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Review

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# Synthetic strategies for dihydrochalcones

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**Dedicated to Professor Hans-Günther Schmalz, on the occasion of his retirement**

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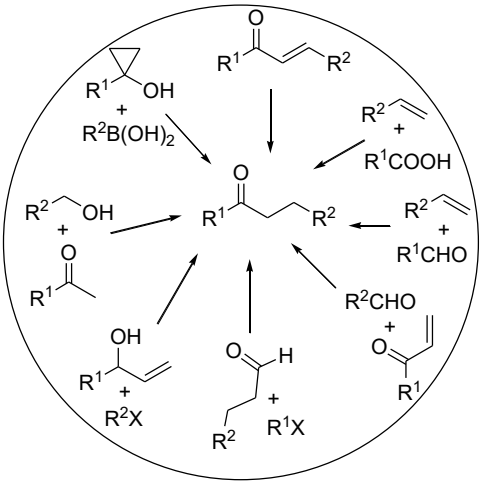
## Abstract

Dihydrochalcones are open chain derivatives of flavanones characterised by the presence of the benzylacetophenone skeleton. They have been reported to exhibit many important biological activities, which make them attractive targets for chemical synthesis. Several synthetic strategies have been developed for the dihydrochalcones. The most widely employed synthetic method involves selective reduction of the double bonds of chalcones. Other methods that have been developed for the synthesis of dihydrochalcones include transition metal-catalysed coupling reactions as well as light-catalysed reactions. This review discusses the synthetic strategies for the dihydrochalcones.




**Keywords:** Dihydrochalcones, reduction, alkylation, metal-catalysed, light-catalysed

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## 1. Introduction

Dihydrochalcones are a minor subclass of flavonoids.[1] They are open-chain derivatives of flavanones characterised by the presence of benzylacetophenone skeleton,[1] which consists of two aromatic rings (A- and B) linked by a three-carbon chain with a carbonyl group adjacent to the A-ring. Retrodihydrochalcones also exist, in which the carbonyl group is connected to the B-ring.[2-4] Dihydrochalcones have been identified and isolated from different plant families, particularly from the families Leguminosae/Fabaceae, Rutaceae, Annonaceae, and Rosaceae.[1, 5, 6] Some glycosides of dihydrochalcones are sweeteners and find applications in the food industry.[1, 7-10] Examples include trilobatin (**1**)[7, 11-13] phloridzin (**2**),[7, 9, 11, 12] and neohesperidin dihydrochalcone (**3**) (Figure 1).[7, 8, 14, 15]

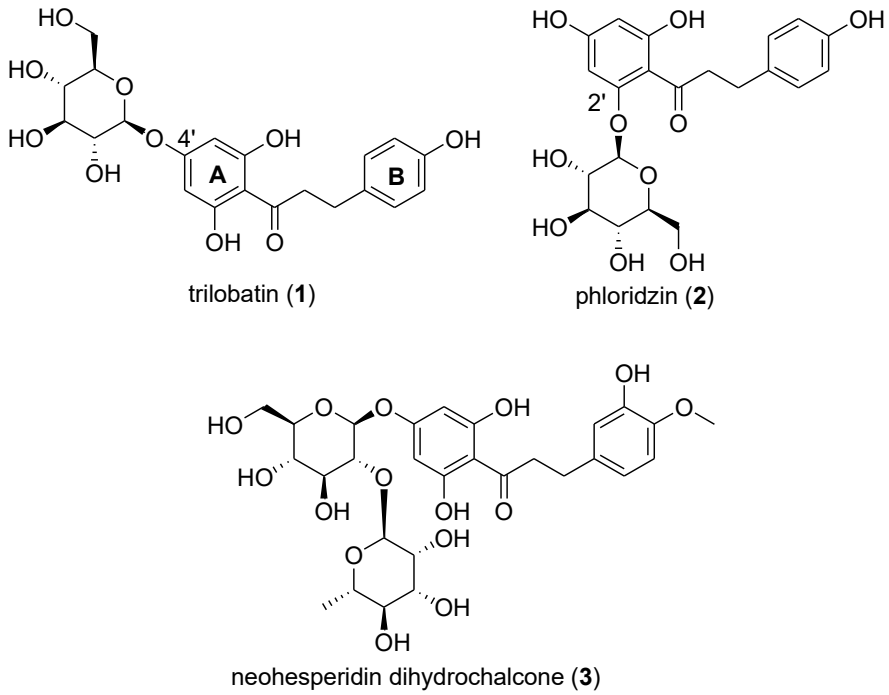



**Figure 1**. Dihydrochalcone sweeteners.

Dihydrochalcones have been reported to exhibit many important biological activities that have made them attractive targets for chemical synthesis.[1, 6, 16] These include antiviral activity against influenza A,[17] antihypertensive and vasorelaxative activities,[18] antimicrobial activity,[19, 20] antiplasmodial activity,[21, 22] antileishmanial activity,[23, 24] chemoprevention and cytotoxic activities,[20, 25-28] and many others.[1, 5, 6, 16]

The biosynthesis of dihydrochalcones was elucidated by Stitch's group based on phloridzin (**2**).[29] They established that *p*-coumaroyl-CoA is reduced into 4-hydroxycinnamoyl-CoA in the presence of NADPH.[29] Condensation of 4-hydroxycinnamoyl-CoA with three units of malonyl-CoA, catalysed by chalcone synthase (CHS) renders the 2',4',6',4-tetrahydroxydihydrochalcone (phloretin), which is glucosylated at the 2'-OH to give phloridzin.[29-31] A *Malus* hydroxycinnamoyl-CoA double bond reductase, which catalyses the NADPH-dependent reduction of *p*-coumaroyl-CoA and feruloyl-CoA to *p*-dihydrocoumaroyl-CoA and dihydroferuloyl-CoA, respectively, was isolated and characterised by Gang's group.[32]

Several synthetic strategies have been developed for the dihydrochalcones. The most widely employed synthetic method involves selective reduction of the double bonds of chalcones.[16, 33-38] Other methods that have been developed include transition metal-catalysed reactions such as carbonylative Negishi coupling,[39] Heck-coupling,[40-42] ruthenium-catalysed aryl migration,[43] coupling with boronic acids/esters,[44-47] and rhodium-catalysed decarbonylative addition.[48] Dihydrochalcones have also been synthesised by alkylation and acylation reactions.[49-51] In some instances, dihydrochalcones have been accessed by β-elimination of flavanones under basic conditions followed by hydrogenation of the resulting chalcones.[13, 52] In this review the synthetic strategies for dihydrochalcones are discussed.

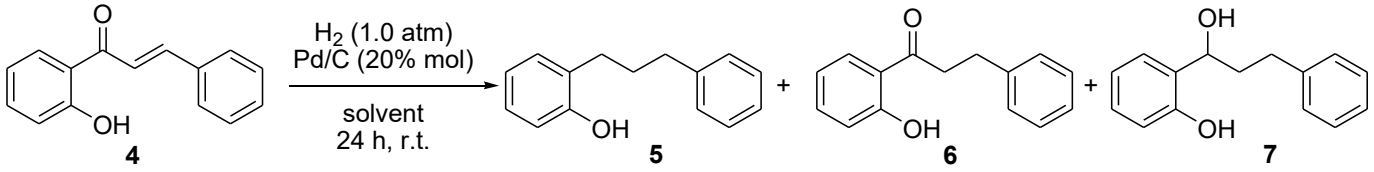
 

## 2. Synthetic Strategies for Dihydrochalcones

### 2.1. Selective reduction of α,β-olefinic bond in chalcones

Most frequently, dihydrochalcones are prepared by selective reduction of the double bonds of chalcones.[16, 33, 35-37, 53-58] Different conditions have been employed for such reduction including hydrogenation over different metal catalysts such as Pd/C, $PtO_2$, $NiCl_2$, Rh-$[(COD)_2]^+[BF_4]^-$ with $PPh_3$ and many others.[53-56, 59-63] Other conditions that have been successfully employed for the selective hydrogenation of α,β-unsaturated carbonyls of chalcones involve the use of cobalt-nickel bimetallic nanocatalyst, CoNi@g$C_3N_4$,[58] and the dinickel complex ($bpy^{\bullet-}$)$Ni^{II}(\mu_2$-H)$_2$NiII($bpy^{\bullet-}$) stabilised on aluminium metal–organic frameworks (MOFs).[64] The use of $NiCl_2$ by Tadigoppula and co-workers facilitated selective reduction of the α,β-olefinic bond of a chalcone bearing a dimethylchromene scaffold, while leaving that of the chromene moiety intact.[65] Other conditions that favored regioselective reduction of the chalcones involved the use of $NaBH_4$ with $InCl_3$.[66] They enabled the reduction of the conjugated double bonds of the chalcones in the presence of geranyl and farnesyl chains.[66] Table 1 exemplifies the solvent-controlled hydrogenation of 2′-hydroxychalcone **4**, which renders either a 1,3-diarylpropane **5**, a dihydrochalcone **6** or a 1,3-diarylpropanol **7**.[54] The dihydrochalcone **6** was obtained predominantly when $CH_2Cl_2$ was used as a solvent (entries 2 and 3), the use of ethanol yielded 1,3-diarylpropane **5** (entry 1), while mixtures of butanol and water rendered either **5** or **7** depending on the ratio used (entries 4 and 5). Thus, differently substituted 1,3-diarylpropanes, dihydrochalcones, and 3-diarylpropanols could be synthesised using the appropriate solvents.[54]

**Table 1.** Studies on the hydrogenation of 2′-hydroxychalcone **4**

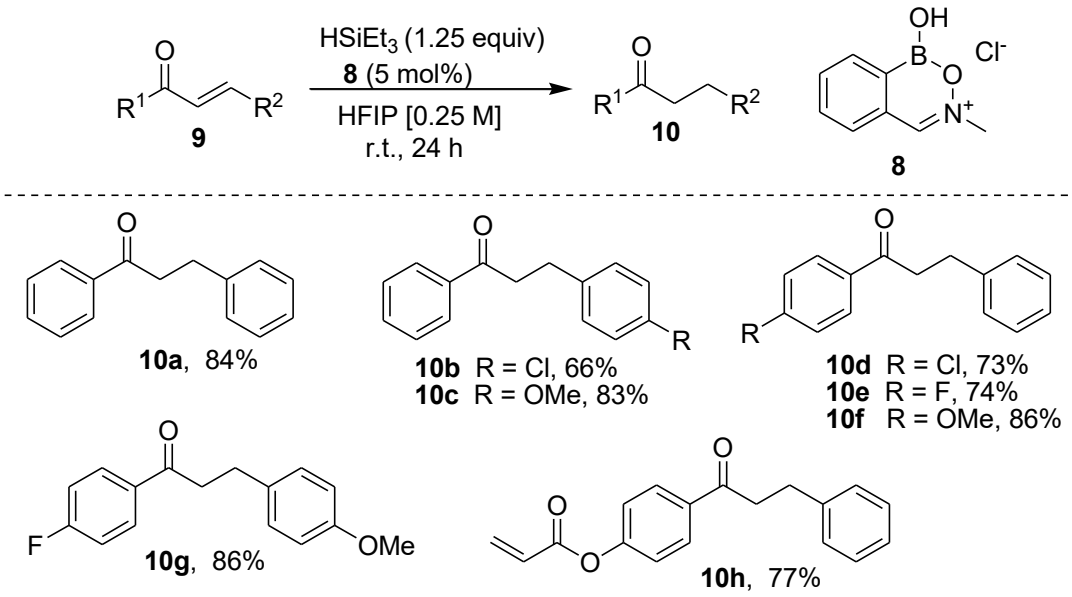



| Entry | Solvent | Conversion [%][a] | | |
|---|---|---|---|---|
| | | **5** | **6** | **7** |
| 1 | EtOH | >98 | 0 | 0 |
| 2 | $CH_2Cl_2$ | 0 | >98 | 0 |
| 3 | $CH_2Cl_2$ [b] | 0 | >98 | 0 |
| 4 | *n*-BuOH/$H_2O$ (1:1) | 0 | 0 | >98 |
| 5 | *n*-BuOH/$H_2O$ (2:1) | 95 | 0 | 5 |

[a] Conversions determined by $^1$H NMR (300 MHz) of the crude reaction mixtures based on compound **4**. [b] Reactions performed for 6 h.

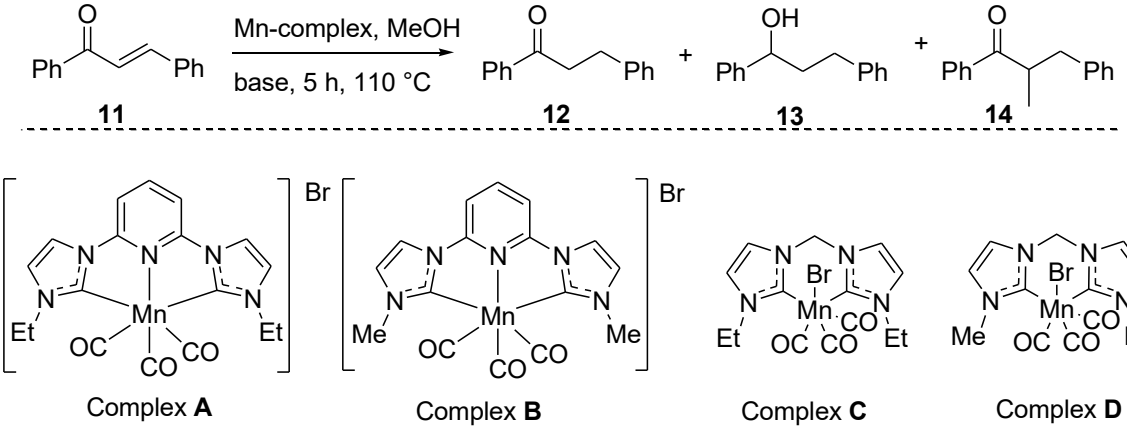
The reduction of α,β-unsaturated carbonyl compounds to corresponding saturated ketones has also been accomplished by silyl reagents.[33, 67, 68] Chalcones have been reduced into dihydrochalcones by in situ hydrogenation using triethylsilane ($Et_3SiH$) with Pd/C or $InCl_3$.[33, 34, 67] Silane reagents have also been used for the reduction of α,β-unsaturated carbonyl compounds including chalcones using catalysts immobilised on MOFs.[69, 70] Rygus and colleagues used $Et_3SiH$ and other silanes in the presence of a hemiboronic acid catalyst **8** in 1,1,1,3,3,3-hexafluoropropan-2-ol (HFIP) for the reduction of α,β-unsaturated ketones **9** into **10** (Scheme 1).[68] The compounds **10** were obtained in 60-88% yields.[68]




**Scheme 1**. Reduction of chalcones using $HSiEt_3$.

**Table 2**. Optimisation of the reaction conditions for the selective transfer hydrogenation of the C=C bond in chalcone using methanol[a]



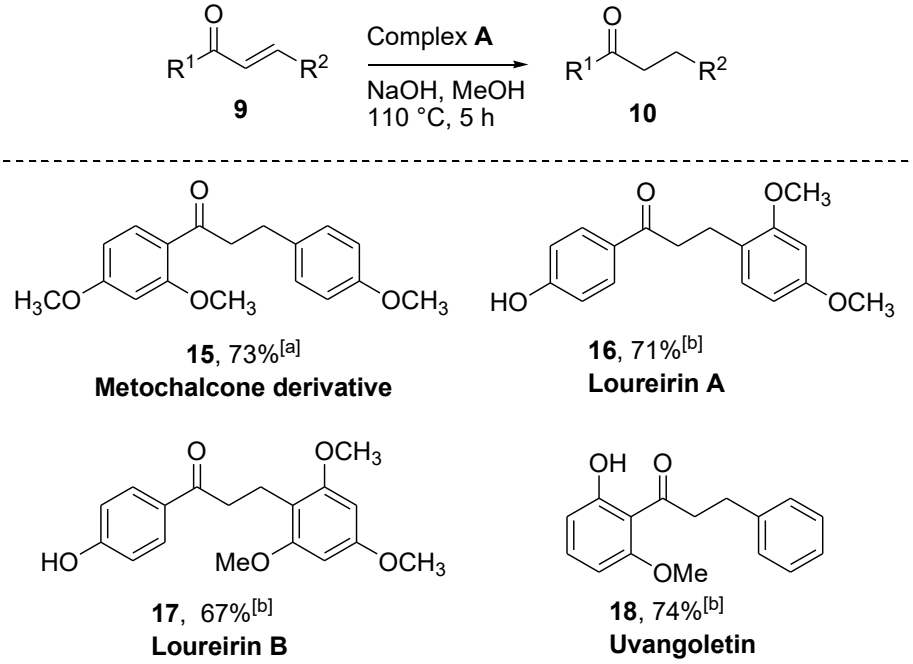

| Entry | Complex [mol %] | Base [mol %] | Yield of **12** % | Yield of **13** % | Yield of **14** % |
|---|---|---|---|---|---|
| 1 | Complex **A** (1) | NaOH (10) | 79 | 16 | - |
| 2 | Complex **A** (1) | NaOH (5) | 88 | 3 | - |
| 3 | Complex **B** (1) | NaOH (5) | 78 | 1 | - |
| 4 | Complex **C** (1) | NaOH (5) | 67 | - | 5 |
| 5 | Complex **D** (1) | NaOH (5) | 53 | - | 2 |
| 6 | Complex **A** (1) | NaOMe (5) | 83 | 1 | - |

[a] Reaction conditions: chalcone (0.25 mmol), Mn complex [mol %], base [mol %], heated in methanol (1 mL) at 110 °C (oil bath temperature) for 5 h; GC (Gas Chromatography) yields (mesitylene was used as internal standard).

There is also great interest in selective transfer hydrogenation (TH) of C=C bonds in α,β-unsaturated carbonyl compounds.[57, 71-75] Yu et al. developed a method for catalytic hydrogen transfer using rhodium

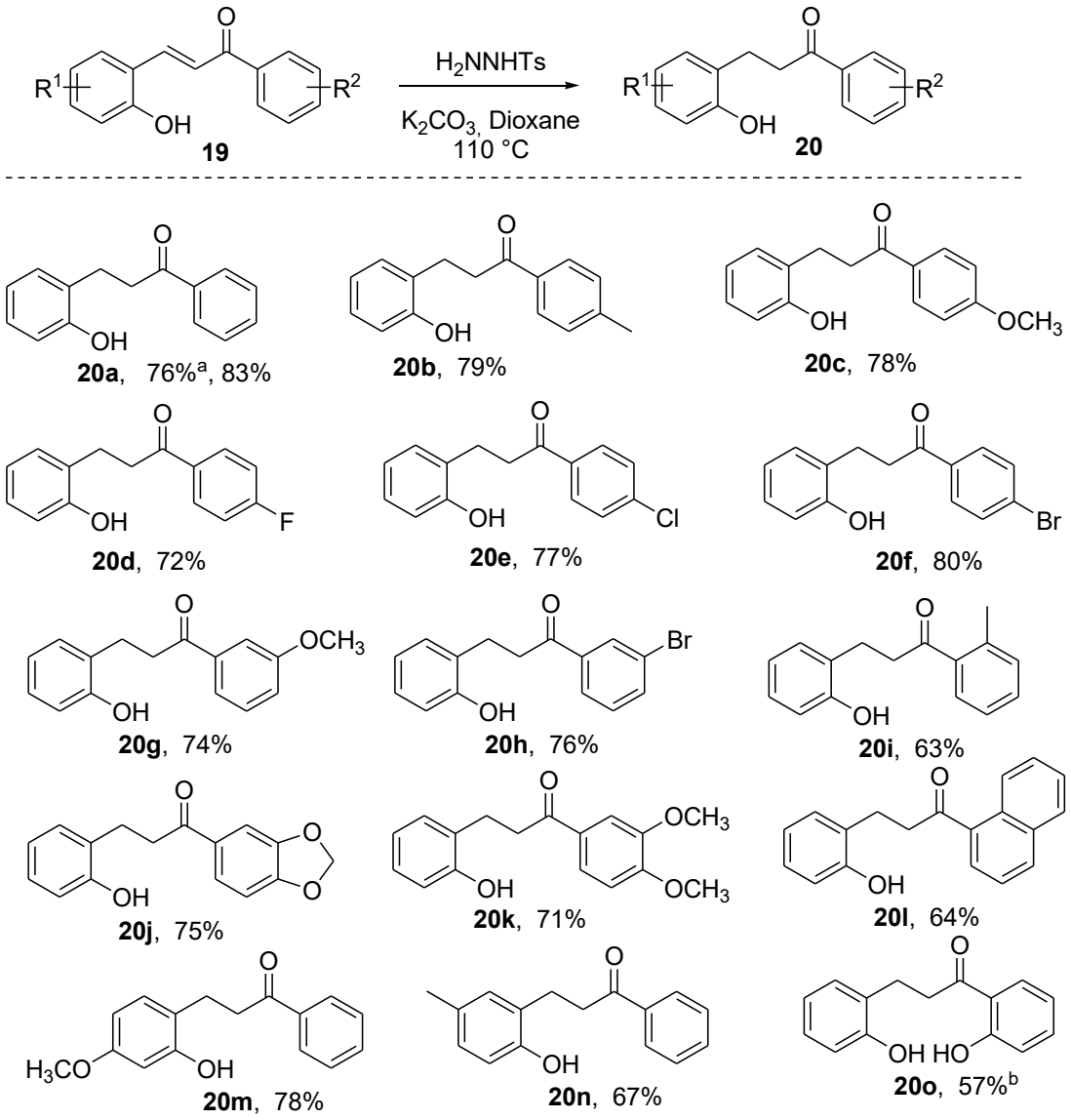
catalyst, $[Cp^*Rh(III)Cl_2]_2$, with isopropanol as hydrogen source and demonstrated its application to the synthesis of various dihydrochalcones from chalcones.[57] In several instances methanol has been used as a hydrogen donor and complexes of Rh(III),[71] Ir(III)[72, 73] and Ru(II)[74] as catalysts. Mandal and colleagues employed *N*-heterocyclic carbene (NHC)-based pincer (CNC)MnI complexes **A**-**D** for the reduction of conjugated alkenes **11** (Table 2).[75] The reaction yielded mainly the saturated ketone **12** and low yields of **13** and **14** were also obtained. Several dihydrochalcones and other saturated ketones were synthesised from their corresponding unsaturated precursors under optimised conditions.[75] The method was further applied to the synthesis of biologically active molecules including natural dihydrochalcones, metochalcone derivative **15**, loureirin A (**16**), loureirin B (**17**) and uvangoletin (**18**) (Scheme 2).[75]




**Scheme 2**. Synthesis of bioactive molecules and natural dihydrochalcones by Mandal and colleagues. Reaction conditions: ketone (0.25 mmol), complex **A** (1 mol %), NaOH (5 mol %), heated in MeOH (1 mL) at 110 °C for 5 h; isolated yields. [a] Complex **A** (2 mol %) and NaOH (10 mol %). [b] Complex **A** (3 mol %) and NaOH (1 equiv.).

Transition metal-free reduction of chalcone double bonds has also been accomplished under different conditions that include the use of activated borane (ActB) with $Et_3SiH$,[36] the $CS_2$/*t*-BuOK system with dimethyl sulfoxide as a hydrogen donor,[37] tetraarylhydrophosphorane in the presence of pinacolborane,[38] and tosyl hydrazine.[35] Using the latter conditions, Shang and co-workers synthesised differently-substituted dihydrochalcones **20** by treatment of chalcones **19** with tosyl hydrazine and $K_2CO_3$, Scheme 3. The dihydrochalcones **20** could further be annulated to afford flavans.[35]

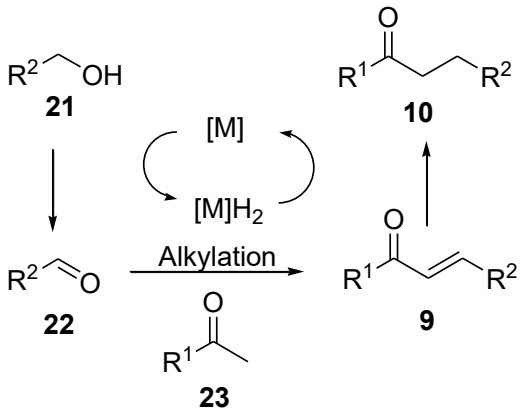



**Scheme 3**. Conjugate reduction of 2-hydroxylchalcones **19.**

## 2.2. Alkylation

There has been great interest in alkylation of ketones with alcohols using hydrogen borrowing and returning methodology,[76] also termed hydrogen autotransfer process.[77] When the reaction is carried out with acetophenones and benzyl alcohols, the resulting products can be chalcones or dihydrochalcones depending on whether the reaction is conducted under inert conditions or under oxygen atmosphere.[78] The process involves a one-pot three steps transformation that starts with oxidation of the alcohol **21** to give an aldehyde **22**, followed by condensation of the aldehyde **22** with an acetophenone **23** and finally reduction of the resulting conjugated system **9** to give a dihydrochalcone **10** (Scheme 4).[78] The first step is facilitated by abstraction of a proton from the alcohol by the metal catalyst, while condensation is enabled by a base, and the last process is hydrogenation (hydrogen return) of the double bond by the metal hydride.[76, 77, 79, 80] The reaction is considered to be cleaner as it mainly produces water as a by-product. It is also possible to avoid metal salts if bases are not used in the reaction or to produce lower quantities of salts by using catalytic amounts of basic salts.[81-85]




**Scheme 4**. The hydrogen-borrowing and returning cycle.

In several instances, researchers have used transition metal-based catalysts for the hydrogen borrowing transformations. These include precious second- and third-row transition-metal catalysts, mainly W,[86] Pd,[78, 79] Ru,[87, 88] Os,[82] Re,[89] and Ir.[80, 81, 87, 90, 91] Non-noble metals such as Ni,[83, 92, 93] Fe,[84] Co,[94] Zn,[85] and Mn[95] have also been used. Tables 3 and 4 summarise the results obtained from different studies. Kwon and colleagues used palladium nanoparticles in aluminum hydroxide [Pd/AlO(OH)] for the α-alkylation of ketones **23** with primary alcohol **21** (Table 3, entry 1). The reaction was initially conducted at 80 °C in the presence of $K_3PO_4$ (3 equiv.), and then at higher temperatures (110 °C) for substrate scope evaluation. The reaction could be completed within shorter reaction times (2.5 h) in most instances at high temperatures. The reaction gave either unsaturated enones when conducted under oxygen or saturated α-alkylated ketones when performed under argon.[78] High yields that ranged from 80 to 98% were determined by GC or after isolation.[78] Cui et al. prepared a silver/molybdenum hybrid catalyst $Ag_6Mo_{10}O_{33}$ (Ag-Mo-22), which they used for hydrogen borrowing reactions (Table 3, entry 2) of acetophenones **23** with benzyl alcohols **21**, resulting in dihydrochalcones **10**. Optimised conditions involved the use of Ag-Mo-22 in the presence of $K_2CO_3$ (20 mol %) as a base. Under optimised conditions, the dihydrochalcones **10** were synthesised in 86-97% yields.[96] Chen and co-workers used amalgamated silver and palladium nanoparticles supported on carbon (Ag-Pd/C) for the hydrogen borrowing reaction of ketones **23** with alcohols **21** (Table 3, entry 3). The optimum conditions involved the use of $K_3PO_4$ (3 equiv.) as a base and toluene solvent at 125 °C for 21 h. Yields of 5 to 97% were obtained during optimisation of conditions leading to the formation of a dihydrochalcone **10**.[79] The reaction was further extended to the synthesis of quinolines.[79] Several research groups utilised iridium-based catalysts including **24**, **25**, and **26** for the alkylation of ketones with alcohols (Table 3, entries 4-6). [80, 81, 90] Li et al. found iridium complex bearing a functional bipyridonate **26** to be an environmentally friendly and highly effective catalyst for the α-alkylation of ketones with primary alcohols (Table 3, entry 6). The optimum conditions involved the use of 1 mol % catalyst **26**, catalytic amounts of a base (0.1 equiv of $Cs_2CO_3$ per substrate), *tert*-amyl alcohol under reflux in an air atmosphere for 6 h. The products were obtained in yields ranging from 82-90% under optimised conditions.[81] Buil and colleagues used the osmium complex [Os($\eta^6$-p-cymene)(OH)(IPr)]OTf **27** for the α-alkylation of arylacetonitriles and alkyl ketones with alcohols. The reaction gave dihydrochalcones **10** when acetophenones **23** and benzyl acohols **21** were used as substrates (Table 3, entry 7).[82] Under optimal conditions, the reactions were performed in toluene under Ar atmosphere at 110 °C using 3 mmol of the corresponding substrate, 1 mol % Os complex **27** and 20% KOH for 1.5 to 6 h for the formation of dihydrochalcones.[82] Using optimised conditions, yields of dihydrochalcones ranged from 91-99%.[82] Zhang et al used tungsten supported with polyaniline (W@PANI) for the reaction of ketones with

alcohols leading to α-alkylated ketones (Table 3, entry 8).[86] The optimised conditions that involved the use of acetophenone **23** (1 mmol), alcohol **21** (1.1 mmol), 120 mg of W@PANI (9.1 mol % W), KOH (1 mmol), and toluene (1 mL) at 110 °C for 6 h were employed for exploring substrate scope. Isolated yields of dihydrochalcones based on **23** ranged from 51 to 85%. Other alkylated ketones were also prepared in good yields.[86]

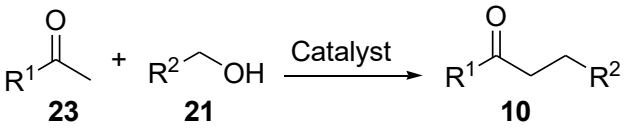
There has been great interest to use base metal catalysts for the hydrogen borrowing reaction.[83, 84, 92, 95] Elangovan and co-workers reported iron-catalysed alkylation of ketones with alcohols (Table 3, entry 9). Different Fe catalysts and catalyst loading were evaluated with $K_2CO_3$ and $Cs_2CO_3$ as bases. Initially, good yields of 74 to 80% were obtained during optimisation of the conditions. Thereafter, the conditions that involved the use of 2 mol % Fe catalyst **28**, 2 mol % $PPh_3$, 10 mol % $Cs_2CO_3$, and toluene at 140 °C for 24 to 48 h were employed to assess the substrate scope of the reaction. Under these conditions, the dihydrochalcones were synthesised in 19 to 72% isolated yields.[84] Nickel catalysts have also been employed as cheap alternatives for the alkylation of ketones with alcohols.[83, 92] Charvieux used nickel supported on silica and alumina for the hydrogen borrowing reaction resulting in α-alkylated ketones (Table 3, entry 10).[83] The optimised conditions involved the use of acetophenone **23** (1.2 equiv.), benzyl alcohol **21** (1 equiv.), supported metal catalyst $Ni/SiO_2$-$Al_2O_3$ (65 wt%), and $K_3PO_4$ (10 mol %) at 175 °C for 14.5 h. Initially, the product was obtained in 86% yield as determined by NMR, and then in 93% isolated yield when the reaction was repeated. Differently substituted dihydrochalcones were synthesised in yields ranging from 15 to 86% under optimised conditions.[83] Alkyl ketones were also synthesised.[83] Lui's group synthesised dihydrochalcones from aryl ketones **23** and benzyl alcohols **21** catalysed by nickel–NHC complexes (Table 3, entry 11). The optimum conditions included the use of Ni-NHC catalyst **29** (3 mol %) and Li$O^t$Bu as a base. Under optimised conditions, the α-alkylated ketones were obtained in 31-90% yields, except for one pyridyl derivative that was obtained in trace quantities.[92] The reaction was also applied to the synthesis of quinolones.[92] Gosh and colleagues prepared manganese oxide nanoparticles ($MnO_2$ NPs) by reduction of $KMnO_4$ with phenolics from mango leaves. The synthesised nanoparticles were used for α-alkylation of ketones with alcohols and for the synthesis of quinolones (Table 3, entry 12). Different parameters were examined for optimisation of reaction conditions. The reaction worked best in toluene, in the presence of 1.0 mol equivalents of K$O^t$Bu or NaOH. Additional derivatives were synthesised under optimised conditions and the dihydrochalcones were obtained in yields ranging from 74 to 94%.[95] Dandia and Chauhan evaluated different catalyst that included $CoCl_2$, $Co(OAc)_2$, as well as phthalocyanine coordinated metal catalysts: zinc(II) phthalocyanine (1 mol %), nickel(II) phthalocyanine (1 mol %), and cobalt(II) phthalocyanine (1 mol %) for the α-alkylation of acetophenones with benzyl alcohols. The best yields were obtained with the cobalt(II) phthalocyanine using K$O^t$Bu as a base and DMSO solvent at 100 °C for 10 h (Table 3, entry 13). Under optimised conditions, differently substituted dihydrochalcones were obtained in 86-97% yields.[94] Zhang and co-workers developed lignin-derived zinc single atom catalyst co-doped with nitrogen and carbon (LCN@Zn-SAC), which was used for the hydrogen borrowing reaction involving ketones and alcohols (Table 3, entry 14). Optimum conditions entailed the use of LCN@Zn-SAC (1.5 mol % Zn), KOH (30 mol %), and toluene (1 mL) at 110 °C for 4 h under argon. The alkylated products were obtained in 34-99% (determined by GC) under optimised conditions.[85]

In other circumstances, the reaction has been carried out between secondary alcohols **30** and primary alcohols **21** to render α-alkylated ketones **10** (Table 4).[87-91, 93] Both noble and non-noble transition-metal catalysts have been utilised for the transformation.[87-91, 93] Musa and colleagues reported ruthenium and iridium-catalysed reactions of secondary alcohols **30** and primary alcohols **21** to furnish alkylated ketones **10**, including dihydrochalcones (Table 4, entry 1). Under optimum conditions that utilised 1 mol % of iridium catalyst **31** or 2 mol % of ruthenium catalyst **32**, KOH base and xylene as solvent at 130 °C, the products were

obtained in 85 to 95% yields.[87] However, self-condensation reactions failed to work, as well as the reaction between 1-phenylethanol and diphenylmethanol.[87] Biswas et al. also used ruthenium catalysts for the synthesis of alkylketones **10** from the reaction of secondary alcohols **30** with primary alcohols **21** (Table 4, entry 2). The best yields were obtained with ruthenium catalyst **33**, using NaOH as a base. Dihydrochalcones were prepared in 40 to 75% yields. Other α-alkylated ketones were also synthesised successfully.[88] Wang and coworkers reported the use of iridium catalyst **25** for the synthesis of dihydrochalcones **10** from secondary alcohols **30** and primary alcohols **21**, in the presence of $AgNTf_2$ and $Cs_2CO_3$ in toluene at 120 °C (Table 4, entry 3). The dihydrochalcones **10** were obtained in isolated yields of 79-98%.[90] Feng's group conducted additional studies involving iridium-catalysed alkylation of secondary alcohols with primary alcohols.[91] Different iridium catalysts were tested. The best yields were obtained with iridium catalyst **26** (Table 4, entry 4). Using this catalyst under optimised conditions, the dihydrochalcones were obtained in 80-90% yields. Other alkyl ketones were synthesised in 79-85% yields.[91] Chakraborty and colleagues reacted secondary alcohols **30** with primary alcohols **21** in the presence of a four-coordinate macrocyclic Ni(II) complex [Ni(MeTAA)] **34** and a base to afford α-alkylated ketones **10** (Table 4, entry 5). Optimised conditions involved the use of $KO^tBu$ base and xylene solvent at 120 °C.[89] The optimum conditions yielded the targeted compound in 81% isolated yield. Thereafter, the substrate scope was evaluated on differently substituted derivatives. The α-alkylated products, particularly dihydrochalcones were synthesised in 63% to 91% yields.[93] Pham and colleagues developed an air-stable rhenium catalyst **35** and used it for the hydrogen borrowing reaction involving a secondary alcohol and primary alcohol (Table 3, entry 6). Optimised conditions included the use of 2 mol % Re catalyst **35** and 20 mol % $Cs_2CO_3$ in *t*-amyl alcohol. A high yield of 99% (determined by $^1H$ NMR) was obtained during optimisation of conditions. The determination of substrate scope led to the synthesis of dihydrochalcones in 63-91% isolated yields.[89]

**Table 3**. Reactions of ketones with alcohols to give α-alkylated ketones including dihydrochalcones




**23** **21** **10**

| Entry | Catalyst (loading) | Optimised Conditions | Yield [%] | Ref. |
|---|---|---|---|---|
| 1 | Pd/AlO(OH) (0.2 mol %) | Acetophenone **23** (1.0 mmol), and alcohol **21** (1.2 mmol), $K_3PO_4$ (3 equiv), 80-120 °C, 2.5 h - 8 h, toluene, Ar. | 87-98%[a] 80-92%[b] | [78] |
| 2 | Ag-Mo-22 ($Ag_6Mo_{10}O_{33}$) (40 mg) | ketone (2 mmol) **23**, benzylic alcohol **21** (10 mmol), Ag-Mo-22 (40 mg), $K_2CO_3$ (20 mol %, 56 mg), 135 °C, 12 h. | 86-97%[b,c] | [96] |
| 3 | Ag-Pd/C (1 mol % of Pd) | Acetophenone **23** (0.25 mmol), benzyl alcohol **21** (0.275 mmol), $K_3PO_4$ (0.75 mmol), toluene (1 mL), 125 °C, 21 h, Ar. | 97%[b,c] | [79] |

**Table 3.** Continued

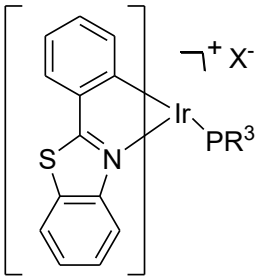
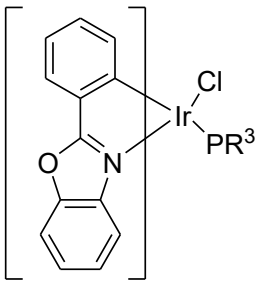
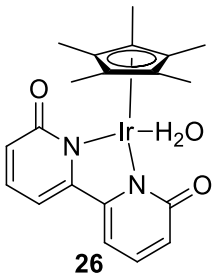
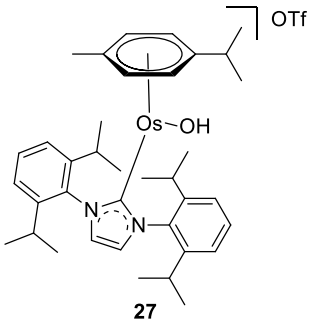
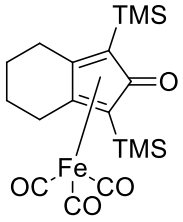
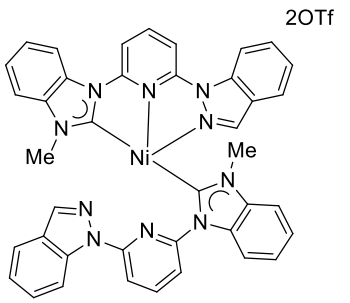
| Entry | Catalyst (loading) | Optimised Conditions | Yield [%] | Ref. |
|---|---|---|---|---|
| 4 |  <br>**24**: R = *n*-Bu, X = OTf<br>iridium–CNP (1 mol %) | Acetophenone **23** (1.0 mmol), alcohol **21** (1.1 mmol), **24** (1 mol %), $Cs_2CO_3$ (1.0 mmol), *tert*-amyl alcohol, 120 °C, 24 h, $N_2$(g). | 57%-98%[c] | [80] |
| 5 |  <br>**25**: R = *n*-butyl<br>**25** (2 mol %), $AgNTf_2$ (2 mol %) | Acetophenone **23** (1.0 mmol), benzyl/alkyl alcohol **21** (1.1 mmol), **25** (2 mol %), $AgNTf_2$ (2 mol %, 0.02 mmol), $Cs_2CO_3$ (1.1 mmol), toluene, 120 °C, 16 h. | 81-96%[c] | [90] |
| 6 |  <br>**26**<br>Cp*Ir catalyst **26** (1 mol %) | Acetophenone **23** (1 mmol), benzyl alcohol **21** (1.1 mmol), catalyst **26** (1 mol %), $Cs_2CO_3$ (0.1 equiv), *tert*-amyl alcohol, reflux, 6 h, under air. | 82-92%[c] | [81] |
| 7 |  <br>**27**<br>[Os($\eta^6$-*p*-cymene)(OH)(IPr)]OTf (1 mol %) | Acetophenone **23** (3 mmol), alcohol **21** (3 mmol), Os **27** (0.01 equiv), KOH (0.2 equiv), toluene, 110 °C, 1.5-6 h, Ar. | 91-99%[c,d] | [82] |

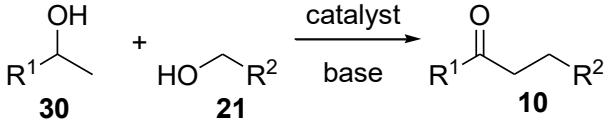
**Table 3.** Continued

| Entry | Catalyst (loading) | Optimised Conditions | Yield [%] | Ref. |
|---|---|---|---|---|
| 8 | Polyaniline-supported tungsten (W@PANI) (9.1 mol % W) | Acetophenone **23** (1 mmol), alcohol **21** (1.1 mmol), 120 mg of W@PANI (9.1 mol % W), KOH (1 mmol), toluene, 110 °C, 6 h. | 51-85%[b,c] | 86 |
| 9 |  **28** Fe complex **28** (2 mol %) | Ketone **23** (1 mmol), alcohol **21** (1.3 mmol), Fe complex **28** (0.02 mmol, 2 mol %), $PPh_3$ (0.02 mmol, 2 mol %), $Cs_2CO_3$ (0.1 mmol, 10 mol %), toluene, 140 °C, 24 – 48 h. | 47-92%[c,d] 19--72%[b,c] | 84 |
| 10 | 65 wt% Ni/$SiO_2$-$Al_2O_3$ (20 mol %) | Acetophenone **23** (11.6 mmol, 1.2 equiv.), benzyl alcohol **21** (9.7 mmol), 65 wt% Ni/$SiO_2$-$Al_2O_3$ (20 mol %), $K_3PO_4$ (10 mol %), neat, 175 °C, 14.5 -24 h. | 34-93%[c,d] 15-86%[b] | 83 |
| 11 |  **29** Ni-NHC Complexes (3 mol %) | Ketone derivatives **23** (0.3 mmol), primary alcohol **21** (0.5 mmol), **29** (0.009 mmol, 3 mol %), Li$O^t$Bu (0.25 mmol), toluene (1.0 mL), 140 °C, 12 h, $N_2$ (g). | 31-90%[c] | 92 |
| 12 | Manganese oxide nanoparticles ($MnO_2$ NPs) (20 mol %, 46.03% w/w) | Acetophenone **23** (0.5 mmol), benzyl alcohol **21** (0.6 mmol), δ-$MnO_2$ NPs (20 mol %, 46.03% w/w), K$O^t$Bu (1.0 equiv.), toluene, 120-140 °C, 24–30 h, in air. | 74-94%[b,c] | 95 |
| 13 | Cobalt (II) phthalocyanine (CoIIPc) (1 mol %) | Acetophenone **23** (1 mmol), alcohol **21** (1 mmol), CoIIPc (1 mol %), K$O^t$Bu (1.2 mmol), DMSO, 100 °C, 10 h, $N_2$(g) | 86-97%[b,c] | 94 |
| 14 | Lignin-derived Zn single atom catalyst co-doped with nitrogen and carbon. (LCN@Zn-SAC) (1.5mol %) | Ketone **23** (0.250 mmol), alcohol **21** (0.375 mmol), LCN@Zn-SAC (10 mg, 1.5 mol-% Zn), KOH (30 mol %), toluene, 110 °C, 4 h, Ar. | 34-99%[a,c] | 85 |

[a]Yields determined by GC, [b]Yields of isolated products, [c]Under optimised conditions, [d]Yields determined by NMR

**Table 4**. Cross coupling reactions of secondary alcohols with primary alcohols to give dihydrochalcones



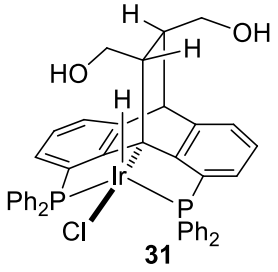
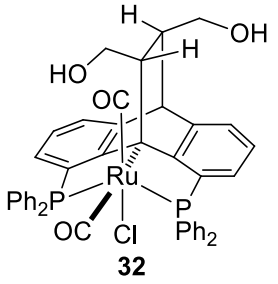
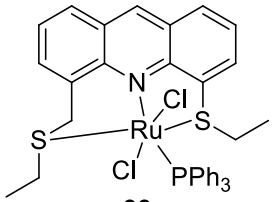
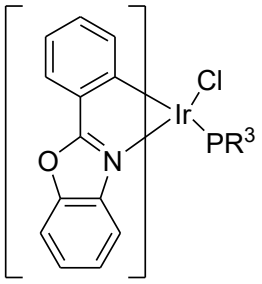
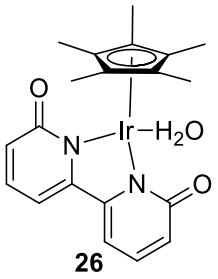
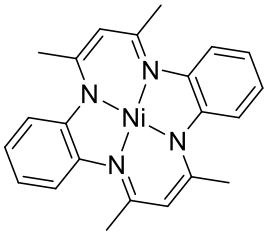
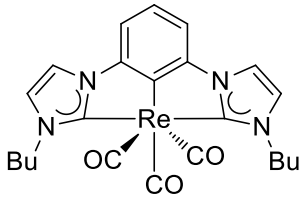

| Entry | Catalyst (loading) | Optimised Conditions | Yield [%] | Ref. |
|---|---|---|---|---|
| 1 |   **31** Catalyst **31** (1 mol %),   **32** Catalyst **32** (2 mol %) | 1 mol % of **31** or 2 mol % of **32**, $R^1OH/R^2OH/KOH$ = 1/1/1, xylene, 130 °C, molecular sieves, 12 h with catalyst **31** and 24 h with catalyst **32**. | 85-95% (using **31**)[a] 87-95% (using **32**)[a] | [87] |
| 2 |   **33** Catalyst **33** (0.5 mol %) | **30** (1 mmol), **21** (1 mmol) catalyst **33** (0.5 mol %), NaOH (25 mol %), 15 mL Ace, pressure tube, neat, 135 °C, 36 h. | 40-75%[b] | [88] |

**Table 4.** Continued

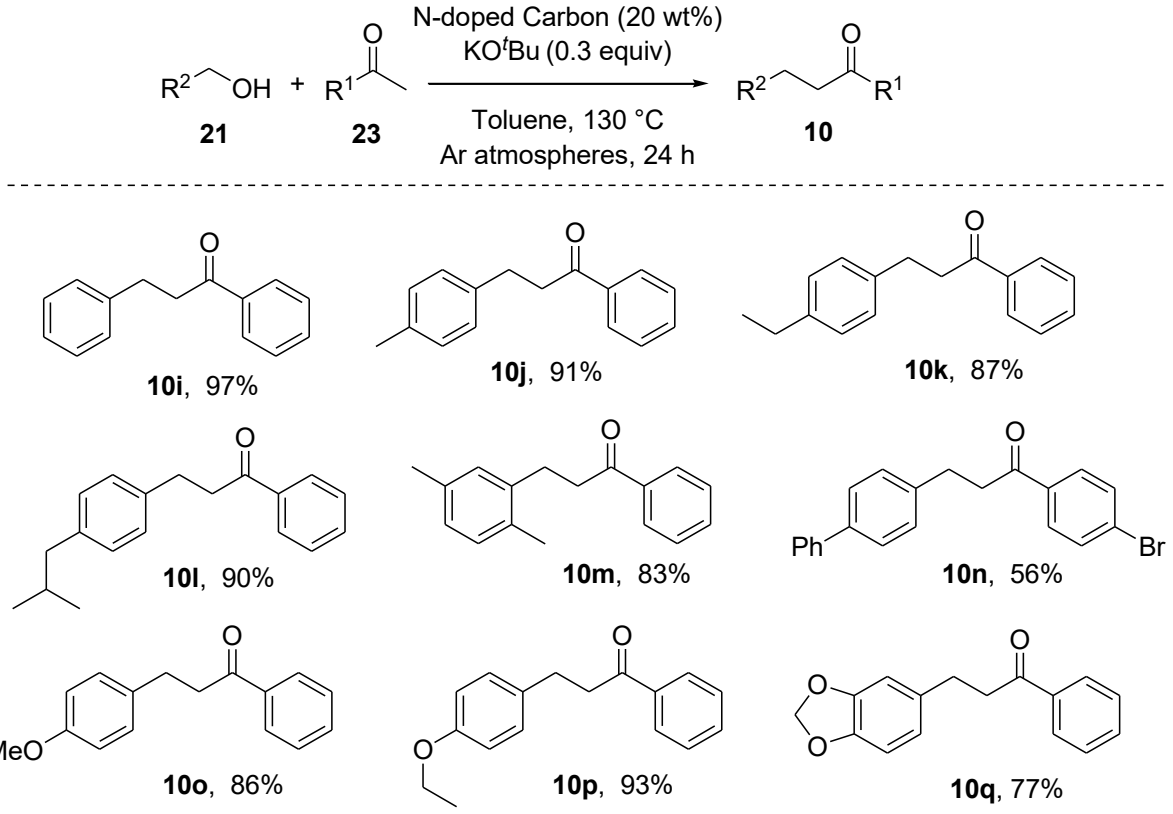
| Entry | Catalyst (loading) | Optimised Conditions | Yield [%] | Ref. |
|---|---|---|---|---|
| 3 |  <br>**25**: R = *n*-butyl<br>**25** Iridium catalyst (2 mol %) | **30** (1.0 mmol), **21** (1.1 mmol), **25** (2 mol %, 0.02 mmol), $AgNTf_2$ (2 mol %, 0.02 mmol), $Cs_2CO_3$ (1.1 mmol), toluene, 120 °C, 16 h. | 79-98%[a,b] | 90 |
| 4 |  <br>**26**<br>[Cp*Ir(2,2'-bpyO)($H_2O$)] (1 mol %) | **30** (1 mmol), **21** (1.1 mmol), **26** (1 mol %), $Cs_2CO_3$ (0.1 equiv), *tert*-amyl alcohol, reflux, 6 h, under air. | 80-90%[b,c] | 91 |
| 5 |  <br>**34**<br>Ni(II) complex [Ni(MeTAA)](1a) (3.0 mol %) | 1-phenylethanol **30** (1.0 mmol), benzyl alcohol **21** (1.3 mmol), KO$^t$Bu (1.0 mmol), **34** (3.0 mol %), xylene, 120 °C, 17 h, Ar. | 63%-91%[a,b] | 93 |
| 6 |  <br>**35**<br>Re catalyst (2 mol %) | **30** (0.25 mmol), **21** (0.30 mmol), 2 mol % Re catalyst **35** (0.0050 mmol), and 20 mol % $Cs_2CO_3$ (0.050 mmol) in /*t*-amyl alcohol (0.4 mL). | 99%[c,d]<br>63-91%[a,b] | 89 |

[a]Isolated yields, [b]Yields of dihydrochalcones under optimised conditions, [c] High yield obtained during optimisation of conditions, [d]Yield determined by $^1$H NMR

Apart from transition metal-catalysed α-alkylation reactions, transition metal-free reactions have been reported that facilitated alkylation of ketones with primary alcohols. Mohan and colleagues reported heterogeneous nitrogen-doped mesoporous carbon catalyst for the hydrogen borrowing reactions.[97] The

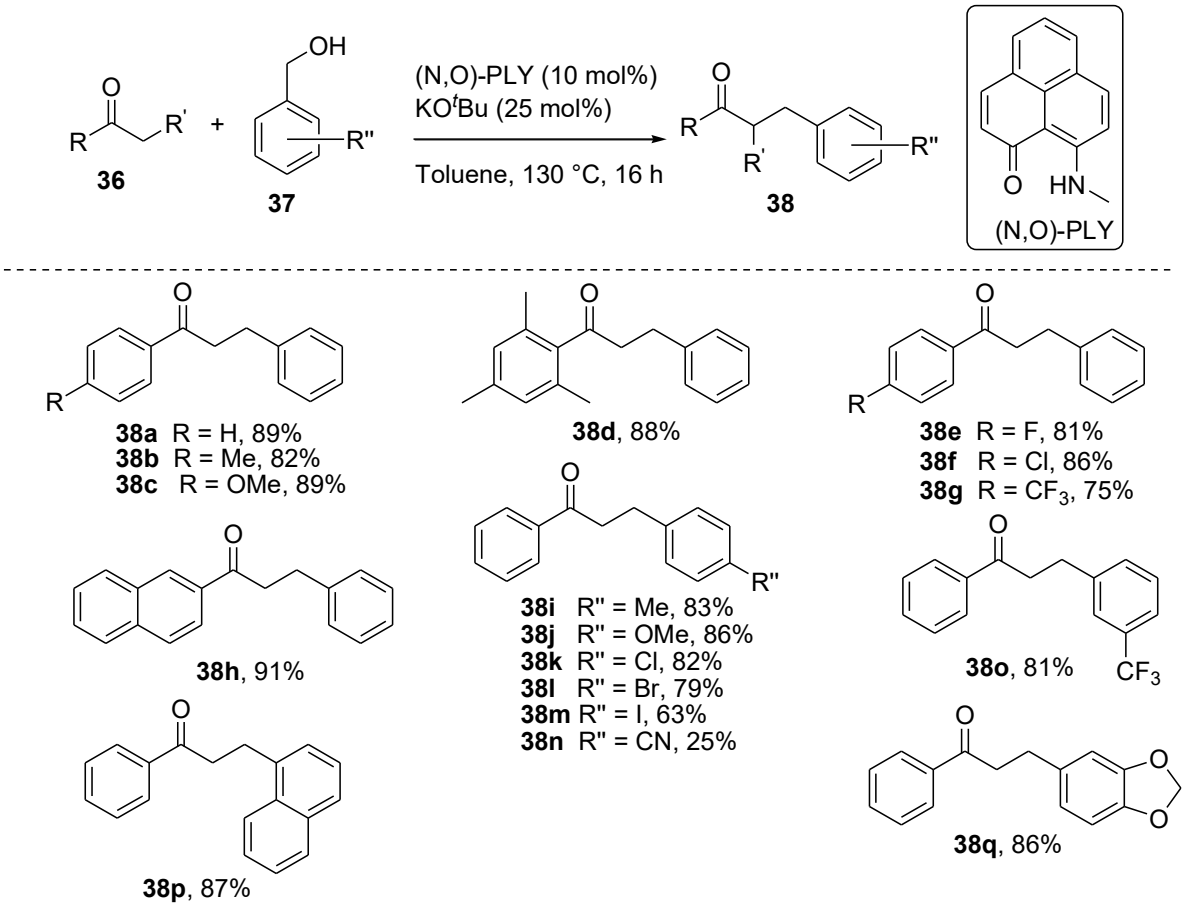
reaction was carried out for 1 h to 24 h in inert atmosphere in the presence of a base. The reaction was used to prepare various amines from benzyl alcohols and anilines, and also for the preparation of dihydrochalcones **10** from benzyl alcohols **21** and acetophenones **23**, Scheme 5. The dihydrochalcones were synthesised in high yields ranging from 77% to 97%, except for one derivative that was obtained in 56% yield.[97]




**Scheme 5**. Synthesis of dihydrochalcones using a heterogeneous nitrogen-doped mesoporous carbon catalyst.

Banik et al. employed the hydrogen borrowing strategy for the synthesis of α-alkylated ketones, including dihydrochalcones, using as a catalyst a phenalenyl-based molecule, 9-(methylamino)-1*H*-phenalen-1-one ((N,O)-PLY) (10 mol %) (Scheme 6).[98] The reaction was performed in toluene at 130 °C for 16 h using KO$^t$Bu (24 mol %) as a base. Under the conditions, differently substituted dihydrochalcones **38** were synthesised from acetophenones **36** and benzylalcohols **37** in 25-91% (Scheme 6). The conditions were also employed for the synthesis of quinolones and alkylated fluorenes.[98]



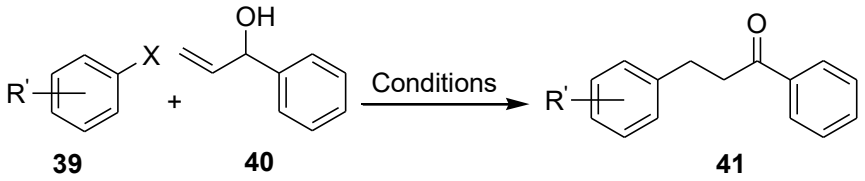

**Scheme 6**. Phenalenyl Catalysed ***α***- Alkylation of Ketone.

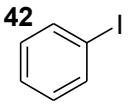
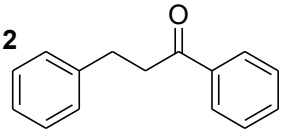
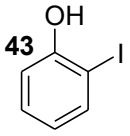
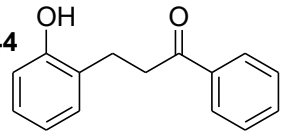
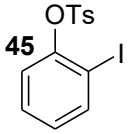
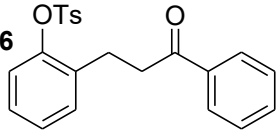
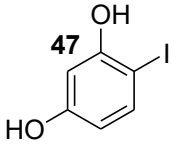
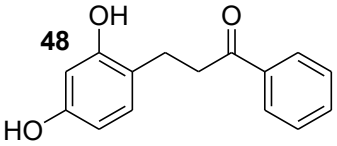
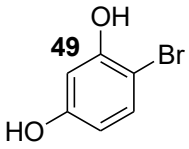
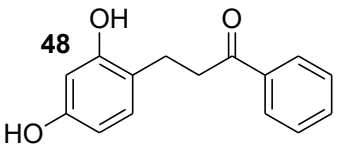
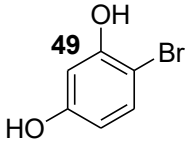
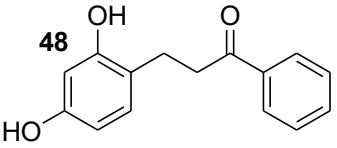
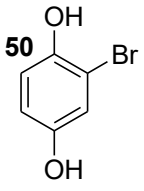
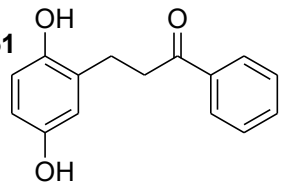
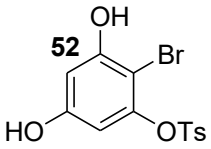
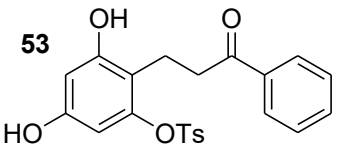
### 2.3. Heck Reaction

Based on the reports by Heck and Chalk,[99-101] who disclosed a Pd-catalysed arylation of but-3-en-2-ols with iodophenols to give benzylacetones, Briot and co-workers developed a Heck-type synthetic route for the preparation of dihydrochalcones.[40] Different conditions were explored that included the use of $Pd(OAc)_2$ with triethylamine ($Et_3N$) (method A), $Pd(OAc)_2$ with cesium carbonate (method B), and 3% Herrmann's catalyst **56** (Figure 2) with sodium acetate (method C).[40] The results are shown in Table 5 and Schemes 7-8. From Table 5 and Scheme 7, it is shown that aryl iodides **42**, **43** and **45** easily coupled with 1-phenyl-2-propen-1-ol **40** under conditions A and B to provide the dihydrochalcones **12**, **44** and **46**. However, reactions failed to work with the 2,4-dihydroxy-1-iodobenzene **47**, possessing the hydroxy group *para* to the iodine substituent, under both method A and method B conditions (Table 5, entry 4). Similarly, the bromoresorcinol **49** gave very low yields (10%) of the dihydrochalcone **48** under method B conditions (Table 5, entry 5) and improved yields (45%) of the dihydrochalcone **48** (Table 5, entries 6 and 7) were obtained using Herrmann's palladacycle **56** (method C). The exception was when coupling was performed on starting materials bearing phloroglucinol-type moiety (Table 5, entry 8, and Scheme 8), which gave low isolated yields of the dihydrochalcones **53** and **62**.

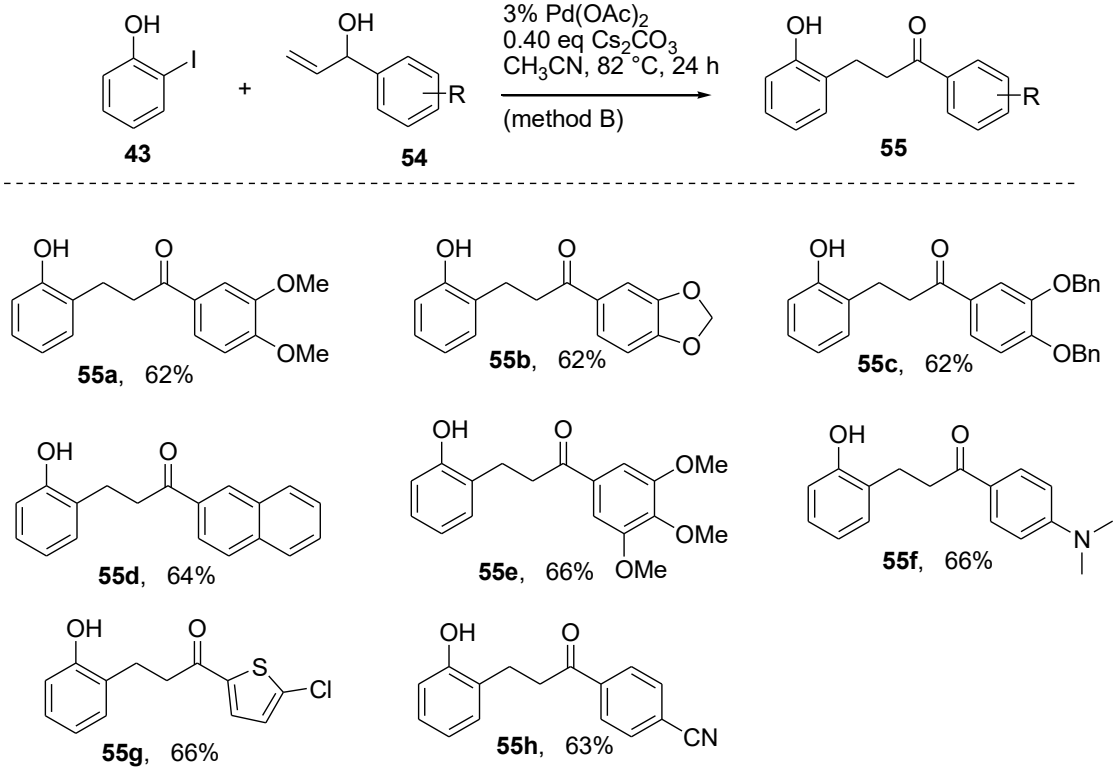
**Table 5.** Coupling of the 1-phenylprop-2-en-1-ol **40** with various aryl halides




| Entry | ArX | DHC | Yield (%)[a] | Conditions[b] |
|---|---|---|---|---|
| 1 |  |  | 74% | A |
| 2 |  |  | 61% | B |
| 3 |  |  | 70% | B |
| 4 |  |  | 0% | A,B |
| 5 |  |  | 10% | B |
| 6 |  |  | 45% | C |
| 7 |  |  | 45% | C |
| 8 |  |  | 12% | C |

[a]Isolated yields. [b] Coupling conditions: (method A) 1% $Pd(OAc)_2$,1.25 equiv of $NEt_3$, $CH_3CN$ reflux, 24 h; (method B) 3% $Pd(OAc)_2$, 0.40 equiv of $Cs_2CO_3$, $CH_3CN$, reflux, 24 h; (method C) 3% Herrmann's catalyst **56**, 2.00 equiv of AcONa, $CH_3CN/DMF/H_2O$, 140 °C, 24 h.




**Scheme 7**. Synthesis of substituted dihydrochalcones using coupling conditions B.

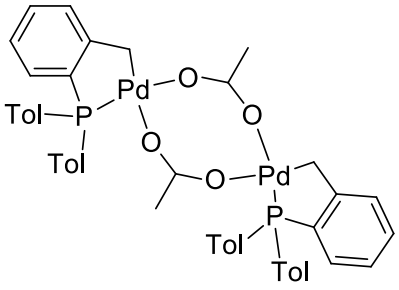
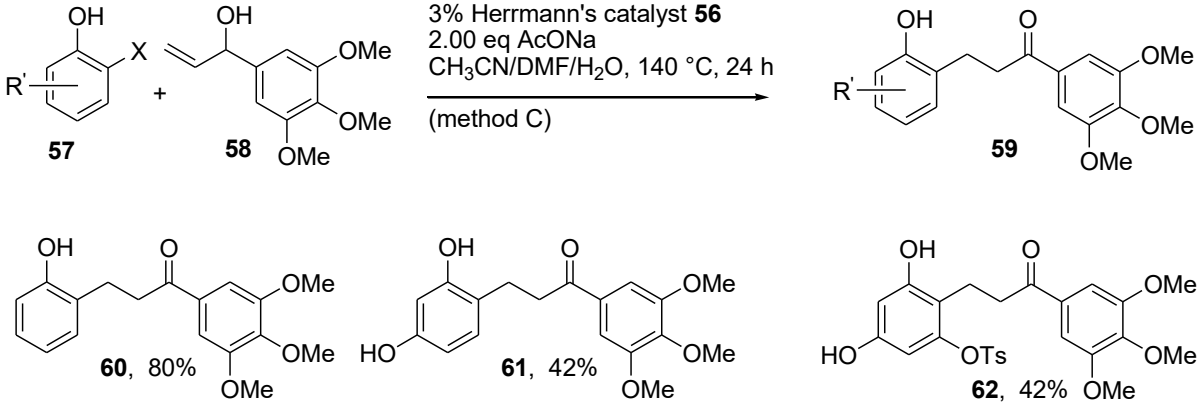



**Figure 2**. Herrmann's catalyst **56.**

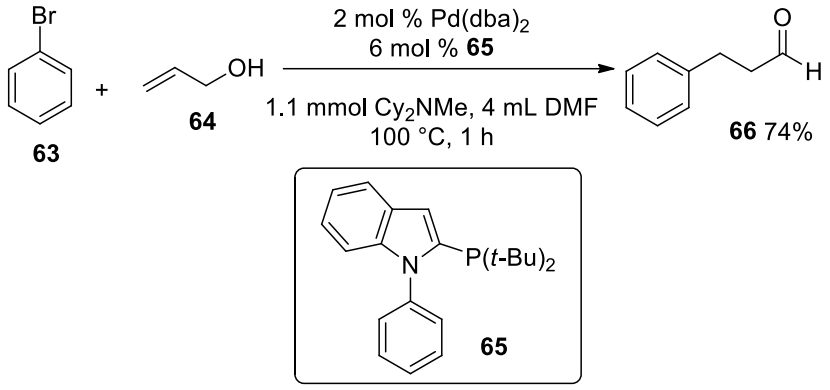



**Scheme 8**. Synthesis of substituted dihydrochalcones using coupling conditions C.

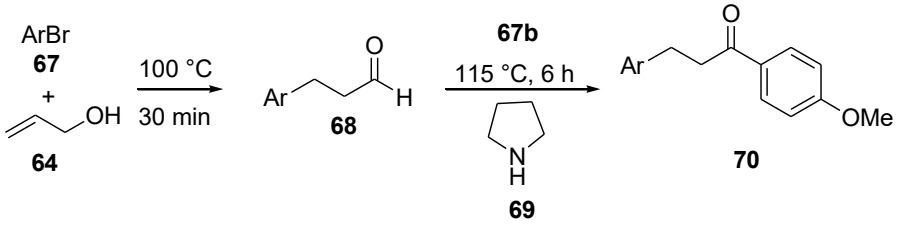
In another study, Suchand and colleagues synthesised dihydrochalcones and diarylbutanones under the conditions like those in Method A ($Pd(OAc)_2$ (3 mol %) and $Et_3N$ (2 equiv) in hot acetonitrile). The synthesised ketones were used as precursors for the preparation of flavans and benzoxepines.[41]

Colbon and co-workers reported a one-pot, two-step protocol that involved Heck coupling of allyl alcohols with aryl halides and subsequent acylation of the resulting aldehydes with aryl halide to afford dihydrochalcones.[102] They first established the conditions for the synthesis of phenylpropanal **66** from bromobenzene **63** and allyl acohol **64**. The optimum conditions, which gave phenylpropanal **66** in 74% yield involved the use of $Pd(dba)_2$ (2 mol %) with the ligand **65** (6 mol %) and $Cy_2NMe$ in DMF at 100 °C (Scheme 9). Differently substituted dihydrochalcones **70** were obtained under optimised conditions as shown in Table 6 in 43% to 66% yields.[101]




**Scheme 9**. Synthesis of phenylpropanal from bromobenzene and allyl alcohol.

**Table 6**. One-pot arylation, isomerisation, and acylation reaction[a]



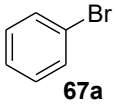
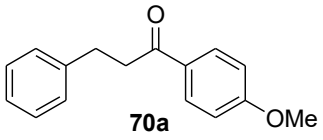
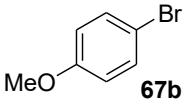
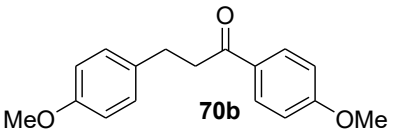
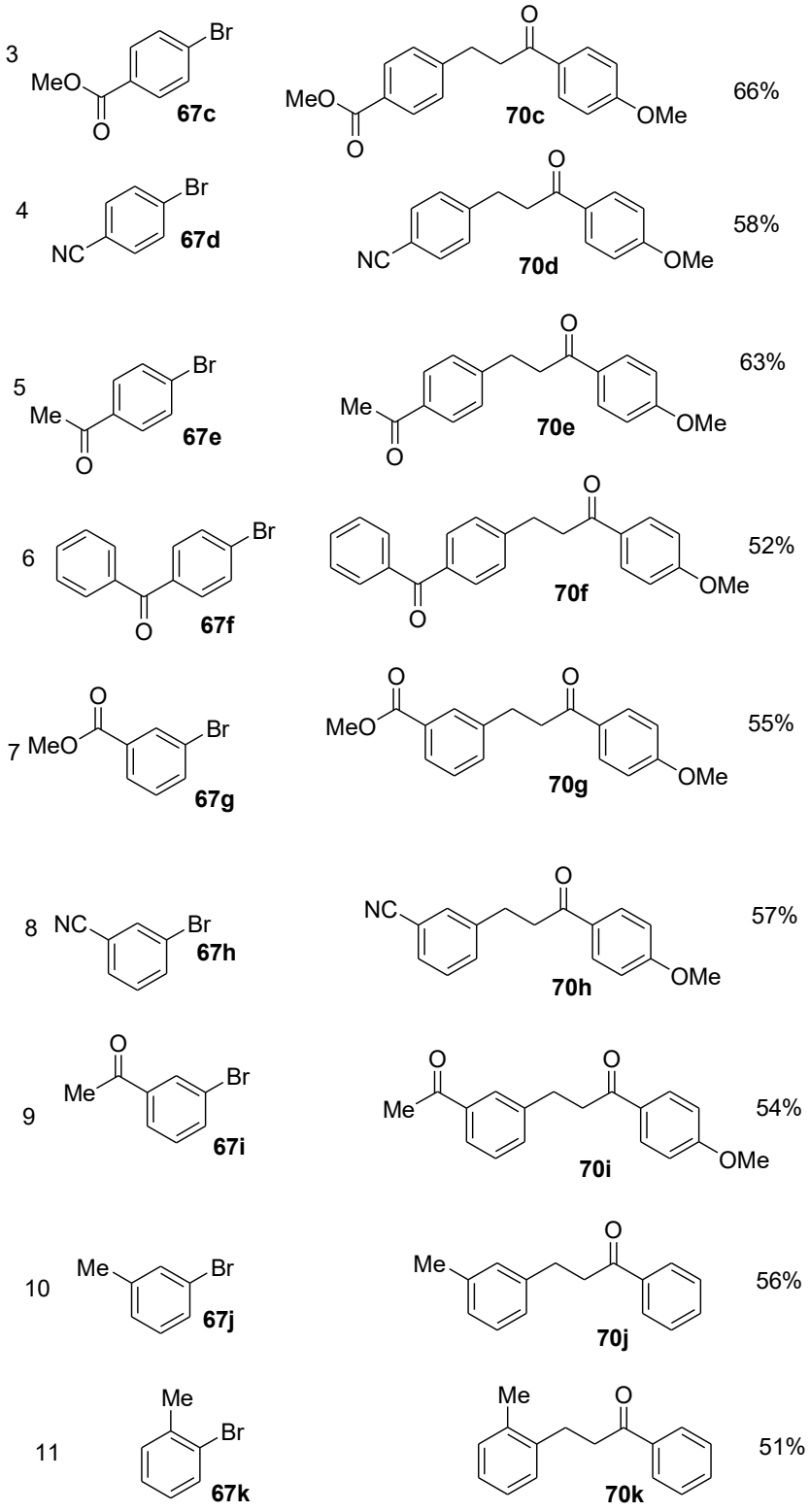

| Entry | ArBr | Product | Yield (%)[b] |
|---|---|---|---|
| 1 |  **67a** |  **70a** | 64% |
| 2 |  **67b** |  **70b** | 43% |

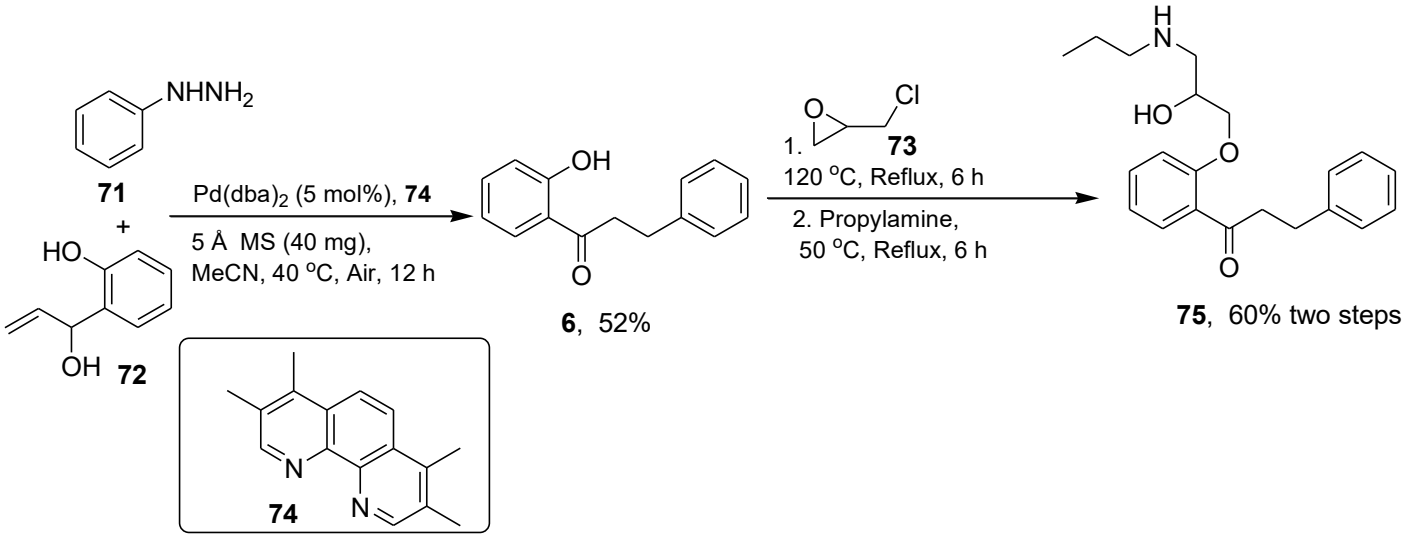
**Table 6.** Continued




[a]Reactions were carried out with arylbromides (2.0 mmol), allylic alcohol (2.0 mmol), $Cy_2NMe$ (2.0 mmol), $K_2CO_3$ (1.0 mmol), 4 Å MS (1 g), $Pd(dba)_2$ (0.02 mmol), and **65** (0.06 mmol) in 4 mL of DMF at 100 °C for 30 min, followed by addition of **67b** (1.0 mmol) and pyrrolidine (1.0 mmol) at 115 °C for 6 h. [b]Isolated yields based on **67b**.

Wang and co-workers reported a modified Heck coupling reaction of arylhydrazines with allyl alcohols to provide dihydrochalcones and other aryl ketones. The reaction proceeded via C-N bond cleavage and could be conducted under air.[42] The reaction released nitrogen and water as by-products. Various conditions were explored for the coupling. Better yields were attained when $Pd(dba)_2$ was used as a catalyst in the presence of **74**, 5 Å molecular sieves and acetonitrile as a solvent.[42] The reaction was extended to the synthesis of various phenethyl ketones and was further applied to the synthesis of a dihydrochalcone propafenone **75**, which is an antiarrhythmic drug. The synthesis of **75** commenced by the preparation of the precursor **6** by the developed palladium-catalysed arylative Heck reaction, followed by alkylation with 2-(chloromethyl)oxirane (**73**) and the reaction of the resulting epoxide with propylamine (Scheme 10).[42]

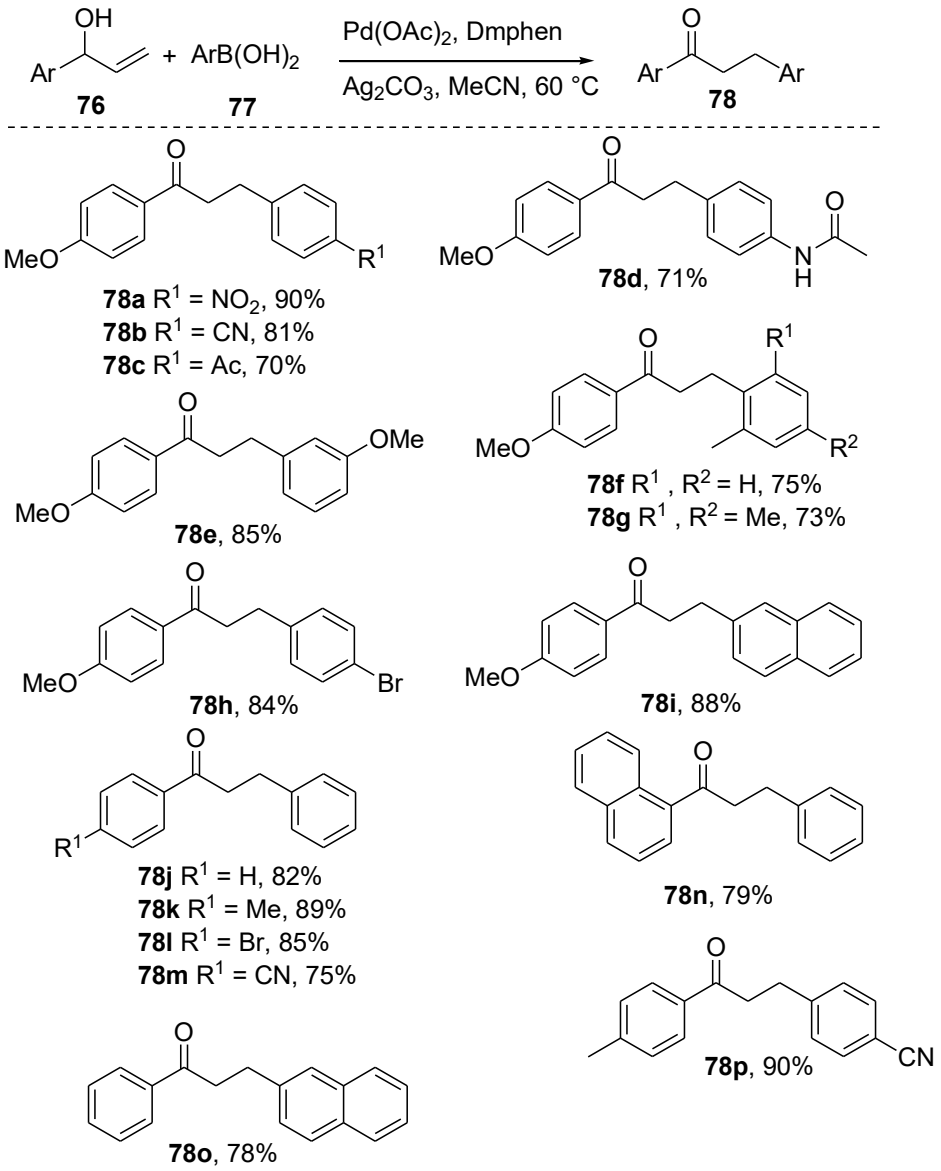



**Scheme 10**. Synthesis of propafenone **75**.

### 2.4. Using boronate esters and boronic acids

Boronic acids and other borate reagents have been utilised to synthesise dihydrochalcones under different conditions.[44-47, 103-105] Vellakkaran and colleagues developed a method for the synthesis of dihydrochalcones and other compounds by the reaction of allyl alcohols with boronic acids catalysed by Pd(II).[44] The optimum conditions involved the use of $Pd(OAc)_2$ with the ligand 2,9-dimethyl-1,10-phenanthroline (dmphen) and oxidant $Ag_2CO_3$ in MeCN at 60 °C. Under optimised conditions, differently-substituted dihydrochalcones **78** were synthesised from allyl alcohols **76** and boronic acids **77** in 71% to 90% yields (Scheme 11).[44] In their follow up study, they used oxygen as oxidant, instead of silver-based reagent to facilitate the reaction between allyl alcohols and boronic acids.[45]

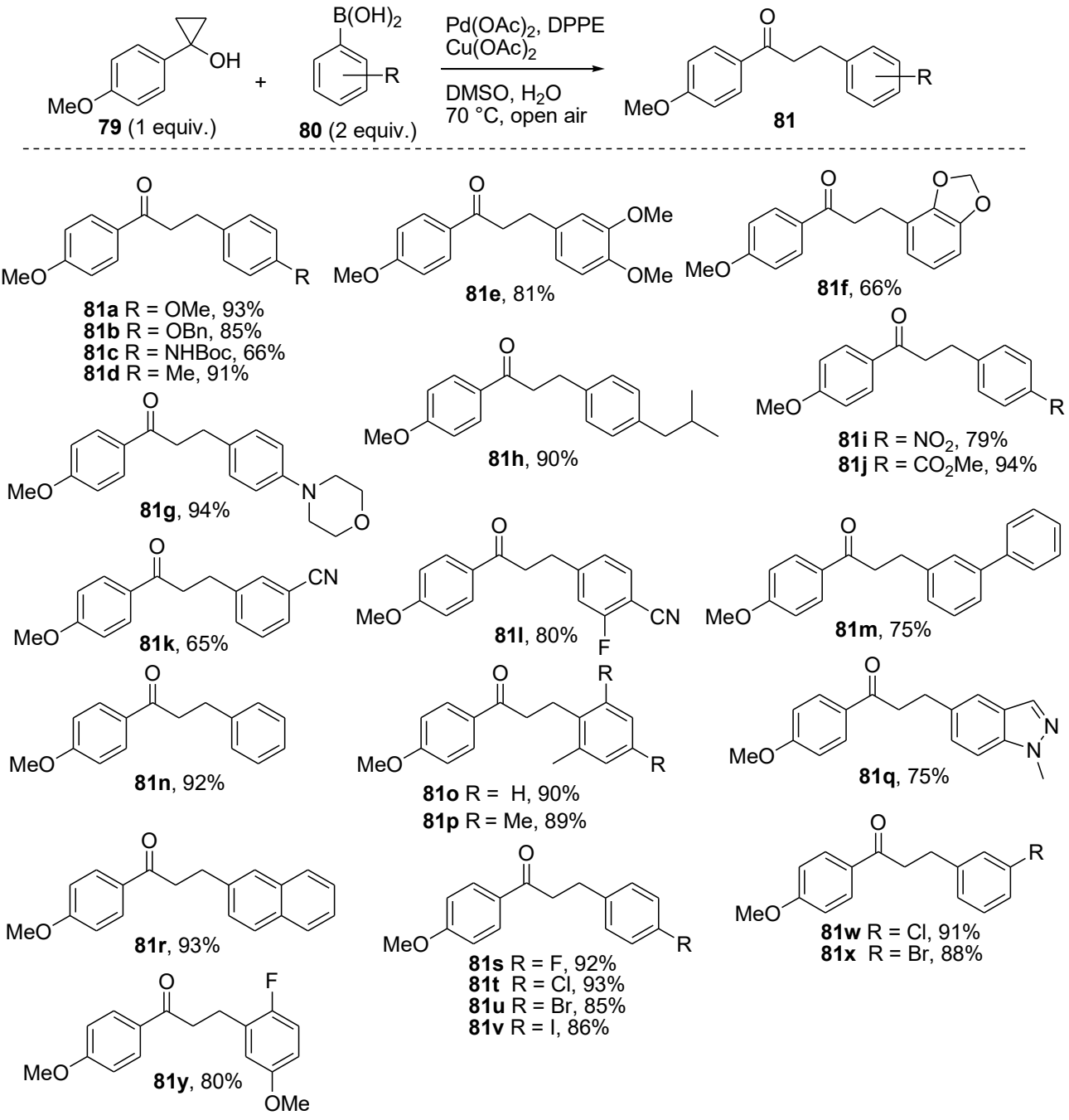
 




**Scheme 11**. Synthesis of dihydrochalcones from allyl alcohols and boronic acids.

Ramar and colleagues investigated the reaction of cyclopropanols with boronic acids to render β-arylated ketones, especially dihydrochalcones.[46] The optimised conditions included the use of cyclopropanols (1 equiv) with boronic acids (2 equiv), catalysed by $Pd(OAc)_2$ in the presence of $Cu(OAc)_2$ (2 equiv) and bis(diphenylphosphino)ethane (DPPE) (0.2 equiv) in DMSO−$H_2O$ (5:1 ratio) under the open-air atmosphere at 70 ℃. The substrate scope was evaluated using cyclopropanol **79** and differently substituted boronic acids **80** (Scheme 12). These experiments afforded dihydrochalcones **81** in 65-94% yields. Other β-arylated compounds were also synthesised.[46]

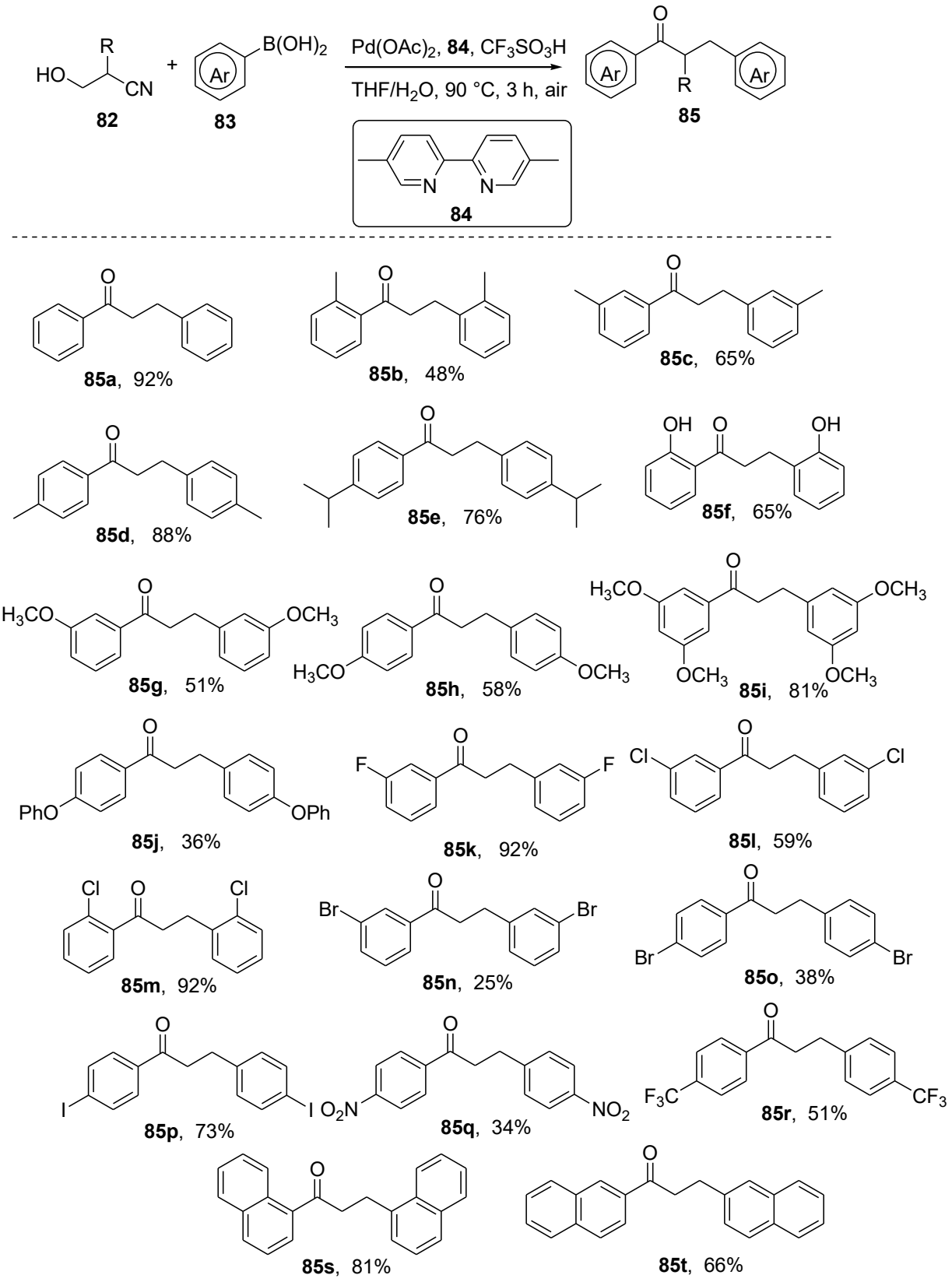
 




**Scheme 12**. Synthesis of dihydrochalcones from cyclopropanol and boronic acids.

Zheng et al. reported the synthesis of dihydrochalcones by 1,3-diarylation of 3-hydroxypropionitrile **82** with boronic acids **83**.[47] The optimum conditions involved conducting the reaction with $Pd(OAc)_2$ (5 mol %), ligand **84** (10 mol %) and $CF_3SO_3H$ (10 equiv) in $THF/H_2O$ (2:1 mL) and air at 90 °C. Under the conditions, homodiarylated products **85** were obtained in 25-92% yields (Scheme 13). The reaction tolerated halogenated substrates; however, their products were prepared in lower yields. Slight modification of the reaction conditions enabled the synthesis of dihydrochalcones from two differently substituted boronic acids **87** and **88** (Scheme 14). The heterodiarylated products **89** were synthesised in yields ranging from 23% to 80%.[47]

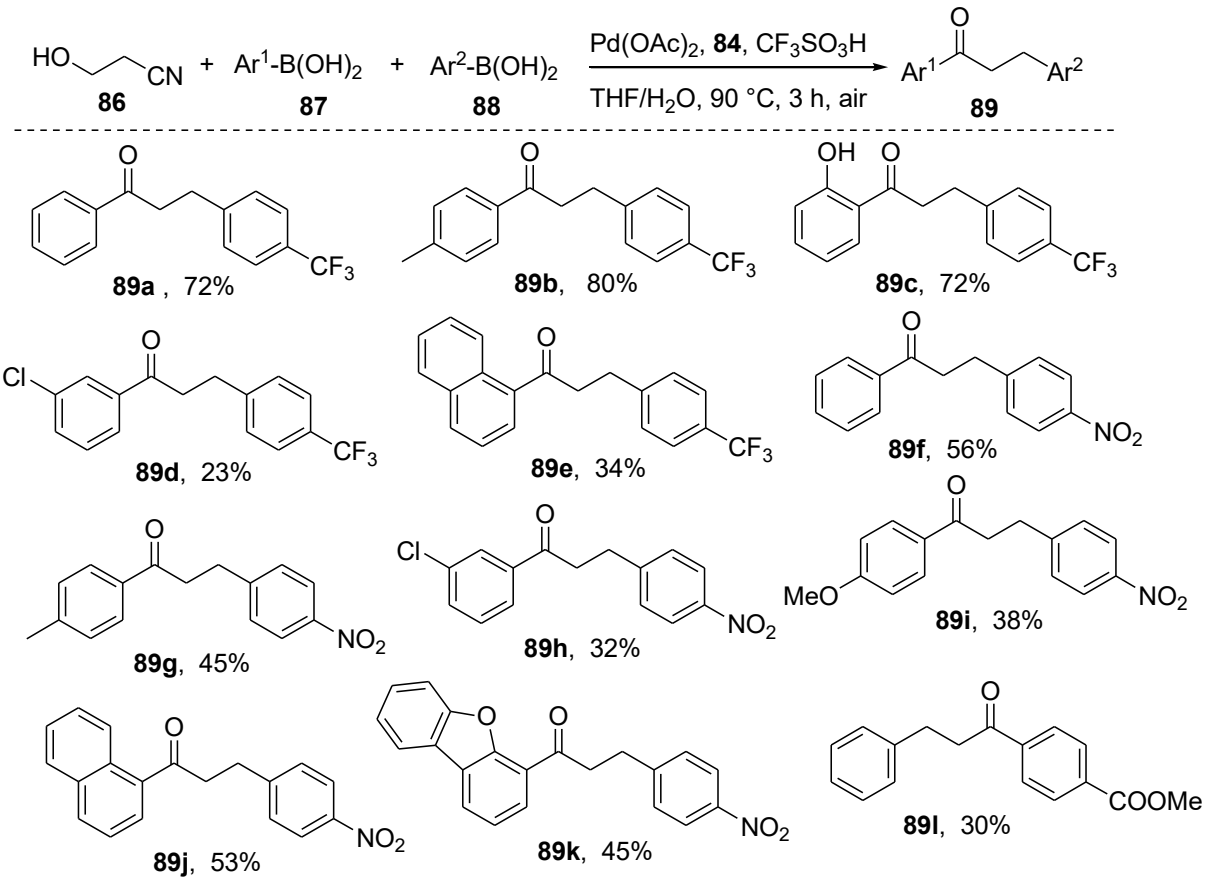
 




[a]Reaction conditions: **82** (0.3 mmol), **83** (4 equiv), $Pd(OAc)_2$ (5 mol %), **84** (10 mol %), $CF_3SO_3H$ (10 equiv), $THF/H_2O$ (2:1 mL), 90 °C, air, 3 h, the isolated yields of **85**.

**Scheme 13**. Synthesis of dihydrochalcones from 3-hydroxypropionitrile and boronic acids.[a]



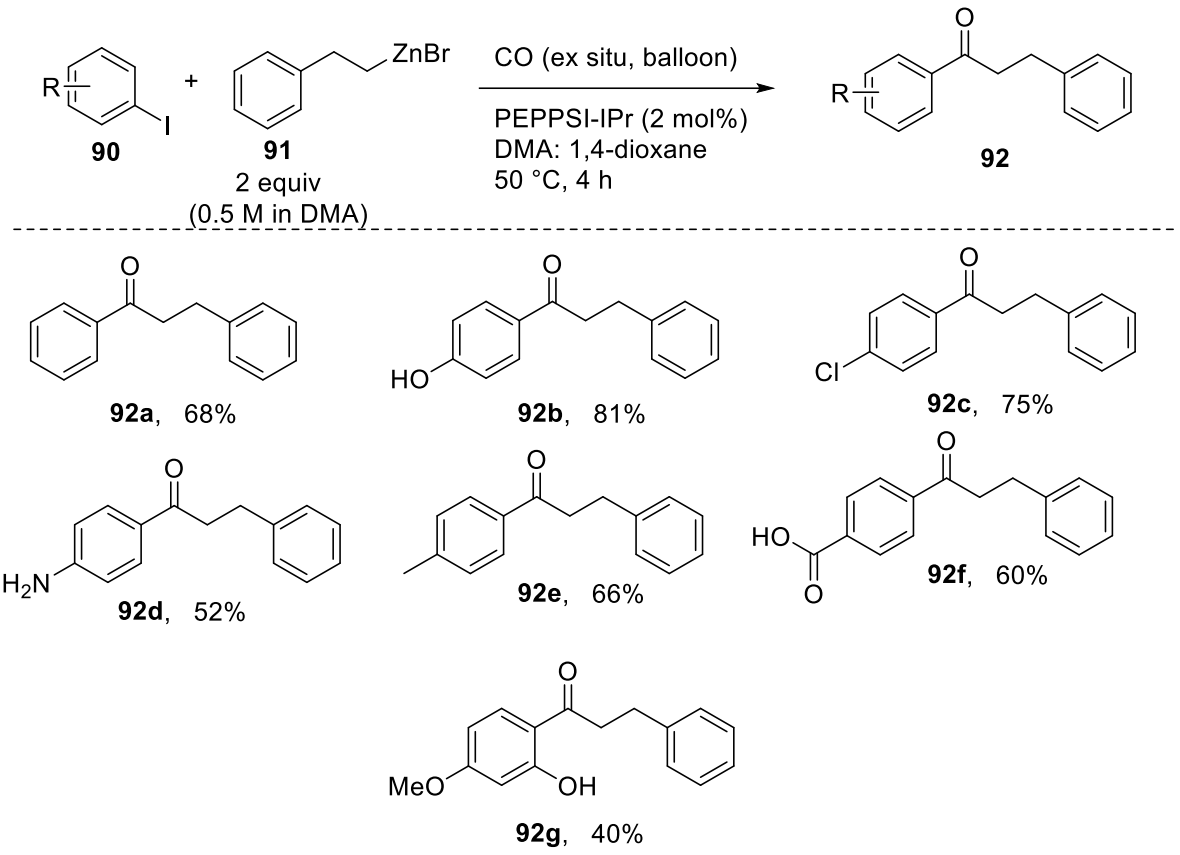

[a]Reaction conditions: **86** (0.3 mmol), $Ar^1B(OH)_2$ (0.6 mmol), $Ar^2B(OH)_2$ (1.8 mmol), $Pd(OAc)_2$ (5 mol %), **84** (10 mol %), $CF_3SO_3H$ (10 equiv), THF/$H_2O$ (2:1 mL), 90 °C, air, 3 h, the isolated yields of **89**.

**Scheme 14**. Synthesis of dihydrochalcones from 3-hydroxypropionitrile and differently substituted boronic acids. [a]

### 2.5. Other transition metal-catalysed coupling reactions

**2.5.1. Negishi coupling.** Kalinin and Ulven prepared dihydrochalcones **92** by carbonylative Negishi coupling reaction involving aryl iodides **90** with organozinc reagent **91** and CO at atmospheric pressure (Scheme 16).[39] The reactions were conducted in the presence of commercial palladium precatalyst [1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene](3-chloropyridyl)palladium(II) dichloride (PEPPSI-IPr), which was identified as the best performing catalyst for the transformation in DMA and dioxane at 50 °C. Under these conditions, dihydrochalcones **92** were prepared in 40-81% yields (Scheme 15).[39]

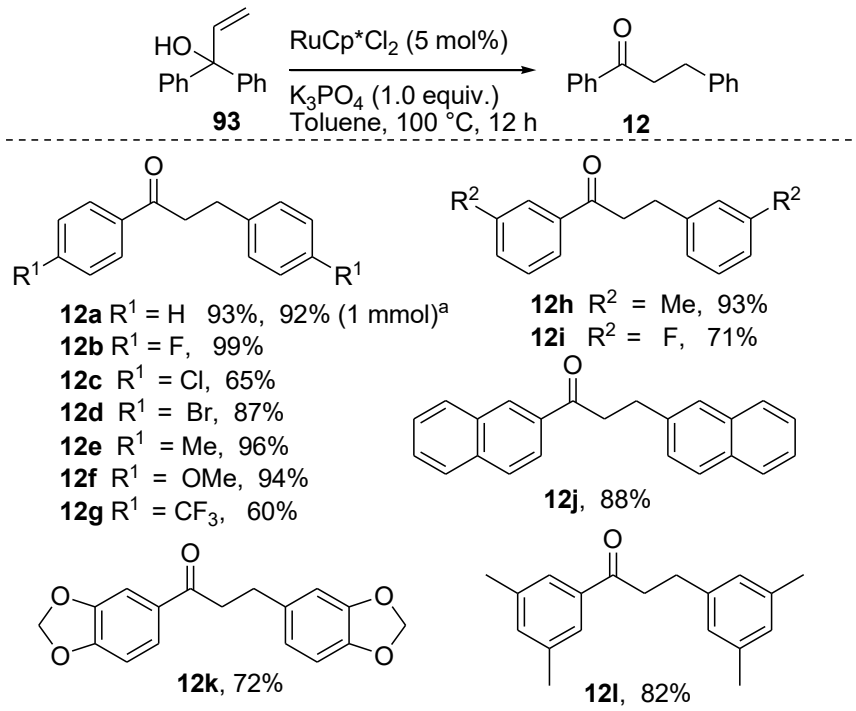
 




**Scheme 15**. Synthesis of dihydrochalcones by carbonylative Negishi coupling reaction.

**2.5.2. Ruthenium-catalysed aryl migration.** Luo et al. reported a ruthenium-catalysed 1,3-aryl migration of allylic alcohols to furnish dihydrochalcones (Scheme 16).[43] After screening different conditions, they identified that the aryl isomerisation was efficiently facilitated by $RuCp^*Cl_2$ (5 mol %) and $K_3PO_4$ (1.0 equiv) base in toluene at 100 $^oC$. Using the conditions, allyl alcohols **93** were successfully transformed into 1,3-diaryl ketones **12** in 60% to 99% yields, Scheme 16. The reaction was further extended to unsymmetrical allylic alcohols. This gave a mixture of the 1,3-aryl migrated regioisomers. It was established that substituted aryl groups were more prone to the migration than the unsubstituted phenyl group, with one exception being the diaryl allyl bearing *p*-$CF_3C_6H_4$ aryl group.[43]



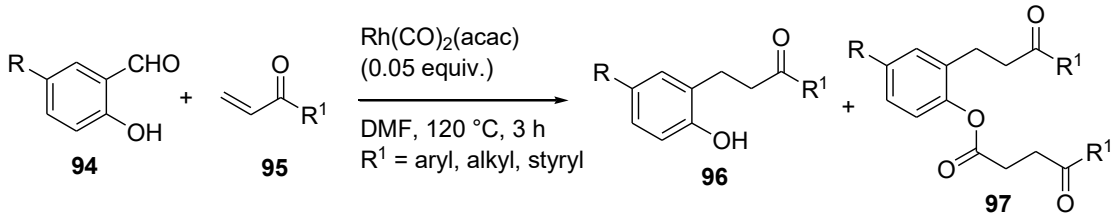

Reaction conditions: **93** (0.1 mmol), RuCp*Cl2 (5 mol %), $K_3PO_4$ (1.0 equiv), toluene (0.5 mL) at 100 °C (oil bath) for 12 h. The yields are isolated yields. [a]The reaction was carried out on a 1 mmol scale.

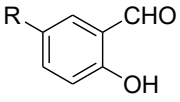
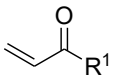
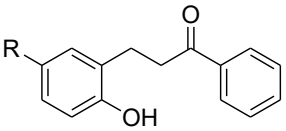
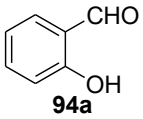
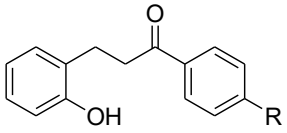
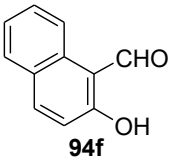
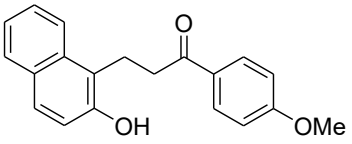
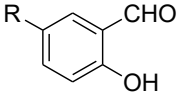
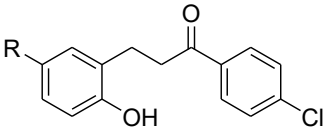
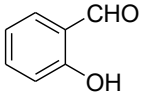
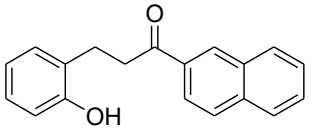
**Scheme 16**. Ruthenium-catalysed 1,3-aryl migration of allylic alcohols to furnish dihydrochalcones.

**2.5.3. Rhodium-catalysed decarbonylative addition.** Rao and Ramakrishna reported a protocol for the synthesis of *o*-hydroxydihydrochalcones from salicylaldehydes and vinyl ketones based on rhodium-catalysed decarbonylative addition.[48] Optimised conditions involved the use of $Rh(CO)_2(acac)$ (0.05 equiv) in DMF at 120 $^oC$ for 3 h. Under these conditions, various salicylaldehydes **94** underwent decarbonylative addition with vinyl ketones **95** to give 2'-hydroxydihydrochalcones **96** together with minor by-products **97** (Table 7). The dihydrochalcones were prepared in 48% to 68% yields. The reaction was also used for the synthesis of the natural dihydrochalcones, taccabulines A-E.[48]

**Table 7**. The reaction of salicylaldehydes with vinyl ketones under rhodium-catalysis[a]



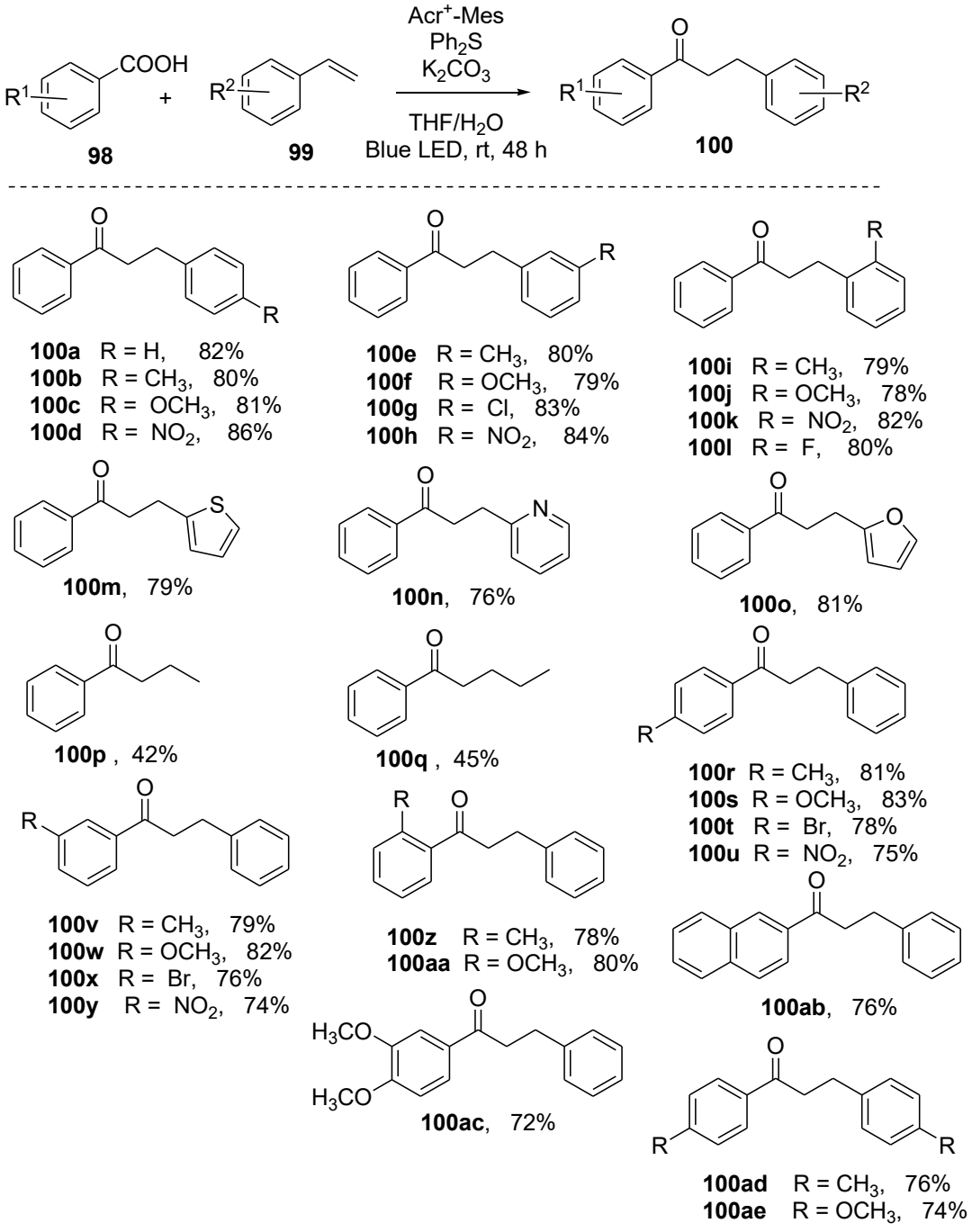

| Entry | Salicylaldehyde | Vinyl Ketone | Product **96** | Product **97** |
|---|---|---|---|---|
| |  |  |  | |
| 1 | **94a** R = H | **95a** R1 = phenyl | **96a** R = H, 61% | **97a**, 21% |
| 2 | **94b** R = Me | | **96b** R = Me, 52% | **97b**, 24% |
| 3 | **94c** R = F | | **96c** R = F, 59% | – |
| 4 | **94d** R = Br | | **96d** R = Br, 54% | – |
| 5 | **94e** R = Ac | | **96e** R = Ac, 54% | – |
| |  **94a** | |  | |
| 6 | | **95b** R1 = *p*-tolyl | **96f** R = Me, 60% | **97f**, 10% |
| 7 | | **95c** R1 = *p*-anisyl | **96g** R = OMe, 62% | **97g**, 14% |
| 8 |  **94f** | **95c** R1 = *p*-anisyl |  **96h**, 68% | – |
| |  | |  | |
| 9 | **94a** R = H | **95d** R1 = *p*-Clphenyl | **96i** R = H, 54% | **96i**, 15% |
| 10 | **94b** R = Me | | **96j** R = Me, 48% | **96j**, 17% |
| 11 | **94c** R = F | | **96k** R = F, 54% | **96k,** 13% |
| |  | |  | |
| 12 | **94a** | **95e** R1 = *B*-naphthyl | **96l**, 57% | – |

[a] Conditions: **94a**–**94f** (0.5 mmol, 1 equiv.), **95a**–**95e** (1 mmol, 2 equiv.), $Rh(CO)_2(acac)$ (0.025 mmol, 0.05 equiv.), DMF (2 mL), 120 °C, 3 h.

### 2.6. Light-catalysed reactions

A method was developed for the synthesis of dihydrochalcones **100** by photocatalytic reaction of benzoic acids **98** with styrenes **99** (Scheme 17).[106] The optimal conditions involved the use of $Ph_2S$ as the additive, which facilitated deoxygenation to afford acyl radicals, Mes−Acr−$MeClO_4$ (5 mol %) as the photocatalyst, $K_2CO_3$ as the base and irradiation with the 10 W blue LED light in THF/$H_2O$ (4:1) with continuous stirring at room temperature for 48 h. Under these conditions, differently substituted dihydrochalcones were obtained in 72% to 82% yields. Other ketones were also synthesised.[106]

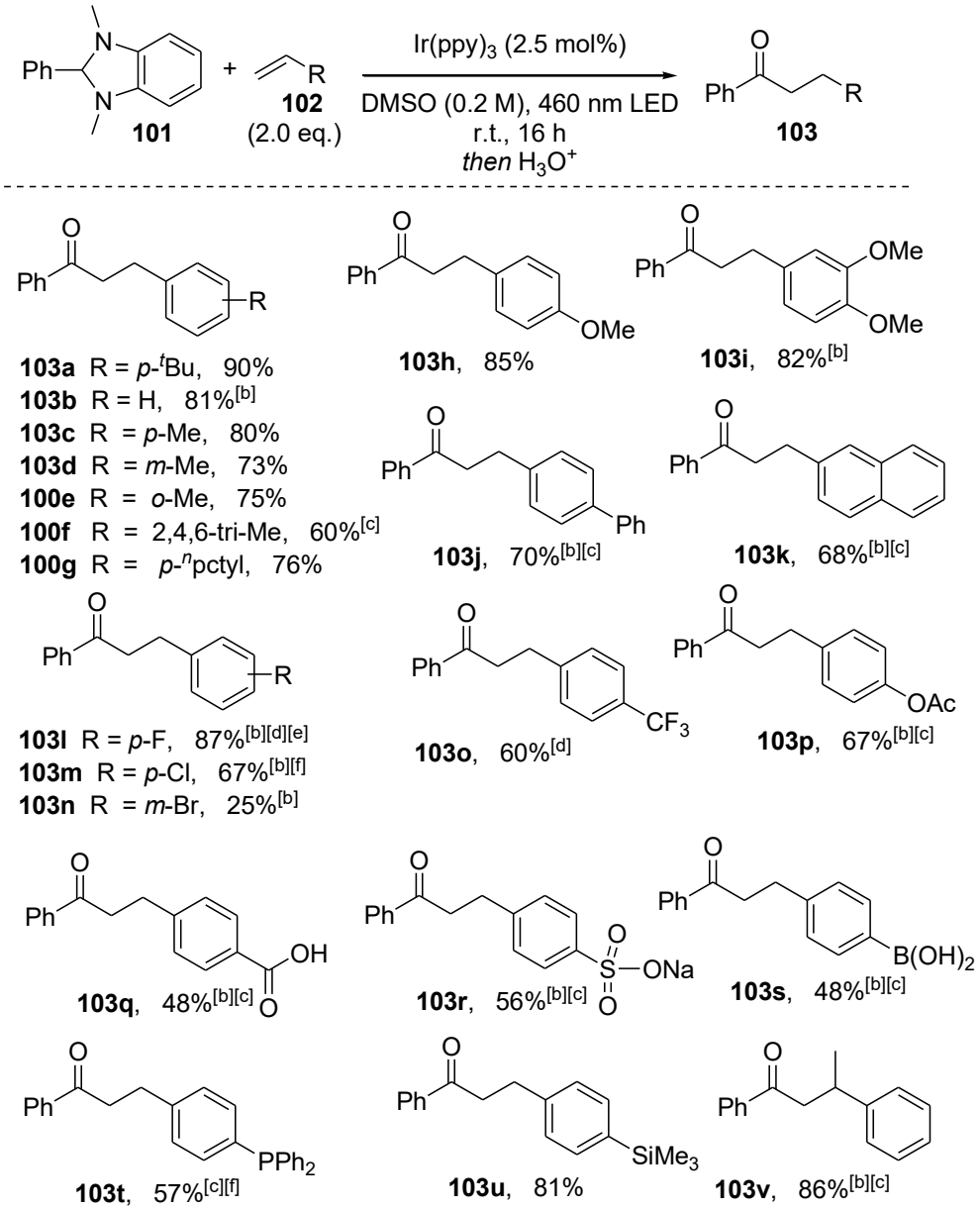
 




**Scheme 17**. Synthesis of dihydrochalcones by light-catalysed reaction of benzoic acids and styrenes.

Saga and colleagues synthesised dihydrochalcones **103** from visible light-catalysed reactions of benzimidazolines **101** and unactivated alkenes **102**, Scheme 18.[107] The benzimidazolines acted as sources of acyl radicals. The reaction was conducted in the presence of a photocatalyst $Ir(ppy)_3$ (2.5%) in DMSO and was irradiated with 460 nm LED light. The substrate scope of the reaction was evaluated using electron-rich and electron-neutral styrenes **102** and also with differently substituted benzimidazolines **101**. The dihydrochalcone products **103** were obtained in yields ranging from 23%-93% (Scheme 21). Most derivatives were obtained in higher yields, lower yields were obtained for a few derivatives.[107]

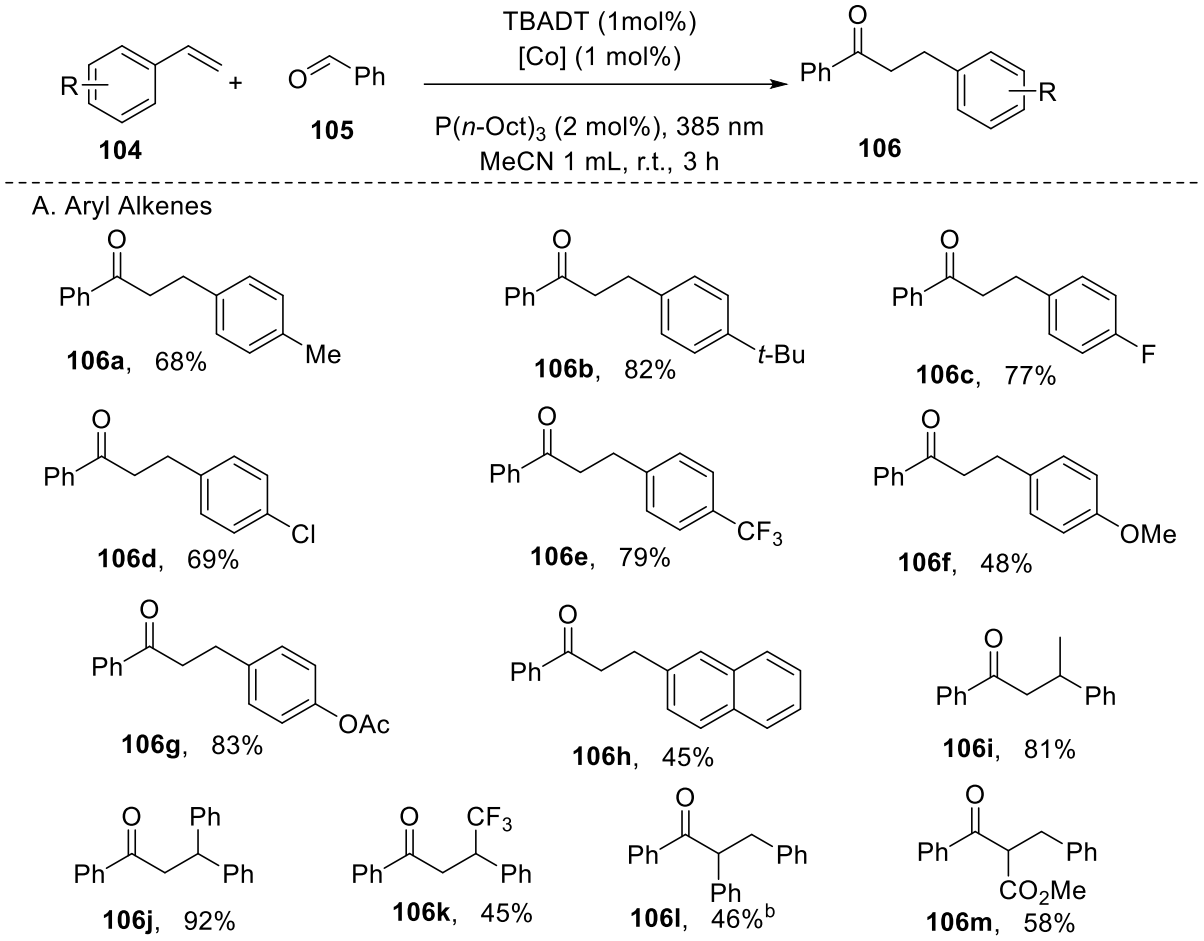



[a]Conditions: **101** (0.10 mmol), alkenes (0.20 mmol), Ir(ppy)$_3$ (2.5 mol %), DMSO (0.5 mL), 460 nm LED, rt, 16 h. Isolated yields are shown. [b]Reaction was run for 40 h. [c]5.0 equiv of alkene was used. [d]10.0 equiv of alkene was used. [e]Ir(4-*t*Bu-ppy)$_3$ was used as the photoredox catalyst. [f]Reaction was performed for 63 h.

**Scheme 18**. Synthesis of dihydrochalcones by visible light-catalysed reactions of benzimidazolines and unactivated alkenes.

Ji et al. conducted photocatalysed reactions of styrenes with aldehydes to afford dihydrochalcones and other ketone derivatives.[108] Their best conditions involved the use of cocatalysts *tetra*-*n*-butylammonium decatungstate (TBADT) and $Co_2(CO)_8$. The optimal performing ligand was trioctylphosphine (P(*n*-Oct)$_3$). The reaction was conducted in acetonitrile and was irradiated with 385 nm LED. Using optimal conditions, the reactions of differently substituted styrenes **104** and aldehydes **105** were evaluated. These gave the corresponding ketones, particularly dihydrochalcones **106** in yields of 45% to 92% (Schemes 19 and 20).[108]

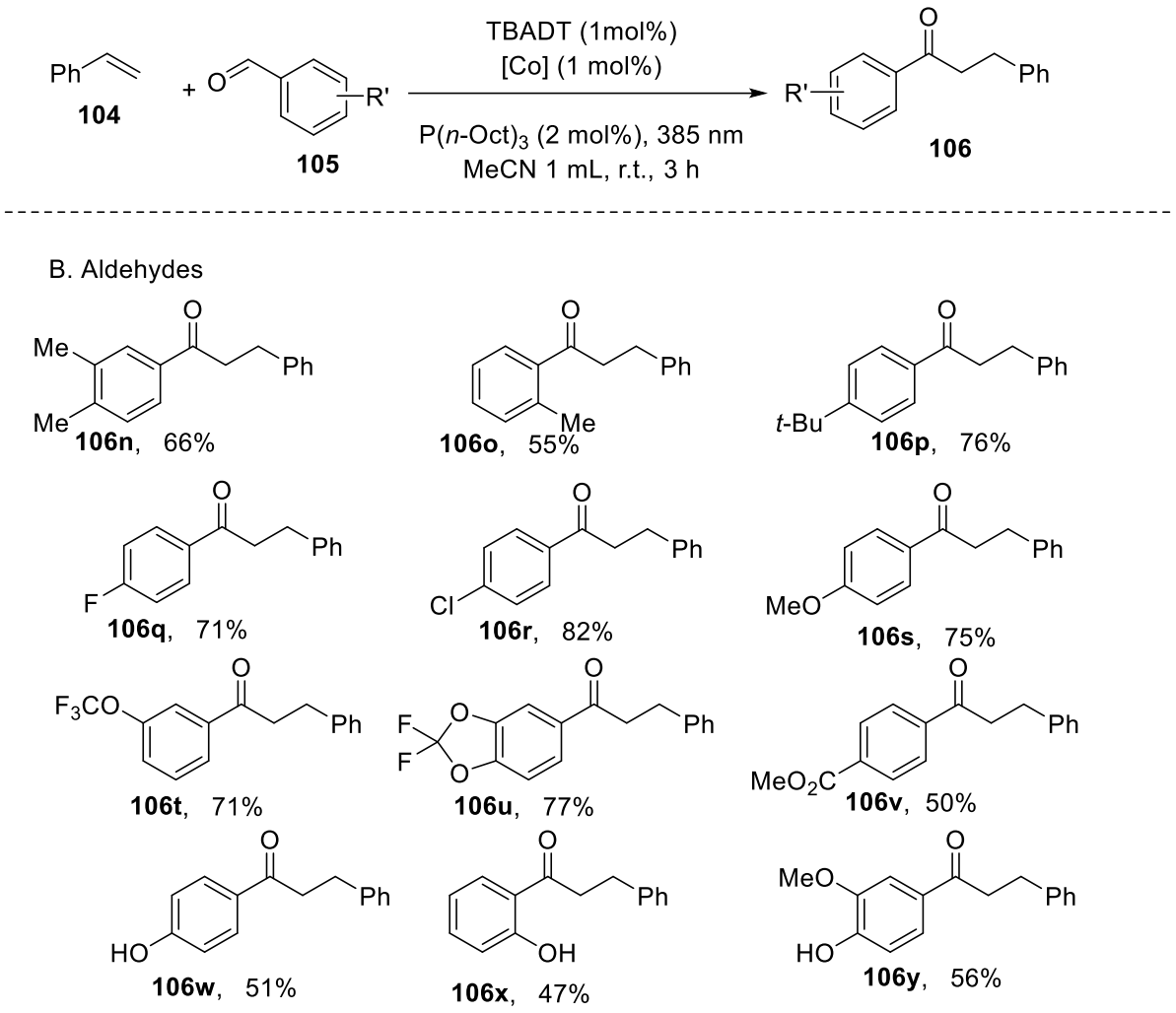
 




[a]Aryl alkene (**104**, 0.38 mmol), aldehyde (**105**, 0.25 mmol), TBADT (2 mol %), $Co_2CO_8$ (0.5 mol %), P(*n*-Oct)$_3$ (2 mol %), acetonitrile (1.0 mL), under purple-LEDs (2W, 385 nm) irradiation for 12 h. [b]Reaction for 24 h.

**Scheme 19**. Synthesis of dihydrochalcones by photocatalysed reaction of styrens with benzaldehydes[a].



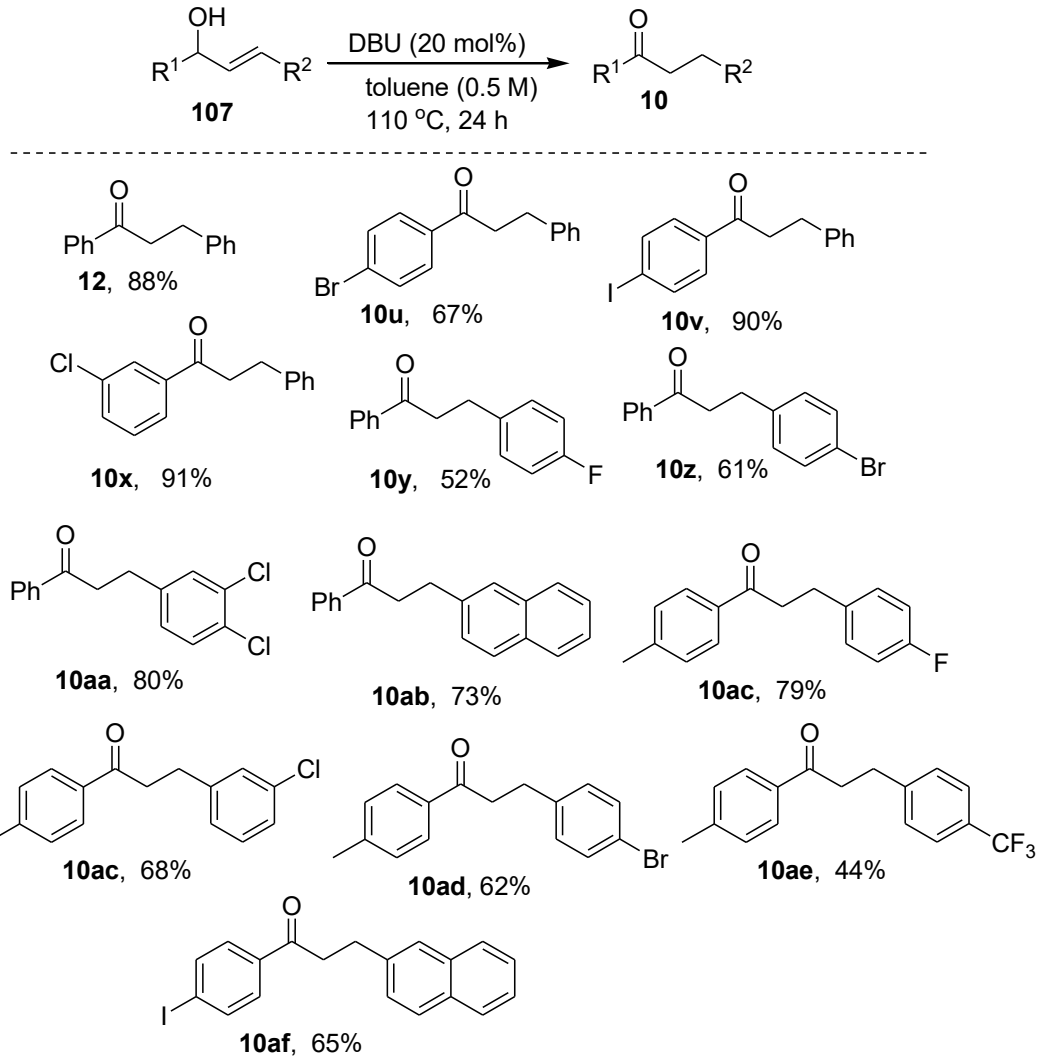

[a]Aryl alkene (**104**, 0.38 mmol), aldehyde (**105**, 0.25 mmol), TBADT (2 mol %), $Co_2CO_8$ (0.5 mol %), P(*n*-Oct)$_3$ (2 mol %), acetonitrile (1.0 mL), under purple-LEDs (2W, 385 nm) irradiation for 12 h.

**Scheme 20**. Synthesis of dihydrochalcones by photocatalysed reaction of styrens with benzaldehydes[a].

### 2.7. Other non-metal catalysed reactions

Qi and colleagues developed a method that involved isomerisation of allylic alcohols **107** into dihydrochalcones **10** under DBU catalysis.[109] The reaction was carried out with 20 mol-% DBU in toluene (0.5 M) at 110 °C for 24 h to afford differently substituted dihydrochalcones in 44-91% yields (Scheme 21).[109]




**Scheme 21**. Isomerization of Allylic Alcohols. Reaction conditions: [a] **107** (1.0 mmol), DBU (20.0 mol %), toluene (2.0 mL, 0.5 M), 110 °C, under an air atmosphere for 24 h. [b] Isolated yields.

## 3. Conclusions and Perspectives

Several synthetic strategies have been developed for the synthesis of dihydrochalcones. The most widely employed method involves selective reduction of double bonds of chalcones. This reaction in several instances has been conducted at lower temparatures. The main disadvantage is the reliance on transition metal catalysts, however, strides have been made on the development of the conditions that do not utilise metal catalysts. The second most employed synthetic strategy for the dihydrochalcones is that of alkylation by the hydrogen borrowing protocol. The method is advantageous in that it releases water as the main by-product, therefore is considered to be cleaner and environmentally friendly. The main disadvantages are that the high tempeartures and harsh basic conditions are often employed that limit the substrate scope of the reactions. Although the method also utilises transition metal catalysts, progress has been made in the development of protocols that use non-noble transition metals as well as metal-free reactions. Other methods that have been developed are transition metal-catalysed reactions that include Heck reaction, Negishi coupling, rhodium-catalysed decarbonylative addition, ruthenium-catalysed aryl migration and coupling reactions involving

boronic acids or boronate esters. Although the reactions utilise transition metals, most of them have wide substrate scope due to benign conditions that include low temparatures. Advancements in the synthesis of dihydrochalcones have been realised in the development of light-catalysed reactions that are mostly conducted at room tempeartaures and without metal catalysts. Another elegant method that has been developed involves DBU-catalysed isomerisation of allylic alcohols. Although several synthetic strategies have been developed for the dihydrochalcones, only a few protocols have been applied to the synthesis of bioactive dihydrochalcones and natural dihydrochalcones. Future research should involve the application of the developed methodologies in the synthesis of bioactive dihydrochalcones and natural dihydrochalcones.

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## 5. References

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Molahlehi Sonopo obtained his MSc degree in Chemistry from the University of the Free State and PhD in Chemistry from the University of KwaZulu-Natal (South Africa). He was awarded a joint post-doctoral research position by the South African Nuclear Energy Corporation (Necsa) and iThemba Pharmaceuticals after completing his PhD studies. Currently he is the research leader for the Radiolabelling section within the Applied Radiation department of research and innovation division (R&I) at Necsa. His current research focuses on radiolabelling of bioactive compounds, natural products isolation, synthetic method development for specific natural products and total synthesis.