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Co-Catalyzed Hydroarylation of Unactivated Olefins

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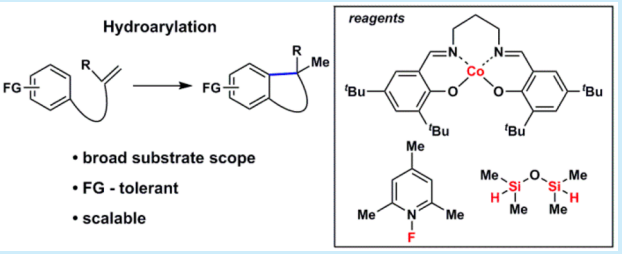
Supporting Information

ABSTRACT: A mild, general, scalable, and functional group tolerant intramolecular hydroarylation of unactivated olefins using a Co(salen) complex, a *N*-fluoropyridinium salt, and a disiloxane reagent was reported. This method, which was carried out at room temperature, afforded six-membered benzocyclic compounds from mono-, 1,1- or *trans*-1,2-di, and trisubstituted olefins.



Benzocyclic frameworks are important structural motifs in biologically active compounds. Among them, α,α-dimethyl benzocycles are frequently found in the structures of retinoic acid synthetic analogs, retinoids.[1] Whereas all-*trans*-retinoic acid (**1**) shows various biological activities associated with toxicity and teratogenicity due to its flexible structure, conformationally restricted retinoids containing an arene ring, known as arotinoids or heteroarotinoids, have historically been considered to show improved chemotherapeutic ratios (efficacy/toxicity) and have the potential to be used as pharmaceuticals, for example, tamibarotene (**2**, potential antineoplastic activity against acute promyelocytic leukemia)[2] and tazarotene (**3**, treatment of acne and psoriasis) (Figure 1).[3] Therefore, a robust synthetic tool for the construction of benzocyclic frameworks is highly desired in medicinal chemistry and synthetic organic chemistry.

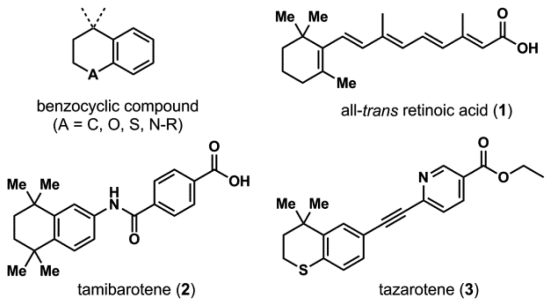
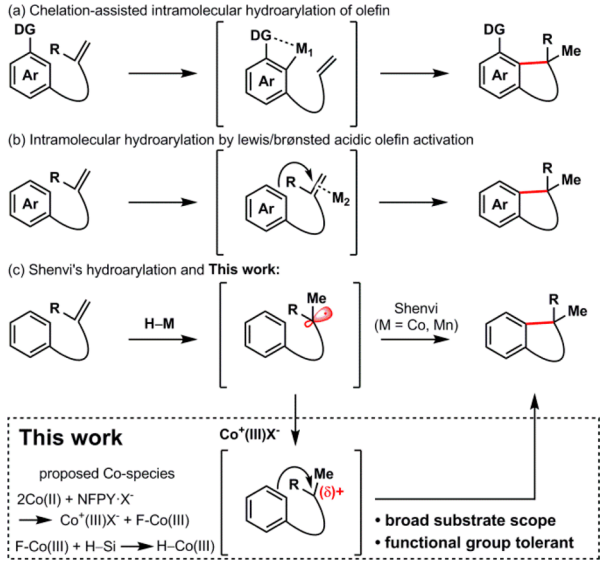


Figure 1. Benzocyclic compound, retinoid, and heteroarotinoids.

From a synthetic point of view, intramolecular hydroarylation of unactivated olefins is a straightforward method for constructing benzocyclic frameworks (Scheme 1). Indeed, many groups have reported this type of reaction using various catalysts. Attractive chelation-assisted intramolecular hydroarylation of olefins was reported by Ellman–Bergman,[4] Rovis,[5] Cramer,[6] Yoshikai,[7] and Sahoo,[8] which essentially required a directing group on the substrate (Scheme 1a). An alternative approach, which involves nucleophilic attack by an arene ring on metal (or Brønsted acid) coordinated olefins, followed by protonation of the metal–carbon bond, was reported by Duñach,[9] Widenhoefer,[10] Sames,[11] Tan,[12] Weghe,[13] and West[14] (Scheme 1b). However, there is much room for improvement in terms of functional group tolerance in these nondirecting group reactions. Besides, there are good examples of intermolecular versions of such reactions.[15]

Scheme 1. Representative Activation Mode of Hydroarylation of Olefins and Our Approach



Recently, Shenvi reported radical hydroarylation protocols using a Co complex (three reactions)[16] or a Mn complex (for the synthesis of arylmenthol)[17] in the presence of phenylsilane, which includes a carbon-radical generated by a hydrogen atom transfer mechanism (Scheme 1c, above). On the other hand, we independently reported an olefin activation protocol using a

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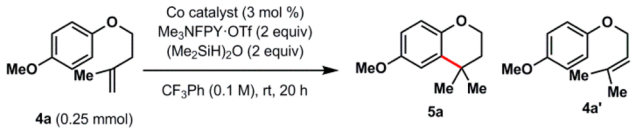
Co(salen) complex, an *N*-fluoropyridinium salt, and a disiloxane reagent to enable intermolecular hydroalkoxylation and intramolecular hydroamination of unactivated olefins with a broad substrate scope and excellent functional group tolerance.[18] Mechanistically, a carbocationic intermediate generated from unactivated olefins via carbon-radical is speculated. Based on this, we envisioned that cyclization can be achieved using an alkenyl arene substrate to afford a benzocyclic framework under identical or modified reaction conditions via generation of a carbocationic intermediate and C−C bond formation (Scheme 1c, below). In light of our previous reports and related examples from other groups,[16,17,19] broad functional group tolerance can be expected. Herein, we report a new method for intramolecular hydroarylation of unactivated olefins using a Co(salen)complex, an *N*-fluoropyridinium salt, and a disiloxane reagent. The mild reaction conditions showed a broad substrate scope, including functionalized complex molecules.

We began our study with the hydroarylation of **4a** under the reaction conditions used for the hydroamination of olefins previously reported by us (Table 1).[18c] The reaction of **4a** catalyzed by Co complex **6** (3.0 mol %) in trifluorotoluene in the presence of *N*-fluoro-2,4,6-trimethylpyridinium trifluoromethanesulfonate ($Me_3NFPY{\cdot}OTf$, 2.0 equiv)[20] and $(Me_2SiH)_2O$ (2.0 equiv) afforded the desired chroman **5a** in 16% yield, together with trisubstituted olefin isomer **4a′** (53%) and a hydrated compound (29%) (entry 1). Then, we evaluated a series of ligands for this reaction (entries 2−4). To our delight, simply changing the diamine unit increased the yield dramatically; product **5a** was obtained in 83% yield using 1,3-propanediamine containing Co complex **8**, together with a hydrogenated byproduct (7%). Lower loadings of $(Me_2SiH)_2O$ offered no appreciable benefit. Further ligand tuning was conducted by changing the aromatic substituents. It was found that only the *tert*-butyl groups at the 3-position (benzaldehyde numbering) of the aromatic ring were essential for obtaining a high yield (entries 5, 6). We evaluated a series of various sized substituents and identified the *tert*-butyl group as optimal (entries 7−10). More results from the catalyst screening are shown in the Supporting Information. Replacing $(Me_2SiH)_2O$ with phenylsilane ($PhSiH_3$) or isopropoxy(phenyl)silane [Ph(*i*-PrO)SiH_2][19y] gave an unsatisfactory result (entries 11, 12). The reaction in the absence of $Me_3NFPY{\cdot}OTf$ gave the desired product in low yield (entry 13). Furthermore, the use of 0.1 equiv of $(Me_2SiH)_2O$ (corresponding to the modified Shenvi's radical protocol) also yielded the same result (entry 14), which clearly indicates the beneficial effect of $Me_3NFPY{\cdot}OTf$ in our cationic pathway.[21]

After establishing the optimal reaction conditions, we explored the scope of the hydroarylation protocol with various alkenyl arenes, **4b−4m** (Table 2). In most cases, hydrogenated byproducts were observed in small amounts (trace to 10%). Alkenyl arene **4b** lacking an electron donating methoxy group was hydroarylated to afford volatile chroman **5b** in 56% yield. Surprisingly, this protocol was also effective for electron-withdrawing groups on the aromatic ring, albeit with a lower yield than that obtained with electron-donating groups (**5c−5e**). This tendency is consistent with the inclusion of a carbocationic intermediate generated from the olefin moiety.

Table 1. Optimum Reaction Conditions



entry	Co cat.	Si−H reagent	yield (%) of **5a** (**4a′**)[a]
1	**6**	$(Me_2SiH)_2O$	16 (53)
2	**7**	$(Me_2SiH)_2O$	34 (7)
3	**8**	$(Me_2SiH)_2O$	**83** (9), 76[b]
4	**9**	$(Me_2SiH)_2O$	0 (0)
5	**10**	$(Me_2SiH)_2O$	34 (4)
6	**11**	$(Me_2SiH)_2O$	82 (0)
7	**12**	$(Me_2SiH)_2O$	51 (39)
8	**13**	$(Me_2SiH)_2O$	69 (trace)
9	**14**	$(Me_2SiH)_2O$	43 (20)
10	**15**	$(Me_2SiH)_2O$	32 (15)
11	**8**	$PhSiH_3$[c]	31 (29)
12	**8**	$PhSiH_2(O^iPr)$	34 (10)
13[d]	**8**	$(Me_2SiH)_2O$	28 (14)
14[d]	**8**	$(Me_2SiH)_2O$[e]	32 (21)

[a]Yield was determined by ^1H NMR analysis of crude reaction mixture using 1,4-bis(trifluoromethyl)benzene as an internal standard unless otherwise noted. [b]Isolated yield. [c]1.3 equiv was used. [d]Without $Me_3NFPY{\cdot}OTf$ [e]0.1 equiv was used.

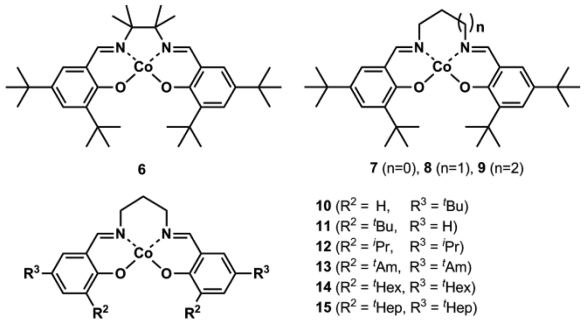
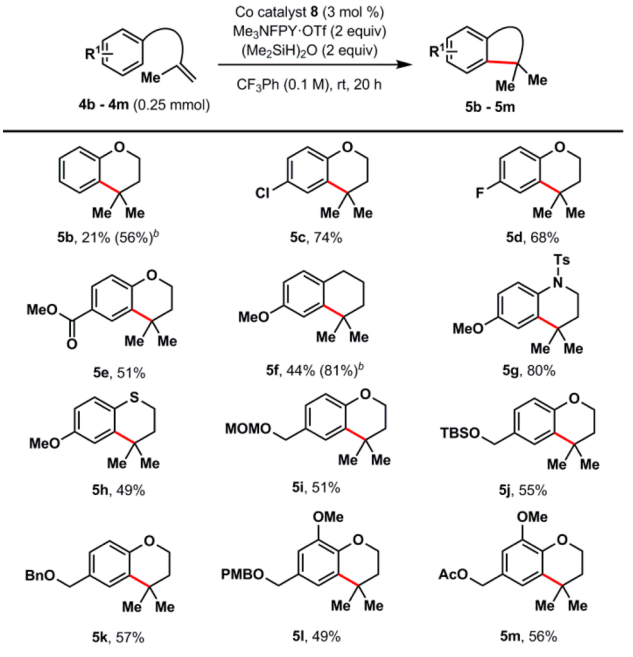


Table 2. Scope of Alkenyl Arene[a]



[a]Isolated yield is shown unless otherwise noted. [b]Yield was determined by ^1H NMR analysis of the crude reaction mixture using 1,4-bis(trifluoromethyl)benzene as an internal standard.

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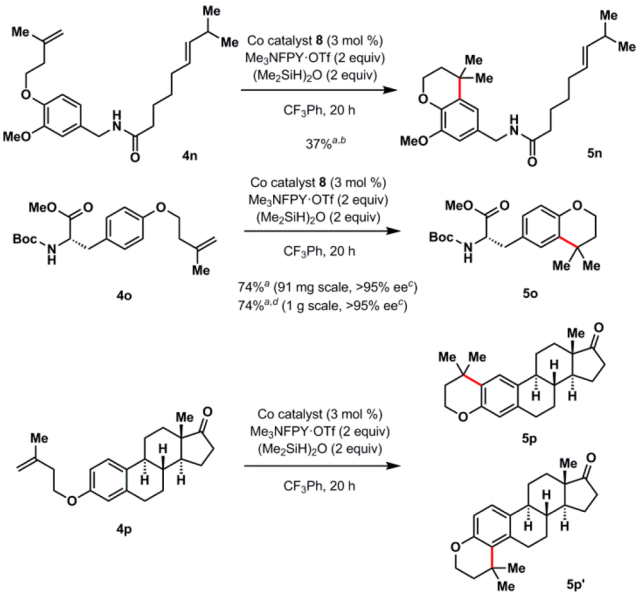
The desired tetralin (**5f**) and tetrahydroquinoline (**5g**) were also obtained by replacing the oxygen atom with methylene or tosyl amide on the tether unit. Notably, a wide range of functional groups was tolerated; for example, sulfide-containing thiochroman (**5h**) was successfully isolated in acceptable yield together with a complex product mixture. Moreover, various chromans were produced from alkenyl arenes bearing an acid-sensitive acetal (**5i**), a fluoroanion-sensitive silyl ether group (**5j**), and a benzyl group (**5k**). Vanillin-derived chromans bearing an acid-sensitive *p*-methoxybenzyl group (**5l**) and base-sensitive acetyl group (**5m**) were also isolated in acceptable yields together with complex product mixtures. At this stage, the method was found to be extremely effective for six-membered ring cyclization (see Supporting Information).

Encouraged by these results, we attempted the synthesis of more complex molecules using this reaction (Scheme 2). As

Scheme 2. Application to Complex Molecule Synthesis



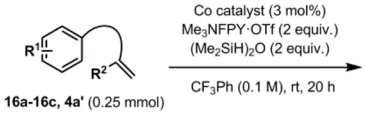
entry	Co catatalyst	yield (%) 5p + 5p'	4p	4p'[e]
1[f]	**6** (3 mol %)	0	0	ND
2[f]	**8** (3 mol %)	45 (1:1)	5	10
3[f]	**10** (3 mol %)	26 (1.5:1)	13	40
4[f]	**11** (3 mol %)	54 (1:1)	6	8
5[f]	**12** (3 mol %)	31 (2:1)	55	trace
6[f]	**12** (6 mol %)	57 (1.5:1)	trace	6
7[a,g]	**12** (6 mol %)	51 (1.5:1)	ND	ND

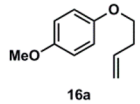
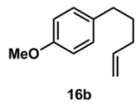
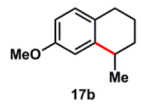
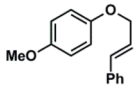
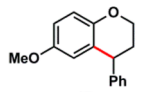
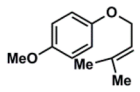
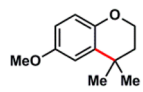
[a]Isolated yield is shown. [b]Purity of commercially available natural capsaicin is 60% containing the inseparable dihydro form of the olefin. As such, **5n** is also a mixture of **5n** and the dihydro product (1:1). [c]Determined by chiral phase HPLC analysis. [d]6 mol % catalyst **8** was used. [e]**4p′** is the trisubstituted olefin isomer of **4p**. [f]0.25 mmol. Yield was determined by ^{1}H NMR analysis of the crude reaction mixture using 1,4-bis(trifluoromethyl)benzene as an internal standard. [g]1 g of **4p** was used.

expected, capsaicin-derived **5n** was obtained from **4n**, with both 1,2-disubstituted olefin and amide tolerated. We also successfully synthesized artificial amino acid derivative **5o** from L-tyrosine-derived compound **4o** without significant racemization, together with a hydrogenated dihydro-product (13%). The scalability was examined using 1 g of **4p** and 6 mol % of catalyst **8**; this attempt also afforded **5p** without any problem. Hydroarylation of estrone-derived **4p** was examined, however, catalyst **8** gave hydroarylated products **5p** and **5p′**, together with a complex product mixture. To our delight, we found that catalyst **12** afforded **5p** and its isomer **5p′** with a minimal amount of byproducts by catalyst rescreening (entries 1−5). Acceptable conversion was achieved by increasing the catalyst loading to give slightly improved yields of **5p** and **5p′** (entry 6). The scalability of this reaction was reexamined using 1 g of **4p**, and **5p** and **5p′** were successfully obtained in acceptable yields (entry 7).

Next, the scope of the olefin moiety was investigated using alkenyl arenes **16a−16c/4a′**, and we found that the optimal catalyst should be selected depending on the olefin substitution pattern (Table 3). In contrast to 1,1-disubstituted olefins,

Table 3. Scope of Olefin Moiety



starting materials	products	catalyst	yield (%)[a]
 16a	 17a	6	85[b]
		6	0[c]
		8	77
 16b	 17b	6	75
 16c	 17c	6	88
		8	0
 4a'	 5a	8	76

[a]Isolated yield is shown. [b]Reaction time was 1.0 h. [c]Without $Me_3NFPY·OTf$.

catalyst **6** was found to be superior to catalyst **8** in the case of monosubstituted olefin **16a**. No **16a** was obtained without using $Me_3NFPY·OTf$; the radical pathway is not involved in the case of monosubstituted olefin. Less nucleophilic arene **16b** could also be used to give tetralin **17b**. The superiority of catalyst **6** for 1,2-*trans*-disubstituted olefin **16c** was quite noticeable; catalyst **6** gave desired product **17c** in excellent yield, in contrast with catalyst **8** which produced no desired product.[22] Trisubstituted olefin **4a′** was found to be applicable to this method using catalyst **8** to obtain compound **5a** in 76% yield, which is comparable to the result shown in Table 1, entry 3. Therefore, there might be two reaction pathways leading to **5a**: direct conversion from **4a** to **5a** and/or via **4a′**.

In summary, we developed the Co-catalyzed intramolecular hydroarylation of unactivated olefins using a Co(salen) complex, $Me_3NFPY·OTf$, and $(Me_2SiH)_2O$. Screening of the salen ligand led to the discovery of effective Co complex **8**, enabling efficient synthesis of α,α-dimethyl benzocycles from 1,1-disubstituted olefins. The mild, general, scalable, and functional group tolerant reaction could be applied to the synthesis of various molecules, including unnatural amino acid and estrone derivatives. Based on the result of the control

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experiment without $Me_3NFPY{\cdot}OTf$ (Table 1, entries 13, 14), our protocol should form a benzocyclic compound via a cationic pathway. Furthermore, the high ligand dependency of this reaction suggests that the cobalt complex could significantly interfere in the transition state of the carbon–carbon bond forming step. Both single-electron oxidation of the carbon radical by the cationic cobalt species and intramolecular nucleophilic trapping by the arene ring might occur simultaneously in a concerted transition state.[23] The origin of the ligand effect of complex **8** is under investigation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01662.

Experimental procedures and analytical data (^1H and ^{13}C NMR) for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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