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COMMUNICATION

A Phosphine-Free Iron Complex-Catalyzed Synthesis of Cycloalkanes via the Borrowing Hydrogen Strategy

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Herein we report a diaminocyclopentadienone iron tricarbonyl complex catalyzed the synthesis of substituted cyclopentane, cyclohexane and cycloheptane compounds using the borrowing hydrogen strategy in the presence of various substituted primary and secondary 1,n diols as alkylating reagents. Deuterium labeling experiments confirm that the diols were the hydride source in this cascade process.

Cycloalkanes constitute a class of compounds omnipresent in organic chemistry. Among these compounds, cyclohexane derivatives are encountered in plethora of natural products, pharmaceuticals or materials.[1] Several strategies have been described in the literature for the preparation of substituted cyclohexanes. As examples, the Diel-Alder reaction,[2] the hydrogenation of aryl derivatives,[3] or the ring closing metathesis[4] can be cited. However, these approaches involve multistep procedures and functionalized precursors. A complementary method could be the double alkylation of a methyl ketone with a double electrophile.[5] However, such strategy implies the formation of an enolate under cryogenic conditions, the use of toxic halides or pseudo-halides compounds and the generation of waste.[6-7]

The α-alkylation of ketones via the borrowing hydrogen or hydrogen autotransfer methodology is a growing and dynamic domain of research and constitutes a greener and safer alternative to the well-known enolate chemistry.[8-9] The alkylating agent is an alcohol, a cheap, ubiquitous and easily accessible starting material. The process, catalyzed by a metal-based complex including Earth-abundant ones, is initiated by the abstraction of a hydrogen atom from the alcohol to form a carbonyl derivative. After an aldol/dehydration sequence, the complex "returns" the hydrogen atom to reduce the in-situ generated activated alkene, leading to the synthesis of functionalized building blocks. This protocol has been well explored for the α-mono-alkylation of ketones with primary alcohols[8-9] and, more recently, with secondary alcohols.[10-11] Few synthesis of α,α-dialkylated ketones have been also recently reported via the alkylation of substituted methylene ketones, consecutive double alkylation of methyl ketones or tandem three-component alkylation.[12-13] The inter/intra-molecular version of the double alkylation methodology with 1,n-diols would lead to the corresponding cycloalkanes. Donohoe and coworkers reported the first inter-/intramolecular double alkylation catalyzed by an iridium complex in the presence of pentamethylphenyl (Ph*) acetophenone, various primary or secondary diols compounds and an excess of base (4 equiv.) at 115 °C (Scheme 1).[14] The success of this process relied on the introduction of the Ph* substituent which generated a twist out of the conjugation with the carbonyl function (and consequently modified the nucleophilic character of the ketone), prevented the self-dimerization in basic conditions. A complex mixture of compounds was obtained in the absence of a starting ortho-disubstituted ketone. Leitner and Maji proposed almost simultaneously to replace the iridium complex by a more abundant metal-based one. The use of pincer type manganese complexes at 140-150 °C allowed the formation of the cycloalkyl pentamethylphenyl ketones in 31-98% yields (Scheme 1).[15-16] Both groups extended also the concept of this cyclization by using secondary benzylic alcohols in the presence of primary diols (Scheme 1).[15-16] The corresponding cycloalkyl alcohols were isolated in moderate to good yields (40-83%, Scheme 1). These results pointed out again the crucial role of the Ph* substituent to prevent overreduction of the resulting cycloalkyl ketones.

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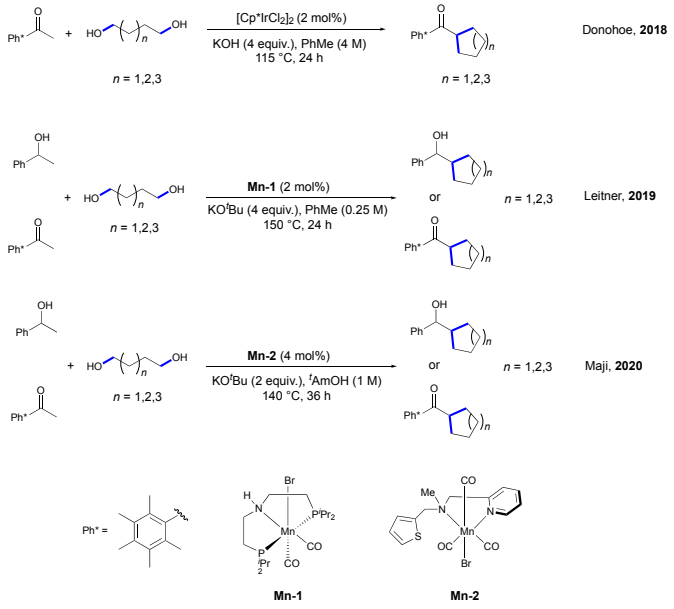
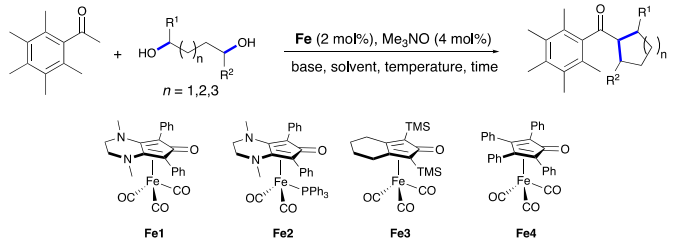
† Footnotes relating to the title and/or authors should appear here.
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x



Scheme 1. Previous syntheses of cycloalkanes via the borrowing hydrogen strategy

We and Morrill have recently highlighted the versatility of the diaminocyclopentadienone iron tricarbonyl complex **Fe1** as pre-catalyst for the formation of C-C bonds in the alkylation of ketones,[10d, 13b, 17a, 18a-b] indoles,[17b, 18a] oxindoles[18a,c] and alcohols,[17c, 18d] and the methylation and ethylation of amines via the hydrogen auto-transfer technology.[18a, 19] Based on these results and previous works by Donohoe and Maji, the synthesis of cycloalkanes (from cyclopentanes to cycloheptanes) was planned via the dialkylation of a ketone with a variety of substituted primary and secondary diols in the presence of the iron complex **Fe1** (Scheme 2).



Scheme 2. Outline of the Fe-catalyzed synthesis of cycloalkanes

As model substrates for the optimization of the reaction conditions, we initially used 1,5-pentan-diol and pentamethylphenyl (Ph*) acetophenone (Table 1 and S1). The latter was chosen as it was the key for the success of the alkylation of ketones with secondary alcohols,[13b] and because the alkylated ketone can be further transformed and functionalized into esters, amides or other aromatic ketones, as elegantly demonstrated by Donohoe.[10a-b, 14]

The iron complexes **Fe1-4** were activated either by addition of Me_3NO[20] or by addition of hydroxide (Hieber's method).[21] A thorough screening of the reaction conditions were accomplished and showed in Table 1 and S1.

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

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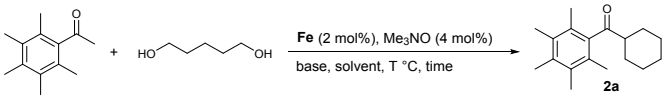


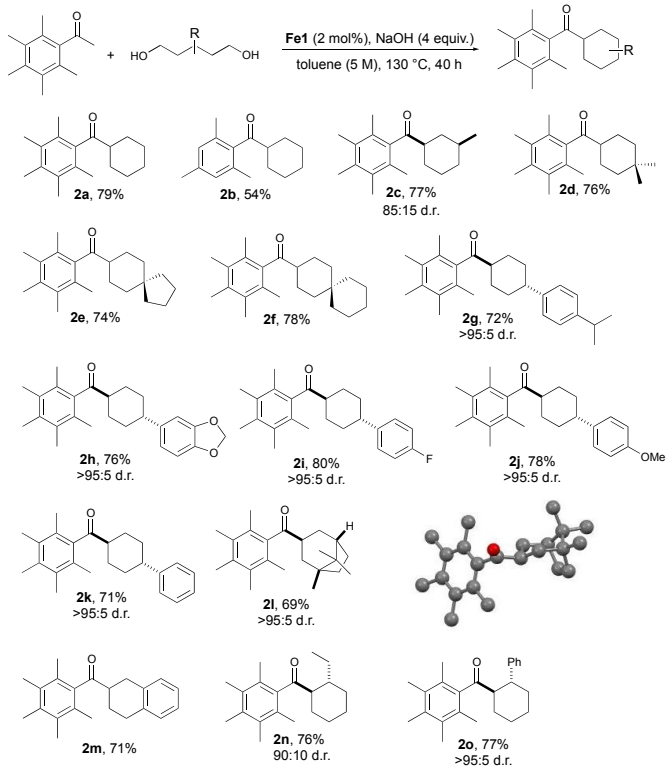
entry	Fe	base (equiv.)	solvent	temp. (°C)	conv.[b] (%)
1	**Fe1**	NaO^{t}Bu (2)	toluene (1 M)	110	-
2	**Fe1**	NaO^{t}Bu (2)	toluene (1 M)	130	19
3	**Fe1**	NaO^{t}Bu (2)	toluene (3 M)	130	20
4	**Fe1**	NaO^{t}Bu (2)	toluene (5 M)	130	26
5	**Fe1**	NaO^{t}Bu (4)	toluene (5 M)	130	36
6	**Fe1**	K_3PO_4 (4)	toluene (5 M)	130	18
7	**Fe1**	K_2CO_3 (4)	toluene (5 M)	130	10
8[c,d]	**Fe1**	NaOH (4)	toluene (5 M)	130	84 (79)[e]
9[c,d]	**Fe1**	NaOH (4)	toluene (5 M)	140	82
10[c,d]	**Fe2**	NaOH (4)	toluene (5 M)	130	61
11[c,d]	**Fe3**	NaOH (4)	toluene (5 M)	130	19
12[c,d]	**Fe4**	NaOH (4)	toluene (5 M)	130	4

[a] General Conditions: ketone (0.5 mmol), diol (1 mmol), **Fe** (2 mol%), Me_3NO (4 mol %), base (4 equiv.), toluene (0.1 mL) for 24 h. [b] Conversions were determined by ^{1}H-NMR analysis of the crude mixture. [c] Reaction performed without Me_3NO. [d] for 40 h. [e] isolated yield in bracket.

A screening of temperature revealed that a temperature threshold of 130 °C was necessary to convert the methyl ketone into the cycloalkyl pentamethylphenyl ketone **2a** in the presence of 2 mol% of iron complex **Fe1** (entries 1-2, Table 1). No improvement was noticed at higher temperature (entries 8-9, Table 1). An excess of diols was also required in this double alkylation (entries 1-2, Table S1). The higher the concentration, the better the conversion (entries 2-5, Table 1). One of the key parameters was the base. Indeed, NaOH provided the product with the highest conversion (84%) within 40 h (entry 8, Table 1), when other bases such as K_2CO_3, K_3PO_4 or NaO*t*Bu furnished the alkylated ketone **2a** in up to 36% conversion (entries 5-7, Table 1). The iron complex **Fe2**, an analog of **Fe1**, catalyzed also the alkylation and provided the cyclohexyl aryl ketone **2a** but in a somewhat lower conversion (entries 8 and 10, Table 1). The other cyclopentadienone iron complexes **Fe3** and **Fe4** were almost inefficient in this process (entries 11-12, Table 1) and no conversion was observed in the absence of iron complex (entry 18, Table S1). When the pentamethylphenyl ketone was replaced by acetophenone, a complex mixture of compounds was observed by ^{1}H-NMR analysis, highlighting the key role of the Ph* substituent in this cascade reaction. In summary the optimized conditions were as follows: 0.5 mmol of pentamethyl phenyl ketone underwent a double alkylation in the presence of 2 equiv. of diol, 2 mol% of complex **Fe1** and 4 equiv. of NaOH at 130 °C in toluene (5 M) to provide the ketone **2a** in 79% yield.

Having established the optimized reaction conditions, the scope of this new iron catalysis was explored.

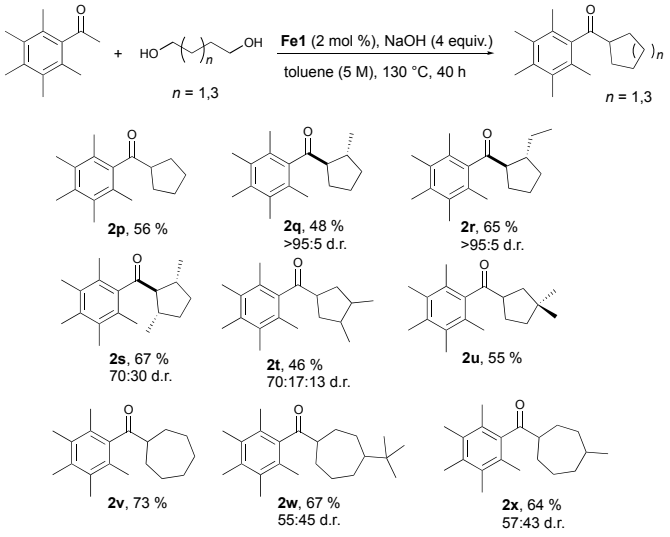
To ensure the synthetic applicability of this methodology, a gram scale alkylation of the pentamethylphenyl ketone with 1,5-pentan-diol was carried out and **2a** was isolated in 78% yield.



Scheme 3. Scope of the iron-catalyzed synthesis of cyclohexanes.

A variety of differently substituted 1,5-diols were engaged in the optimized conditions for the synthesis of functionalized cyclohexyl derivatives (Scheme 3). Electron-donating (alkyl, methoxy, acetal) and electron-withdrawing groups (fluoride) on the aryl ring were tolerated in these conditions. Ketones **2g-k**, **2m** and **2o** were isolated in good yields (71-80%, Scheme 3). Alkyl substituent can also be introduced on the diols and the corresponding ketones **2a-f**, **2l** and **2n** were obtained in moderate to good yields (54-79%, Scheme 3). Starting from 3-substituted 1,5-pentan-diols, only the *trans*-1,4-disubstituted cyclohexanes **2g-k** were isolated (Scheme 3). The control of the diastereoselectivity was lower when 2-methyl-1,5-pentan-diol was used as electrophile. The corresponding ketone **2c** was obtained in a 85:15 diastereomeric ratio (Scheme 3). Gratifyingly, 1,2-disubstituted cyclohexanes **2n** and **2o** were also produced with a good control of the diastereoselectvity (d.r. = 90:10 to >95:5, Scheme 3). Finally, the reduction of (+)-camphor acid led to a diol, which provided the ketone **2l** upon double alkylation in good yield (69%) and high diastereomeric ratio (95:5). To unambiguously establish the atom connectivity in **2l**, single crystals were grown by slow evaporation of methanol. Suitable single crystals were obtained and subjected to X-ray diffraction. Thermal ellipsoid representation is shown in Scheme 3 and highlight the syn-relationship between the CO group, the methyl substituent and the hydrogen atom.

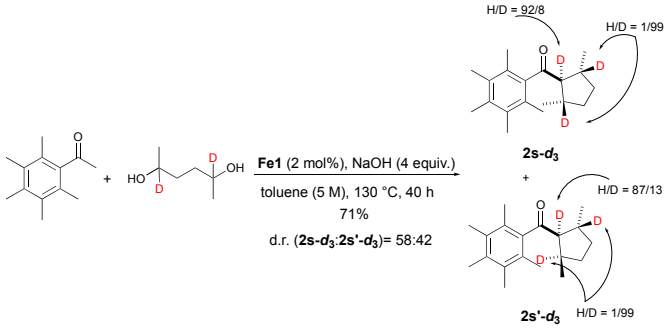
We then extended this work to the synthesis of cyclopentanes and cycloheptanes and the use of 1,4- and 1,6-diols (Scheme 4). Cyclopentane compounds **2p-u** were isolated in moderate yields (46-67%, Scheme 4). As observed previously with substituted 1,5-diols, diastereoselectivity of the alkylation depends on the position of the substituent. 1,2-disubstituted cyclopentanes **2q** and **2r** were obtained as a single *trans*-diastereomer (d.r. = >95:5) while the 1,3,4- and 1,2,5-trisubstituted cyclopentanes **2s** and **2t** were isolated as a mixture of diastereomers (70:30 in favor of the *meso*-diastereomer and 70:17:13, respectively, Scheme 4). A geminal dimethyl group in diol did not hamper the reactivity and afforded the alkylated product **2u** in 55% yield. Pleasingly, the reaction between the Ph* ketone and 1,6-hexane diol led to cycloheptane **2v** in 73% isolated yield. As noticed in previous works, substituted cyclopheptanes were prepared in good yields but with a moderate control of the diastereoselectivity (Scheme 4). Disubstituted cycloheptanes **2w** and **2x** were synthesized in 67 and 64% yield, respectively, as almost a 1:1 mixture of diastereomers (Scheme 4).



Scheme 4. Scope of the iron-catalyzed synthesis of cyclopentanes and cycloheptanes.

To gain mechanistic insights on the mechanism of this alkylation reaction, a deuterium labeling experiment was performed (Scheme 5). Under optimized conditions, the reaction using the deuterated hexane-2,5-diol yielded **2s-*d*$_3$** and **2s'-*d*$_3$** in 71% as a mixture of two diastereomers (d.r. = 58:42, the meso-diastereomer as the major compound). Chemical yield is comparable to the non-deuterated alkylation (Scheme 4). Deuterium was incorporated in position 2 and 5 of cyclopentanes for both diastereomers, suggesting that the diol is the hydride source in the overall process and the mechanism implies an inter- and an intramolecular alkylation via the reduction of two enone intermediates (see the proposed mechanism in the Supplementary Information, Scheme S2).

In conclusion, we have developed the first phosphine-free iron complex-catalyzed synthesis of cycloalkanes using methyl ketones and diols compounds via the hydrogen autotransfer strategy. Various primary as well as secondary diols were introduced in this alkylation and afforded cycloalkanes in moderate to good yields. Labeling experiments confirm that the diol was the source of hydrides in this process. These results tend to promote the interest of phosphine-free iron complexes in catalysis and encourage the development of new reactivities.



Scheme 5. Deuterium labeling experiment.

Conflicts of interest

There are no conflicts to declare

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