C–H Activation

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Substrate-Directed Hydroacylation: Rhodium-Catalyzed Coupling of Vinylphenols and Nonchelating Aldehydes**

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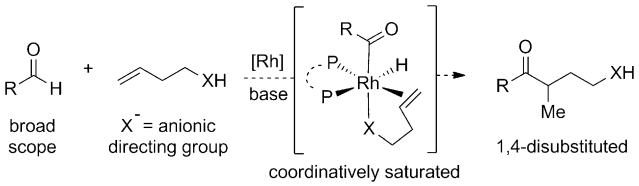
Abstract: *We report a protocol for the hydroacylation of vinylphenols with aryl, alkenyl, and alkyl aldehydes to form branched products with high selectivity. This cross-coupling yields α-aryl ketones that can be cyclized to benzofurans, and it enables access to eupomatenoid natural products in four steps or less from eugenol. Excellent reactivity and high levels of regioselectivity for the formation of the branched products were observed. We propose that aldehyde decarbonylation is avoided by the use of an anionic directing group on the alkene and a diphosphine ligand with a small bite angle.*



Scheme 1. Proposed regioselective hydroacylation of alkenes bearing an anionic directing group.

Substrate-directed hydroacylation enables the regioselective construction of ketones with high atom economy.[1–3] By using a directing group on the alkene component (for example, 1,5-dienes,[4] homoallylic sulfides,[5] allylic alcohols,[6] or homoallylic alcohols[7]), the linear selectivity of rhodium-catalyzed hydroacylation can be overturned to yield branched ketones.[8] However, most hydroacylation processes are limited by the need for chelating aldehydes, such as salicylaldehydes,[9] 2-aminobenzaldehydes,[10] β-sulfur-substituted aldehydes,[11] or (2-pyridyl)aldimines,[12] to facilitate C–H bond activation and suppress competitive decarbonylation. The development of new catalysts for the branched-selective hydroacylation of olefins with nonchelating aldehydes remains challenging. As alternatives to Rh catalysis, the research groups of Krische and Ryu applied ruthenium hydrides for the branched-selective addition of nonchelating aldehydes to enones and 1,3-dienes.[13] Recently, Glorius and co-workers reported an N-heterocyclic-carbene-catalyzed method for the efficient linear-selective coupling of benzaldehydes and electron-deficient styrenes.[14] Additionally, a few promising examples of branched-selective coupling with electron-rich styrenes were reported, albeit with low-to-moderate yields. In light of this challenging transformation, we hypothesized that an anionic directing group on the alkene could enable branched-selective hydroacylation with broad scope in terms of the aldehyde substrate (Scheme 1).

The choice of an anionic directing group allows the use of a neutral Rh catalyst, which is highly electron-rich as compared to the commonly used cationic catalysts. Neutral Rh complexes, such as the complex $[(Me_3P)_3RhCl]$ described by Milstein and the Brookhart catalyst $[Cp^*Rh(olefin)_2]$ (Cp^* = pentamethylcyclopentadienyl), are reactive towards nondirected aldehyde C–H bond activation.[15] On the basis of our double-chelation-assisted hydroacylations with salicylaldehydes,[5–7] we reasoned that an anionic group should promote binding of the alkene and guide the formation of the branched ketone. We focused on the use of bidentate phosphines to make the acyl rhodium(III) hydride coordinatively saturated and therefore stable toward decarbonylation.[16]

In principle, a wide range of acidic functional groups could be used to generate the requisite anionic directing group in the presence of a catalytic base. Owing to the prevalence of phenols and their wide range of pK_a values, we chose vinylphenols as the alkene substrates for initial studies (Scheme 2). Willis and co-workers recently reported a method to access furans through alkyne hydroacylation.[17] Their method relied on the coupling of β-sulfur-substituted aldehydes with propargylic alcohols, and the sulfide directing group was retained in all of the furan products. In our case, the products of vinylphenol hydroacylation can be cyclized into a wide variety of benzofurans, including biologically relevant eupomatenoids.

To test our hypothesis, we examined the coupling of hydrocinnamaldehyde with 4-chloro-2-vinylphenol in the presence of a catalytic base, Rh, and various ligands (Table 1). We maintained a 2:1 P/Rh ratio to generate the proposed saturated acyl rhodium(III) hydride intermediate (Scheme 1). Both $P(OMe)_3$ and bis(diphenylphosphino)methane (dppm) were effective ligands and provided the branched product with > 20:1 branched/linear (b/l) selectivity (Table 1, entries 1 and 2). Weller, Willis, and co-workers used

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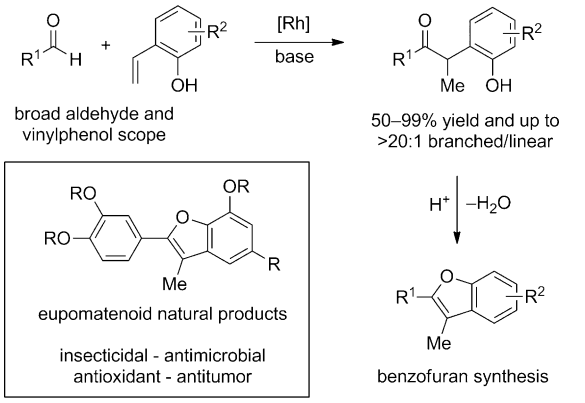
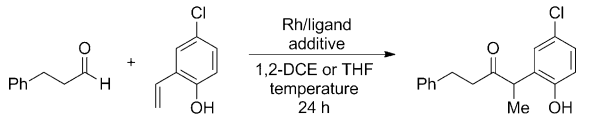


Scheme 2. Hydroacylation of vinylphenols with alkyl, alkenyl, and aryl aldehydes.

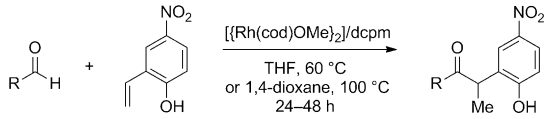
Table 1: Optimization of the reaction conditions.[a]



Entry	Rh	Ligand	Additive	*T* [°C]	Yield [%]
1[b]	$[\{Rh(cod)Cl\}_2]$	$P(OMe)_3$	K_3PO_4	80	75
2[c]	$[\{Rh(cod)Cl\}_2]$	dppm	K_3PO_4	60	90
3[c]	$[\{Rh(cod)Cl\}_2]$	dcpm	K_3PO_4	60	99
4[d]	$[\{Rh(cod)OMe\}_2]$	dcpm	none	60	99

[a] The b/l ratio was >20:1 in all cases, as determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [b] Rh dimer (5 mol%), ligand (20 mol%), K_3PO_4 (10 mol%), 1,2-DCE solvent, 0.4 M in the vinylphenol. [c] Rh dimer (2.5 mol%), ligand (5 mol%), K_3PO_4 (10 mol%), 1,2-DCE solvent, 0.4 M in the vinylphenol. [d] Rh dimer (2 mol%), ligand (4 mol%), THF solvent, 1 M in the vinylphenol. cod = 1,5-cyclooctadiene, 1,2-DCE = 1,2-dichloroethane.

Table 2: Scope of the hydroacylation with respect to the aldehyde.[a,b]



Entry	Aldehyde		Yield [%]	b/l
1		R = Bn	96	>20:1
2		R = Bu	99	>20:1
3		R = *i*Pr	91	>20:1
4		R = Ph	98	>20:1
5		R = CH_2OTBS	68	>20:1
6[c]			99	>20:1
7			94	>20:1
8			91	>20:1
9		R^1 = Ph; R^2,R^3 = H	95	>20:1
10		R^1,R^2 = Me; R^3 = H	62	10:1
11		R^1,R^2 = H; R^3 = Me	31	>20:1
12		R = NMe_2	77	>20:1
13		R = OMe	79	>20:1
14		R = H	78	16:1
15		R = CO_2Me	94	12:1
16			82	19:1

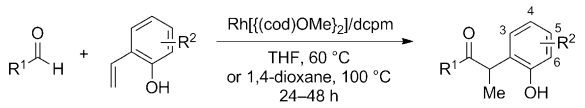
[a] The b/l ratios were determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [b] With alkyl aldehydes: $[\{Rh(cod)OMe\}_2]$ (2 mol%), dcpm (4 mol%), THF, 60°C; with alkenyl and aryl aldehydes: $[\{Rh(cod)OMe\}_2]$ (4 mol%), dcpm (8 mol%), 1,4-dioxane, 100°C. All reactions were carried out at a concentration of 1 M with respect to the vinylphenol. [c] The product had a diastereomeric ratio of 1:1.

similar small-bite-angle diphosphines to enable the hydroacylation of alkenes and alkynes with β-sulfur-substituted aldehydes, and they suggested that the small bite angle promotes reductive elimination.[11e] A more sterically demanding and basic ligand, bis(dicyclohexylphosphino)methane (dcpm), provided a faster reaction rate and higher yield (Table 1, entry 3; 99% yield). Diphosphines with larger bite angles were completely ineffective, and the dearth of chiral small-bite-angle diphosphines precluded an enantioselective process. A change in the solvent from 1,2-DCE to THF and an increase in the vinylphenol concentration to 1M further increased the reaction rate. In line with the observation by Bergman and co-workers that rhodium–alkoxide complexes undergo rapid exchange with phenols,[18] $[\{Rh(cod)OMe\}_2]$ was found to be an effective catalyst in the absence of an added base (Table 1, entry 4; 99% yield). Conveniently, this protocol requires commercially available catalyst components, and unlike the cationic rhodium diphosphine catalysts currently used for hydroacylation, does not require hydrogenation to activate the catalyst.

Aldehydes with diverse steric and electronic properties are excellent coupling partners (Table 2). Primary and secondary aliphatic aldehydes were routinely transformed into ketones in yields above 90% (Table 2, entries 1–8), and acidic α-hydrogen atoms (entry 4) and potentially labile β-silyloxy groups (entry 5) were tolerated. Alkenyl aldehydes are traditionally challenging substrates in hydroacylation owing to issues of chemoselectivity and their tendency to form π-complexes with Rh.[15c] Nonetheless, we report the first rhodium-catalyzed hydroacylation reactions with alkenyl aldehydes in the absence of an aldehyde directing group (Table 2, entries 9–11). These substrates react at a slightly higher temperature and catalyst loading (100°C, 4 mol% $[\{Rh(cod)OMe\}_2]$, 8 mol% dcpm). With electron-rich benzaldehydes (Table 2, entries 12 and 13), the >20:1 b/l ratio observed for most other substrates was maintained, whereas the use of electron-neutral and electron-deficient variants led to slightly lower but synthetically useful regioselectivities (entries 14 and 15). Vanillin was effectively transformed in 82% yield into the corresponding α-aryl ketone product (Table 2, entry 16). The scope of this protocol with respect to the aldehyde is among the broadest reported for hydroacylation to date, thus highlighting the unique reactivity of neutral [Rh(X)(dcpm)] fragments towards the activation of aldehyde C–H bonds.

Vinylphenols with highly varied pK_a values coupled with hydrocinnamaldehyde in 50–93% yield with >20:1 b/l regioselectivity (Table 3, entries 1–4). Sterically demanding vinylphenols were suitable substrates (Table 3, entries 5–7), but the 6-Me-substituted substrate was converted into the desired product in only 11% yield owing to competitive aldol condensation. We predicted a concentration-dependent chemoselectivity for aldol condensation and hydroacylation as a result of the strong binding of the vinylphenol to Rh. In line with this hypothesis, we observed an increased yield of 50% upon fivefold dilution of the reaction mixture. A disubstituted vinylphenol (2-propenylphenol) and a further homologated substrate (2-allylphenol) were unreactive with hydrocinnamaldehyde. Secondary aldehydes were generally transformed in higher yields than primary aldehydes, presumably because they are resistant to aldol condensation (Table 3, entries 8–11; 74–95% yield). These bulkier substrates exhibited slightly diminished regioselectivity with electron-rich vinylphenols. The third substrate class, alkenyl aldehydes, gave almost identical results to hydrocinnamaldehyde (Table 3, entries 12–15). Transformations with benzaldehyde displayed varied regioselectivities (from 9:1 to >20:1) depending on the electronic nature of the vinylphenol (Table 3, entries 16–20).

Table 3: Scope of the hydroacylation with respect to the alkene.[a,b]

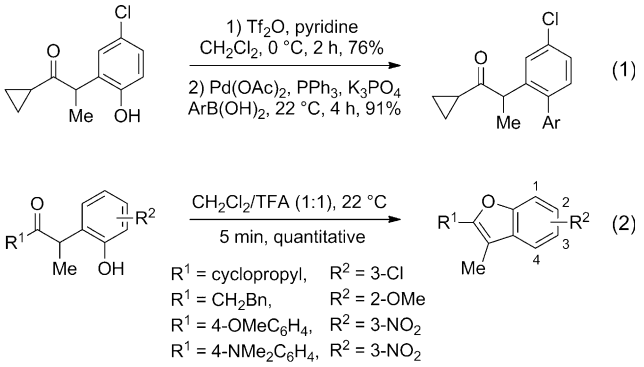


Entry	Product	R^2	Yield [%]	b/l
1		6-OMe	80	>20:1
2		5-OMe	50	>20:1
3		4-OMe	55	>20:1
4		4-F	93	>20:1
5		6-Me	11 (50[c])	>20:1
6		3-Me	93	>20:1
7		4,6-tBu$_2$	67	>20:1
8		6-OMe	93	11:1
9		4-OMe	74	10:1
10		6-Me	91	>20:1
11		3-Me	95	>20:1
12		6-OMe	92	>20:1
13		4-OMe	52	>20:1
14		6-Me	62	>20:1
15		3-Me	96	>20:1
16		6-OMe	88	19:1
17		4-OMe	53	9:1
18		6-Me	81	>20:1
19		3-Me	77	>20:1
20		4,6-tBu$_2$	84	>20:1

[a] The b/l ratios were determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [b] With alkyl aldehydes: [{Rh(cod)OMe}$_2$] (2 mol%), dcpm (4 mol%), THF, 60°C; with alkenyl and aryl aldehydes: [{Rh(cod)OMe}$_2$] (4 mol%), dcpm (8 mol%), 1,4-dioxane, 100°C. Reactions were carried out at a concentration of 1 M with respect to the vinylphenol unless otherwise noted. [c] Yield for a reaction carried out at a concentration of 0.2 M with respect to the vinylphenol. Cy = cyclohexyl.

Sterically demanding alkene substrates, including a bulky 4,6-tBu$_2$-substituted vinylphenol, were excellent coupling partners for benzaldehyde (Table 3, entries 18–20).

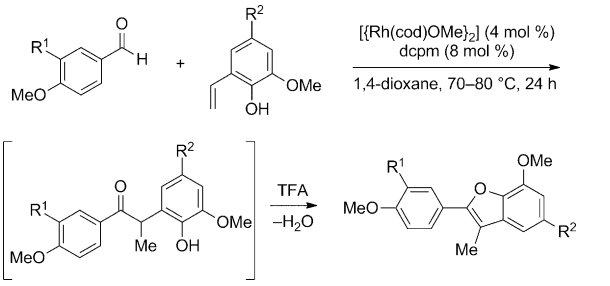
This method provides an alternative approach to the synthesis of *ortho*-substituted α-aryl ketones, which are typically difficult to access by traditional ketone α-arylation.[19] The products of this directed olefin hydroacylation can be further elaborated in a straightforward manner. For example, the phenol component can be triflated and subjected to Suzuki–Miyaura cross-coupling [Scheme 3, Eq. (1)].[20] Alternatively, treatment of the resulting ketones with trifluoroacetic acid (TFA) induces cyclocondensation to the corresponding benzofurans in quantitative yield [Scheme 3, Eq. (2)].[21]



Scheme 3. Derivatization of hydroacylation products. Ar = 4-methoxyphenyl, Bn = benzyl, Tf = trifluoromethanesulfonyl.

This benzofuran synthesis prompted us to target the eupomatenoid class of neolignans (Table 4), which exhibit insecticidal, antimicrobial, antioxidant, and antitumor activity.[22] Most of the recent syntheses of these compounds establish the benzofuran core first and rely on either Stille or Kumada coupling to append propenyl or allyl units.[23] In contrast, we derived a fully functionalized vinylphenol from

Table 4: Eupomatenoid natural product synthesis.



Entry	Name	R^1	R^2	T [°C]	Yield [%]
1	eupomatenoid 12	OMe	1-propenyl	80	70
2	eupomatenoid 16	H	1-propenyl	80	80
3	eupomatenoid 17	H	allyl	70	78
4	eupomatenoid 18	OMe	allyl	70	82

eugenol and used hydroacylation and cyclocondensation to forge the benzofuran core. These coupling partners are highly reactive and allow hydroacylation to occur at moderate temperatures of 70–80 °C. Our approach enabled three-step syntheses of eupomatenoids 17 and 18, and four-step syntheses of eupomatenoids 12 and 16. The alkene proximal to the phenol reacted chemoselectively in the presence of distal allyl and propenyl units (depicted as R^2).

In summary, we have developed a catalyst system for the branched-selective hydroacylation of alkenes bearing anionic directing groups with a wide range of aryl, alkenyl, and alkyl aldehydes. High branched selectivity and high reactivity were generally observed. In combination with a cyclocondensation, we applied this method to access several neolignan natural products. On the basis of these studies, we expect that it will be possible to use other acidic functional groups (e.g. anilines, sulfonamides, hydroxy groups, and carboxylic acids) to generate anionic directing groups in situ and thus further expand the application of hydroacylation. Given the mild reaction conditions, neutral [Rh(X)(dcpm)] fragments are highly reactive towards aldehyde C–H bond activation and hold promise for future hydroacylation reactions with nonchelating aldehydes. A detailed mechanistic study is under way to elucidate the factors leading to this high reactivity and selectivity.

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[1] For a review on substrate-directable reactions, see: A. H. Hoveyda, D. A. Evans, G. C. Fu, *Chem. Rev.* **1993**, *93*, 1307.
[2] a) B. M. Trost, *Science* **1991**, *254*, 1471; b) B. M. Trost, *Acc. Chem. Res.* **2002**, *35*, 695.
[3] For a review on hydroacylation, see: M. C. Willis, *Chem. Rev.* **2010**, *110*, 725.
[4] a) M. Tanaka, M. Imai, Y. Yamamoto, K. Tanaka, M. Shimowatari, S. Nagumo, N. Kawahara, H. Suemune, *Org. Lett.* **2003**, *5*, 1365; b) M. Imai, M. Tanaka, K. Tanaka, Y. Yamamoto, N. Imai-Ogata, M. Shimowatari, S. Nagumo, N. Kawahara, H. Suemune, *J. Org. Chem.* **2004**, *69*, 1144.
[5] M. M. Coulter, K. G. M. Kou, B. Galligan, V. M. Dong, *J. Am. Chem. Soc.* **2010**, *132*, 16330.
[6] S. K. Murphy, M. M. Coulter, V. M. Dong, *Chem. Sci.* **2012**, *3*, 355.
[7] S. K. Murphy, D. A. Petrone, M. M. Coulter, V. M. Dong, *Org. Lett.* **2011**, *13*, 6216.
[8] Alternatively, a directing group placed at a suitable position can reinforce linear selectivity while promoting reactivity. For example, the cross-coupling of a variety of nonchelating aldehydes and acrylamides with high linear selectivity has been reported: a) K. Tanaka, Y. Shibata, T. Suda, Y. Hagiwara, M. Hirano, *Org. Lett.* **2007**, *9*, 1215; b) Y. Shibata, K. Tanaka, *J. Am. Chem. Soc.* **2009**, *131*, 12552.
[9] For hydroacylation with salicylaldehydes, see Refs. [4–7] and: a) K. Kokubo, K. Matsumasa, M. Miura, M. Nomura, *J. Org. Chem.* **1997**, *62*, 4564; b) K. Kokubo, K. Matsumasa, Y. Nishinaka, M. Miura, M. Nomura, *Bull. Chem. Soc. Jpn.* **1999**, *72*, 303; c) R. T. Stemmler, C. Bolm, *Adv. Synth. Catal.* **2007**, *349*, 1185; d) Y. Inui, M. Tanaka, M. Imai, K. Tanaka, H. Suemune, *Chem. Pharm. Bull.* **2009**, *57*, 1158; e) D. H. T. Phan, K. G. M. Kou, V. M. Dong, *J. Am. Chem. Soc.* **2010**, *132*, 16354.
[10] 2-Aminobenzaldehydes have recently been demonstrated to undergo efficient coupling with alkynes under Rh catalysis: M. Castaing, S. L. Wason, B. Estepa, J. F. Hooper, M. C. Willis, *Angew. Chem.* **2013**, *125*, 13522; *Angew. Chem. Int. Ed.* **2013**, *52*, 13280.
[11] For hydroacylation with β-sulfur-substituted aldehydes, see: a) M. C. Willis, S. J. McNally, P. J. Beswick, *Angew. Chem.* **2004**, *116*, 344; *Angew. Chem. Int. Ed.* **2004**, *43*, 340; b) G. L. Moxham, H. E. Randell-Sly, S. K. Brayshaw, R. L. Woodward, A. S. Weller, M. C. Willis, *Angew. Chem.* **2006**, *118*, 7780; *Angew. Chem. Int. Ed.* **2006**, *45*, 7618; c) G. L. Moxham, H. E. Randell-Sly, S. K. Brayshaw, A. S. Weller, M. C. Willis, *Chem. Eur. J.* **2008**, *14*, 8383; d) J. D. Osborne, M. C. Willis, *Chem. Commun.* **2008**, 5025; e) A. B. Chaplin, J. F. Hooper, A. S. Weller, M. C. Willis, *J. Am. Chem. Soc.* **2012**, *134*, 4885; f) I. Pernik, J. F. Hooper, A. B. Chaplin, A. S. Weller, M. C. Willis, *ACS Catal.* **2012**, *2*, 2779.
[12] For (2-pyridyl)aldimines, see: a) J. W. Suggs, *J. Am. Chem. Soc.* **1979**, *101*, 489; b) C.-H. Jun, J.-B. Kang, J.-Y. Kim, *J. Organomet. Chem.* **1993**, *458*, 193; c) C.-H. Jun, J.-S. Han, J.-B. Kang, J.-Y. Kim, *Tetrahedron Lett.* **1993**, *34*, 6431; d) C.-H. Jun, J.-S. Han, J.-B. Kang, S.-I. Kim, *J. Organomet. Chem.* **1994**, *474*, 183; e) M. C. Willis, S. Sapmaz, *Chem. Commun.* **2001**, 2558.
[13] For branched-selective hydroacylation by complementary ruthenium hydride catalysis, see: a) T. Fukuyama, T. Doi, S. Minamino, S. Omura, I. Ryu, *Angew. Chem.* **2007**, *119*, 5655; *Angew. Chem. Int. Ed.* **2007**, *46*, 5559; b) S. Omura, T. Fukuyama, J. Horiguchi, Y. Murakami, I. Ryu, *J. Am. Chem. Soc.* **2008**, *130*, 14094; c) F. Shibahara, J. F. Bower, M. J. Krische, *J. Am. Chem. Soc.* **2008**, *130*, 14120; for a review of hydroacylation methods that proceed by a mechanism other than aldehyde C–H bond activation, see: J. C. Leung, M. J. Krische, *Chem. Sci.* **2012**, *3*, 2202.
[14] M. Schedler, D.-S. Wang, F. Glorius, *Angew. Chem.* **2013**, *125*, 2645; *Angew. Chem. Int. Ed.* **2013**, *52*, 2585.
[15] Almost all examples of isolable acyl rhodium(III) hydrides derived from nonchelating aldehydes are neutral complexes; see: a) D. Milstein, *Organometallics* **1982**, *1*, 1549; b) D. Milstein, *J. Chem. Soc. Chem. Commun.* **1982**, 1357; c) C. Bianchini, A. Meli, M. Peruzzini, J. A. Ramírez, A. Vacca, F. Vizza, F. Zanobini, *Organometallics* **1989**, *8*, 337; d) K. Wang, T. J. Emge, A. S. Goldman, C. Li, S. P. Nolan, *Organometallics* **1995**, *14*, 4929; e) R. Goikhman, D. Milstein, *Angew. Chem.* **2001**, *113*, 1153; *Angew. Chem. Int. Ed.* **2001**, *40*, 1119; f) V. Cîrcu, M. A. Fernandes, L. Carlton, *Inorg. Chem.* **2002**, *41*, 3859.
[16] Coordinatively saturated acyl rhodium(III) hydrides must dissociate a ligand to undergo decarbonylation, and this dissociation is often rate-limiting; for example, see Ref. [15a].
[17] P. Lenden, D. A. Entwistle, M. C. Willis, *Angew. Chem.* **2011**, *123*, 10845; *Angew. Chem. Int. Ed.* **2011**, *50*, 10657.
[18] S. E. Kegley, C. J. Schaverien, J. H. Freudenberger, R. G. Bergman, *J. Am. Chem. Soc.* **1987**, *109*, 6563.
[19] For seminal reports, see: a) B. C. Hamann, J. F. Hartwig, *J. Am. Chem. Soc.* **1997**, *119*, 12382; b) M. Palucki, S. L. Buchwald, *J. Am. Chem. Soc.* **1997**, *119*, 11108; c) T. Satoh, Y. Kawamura, M. Miura, M. Nomura, *Angew. Chem.* **1997**, *109*, 1820; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1740; d) for an account, see: D. A. Culkin, J. F. Hartwig, *Acc. Chem. Res.* **2003**, *36*, 234.
[20] A. Suzuki, *Pure Appl. Chem.* **1985**, *57*, 1749.
[21] Benzofurans have been previously synthesized by the TFA-mediated cyclocondensation of α-(2-hydroxyaryl) ketones; see Refs. [7, 23a].
[22] For isolation, see: a) B. F. Bowden, E. Ritchie, W. C. Taylor, *Aust. J. Chem.* **1972**, *25*, 2659; b) K. Picker, E. Ritchie, W. C. Taylor, *Aust. J. Chem.* **1973**, *26*, 1111; c) R. W. Read, W. C.

Taylor, *Aust. J. Chem.* **1979**, *32*, 2317; d) A. R. Carroll, W. C. Taylor, *Aust. J. Chem.* **1991**, *44*, 1615; e) A. R. Carroll, W. C. Taylor, *Aust. J. Chem.* **1991**, *44*, 1627; for biological properties, see: f) D. C. Chauret, C. B. Bernard, J. T. Arnason, T. Durst, H. G. Krishnamurty, P. Sanchez-Vindas, N. Moreno, L. San Roman, L. Poveda, *J. Nat. Prod.* **1996**, *59*, 152; g) I.-L. Tsai, C.-F. Hsieh, C.-Y. Duh, *Phytochemistry* **1988**, *27*, 1371; h) M. Carini, G. Aldini, M. Orioli, R. M. Facino, *Planta Med.* **2002**, *68*, 193; i) B. Freixa, R. Vila, E. A. Ferro, T. Adzet, S. Cañigueral, *Planta Med.* **2001**, *67*, 873.

[23] For syntheses of eupomatenoids, see: a) C. Eidamshaus, J. D. Burch, *Org. Lett.* **2008**, *10*, 4211; b) O. Miyata, N. Takeda, T. Naito, *Org. Lett.* **2004**, *6*, 1761; c) T. Bach, M. Bartels, *Synthesis* **2003**, 925.

