate inhibit the reaction (entries 1−4). Dichloromethane was found to be the optimum solvent. Among the activators, NaBARF was found to be the best (and a unique) choice, leading to nearly quantitative yield of the product(s), with outstanding regioselectivity for the preferred 1,2-adduct with the proper choice of ligands (entries 1, 5, and 8). We found that ZnX_2,[54] $InBr_3$,[51] and various Ag salts which have been previously used in related reactions lead to other side reactions, including hetero-Diels−Alder reactions (especially with Ag salts).[62]

Ligand Effects. Next we turned to an examination of the ligand effects seeking the best activity and highest regio- and enantioselectivity. The most important results obtained are shown in an abbreviated form in Table 2, with a more complete table with additional ligands and reaction conditions included in the Supporting Information (see Table S2 for details). Among the traditional 1,*n*-bis-diphenylphosphinoalkane ligands (Ph_2P-$(CH_2)_n$-PPh_2, n = 1−4), only dppp (1,3-bis-diphenylphosphinopropane) led to good yields of the hydroacylation products, but giving a mixture of mostly 1,2- and 1,4- (Z + E) adducts in a ratio of 43:54. Similar mixtures of products were obtained with chiral bis-phosphines, (*S*,*S*)-BDPP, (*R*,*R*)-QuinoxP*, and (*S*,*S*)-BenzP* (entries 2, 5, and 6). Other chiral bis-phosphines (see Supporting Information), among them (*R*)-Prophos, (*S*,*S*)-Chiraphos, (*R*,*R*)-DIOP, Ph-BIBOP, 2,2′-bis-phosphino-1,1-biaryls like (*S*)-BINAP, (*S*)-SegPhos, and (*R*)-binaphane, and bis-phospholano ligands (*S*,*S*)-Me-BPE, (*R*,*R*)-Et-BPE, and (*R*,*R*)-TangPhos, gave no detectable amount of hydroacylation products (see Supporting Information, Table S2 for details and p S20 for structures of the ligands).[62] A number of sterically and electronically modified phosphinooxazoline (PHOX) ligands which were successfully used elsewhere for Co(I)-catalyzed hydroboration[60] and [2+2]-cycloaddition[61] reactions also failed in the hydroacylation. Most notably, catalysts from several ligands completely consumed the starting 1,3-diene without producing any of the hydroacylation products, presumably leading to high-molecular-weight oligomers (entries 4, 8, and 10).[63]

The best ligands for 1,2-selective hydroacylation were found to be bulky electron-rich phosphines such as 1,2-bis-dicyclohexylphosphinoethane (Table 2, entry 1) and chiral ligands *t*-Bu-BIBOP (entry 3), *i*-Pr-DUPHOS (entry 7), and Ph-BPE (entry 9). The extreme sensitivity of the reaction to the ligand structure is revealed by a pairwise comparison of the activities

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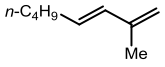
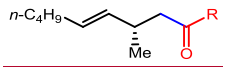
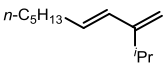
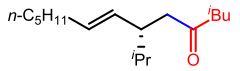
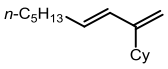
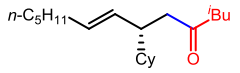
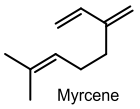
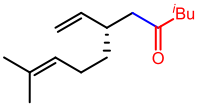
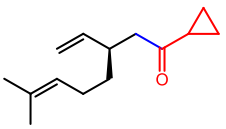
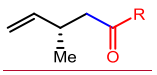
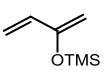
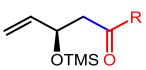
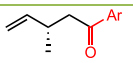
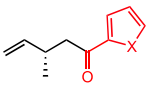
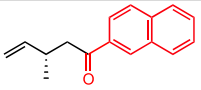
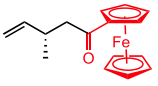
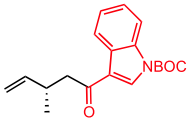
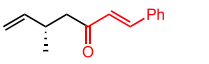
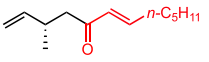
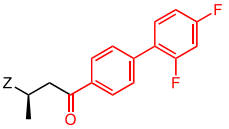
Table 3. Selectivity in Hydroacylation of 2,4-Di- and 2-Monosubstituted 1,3-Dienes: Vicinal Additions Giving Linear Ketones[a]

From Dienes and Diverse Aliphatic Aldehydes				
No.	Diene	adduct	yield/rr	er
1.				
		1a. R = *i*-Pr	75/9:1	97:3
		1b. *n*-hexyl	67/7:1	91.5:8.5
		1c. *n*-butyl	63/7:1	92:8
		1d. *i*-butyl	72/7:1	96.5:3.5
		1e. cyclopentyl	66/7:1	96.5:3.5
2.		 **2**	66/4:1	97:3
3.		 **3**	54/6:1	91:9[b]
4.		 **4a**.	84/6:1	>90:10[b]
		 **4b**.	57/9:1[c]	99:1
5.				
		5a. R = *i*-butyl	83/16:1	96:4
		(*S*)-Dihydrotagetone		
		5b. *n*-hexyl	89/7:1	94:6
		5c. CH_2CH_2Ph	31/7:1	93.5:6.5
		5d. cyclopentyl	90/11:1	95:5
		5e. Cy	84/19:1	96:4
6.				
		6a. R = Cy	76/4:1[c]	94:6
		6b. R = Ph	50/1:1[c]	99:1

From Isoprene and Aromatic Aldehydes			
No.	adduct	yield/rr	er
7.			
	7a. Ar = Ph	96/7:1	99.5:0.5
	7b. 3,4-di-OMe-C_6H_4	79/9:1	99.5:0.5
	7c. 4-CF_3- C_6H_4	98/3:1	99.5:0.5
	7d. 4-CO_2Me- C_6H_4	94/6:1	>90:10[b]
	7e. 4-Br- C_6H_4	95/4:1	>99:1
8.			
	8a. X = O 2-furanyl	65/9:1	99.5:0.5
	8b. X = S 2-thiophenyl	76/3:1	98.5:1.5
9.	 **9**	95/3:1	99:1
10.	 **10**	85/20:1	99:1
11.	 **11**	26/9:1	>99:1
12.	 **12a**	78/>20:1	99.5:0.5
	 **12b**	72/9:1	nd
13.		Z=Vinyl 97/12:1[d]	Z=Vinyl >99:1
	(*R*)-**13a** Z=vinyl	Z=COOH 95/1:0	Z= COOH >99:1
	13b Z= CO_2H (*R*)-Flobufen		

[a]See eq 5 in Table 1 for procedure; (*S*,*S*)-Ph-BPE used as ligand. Cy = cyclohexyl. Isolated yields of combined product. rr = ratio of major product to the other regioisomers. nd = not determined. [b]Minimum value (estimated because of incomplete separation of enantiomers). [c](*R*,*R*)-*i*-Pr-DUPHOS used as ligand instead of (*S*,*S*)-Ph-BPE. For the use of single-component $[Co]^+$ catalysts for these reactions see eq 7 in Table 5. [d](*R*,*R*)-Ph-BPE used as ligand instead of (*S*,*S*)-Ph-BPE.

of ligands shown in entries 3/4, 7/8, and 9/10. In each case, a small change in alkyl substitution pattern of the ligand shows a dramatic effect on the reaction. Among the active ligands, the (*S*,*S*)-Ph-BPE gave the best overall yield and regio- and enantioselectivity. This ligand was chosen for further studies to explore the scope and limitations of the asymmetric hydroacylation.

Scope of Aldehydes and 1,3-Dienes. Having established a useful protocol for hydroacylation, the scope of coupling of various aldehydes containing primary, secondary, and cycloalkyl substituents with 2,4-di- and 2-monosubstituted 1,3-dienes (including isoprene and myrcene) was explored using the ligand (*S*,*S*)-Ph-BPE [and (*R*,*R*)-*i*-Pr-DUPHOS in selected cases], and the results are shown in Table 3. 2-Methyl-1,3-octadiene reacts with both primary (*n*-hepanal, *n*-pentanal, 3-

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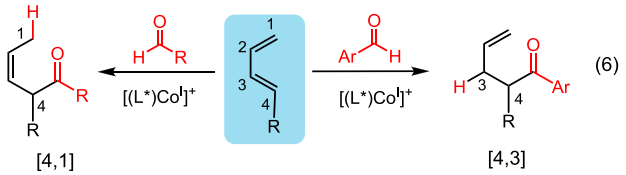
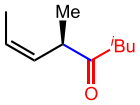
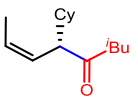
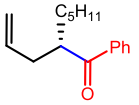
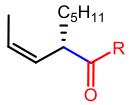
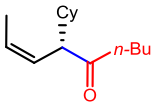
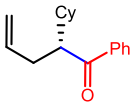
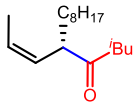
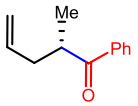
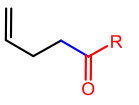
Table 4. Hydroacylation of 1,3-Butadiene and Monosubstituted 1,3-Dienes[a]



adduct	yield/rr[b,c]	er[c]	adduct	yield/rr[b]	er[c]	adduct	yield/rr[b]	er[c]
 **14**[d]	83/13:1	(*Z*): 96:4 (*E*): 97:3	 **18**	68/>20:1	99:1	 **21**	60/12:1	97.5:2.5
 **15/16**	R = *i*-Pr 58/7:1 R = *i*-Bu 64/19:1	>97:3 nd[e]	 **(*Z*)-19**	74/99:1	>90:10	 **22**	52/99:1	97.5:2.5
 **17**	69/12:1	nd[e]	 **20**	64/32:1	98.5:1.5	 **23/24**[d,f]	R = Ph 82/>19:1 R = *n*-Hex 81/>19:1	achiral

[a]See eqs 5 and 6 and Tables 1 and 4. For procedure and experimental details, see Supporting Information, p S11. See Table S3 in the Supporting Information for optimization of ligands. [b]Ratio of major isomer ([4,1] or [4,3]) to the others. Ratio for Z:E can be found in the Supporting Information. [c]Determined by GC. [d](*R,R*)-*i*-Pr-DUPHOS used as ligand instead of (*S,S*)-Ph-BPE(for **14**, **23**, **24**). [e]Not determined. [f]Using 15% by weight 1,3-butadiene in hexanes.

methylbutanal) and secondary (isobutyraldehyde and cyclopentanecarboxaldehyde) aldehydes, giving products in good yields and excellent enantioselectivities (entry 1). Thus, the isopropyl (**1a**), isobutyl (**1d**), and cyclopentyl (**1e**) ketones are produced in an enantiomeric ratio of 96.5:3.5 or higher and the corresponding *n*-hexyl and *n*-butyl derivatives in slightly lower er. In general, the regioselectivity (regioisomeric ratio, rr) for the 1,2-adduct, as measured by the ratio of the desired 1,2-adduct (**1a**−**1e**) to the sum of 1,4- and the other minor adducts (eq 5), varies from 16:1 to 4:1. Replacing the 2-methyl substituent in the diene with an isopropyl group (entry 2) retains the high enantioselectivity in the formation of the corresponding isobutyl ketone (er: 97:3). Enantioselectivities in the reactions of a feedstock 1,3-diene, myrcene (entry 4), depend on the aldehyde, with cyclopropylcarboxaldehyde giving a product (**4b**) in an er of 99:1. Reactions of yet another feedstock 1,3-diene, isoprene, are also noteworthy because of the high regio- and enantioselectivities seen (er: 93.5:6.5 to 96:4, entries **5a**−**5e**). The absolute configuration of ketone **5a** was established from the comparison of specific rotation with that of (*S*)-Dihydrotagetone, a natural product of known configuration (Figure 1B).[57a] The configurations of the other aliphatic ketones (entries 1−6) were assigned by analogy.

One of the most useful substrates is 2-trimethylsiloxy-1,3-butadiene (entry 6), which gives protected aldol products **6a** and **6b** with a latent alkene suitable for further elaboration of the carbon chain. Excellent enantioselectivities are observed for the protected aldol products from cyclohexanecarboxaldehyde (er = 94:6 er) and benzaldehyde (er = 99:1). Configuration of the desilylated aldol **6a** was confirmed by comparison of optical rotation with that of a closely related analog.[64] This catalytic enantioselective route to aldol products, usually derived from methyl ketones or equivalents, might offer an attractive alternative (through a different disconnection) to other more traditional chiral Lewis acid-catalyzed aldol reactions starting with silyl enolates.[65,66] A hydroacylation route to aldol-like products has not been disclosed before.

Reactions of Isoprene. Since isoprene (US$1.40/kg) is one of the cheapest feedstock dienes, we have examined the full scope of aldehydes (in addition to the examples in entry 5 in Table 3) that would engage this precursor in an enantioselective 1,2-hydroacylation, and the additional results are shown in entries 7−13 in Table 3. Aromatic aldehydes including various substituted benzaldehydes with electron-withdrawing and electron-donating groups (**7a**−**7e**), heteroaryl aldehydes (2-furan- and 2-thiophene-carboxaldehyde, **8a** and **8b**), naphthalene-2-carboxaldehyde (**9**), and ferrocene-carboxaldehyde (**10**) underwent enantioselective hydroacylation with isoprene, giving excellent er's, several in the range of 98.5:1.5 or higher. Products from α,β-unsaturated aldehydes, (*E*)-cinnamaldehyde (**12a**) and (*E*)-2-octenal (**12b**), are highly functionalized ketones carrying two different alkenyl substituents, useful for further elaboration of these nearly enantiomerically pure building blocks.

Hydroacylation of Terminally Monosubstituted 1,3-Diene. These dienes (Table 4) belong to yet another important class of readily available precursors, whose enantioselective hydroacylation yields α-chiral ketones, important precursors in their own right for further synthesis. These substrates revealed a striking dependence of the regioselectivity on the nature of the aldehyde. Details of the optimization of the reaction are included in the Supporting Information (Table S3). Thus, commercially available (*E*)-1,3-pentadiene gave a

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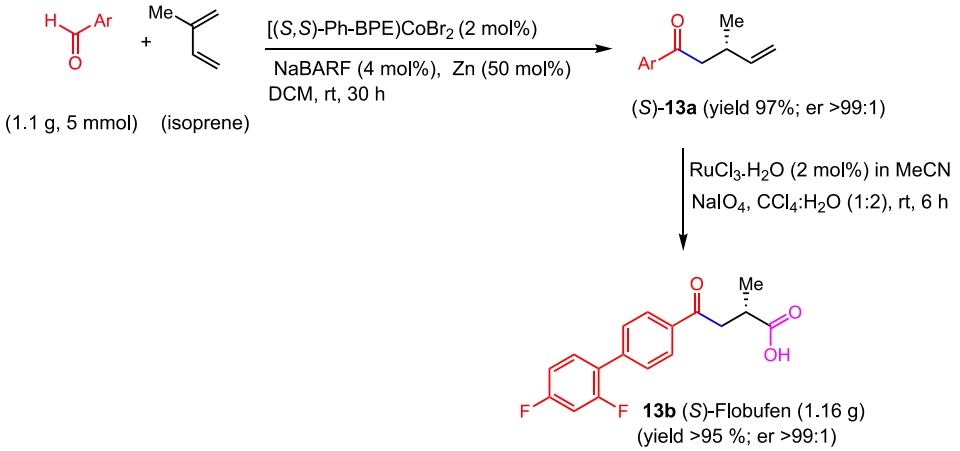

Figure 2. Two-step, gram-scale synthesis of (*S*)-Flobufen from isoprene. Flobufen represents an example of the synthesis of an α-substituted γ-keto acid, a widely used pharmacophore in medicinal chemistry.

good yield of the [4,1]-adduct (rr [(4,1):(4,3)] = 93:7, er = 97.5:2.5) upon reaction with isovaleraldehyde (**14**, Table 4), while giving almost exclusively a [4,3]-adduct (**20**, rr [(4,3):(4,1)] = 97:3, er = 98.5:1.5) with benzaldehyde. Similar regiodivergent selectivity was observed for the other dienes with aliphatic and aromatic aldehydes listed in Table 4. The absolute configuration of the product **20** was ascertained by comparison of its specific rotation with those of authentic samples previously reported in the literature,[67] and other configurations were assigned by analogy. Finally, 1,3-butadiene itself undergoes almost exclusive 1,2-hydroacylation, irrespective of the nature of the aldehyde, giving γ,δ-unsaturated ketones **23** and **24** (Table 4).

Gram-Scale, Two-Step Synthesis of (*S*)-(−)-Flobufen from Isoprene. In addition to the previously described synthesis of the flavoring agent (*S*)-Dihydrotagetone (Table 3, **5a**), a gram-scale synthesis of the anti-inflammatory agent, (*S*)-(−)-Flobufen (a representative example of α-substituted γ-keto acids, a large class of medicinally important compounds that include metalloproteinases, renin, and angiotensin-converting inhibitors, Figure 1, **B**), was carried out starting from the isoprene-derived alkene **13a** (Table 3, entry 13) by oxidation with aqueous $NaIO_4$ and $RuCl_3$ (Figure 2). The absolute configuration of the product was deduced by comparison with the known specific rotations of authentic enantiomers.[58b,62]

Role of Cationic Co(I) Intermediates in Hydroacylation. Two distinct mechanisms have been invoked for the cobalt-catalyzed hydroacylation of alkenes, involving activation of the aldehyde hydrogen such as by a Co(I) reagent $CpCo(I)L_2$[52] in an *intermolecular* reaction or by a Co(0) reagent as in (**P**∼**P**)Co(0) in the context of an enantioselective *intramolecular* reaction.[68,69] Alternatively, an oxidative cyclization involving the (**P**∼**P**)Co(I) catalyst followed by a β-hydride elimination and subsequent reductive elimination has been proposed for an intermolecular hydroacylation of 1,3-dienes.[51,70] Based on several anecdotal observations during our previous investigations[30] on the applications of cationic complexes $[(\mathbf{P}\sim\mathbf{P})Co(I)]^+[X]^-$, and a detailed mechanistic investigation of the heterodimerization of 1,3-dienes and methyl acrylate,[71] we believe that the oxidative addition route (Figure 3) is the preferred pathway for the hydroacylation reaction. Our recently completed mechanistic study of cycloisomerization/hydroalkenylation of 1,6-enynes catalyzed by similar cationic Co(I) complexes[72] also

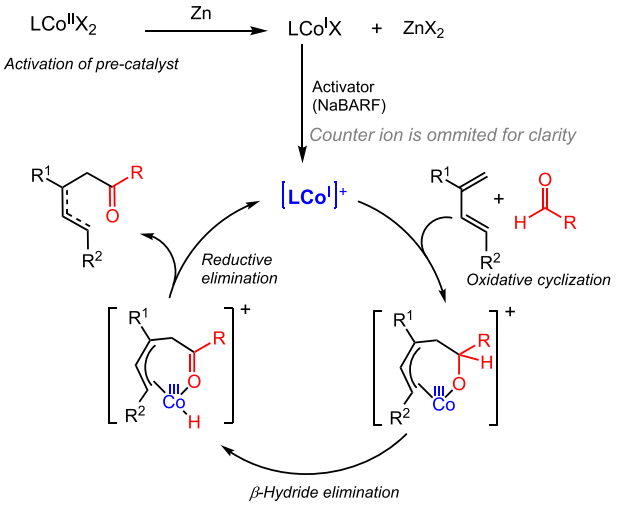

Figure 3. An oxidative dimerization mechanism initiated by a cationic Co(I) species explains the various solvent counterion effects and the predominant (*Z*)-stereoselectivity seen in 4,1/1,4-additions.

gives some support to an oxidative pathway for reactions of these species. The regioselectivity, the *Z*-configuration for the 4,1/1,4-adducts, the lack of decarbonylation, and the counterion and solvent effects on the reaction (Table 1) all suggest a key role for a cationic cobalt(I) intermediate in this highly effective hydroacylation protocol that proceeds at room temperature. Several experiments based on isolated cationic Co(I) complexes (Figure 4) which support this conjecture are shown in Table 5.

In order to clarify the role of such a cationic intermediate and to rule out a mechanism involving a Co(0)/Co(II) redox cycle, we prepared a number of discrete Co(I) complexes (*free of any reducing agents or other residual metal salts*), including cationic ones, and examined them for catalytic activity. The most extensive among these studies were conducted using (*R*,*R*)-[*i*-Pr-DUPHOS]CoX_2 [X = Cl, Br, (**25a**, **25b**)], which served as a source of several catalytically viable cationic Co(I) complexes (Figure 4). (*R*,*R*)-*i*-Pr-DUPHOS complexes were used in this study (Table 5) even though they gave less selective reactions compared to (*S*,*S*)-Ph-BPE ligands (Table 3) because the former set gave highly crystalline intermediates. The Co(I) complex **26**, a known compound previously prepared by Chirik by an alternate route from **25a**,[73] is most

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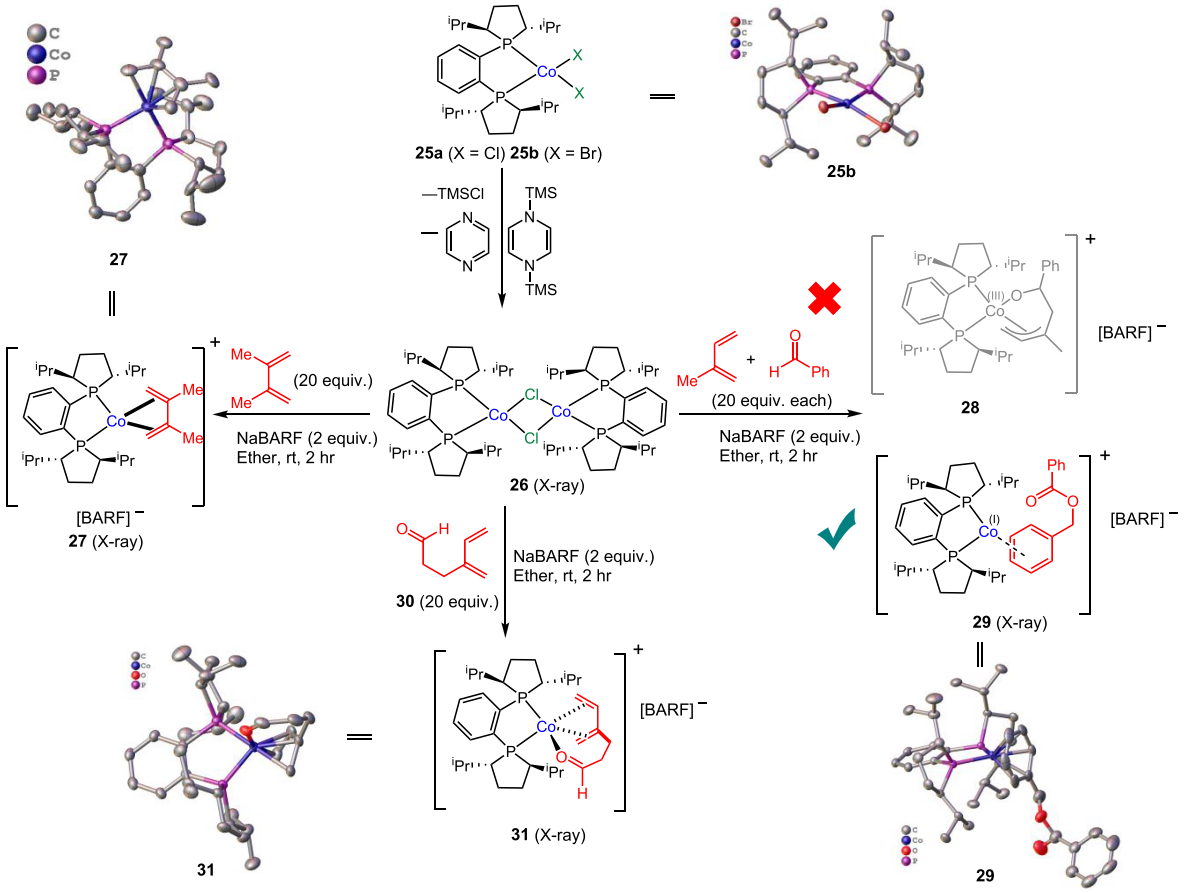
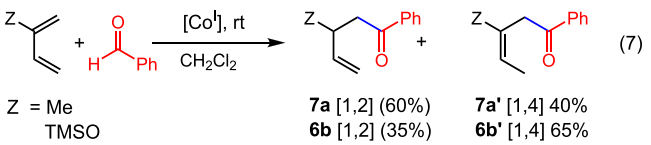


Figure 4. New synthesis of a neutral Co(I) complex and its use for the generation of cationic complexes useful as single-component catalysts for hydroacylation. BARF counterions are omitted for clarity in representations of the solid-state structures.

Table 5. Role of Cationic Complex [P~P]Co(I)]$^+$[BARF]$^-$ in Hydroacylation[a]



(7)

entry	Z	catalyst (mol%)	t (h)	conv (%)	er for **7a** or **6b**
1	Me	{[*i*-Pr-DUPHOS] $Co^ICl\}_2$ (2.5)	24	0 (0)[b]	–
2	Me	{[*i*-Pr-DUPHOS] $Co^ICl\}_2$ (2.5) NaBARF (7.5)	24	60 (100)[b]	98:2
3	Me	[*i*-Pr-DUPHOS]$CoBr_2$ (5) Zn (50), NaBARF (7.5)	24	93	98:2
4	Me	[*i*-Pr-DUPHOS]$CoBr_2$ (5) Zn (50), NaBARF (0)	24	<5	–
5	Me	[*i*-Pr-DUPHOS] $[Co^I(2,3\text{-}Me_2BD)]^+$ (**27**)	40	60	98:2
6	TMSO	$[Co^I]^+$ catalyst **29** (5)	30	95	99:1
7	TMSO	$[Co^I]^+$ catalyst **31** (5)	48	73	99:1

[a]For a more complete table, see Table S4 in the Supporting Information; procedure F (Supporting Information, p S14) gives details. [b]In ether, where the cationic species appears to be more stable.

conveniently prepared by reduction of **25a** by 1,4-bis-trimethylsilylpyrazine.[74] Unlike the corresponding (*S,S*)-BDPP Co(I) complex,[75] which forms a ligand-bridged dimer,[60] the DUPHOS complex is formed as a chloride-bridged dimer (**26**). This dimer **26** itself is not a catalyst for the reaction (Table 5, entry 1), but upon addition of NaBARF, a reaction ensues (entry 2) giving the same products as with our in situ-generated catalyst (Table 3, entry 7, product **7a**). The role of the BARF counterion is also obvious from the in situ procedure shown in entry 4, but devoid of NaBARF, there was no reaction. The cationic 2,3-dimethylbutadiene complex **27** is a viable catalyst, albeit a less efficient one (entry 5).

Attempts to isolate a possible intermediate (**28**) in the hydroacylation led to a Tishchenko reaction product, which made a stable complex (**29**) with the $[(P\sim P)Co(I)]^+$ fragment. This complex (**29**) is also a catalyst for hydroacylation reactions, especially for the reactions of the more reactive 2-trimethylsiloxy-1,3-butadiene (entry 6), where the isolated single-component catalysts have a distinct advantage in that the competitive Mukaiyama aldol reaction between the 2-siloxy-1,3-diene and the aldehyde is significantly slowed down. Finally, a model complex (**31**), prepared from a dienyl aldehyde (**30**), complex **26**, and NaBARF, offers further support for the ability of $[(L)Co(I)]^+$ to assemble the reacting components in its coordination sphere. This complex (**31**) is also a competent catalyst for the hydroacylation of the more reactive 2-trimethylsiloxy-1,3-diene (entry 7).

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CONCLUSIONS

We disclose a general procedure for the regio- and enantioselective addition of the hydrogen and the acyl group of an aldehyde (hydroacylation) to three classes of substituted 1,3-dienes to produce a wide variety of functionalized ketones with α- or β-alkyl/alkenyl-bearing chiral centers in enantiomeric ratios up to >99:1. In this cobalt-catalyzed reaction, inexpensive feedstock dienes and aldehydes that are used include 1,3-butadiene, isoprene, myrcene, piperylene, butyraldehyde, benzaldehyde, and furfural. While reactions of most diene substrates can be carried out using very practical, in situ-generated $[(\mathbf{L})\mathrm{Co(I)}]^+$ catalysts, use of single-component catalysts that were prepared to establish the intermediacy of such species in these reactions may have significant advantages in reactions of highly sensitive substrates such as trimethylsiloxydienes, where these catalysts preclude a competitive Mukaiyama aldol reaction yet promote very efficient hydroacylation. This reaction provides a new, hitherto undisclosed enantioselective route to aldols. Application of this chemistry for a two-step, gram-scale synthesis of (*S*)-Flobufen from isoprene (92% yield and enantiomeric ratio >99:1) illustrates the power of the new protocols for the preparation of pharmaceutically relevant compounds.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c06245.

> Full experimental details for the preparation of all new compounds, and their spectroscopic and chromatographic data, including Tables S1−S8 with details of several optimization studies and Figure S1 showing names, structures, and sources of all chiral ligands (PDF)

Accession Codes

CCDC 2016106 and 2074144−2074147 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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