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Development of new iron catalysts for the tandem isomerization–aldol condensation of allylic alcohols

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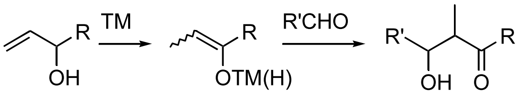
Abstract—(bda)Fe(CO)$_3$ and (COT)Fe(CO)$_3$ are shown to be excellent catalysts for the tandem isomerization–aldol reaction of allylic alcohols with aldehydes and to significantly increase the scope of this aldolization process, especially, in the case of sterically hindered aldehydes.

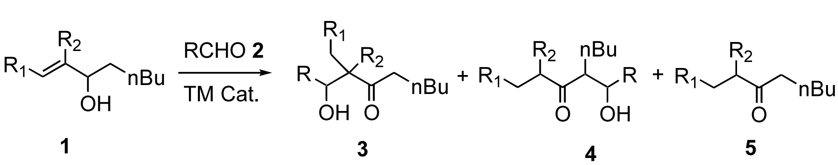
The aldol reaction is a fundamental process for the creation of C–C bonds.[1] We have discovered recently a novel approach to this reaction via a tandem isomerization–aldolization of allylic alcohols, mediated by transition metal catalysts.[2] Following a known process,[3] the allylic alcohol is isomerized by the catalyst into a complexed enol and/or transition metal enolate which can be trapped in situ by an aldehyde to give the aldol adduct (Scheme 1).[2] This new aldol type reaction is a complete atom economy process which furthermore occurs under mild and neutral conditions.

As a first example, Fe(CO)$_5$ proved to be a versatile catalyst for this reaction, allowing addition of various types of allylic alcohols **1** with aldehydes **2**: at only 2–5 mol% and under irradiation, it afforded mainly the aldols **3** with small amounts of the regioisomers **4** and ketones **5** (Scheme 2). However, some limitations have been recognized, especially with sterically hindered carbonyls affording low yields of aldol products. In order to improve this new reaction, experiments in different directions have been already reported. A first possibility was the extension to other metals: rhodium as well as ruthenium catalysts proved to be completely regioselective, however, with a more limited scope for the addition.[4] The latter approach could also be combined with the use of other solvents such as water or ionic liquids, however with similar results.[5]



Scheme 1.

For the iron carbonyl mediated reaction a mechanism has been proposed, where Fe(CO)$_3$ was postulated to be the active catalytic species.[2] Therefore, in order to improve this reaction another attractive possibility was to screen various iron carbonyl complexes (Fig. 1). We report here our results establishing that (bda)Fe(CO)$_3$ and (COT)Fe(CO)$_3$ are efficient catalysts that further extend the scope of this tandem isomerization–aldolization reaction.



Scheme 2.

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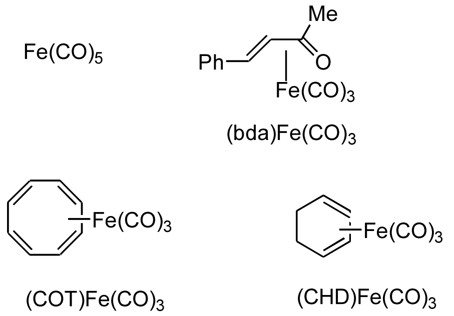
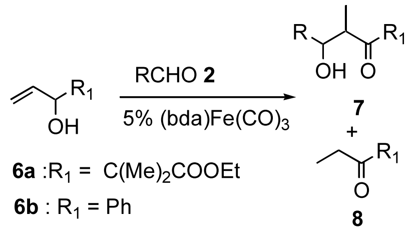


Figure 1.

As (bda)Fe$(CO)_3$ is a well known Fe$(CO)_3$ donor,[6] we first tried it as a catalyst. The results are given in Tables 1 and 2. The irradiation[7] of a THF solution of the allylic alcohol and the aldehyde in the presence of the catalyst at 5 mol% gives good isolated yields of the mixture of the aldols with a good regioselectivity but a low diastereoselectivity.[8] Ketone **5** is also isolated, albeit in low yield. The reaction is compatible with the presence of alkyl substituents on both positions of the double bond as well as with different side chains in the allylic alcohol moiety. It is particularly interesting to note that the reaction is compatible with different aldehydes, including one with an amide nitrogen atom (entry e, Table 1). It can also be observed that the reaction of allylic alcohol **6a** (Scheme 3, Table 2) gives the two aldols with a good diastereomeric ratio (~6/1) and good yields, even with the sterically hindered isobutyraldehyde (entry b).

It can be noted that, in most cases, the isolated yields are higher than those obtained when Fe$(CO)_5$ is used as a catalyst. Finally, it is important to underline that this tandem isomerization–aldolization is not observed when (bda)Fe$(CO)_3$ is used under thermal reaction conditions;[9] therefore, irradiation is necessary for the reaction to occur, as it was previously established for the reaction catalyzed by Fe$(CO)_5$. As (bda)Fe$(CO)_3$ is a well known Fe$(CO)_3$ donor under thermal conditions, an attractive hypothesis to explain this result would be the presence of a higher energy step requiring photochemical activation in the reaction pathway.[10] Although this mechanistic point needs further studies, it is possible to conclude that (bda)Fe$(CO)_3$ appears as a useful alternative catalyst for this reaction.



Scheme 3.

Next, we investigated the reactivity of (COT)Fe$(CO)_3$. This complex has been the subject of in-depth physicochemical studies (structure and fluxional behavior for instance), as well as reactivity studies.[11] However, to the best of our knowledge, it has never been reported as a Fe$(CO)_3$ transfer agent. Therefore, we first screened different aldehydes, octen-3-ol being taken as the model allylic alcohol (Table 3). A remarkable increase of the reactivity, as compared to Fe$(CO)_5$, was observed: with only 2–4 mol% of the catalyst, the reaction is complete within 20–60 minutes and the aldols are obtained in good yields, even in the case of very bulky aldehydes. It is important to note that under Fe$(CO)_5$ catalysis only low yields (<20%) of aldols were obtained with cyclohexane carboxaldehyde or isobutyraldehyde for instance.[2] When (COT)Fe$(CO)_3$ is used, the corresponding aldols are isolated in ca. 63% yield (entries d and e, Table 3). However, the diastereoselectivity remains similar to that obtained with Fe$(CO)_5$ as the catalyst. Furthermore, it is particularly interesting to note that the reaction of aldehydes bearing an isolated double bond occurs with no bond shift, as shown by

Table 1. Tandem isomerization–aldolization condensation of alcohol **1** using bdaFe$(CO)_3$ as the catalyst

Entry	R	R_1	R_2	Time (min)	**3**+**4** (yield %)	**3**+**4** Fe$(CO)_5$ as cat.[2]	**3***syn*/**3***anti*/**4**/**4′**	**5** (yield %)
a	Ph	H	H	40	91	74	49/46/3/2	5
b	Ph	Me	H	75	70	46	57/32/7/4	15
c	Ph	H	Me	120	85	73	90/–/6/4	5
d	$(Me)_2CH$	H	H	120	62	<20	61/32/4/3	17
e	*p*-AcNHPh	H	H	90	58	[a]	37/60/3<1[b]	

[a] Unknown.

[b] Ratio calculated on the mixture after chromatography.

Table 2. Tandem isomerization–aldolization condensation of alcohols **6a** and **6b** using bdaFe$(CO)_3$ as the catalyst

Entry	R	R_1	Time (min)	**7** (yield %)	**7** Fe$(CO)_3$ as cat.[2]	**7***syn*/*anti*	**8** (yield %)
a	Ph	$C(Me)_2COOEt$	60	83	73	86/14	[a]
b	$(Me)_2CH$	$C(Me)_2COOEt$	240	70	[a]	86/14	12
c	Ph	Ph	90	74	73	39/61	12

[a] Unknown.

Table 3. Tandem isomerization–aldolization condensation of alcohol **1** using (COT)$Fe(CO)_3$ as the catalyst

Entry	R	R_1	R_2	Cat. (%)	Time (min)	**3**+**4** (yield %)	**3**+**4** $Fe(CO)_5$ as cat.[2]	**3***syn*/**3***anti*/**4**/**4′**	**5** (yield %)
a	Ph	H	H	2	20	84	74	64/28/5/3	12
b	H	H	H	4	45–60	84	64	94/–/6	9
c	Me_2CHCH_2	H	H	3	35	72	54	63/27/5/5	19
d	Me_2CH	H	H	3	35	63	<20	53/34/7/6	27
e	Cy	H	H	3	35	64	<20	59/35/4/2	27
f	Et_2CH	H	H	3	35	36	[a]	65/33/2/–	42
g	$EtCH{=}CH(CH_2)_2$	H	H	4	180	78	[a]	55/36/5/4	6
h	*p*-AcNHPh	H	H	5	180	54	[a]	57/36/4/3	4
i	Ph	Me	H	5	4 h	<20% conv.	46		
j	Ph	H	Me	5	4 h	<20% conv.	73		

[a] Unknown.

the reaction with 5-hepten-1-al (entry g, Table 3). Next we studied the reactions starting from various allylic alcohols. We observed that they did not go to completion (<20% conversion) when an alkyl substituent is present on the double bond (entries i and j, Table 3). The same fall in reactivity was observed starting from alcohol **6a**: an NMR control after 4 h of reaction establishes the ketone as the major product whereas a ~7/3 ratio of allylic alcohol/aldols is obtained. We can conclude that (COT)$Fe(CO)_3$ gives better results than $Fe(CO)_5$ in the case of bulky aldehydes but is inefficient in the case of bulky allylic alcohols.

Next, we investigated the structurally close (CHD)$Fe(CO)_3$: the reaction could be completed only when unsubstituted allylic alcohols (such as **1a**) and reactive aldehydes (e.g. PhCHO) were used. Therefore, this iron complex can not be used for this transformation. Although the results obtained with (COT)$Fe(CO)_3$ and (CHD)$Fe(CO)_3$ indicate that these catalysts are probably not acting as simple $Fe(CO)_3$ donors under the reaction conditions, the origin of the change in reactivity remains to be elucidated.

In conclusion, we have investigated three new iron catalysts in the tandem isomerization–aldol condensation of allylic alcohols. Two of them, (bda)$Fe(CO)_3$ and (COT)$Fe(CO)_3$, show higher reactivity compared to the previously used $Fe(CO)_5$. In particular, (COT)$Fe(CO)_3$ appears especially useful in the challenging case of bulky aldehydes. Furthermore, we have also demonstrated that both catalysts can perform the reaction with aldehydes bearing either a protected nitrogen atom or an isolated double bond. The third one, (CHD)$Fe(CO)_3$ is less reactive. So we have developed two alternate catalysts that significantly extend the scope of this tandem isomerization–aldol condensation. We are currently studying the mechanism of these reactions, as well as some applications to the synthesis of natural products and structural analogues.

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7. *Representative experimental procedure*: In a two-necked pyrex flask was placed (COT)$Fe(CO)_3$ (2–4 mol%) under nitrogen. Dry THF (8 mL), allylic alcohol (1 mmol) and freshly distillated aldehyde (1.2 mmol) were added sequentially. The reaction mixture was irradiated with a Philips HPK 125 W lamp until disappearance of the allylic alcohol. The reaction mixture was filtered through silica gel (7 g) and purified by chromatography to afford ketone and subsequently the aldol products. Most of the diastereomers were separated and fully characterized. All diastereomeric mixtures of aldol products gave spectra (IR, ^1H, ^{13}C NMR) consistent with their assigned structure and satisfactory high resolution mass measurement and/or combustion analysis.
8. The regio- and stereomeric ratios were established by ^1H or/and ^{13}C NMR on the crude mixture.[2] The relative configurations were established according to Ref. 2 and to the following empirical rule: the C of the CHOH group is deshielded in the *anti* adduct compared to the *syn* adduct and the H of the CHOH group is shielded in the *anti* adduct compared to the *syn* adduct.
9. At 80°C in toluene, neither aldol condensation nor isomerization was observed starting from **1a** ($R_1 = R_2 = H$)

and PhCHO. After 3 h at higher temperature (110°C), only a partial conversion ($\sim$50%) to the ketone was observed, without any evidence (TLC, NMR) for the aldol products.

10. It is worth noting that no (or very little, <10%) retroaldol reaction was observed on heating **3a** ($R_1=R_2=H$, $R=Ph$) for 1.5 h at 110°C. However, in the presence of catalytic bdaFe$(CO)_3$, a fast retroaldolization was observed.
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