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C-H Bond Functionalization via Hydride Transfer: Synthesis of Dihydrobenzopyrans from *ortho*-Vinylaryl Akyl Ethers

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Abstract

The hydride transfer initiated cyclization ("HT-cyclization") of aryl alkyl ethers, which leads to direct coupling of sp^3 C-H bonds and activated alkenes, is reported. Readily available salicylaldehyde derived ethers are converted in one step to dihydrobenzopyrans, an important class of heteroarenes frequently found in biologically active compounds. This process has not been previously reported in contrast to known HT-cyclizations of the corresponding *tert*-amines ("*tert*-amino effect" reactions).

In the context of a broad research program in the area of C-H bond functionalization,[1] we have been interested in direct coupling of sp^3 C-H bonds and alkenes, to afford α-alkylation of ethers and amines under catalytic, non-basic conditions. As an alternative to the transition metal catalyzed process, where the coupling is initiated by the metal-mediated cleavage of the C-H bond,[2,3] we have been developing a different approach based on intramolecular hydride transfer (Scheme 1).[4] In this process, activation of an electron-deficient alkene by a Lewis acid triggers a 1,5-hydride transfer and formation of a zwitterionic intermediate (intramolecular redox event), which is followed by the cyclization via ionic C-C bond formation.

This overall cyclization is initiated by an intramolecular redox process and thus does not require a stoichiometric oxidant.[5] For example, we previously reported that the relatively reactive benzyl ethers undergo facile cyclization in the presence of boron trifluoride etherate (Scheme 2A).[4a] The less reactive substrates, such as pyrrolidine carbamate **3**, however, require stronger activation with $PtCl_4$, to give the cyclization product **4** in good yield (Scheme 2B). The higher hydridophilicity of the double bond may also be accomplished by using doubly activated alkenes and a suitable Lewis acid capable of chelating the diester unit, as illustrated by the α,β-unsaturated malonate ester **5** and $Sc(OTf)_3$ (Scheme 2C). More recently, we showed that even primary ethers could be induced to undergo the HT-cyclization, by the action of a simple yet powerful activation protocol employing $BF_3{\cdot}Et_2O$ and ethylene glycol, which generates highly reactive alkenyl-oxocarbenium intermediates from the corresponding enones *in situ*

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Supporting Information Available: Experimental procedures and spectroscopic data for starting materials and products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(Scheme 2D).[4c] Increasing the hydridophilicity of the alkene led to expansion of the scope of the HT-cyclization reactions, and it appears that the boron trifluoride/ethylene glycol activation of enones and the scandium triflate activation of α,β-unsaturated malonates are the most effective systems in this regard (Scheme 2).

In this study, we examined the reactivity of aryl alkyl ethers (Scheme 3). These compounds are attractive substrates as they are prepared in two steps from readily available salicylaldehydes, and in one step, would furnish dihydrobenzopyrans (or chromans),[6] an important structural class found in many natural products and biologically active compounds.[7]

As expected, the aryl alkyl ethers were less reactive in comparison to the dialkyl ethers, owing to the electron withdrawing nature of the arene ring (and thus lower carbocation stabilizing ability of the aryl ether oxygen). The benzyl ether-enone **9** gave no reaction even under the highly activating conditions using $BF_3{\cdot}Et_2O$ and ethylene glycol (Scheme 3A). Thus, we examined the alkenes with two electron-withdrawing groups (compounds of type **I**, Scheme 3B), and found that these substrates underwent the desired HT-cyclization in the presence of $Sc(OTf)_3$. The corresponding N-arylamines (compounds of type **II**) are much more reactive in comparison and are known to undergo HT-cyclization either thermally or in the presence of acid catalysts (these reactions are often referred to as the "*tert*-amino effect").[8,9] To the best of our knowledge, the HT-cyclization has not been previously reported with phenol-derived substrates.[10]

The desired substrates were synthesized in short order by the alkylation of the phenol, followed by the Knoevenagel condensation with the selected carbonyl partner (Scheme 4). We chose substrate **13** to examine an array of Lewis acids and to optimize the reaction conditions (Table 1). As noted above, the aryl ether substrates are quite unreactive as seen from low or no conversion with many Lewis acids. Importantly, complete conversion of the starting material and excellent isolated yield of the desired product was accomplished by heating with $Sc(OTf)_3$ as the catalyst. It should be noted that no reaction was observed in the absence of catalyst under these conditions (Table 1, entry 1), which stands in contrast to the corresponding *tert*-amine substrates that are known to undergo the HT-cyclization upon heating.[8,9]

We next focused our efforts on exploring the substrate scope with respect to the hydride donor and acceptor components of the substrate. The HT-cyclization occurred readily with cyclic and acyclic aliphatic ethers to afford excellent yields of the dihydrobenzopyran products (Table 2, entries 1 and 2). The benzyl ether **17** (Table 2, entry 3), however, gave lower yield and required increased catalyst loading, which is likely due to the cleavage of the benzyl ether bond. The low efficiency of the HT-cyclization of the allyl ether substrate **19** is in part due to a competing Claisen rearrangement.[11]

In regard to the hydride acceptor component, the best results were obtained with the di-ester substrates such as compounds **13** and **15** or the keto-ester substrates such as **21.** The diketone substrates with cyclic and acyclic hydride donor moieties did undergo the HT-cyclization (Table 2, entries 6 and 7), but in these cases a significant amount of the product was lost to competing side reactions (see Supporting Information). The keto-sulphone **27** was also converted to the expected product **28**, albeit in modest yield due to lower reactivity under these reaction conditions (Table 2, entry 8).

We next examined the substitution of the arene ring, which revealed its strong effect on the reactivity. For instance, compound **29** with the methoxy group in the C-4 position is an excellent substrate providing high yield of the desired dihydrobenzopyran **30** (Table 3, entry 1). This is consistent with the ability of the methoxy group to stabilize the developing oxocarbenium ion in the *para*-position through the resonance effect. In contrast, the regioisomer **31** containing

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the methoxy group at the C-5 position was much less reactive, providing the corresponding product in modest yield, requiring higher catalyst loading and longer reaction time. This observation can be rationalized by decreasing the hydridophilicity of the alkene by the electron-donating resonance effect of the methoxy group (in the *para*-position with respect to the alkene), as well as by reducing the hydride donor ability of the *iso*-propoxy group by the σ-effect of the methoxyl oxygen atom. The deactivating bromine substituent was well tolerated at the C-4 position, although it significantly reduced the reactivity of substrate **33** as longer reaction time was required to reach completion, affording high yield of dihydrobenzopyran **34** (Table 3, entry 3). However, bromine at the C-5 position completely shut down the cyclization reaction (Table 3, entry 4). We rationalize this result by the σ-electron withdrawing effect of the bromine atom, which severely decreases the hydride donor ability of the *iso*-propoxy group when the bromine substituent is situated closer. Similar to compound **31**, substrate **37** containing the diethylamino group at the C-5 position was deactivated and required excess Lewis acid to achieve 60% conversion in 48 hours. Lastly, we were pleased to find that **39** was converted to product **40** in high yield (Table 3, entry 6), illustrating the compatibility of this method with relatively complex substrates.

In summary, we developed a new and concise synthetic approach to highly substituted dihydrobenzopyrans via the HT-cyclization of *ortho*-vinylaryl alkyl ethers. Applying this method, widely available salicylaldehydes can be converted in three steps to the desired dihydrobenzopyrans, an important class of heterocycles frequently found in biologically active compounds. The *ortho*-vinylaryl alkyl ethers are significantly less reactive, which limits the scope of the HT-cyclization of these substrates, compared to the analogous *tert*-amines. Nevertheless, guided by the results of this study, a wide spectrum of interesting structures can be accessed in a three-step synthetic sequence.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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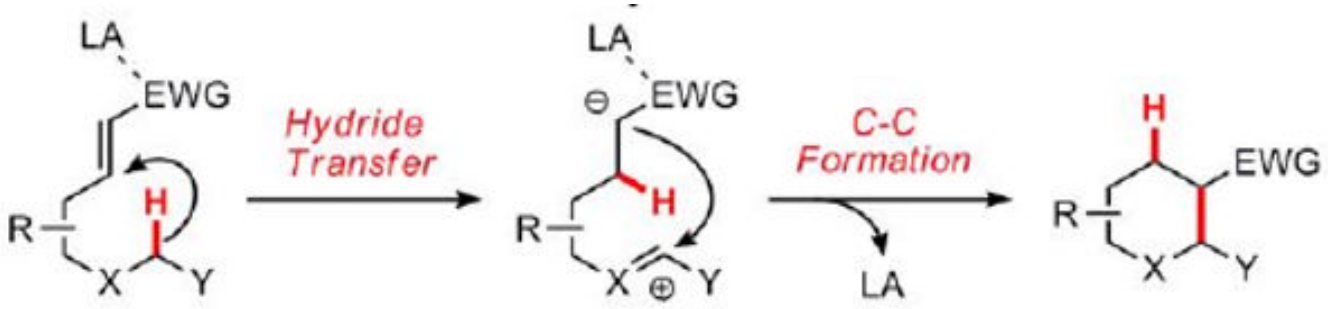

Scheme 1.

The Mechanistic Concept for the α-Alkylation of Ethers and Amines via Hydride Transfer
EWG = electron withdrawing group; LA = Lewis acid; X and Y = cation stabilizing substituent (alkyl, alkenyl, aryl, heteroatom)

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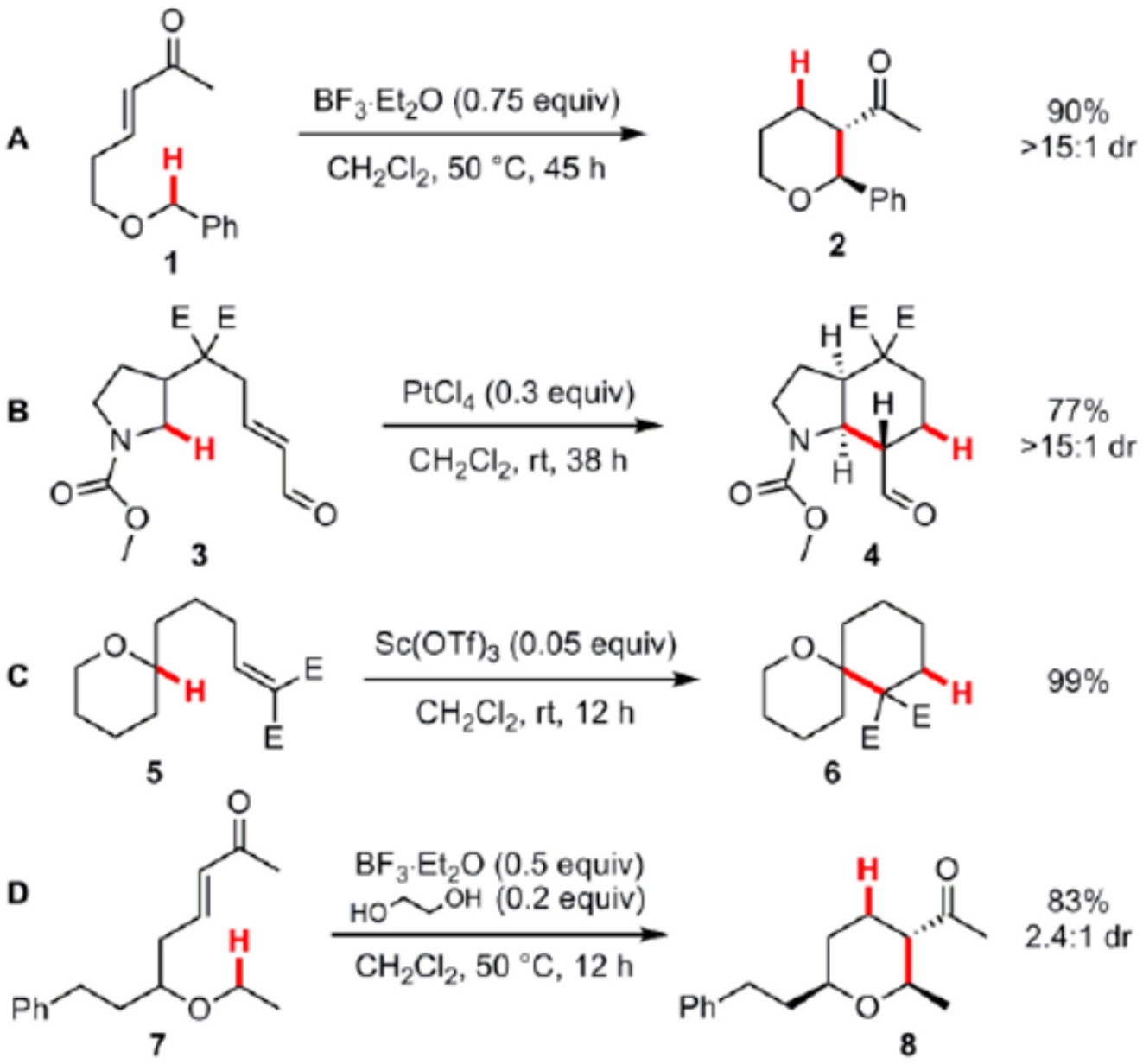

Scheme 2.
Development of Numerous Activation Protocols for HT-Cyclization Reactions

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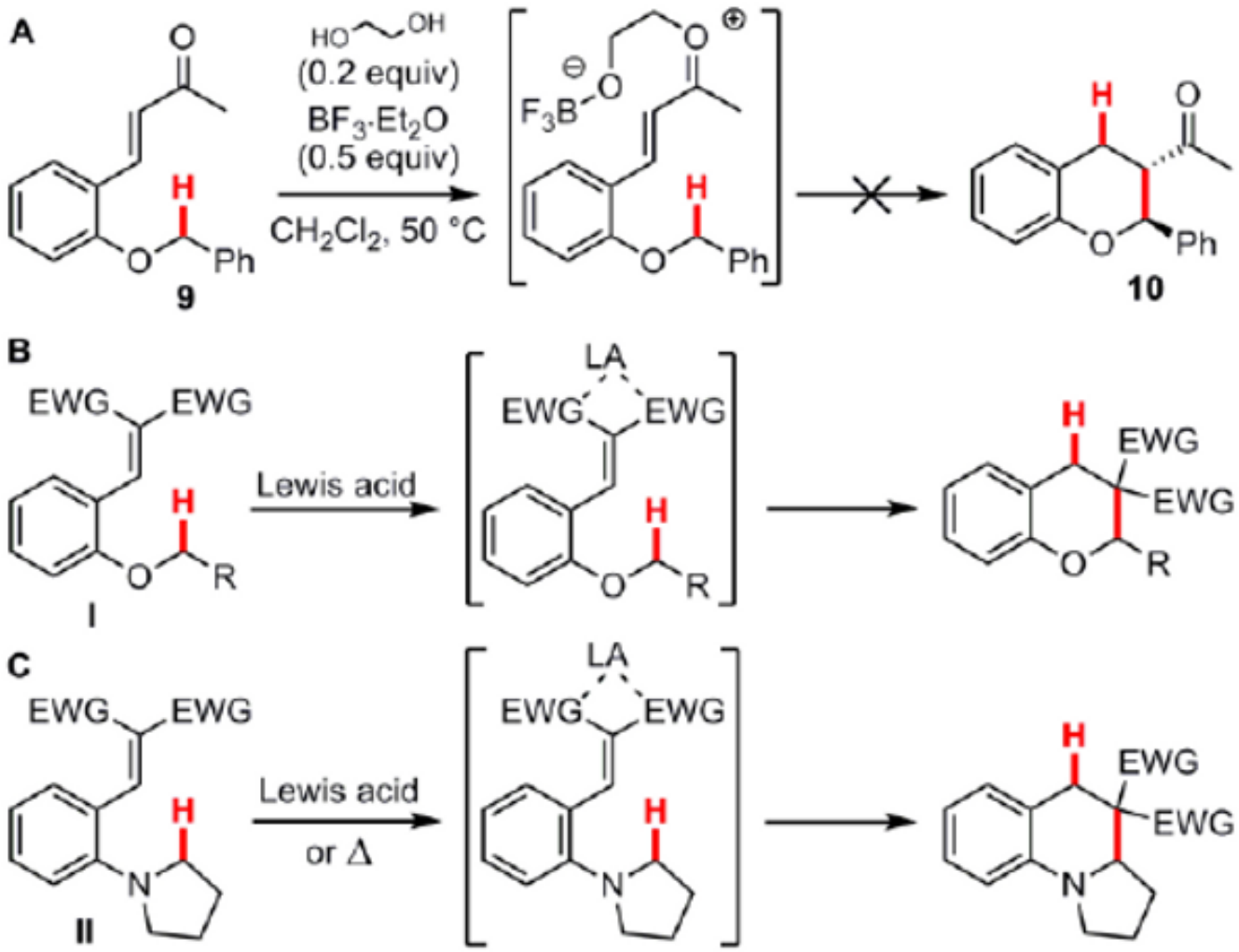
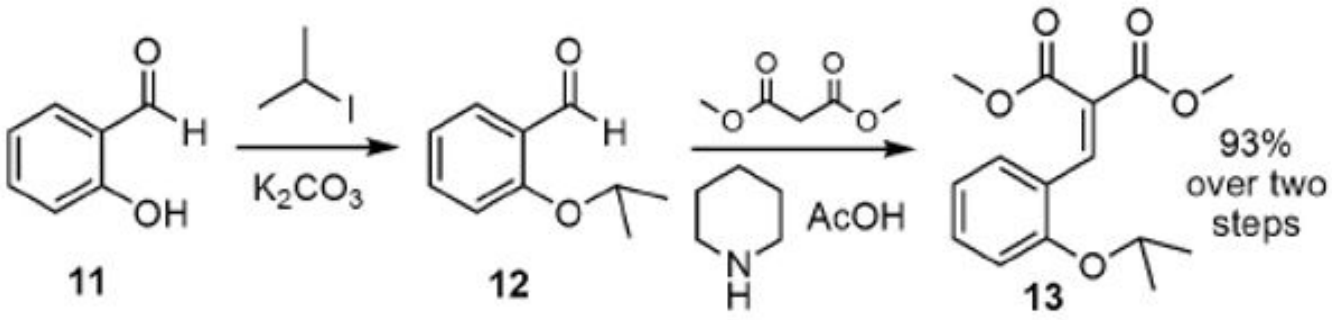


Scheme 3.
Activation of Aryl Ethers and Aryl Amines



Scheme 4.
Synthesis of Substrates from Salicylaldehydes

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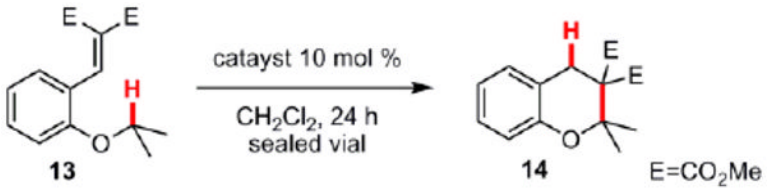
Table 1

Screen for Catalyst Activity [a]



entry	catalyst	temp(°C)	13(%)[b]	14(%)[c]
1	None	80	99	0
2	$BF_3{\cdot}Et_2O$		82	0
3	$PtCl_4$		80	0
4	$InCl_3$		92	9
5	$ScCl_3$		97	2
6	$TiCl_4$		84	6
7	$AlCl_3$		12	77
8	$In(OTf)_3$		44	47
9	$Zn(OTf)_3$		92	0
10	$Cu(OTf)_2$		65	1
11	$Gd(OTf)_3$		87	9
12	$Yb(OTf)_3$		69	21
13	$Sc(OTf)_3$	80	0	91[d]
14	$Sc(OTf)_3$	50	80	12

[a] All reactions were performed at 0.025 M concentration with dodecane as an internal standard and monitored by GC.

[b] Percentage of starting material remaining relative to internal standard.

[c] Product formed relative to internal standard.

[d] Isolated yield.

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product	time (h)	cat. (equiv)	yield (%)[b]
14	24	0.1	91
16	36	0.1	95
18	36	0.3	75

product	time (h)	cat. (equiv)	yield (%)[b]
20	60	0.4	32
21	36	0.1	90

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product	time (h)	cat. (equiv)	yield (%)[b]
24	30	0.1	35
26	24	0.1	58

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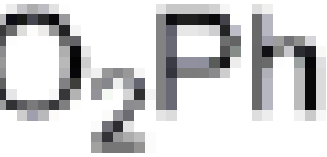
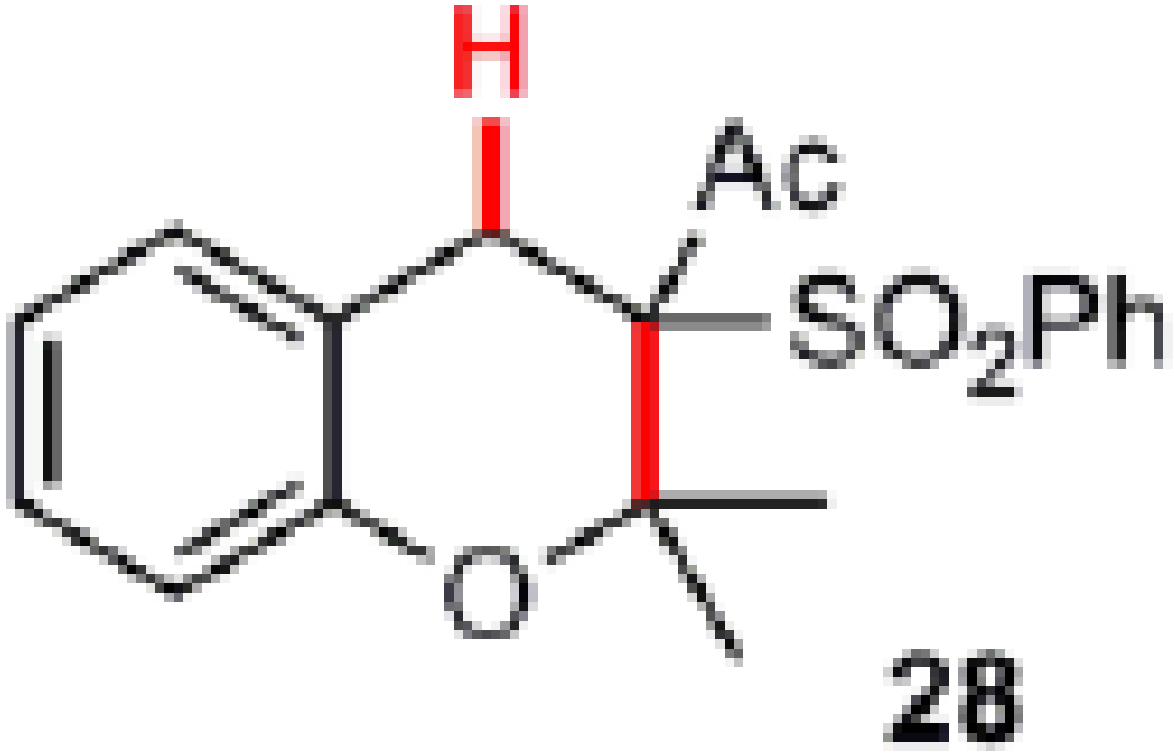
product	time (h)	cat. (equiv)	yield (%)[b]
 27	28	0.5	45
E = CO_2Me	Ac = COMe		
 28			
E' = CO_2Et			

unt of $Sc(OTf)_3$ catalyst.

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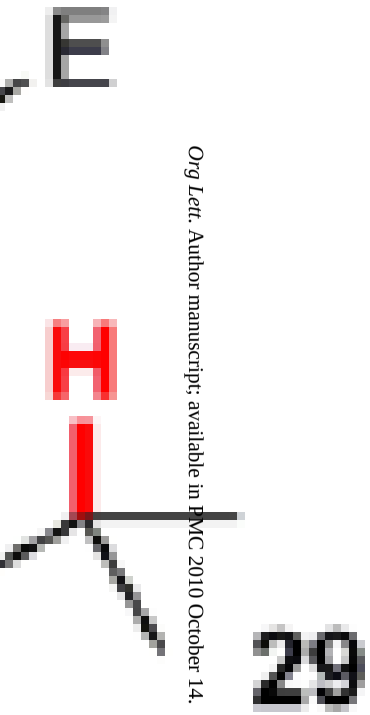
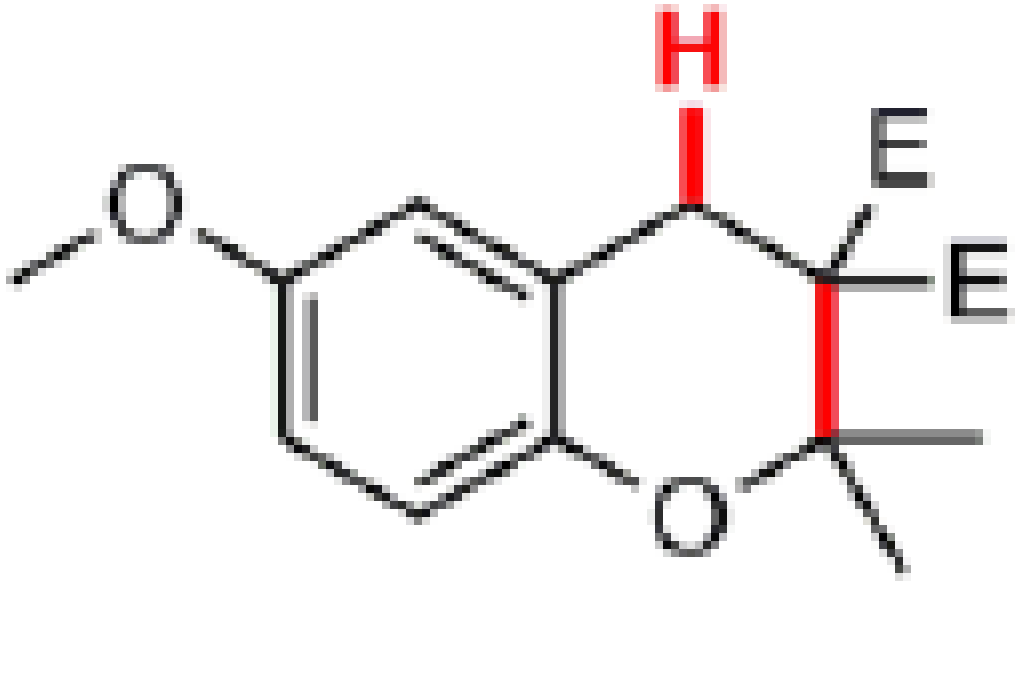
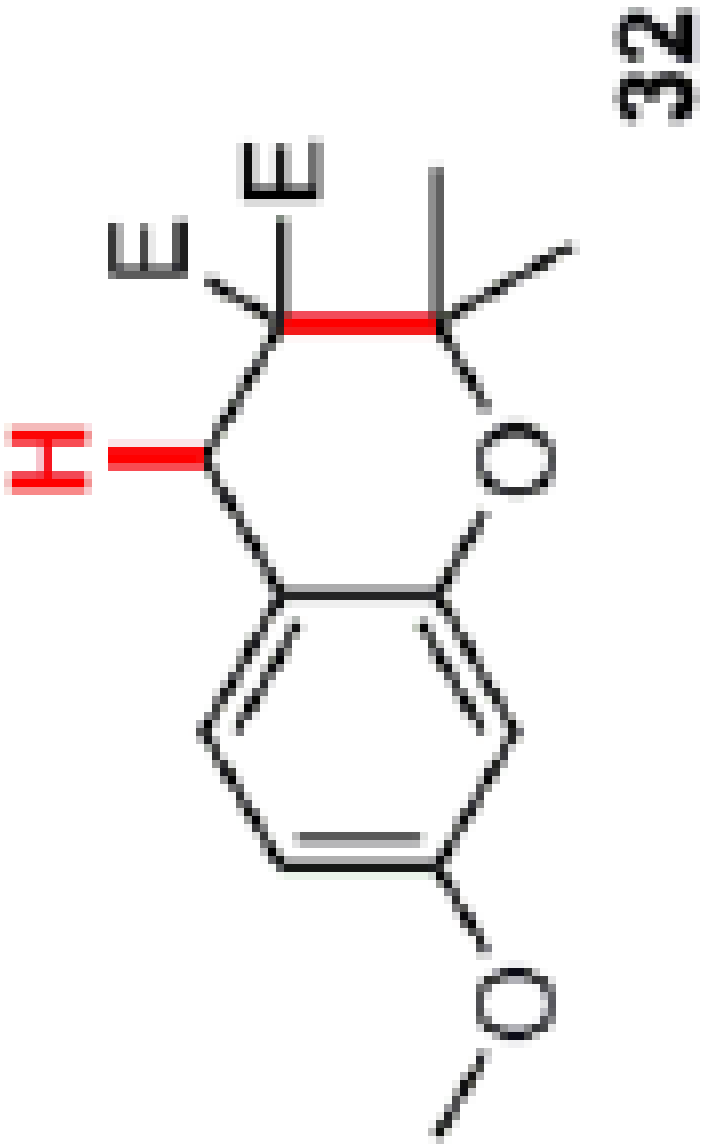
	product	time (h)	cat. (equiv)	yield (%)[b]
		12	0.1	95
29	30			

product	time (h)	cat. (equiv)	yield (%)[b]
	60	0.5	56

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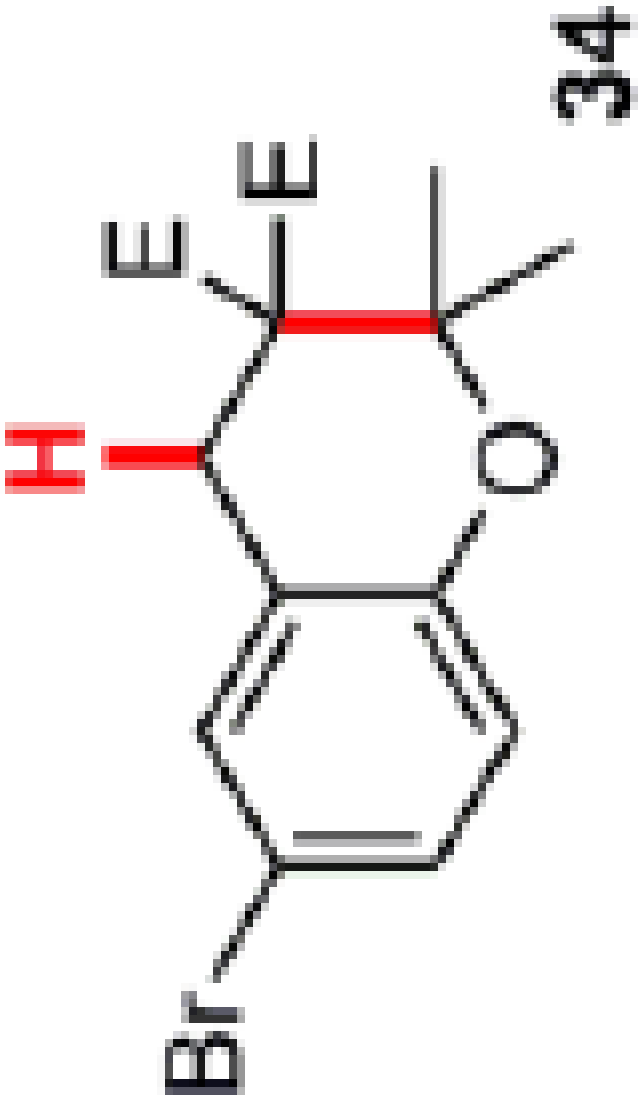
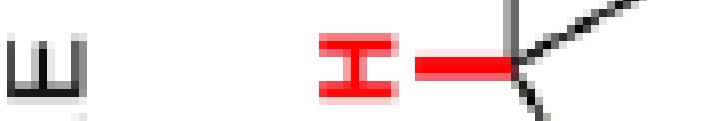
product	time (h)	cat. (equiv)	yield (%)[b]
 34	36	0.1	95
 33			

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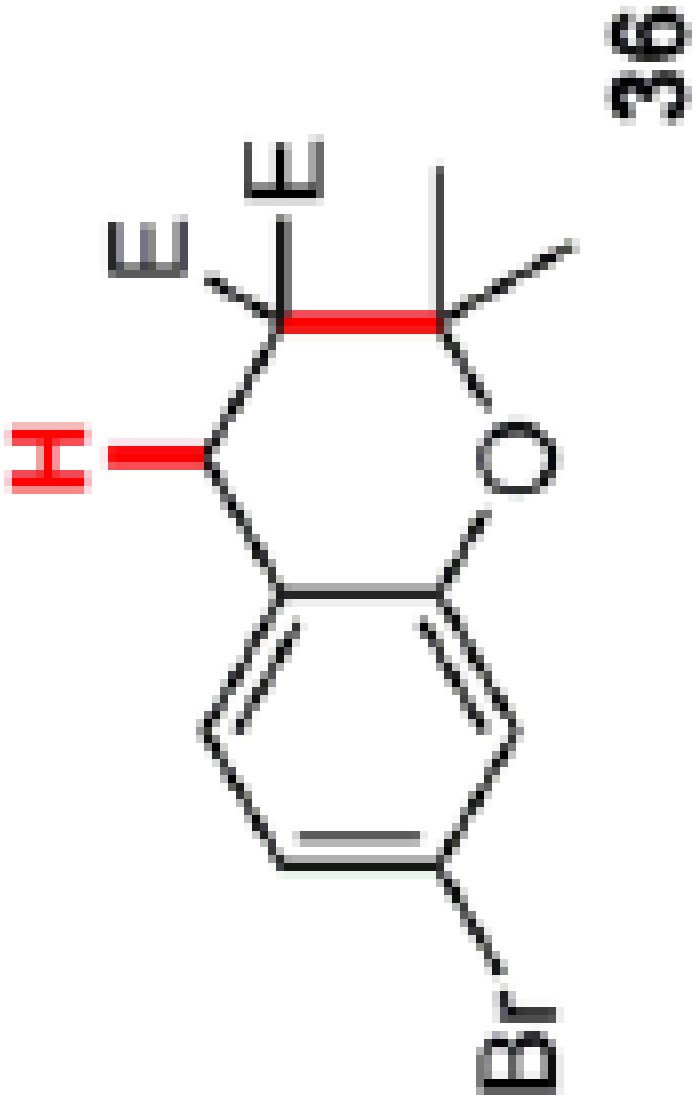
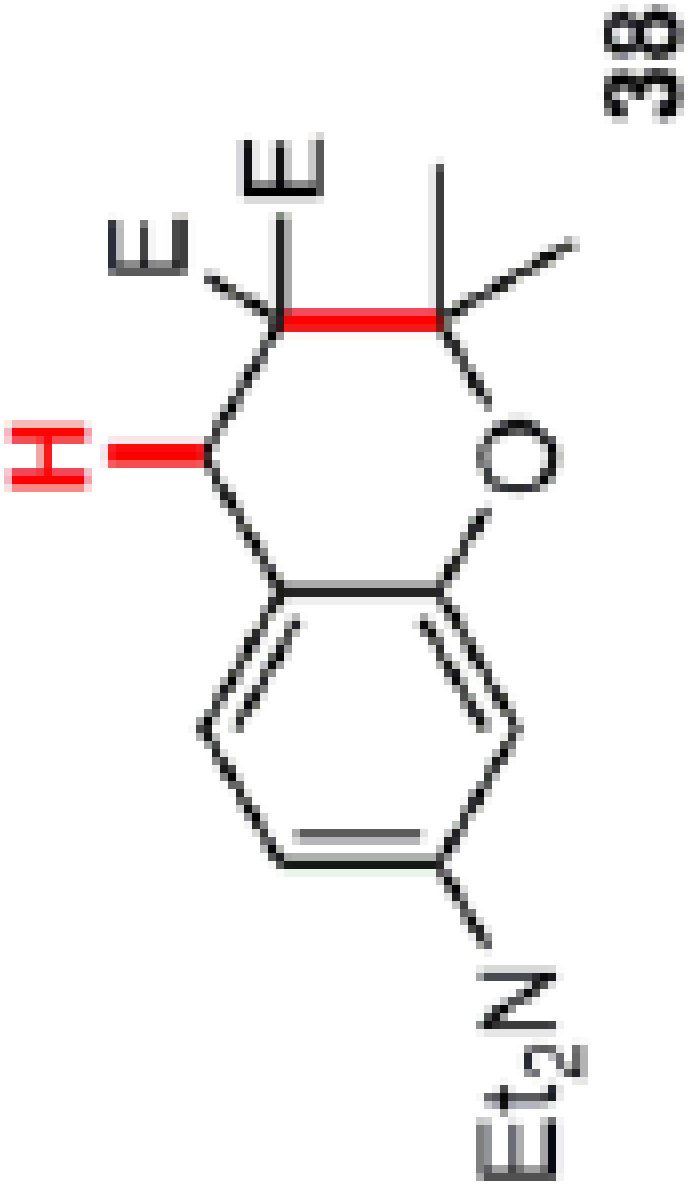
product	time (h)	cat. (equiv)	yield (%)[b]
	96	0.1	NR[c]

product	time (h)	cat. (equiv)	yield (%)[b]
	48	2.0	32[d]

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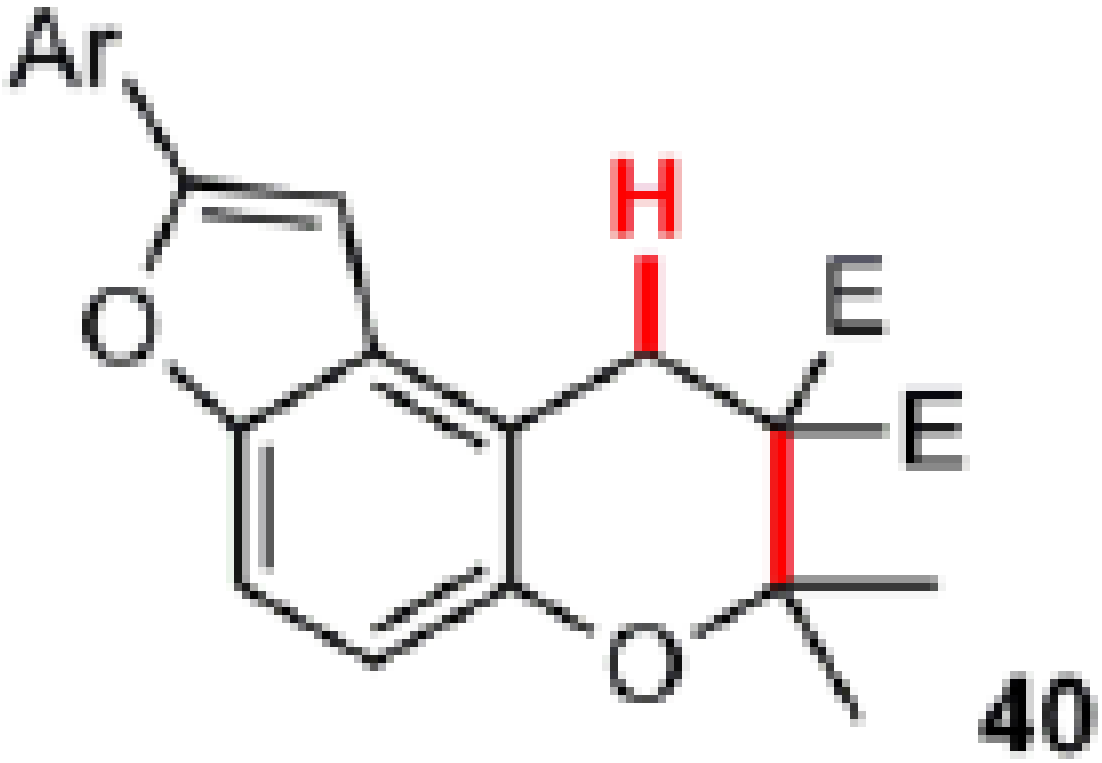
product	time (h)	cat. (equiv)	yield (%)[b]
 **40**	48	0.1	85

E = CO_2Me

Ar = 4-MeO-C_6H_4

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icated amount of $Sc(OTf)_3$ catalyst.