Cascade reductive Friedel-Crafts alkylation catalyzed by robust iridium(III) hydride complexes containing a protic triazolylidene ligand

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ABSTRACT: The synthesis of complex molecules like active pharmaceutical ingredients typically requires multiple single-step reactions, in series or in a modular fashion, with laborious purification and potentially unstable intermediates. Cascade processes offer attractive synthetic remediation as they reduce time, energy, and waste associated with multistep syntheses. For example, triarylmethanes are traditionally prepared via several synthetic steps, and only a handful of cascade routes are known with limitations due to high catalyst loadings. Here we present an expedient catalytic and atom-economic cascade process to produce triarylmethanes. For this purpose, we have developed a bifunctional iridium system as efficient catalyst to build hetero-triaryl synthons via reductive Friedel-Crafts alkylation from ketones, arenes, and hydrogen. The catalytically active species was generated in situ from a robust triazolyl iridium(III) hydride complex and acid, and is comprised of a metal-bound hydride and a proximal ligand-bound proton for reversible dihydrogen release. These complexes catalyze the direct hydrogenation of ketones at slow rates followed by dehydration. Appropriate adjustment of the conditions successfully intercepts this dehydration and leads instead to efficient C–C coupling and Friedel-Crafts alkylation. The scope of this cascade process includes a variety of carbonyl substrates such as aldehydes, (alkyl)(aryl)ketones, and diaryl ketones as precursor electrophiles with arenes and heteroarenes for Friedel-Crafts coupling. The reported method has been validated in a swift one-step synthesis of the core structure of a potent antibacterial agent. Excellent yields and exquisite selectivities were achieved for this cascade process with unprecedentedly low iridium loadings (0.02 mol%). Moreover, the catalytic activity of the protic system is significantly higher than that of an *N*-methylated analogue, confirming the benefit of the Ir–H/N–H hydride-proton system for high catalytic performance.

INTRODUCTION

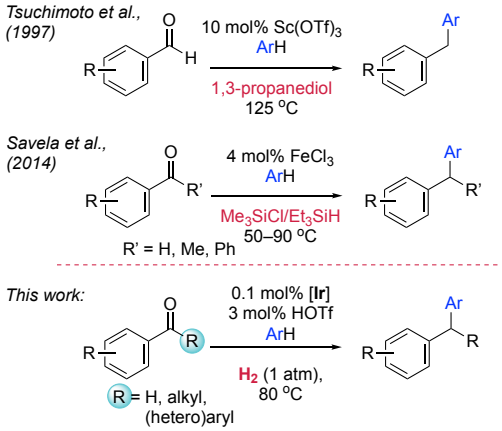
Cascade reactions offer attractive synthetic opportunities by improving resource efficiency on multiple levels.[1-3] This concept usually implies reducing the overall load of required solvents and reagents, as well as decreasing the amount of waste and by-products. Moreover, it optimizes labor costs, as a usually only a single workup and purification step is required. Many cascade reactions involve (reversible) hydrogen transfer to produce reactive intermediates *in situ* via hydrogen borrowing processes.[4, 5] Direct hydrogenation has been applied in tandem with other reactions as an efficient and atom economical method for advanced substrate functionalization.[6-9] The activation of H–H bond by transition metal complexes has been dominated in the field for a long time. In many classical examples in homogeneous catalysis, such transformations occur at the metal center by oxidative addition, homolytic or heterolytic cleavage, while the ligands remain unchanged over the course of the reaction.[10] More recent discoveries introduced the concept of metal-ligand bifunctional catalysis, were ligands participate directly in the bond activation step and undergo a reversible chemical transformation.[11, 12] Such cooperation between the metal as hydride acceptor, and the ligand as internal Lewis base proceeds synergistically[13] and substantially lowers the otherwise high H–H bond dissociation energy (435.8 kJ/mol)[14] and the unattractively high pKa (~35 in THF),[15] even though the acidity changes drastically once hydrides are formed.[16, 17]

This concept has led to a surge of ligands with reliable metal coordination to accommodate metal hydrides and sterically constrained basic ligand sites for proton harboring.[18-29] Despite the striking benefits of this concept, it has been only rarely applied with N-heterocyclic carbenes (NHCs), though the emergence of protic imidazole-derived NHCs has resurrected interest.[30, 31] Remarkably, the synthetically much more easily accessible and synthetically versatile triazolylidene subclass of NHC ligands[32-34] have not been considered for such applications until now. Here we demonstrate that protic triazolylidene iridium complexes are readily accessible and provide attractive catalytic performance in the reductive Friedel-Crafts alkylation using abundant ketones and aldehydes as alkylating agent, thus considerably expanding the range of alkyl halide surrogates for aromatic substitution. Previously, benzyl alcohols have been used as the main substitutes of alkyl halides in Friedel-Crafts transformation for the synthesis of diaryl- and triarylmethanes. [28, 35-41] Other precursors such as ethers,[28, 42, 43] benzyl carboxylic esters,[28] styrenes,[42] and sulfones,[44] have also been explored as alkylating agents. Aldehydes, when involved in Friedel-Crafts alkylation, undergo often undesired double benzylation with formation of triarylmethanes.[45-48] Under reducing conditions, ketones, as alkylating agents, can be attractive alternatives for the production of unsymmetrical triarylmethanes, especially when considering the synthetic accessibility of structurally diverse carbonyl compounds.[49, 50]

Cascade direct hydrogenation/Friedel-Crafts alkylation reaction as an efficient method for the functionalization of arenes has not been explored yet, although reductive Friedel-Crafts alkylation has some few precedents (Scheme 1).[42, 51, 52] Tsuchimoto *et al.* used benzaldehydes and 1,3-propanediol in the presence of 10 mol% $Sc(OTf)_3$ to form a reactive acetal as alkylating agent.[51] By using a NHC-Ir complex and 2-propanol as a reducing agent, Prades *et al.* expanded the substrates to benzophenone.[42] Finally, Savela *et. al.* reported an iron-catalyzed Friedel-Crafts alkylation with ketones and aldehydes mediated by organosilanes.[52] The process utilizes Et_3SiH for the hydrosilylation of the carbonyl compound and Me_3SiCl for the following nucleophilic

substitution to form the corresponding alkyl chloride involved in iron(III)-catalyzed Friedel-Crafts alkylation.

Scheme 1. Strategies for reductive Friedel-Crafts alkylation.

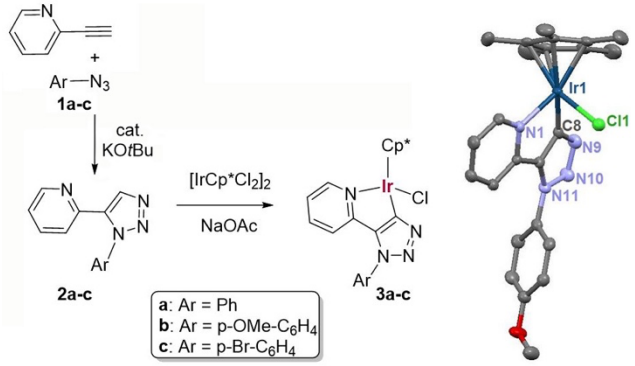


We reasoned that an atom-efficient procedure may be accessible by using hydrogen as reducing agent combined with a bifunctional catalyst comprised of a metal center for hydride stabilization and a ligand site for transient proton binding. Herein, we demonstrate the iridium(III) hydride complexes bearing an 1,2,3-triazolyl ligand with an unsubstituted nitrogen that is available for protonation provides access to Ir–H/N–H complexes that are efficient catalysts in the reductive Friedel-Crafts alkylation. These catalysts are remarkably robust under acidic conditions and provide an efficient and atom-economic access to hetero-triarylmethanes from aromatic carbonyl compounds in the presence of atmospheric pressure of H_2.

RESULTS AND DISCUSSION

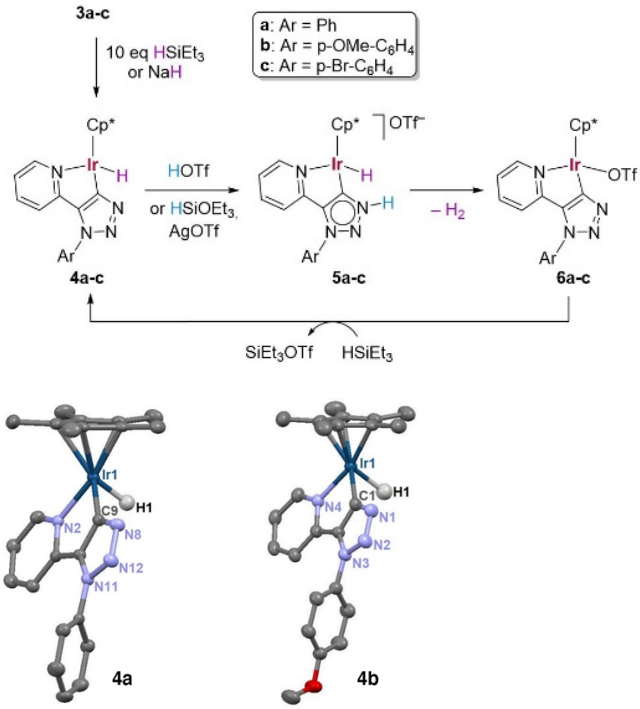
Synthesis of the iridium(III) complexes. The target iridium complexes were prepared starting from the appropriate aryl azide **1a-c** through base-catalyzed click reaction with 2-ethynylpyridine to give the 1,5-substituted 1,2,3-triazoles **2a-c** followed by metalation with $[IrCp^*Cl_2]_2$ in the presence of NaOAc (Scheme 2).[53] The iridium(III) complexes **3a-c** featured the iridium-bound triazolyl carbon nuclei at δ_C 161.5±1 in the $^{13}C\{^1H\}$ NMR spectrum and X-ray diffraction analyses of complexes **3a** and **3b** confirmed the postulated connectivity (Fig. S79).

Scheme 2. Synthesis of iridium (III) complexes **3a-c** bearing 1,2,3-triazolyl ligands and ORTEP plot of complex **3b** (30% probability).



The corresponding iridium(III) hydride complexes **4a-c** were obtained by chloride abstraction using either $HSiEt_3$ or NaH (Scheme 3). Although the silane was utilized in large excess, this reaction was highly selective and allowed the product to be conveniently isolated by crystallization. Less $HSiEt_3$ was required when the reaction was performed in the presence of a silyl scavenger such as NaOTf or AgOTf, but the formed by-products complicated product isolation and purification. Formation of the hydride complexes was confirmed by ^1H NMR spectroscopy, revealing a diagnostic hydride resonance at around –15.20 ppm for complexes **4a–c**. All hydride complexes **4a–c** are moderately air- and moisture-stable in crystalline form and can be stored without protection for up to a week. Extended storage leads to gradual decomposition, indicated by loss of the hydride signal and concomittant appearance of a series of new signals in the ^1H NMR spectrum. However, these complexes rapidly decompose in moist solution. Suitable crystals for X-ray diffraction analysis were obtained for complexes **4a** and **4b** from a saturated dry THF solution by slow diffusion of ether and hexane, respectively (Fig. S80).

Scheme 3. Synthesis of triazolyl iridium(III) hydride complexes **4a-c** and formation of *N*-protonated carbene iridium(III) hydride complexes **5a-c** and subsequent dehydrogenation to **6a-c**, and ORTEP plots of **4a** and **4b**.



During optimization of the procedure for the synthesis of hydride complex **4a**, we noted that using two equivalents of AgOTf with three equivalents of $HSiEt_3$ yielded a new compound, which was assigned to the protonated iridium hydride **5a** based on the downfield shifted hydride resonance at δ_H = –14.5 ppm in protonated THF (*vs* –15.20 ppm for **4a**) and a diagnostic sharp singlet at 15.89 ppm attributed to the N-H proton.[54, 55] Protonation may be imparted by the silver(I)-mediated

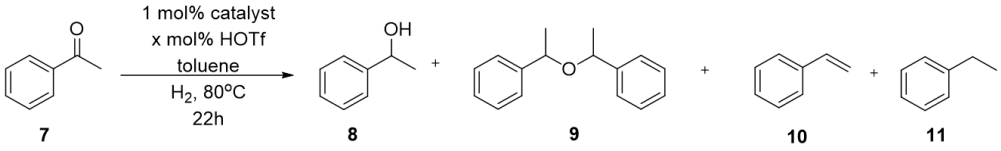
oxidation of hydrosilane to form trifluoromethanesulfonic acid (HOTf) *in situ*.

Indeed, when THF solutions of iridium(III) hydride complexes **4a–c** were treated with anhydrous HOTf under an inert atmosphere, carbene complexes **5a–c** formed instantaneously via protonation of the triazole N3 position (Scheme 3). Formation of the protic carbene complexes **5a–c** was supported by a sharp ^{1}H NMR signal around 15.85 (±0.08) ppm, while the hydride signal shifted downfield and appeared at δ = –14.45 (±0.02) ppm (Table S1). Although these NH-carbene iridium hydride complexes **5a–c** dehydrogenated within minutes, they were sufficiently stable to record ^{1}H NMR spectra, yet more time-consuming NMR spectroscopic experiments were not possible.[56] Using more concentrated samples or working at lower temperature resulted in even faster degradation. Attempts to run this reaction in CD_3NO_2 or MeCN did not prevent rapid precipitation, while using CD_2Cl_2 instead of THF altered the reactivity and led to ligand protonation as well as hydride abstraction. Weaker acids such as NH_4PF_6, trifluoroacetic acid, formic acid, or anhydrous ethereal HCl did not induce protonation of **4a**, indicating a remarkably low basicity of the triazolyl nitrogen site.

All three protic carbene complexes **5a–c** were unstable and released H_2, identified by an NMR signal at δ_H = 4.55 ppm in the reaction mixtures (THF-d_8). Concomitantly, a red precipitate assigned to **6a–c** formed (Fig. S31),[57] which was insoluble in most common polar or nonpolar solvents except CD_3NO_2.[58] While standard ^{1}H and ^{13}C NMR spectroscopy did not allow to distinguish complexes **6a–c** from a dimeric form with non-coordinating OTf^- counterions,[59-61] DOSY analysis of the mixture of **6b** and **3b** revealed highly similar diffusion coefficients for both compounds, indicating similar molecular volumes of both species (Fig. S44) and hence a monomeric structure of **6b**. Mass spectra of **6a–c** showed the pertinent $[M+H]^+$ signals, in agreement with a coordinated triflate anion in a monomeric complex (*e.g.* m/z 669.1207 for **6a**). No signal for a dimeric species was detected. Remarkably, addition of $HSiEt_3$ to a suspension of **6a-c** in THF regenerated the iridium hydride complexes **4a–c**, thus identifying the triazolyl iridium scaffold as a competent system for shuttling H_2. Moreover, these reactivities indicate a high robustness of the triazolylidene iridium scaffold towards acidolysis even in the presence of strong acids such as HOTf or HCl.[62]

Direct hydrogenation catalysis. The facile dehydrogenation of complexes **5a–c** suggests these species as well as complexes **6a–c** as potential hydrogen transfer catalysts. Neither iridium(III) chloride complex **3a** nor iridium(III) hydride complex **4a** catalyze the hydrogenation of acetophenone under atmospheric pressure of H_2 (Table 1, entries 1, 2). However, addition of 1 equiv. HOTf per iridium center, *i.e.* conditions that form complexes **5a–c**, activates catalytic turnover (entries 3–8). The selectivity was modest, affording phenethyl alcohol **8** from hydrogenation together with the corresponding ether **9** from subsequent dehydration, traces of styrene **10** as the other product of dehydration, as well as ethyl benzene **11** due to styrene hydrogenation. The fact that only traces of styrene are observed suggests that hydrogenation of olefins is faster than that of ketones. In contrast to complexes **3** and **4**, iridium species **6a–c** catalyze hydrogenation without the addition of TfOH (entries 9–11), and with activities and selectivities that are essentially identical to iridium complex **3a-c** and **4a-c** upon HOTf activation, indicating the same catalytically active species, and revealing full stability of the Ir–C bond under acidic conditions as demonstrated previously for related Ir carbene complexes.[62, 63] When AgOTf was used as an additive instead of the acid, much lower conversion of acetophenone was observed under otherwise identical conditions (entry 13). Likewise, HBF_4 or CF_3COOH failed to induce catalytic activity (entry 14).

Table 1. Hydrogenation of acetophenone.[a]



Entry	Precatalyst	Acid loading	Conversion	Yield			
				8	**9**	**10**	**11**
1	**3a**	-	<2%	-	-	-	-
2	**4a**	-	<2%	-	-	-	-
3	**3a**	1 mol%	67%	29%	18%	<3%	17%
4	**3b**	1 mol%	68%	29%	19%	<3%	17%
5	**3c**	1 mol%	48%	22%	10%	5%	10%
6	**4a**	1 mol%	70%	30%	23%	<3%	15%
7	**4b**	1 mol%	69%	29%	21%	<3%	17%
8	**4c**	1 mol%	49%	24%	9%	5%	10%
9	**6a**	-	68%	30%	12%	<3%	22%
10	**6b**	-	67%	28%	15%	<3%	22%
11	**6c**	-	48%	23%	8%	<3%	12%
12	**3a**	0.5 mol%	10%	8%	-	<3%	<3%

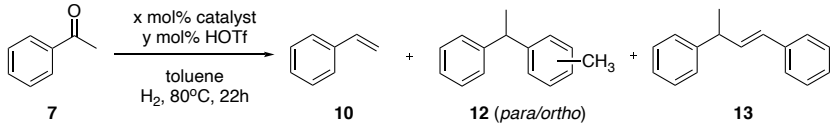
13[b]	**3a**	3 mol%	22%	6%	-	<3%	13%
14[c]	**3a**	1 mol%	<2%	-	-	-	-
15	-	1 mol%	27%[d]	-	-	-	-
16[e]	**3a**	3 mol%	52%[d]	-	-	-	-

[a)] Reaction conditions: acetophenone (2.1 mmol) iridium complex (21 μmol) toluene (10 mL), H_2 (1 bar), HOTf; [b)] AgOTf instead of HOTf; [c)] HBF_4•OEt_2 or CF_3COOH instead of HOTf; [d)] 1,3,5-triphenylbenzene was formed, [e)] in absence of H_2.

The aryl substituent on the triazole had only a mediocre influence on catalytic activity, which is in agreement with the only minor chemical shift differences of the hydride NMR frequencies of complexes **5a–c** (Table S1). Notably, bromide substituents led to lower catalytic performance of complex **6c** and likewise **3c** and **4c**, which may be attributed to their electron-withdrawing nature and the ensuing lower proton affinity of the triazole.[64] However the electron-donating methoxy group in complex **6b** did not lead to enhanced catalytic activity, even though the stability of the hydrogenated complex **5b** was higher compared to **5a** and **5c** (see above).

Reductive Friedel-Crafts alkylation. The slow conversion of acetophenone under atmospheric H_2 pressure paired with the high stability of the complexes towards Brønsted acids was exploited in reductive Friedel-Crafts alkylation by slightly increasing the amount of HOTf with respect to the iridium precatalyst. This modification radically switched the chemoselectivity of the reaction towards electrophilic alkylation of the aromatic solvent. Thus, toluene is alkylated in the presence of either **3a** or **4a** when acetophenone was reacted in the presence of 3 mol% acid and 1 mol% iridium complex to yield the cross-coupled diaryl-ethane as a mixture of *ortho* and *para* substitution (Table 2, entries 1,2), in line with general selectivity principles.[65] In addition, minor quantities of compound **13** were formed due to homocoupling of the intermediate from acetophenone hydrogenation and dehydration. Reducing the loading of the iridium precatalyst to 0.1 mol% significantly improved selectivity and yielded exclusively the cross-coupled product **12** (entry 3). Further lowering of the iridium loading to 0.02 mol% is tolerated, yet the HOTf portion is critical as selectivity and activity erode when HOTf is reduced from 3 to 1 mol% (entries 4–6). Increasing the acid concentration did not lead to any improvement (entry 7). Iridium complex **3b** was as efficient as **3a**, while the bromide-functionalized complex **3c** was again less active (entries 8,9), in agreement with the activity observed for hydrogenation (*cf.* Table 2). Iridium complexes **4a** and **6a** showed identical selectivity and activity patterns as **3a**, suggesting the formation of a common active species (entries 6,10,13). The same conclusion emerges when comparing **3b**, **4b,** and **6b**, and **3c**, **4c,** and **6c**, respectively. The availability of a protic N–H and hydridic Ir–H unit appeared to be essential for imparting reductive Friedel-Crafts alkylation. Neither $[IrCp^*Cl_2]_2$ nor free ligand **2a** nor blank reactions showed catalytic activity towards reductive Friedel-Crafts alkylation and only formed minor quantities of 1,3,5-triphenylbenzene from trimerization of the styrene intermediate (entries 16–18). Likewise, chloride abstraction with other reagents (*e.g.* 2 mol% KOTf or AgOTf) did not lead to significant cross coupling (entries 19-20).

Table 2. Reductive Friedel-Crafts alkylation of toluene. [a]

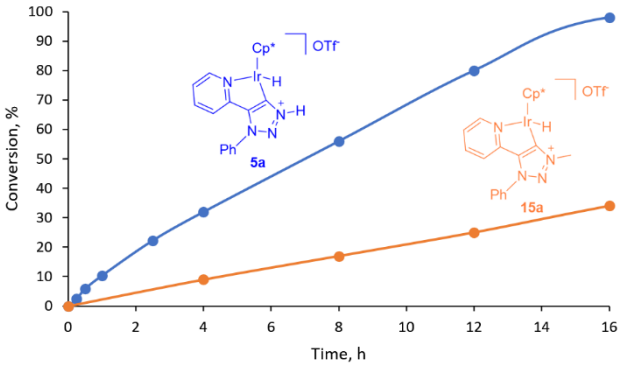


Entry	Precatalyst		Acid loading	Conversion	Yield		
					10	**12** (para/ortho)	**13**
1	3a	1 mol%	3 mol%	100%	-	63% (4.7/1)	37%
2	4a	1 mol%	3 mol%	100%	-	60% (5.7/1)	39%
3	3a	0.1 mol%	3 mol%	100%	-	99% (4.5/1)	-
4	3a	0.02 mol%	1 mol%	34%	12%	10% (1.0/0)	10%
5	4a	0.02 mol%	1 mol%	35%	12%	11% (1.0/0)	10%
6	3a	0.02 mol%	3 mol%	100%	-	96% (5.0/1)	<3%
7	3a	0.02 mol%	5 mol%	100%	-	95% (5.3/1)	<3%
8	3b	0.02 mol%	3 mol%	100%	-	94% (5.3/1)	<3%
9	3c	0.02 mol%	3 mol%	63%	<3%	42% (4.3/1)	17%
10	4a	0.02 mol%	3 mol%	100%	-	95% (4.8/1)	<3%
11	4b	0.02 mol%	3 mol%	100%	-	96% (5.0/1)	<3%
12	4c	0.02 mol%	3 mol%	64%	<3%	45% (4.0/1)	15%
13	6a	0.02 mol%	3 mol%	100%	-	97% (5.1/1)	<3%

14	6b	0.02 mol%	3 mol%	100%	-	95% (5.3/1)	<3%
15	6c	0.02 mol%	3 mol%	63%	5%	38% (5.3/1)	18%
16	$[IrCp^*Cl_2]_2$	0.1 mol%	3 mol%	21% [b]	-	-	-
17	2a	0.1 mol%	3 mol%	32% [b]	-	-	-
18	-	-	3 mol%	52% [b]	-	-	-
19[c]	3a	1 mol%	1 mol%	57%	40%	<3%	13%
20[d]	3a	1 mol%	1 mol%	100%	10%	29% (1.0/0)	57%

[a)] Reaction conditions: acetophenone (2.1 mmol) and iridium complex in toluene (10 mL), H_2 (1 bar), HOTf; [b)] formation of 1,3,5-triphenylbenzene; [c)] plus 2 mol% KOTf; [d)] plus 2 mol% AgOTf.

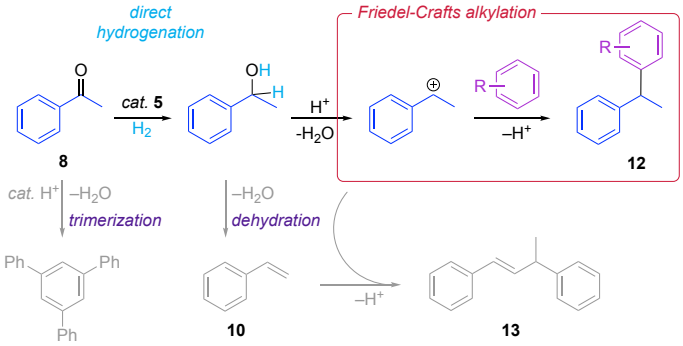
Figure 1. Time-conversion profiles for the consumption of acetophenone in the reductive Friedel-Crafts alkylation of acetophenone with toluene in the presence of 0.02 mol% **5a**, generated in situ from **3a**, (blue) and **15a** (orange; conversion of acetophenone monitored by ^1H NMR spectroscopy, dioxane as internal standard).



The relevance of the protic triazolylidene unit was further demonstrated by comparison with the analogous iridium complex **15a** containing an *N*-methylated ligand, which was obtained by post-modification of **3a** with MeOTf. Complex **15a** also required HOTf to become catalytically active, though conversions were slower than with the protic analogue **3a** (entries 19,20; Fig. 1).

This reductive Friedel-Crafts alkylation is presumed to be the product of a cascade reaction starting from the iridium-catalyzed hydrogenation of the ketone to the corresponding alcohol (*vide supra*), followed by acid-mediated dehydroxylation and formation of a carbocation for Friedel-Crafts alkylation (Scheme 4). In agreement with the proposed mechanism, HOTf on its own catalyzes Friedel-Crafts alkylation of toluene with 1-phenylethanol, although the reaction is dominated by the formal homocoupling of alcohol and yields **13** as the major product (Scheme 5). Hence, key to the cascade process presented here is the slow formation of alcohol, which keeps its concentration constantly low. In the presence of sufficiently large excess of arene, this alcohol in acidic media leads to selective Friedel-Crafts alkylation rather than elimination, *viz.* formation of styrene and homocoupling products. In support of this model, the chemoselectivity of the process strongly depends on the relative amounts of toluene and ketone in the reaction mixture (Table S2). At low toluene:ketone ratios (up to 5:1), dehydration of the alcohol leads to significant amounts of the homo-coupled product **13** and the trimerization product **14**. Higher toluene ratios increase the selectively towards reductive Friedel-Crafts alkylation, and with 40 equivalents toluene, up to 96% conversion to **12** was achieved with exquisite selectivity, and efficient suppression of **13** or **14**. This high toluene/ketone ratio can also be achieved with lower toluene quantities and by addition of the ketone in small portions, which allows to use the aryl component only in small excess.

Scheme 4. Proposed transformation pathways for acetophenone in the presence of catalyst **5a** under acidic conditions; with diaryl ketones and aldehydes, dehydration leads to ether rather than olefin formation.



Scheme 5. Conversion of 1-phenylethanol **8** in the presence of HOTf.

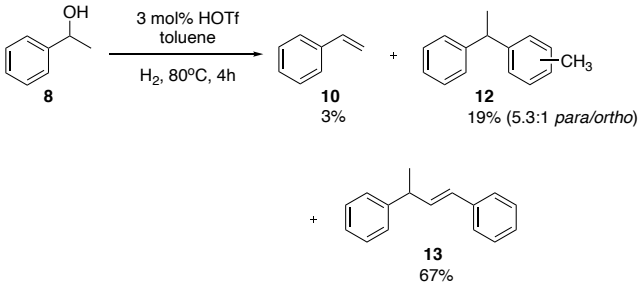
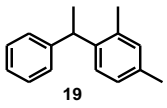
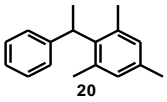
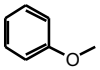
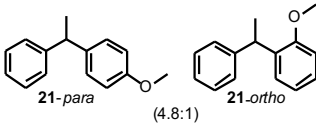
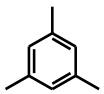
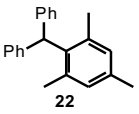
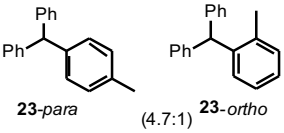
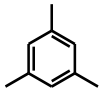
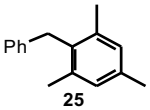
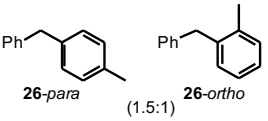
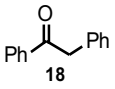
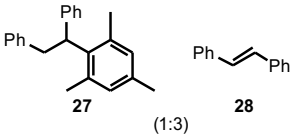


Table 3. Substrates scope for reductive Friedel-Crafts alkylation.[a]

Entry	Carbonyl compound	Aryl compound	Product	Isolated yield (conversion)

1	 **7**		 **19**	94% (100%)
2	 **7**		 **20**	98% (100%)
3	 **7**		 **21**-*para* (4.8:1) **21**-*ortho*	98% (100%)
4	 **16**		 **22**	97% (100%)
5	 **16**		 **23**-*para* (4.7:1) **23**-*ortho*	97% (100%)
6	 **16**		 **24**	79% (100%)[b]
7	 **17**		 **25**	98% (100%)
8	 **17**		 **26**-*para* (1.5:1) **26**-*ortho*	95% (100%)
9	 **18**		 **27** (1:3) **28**	95% (100%)

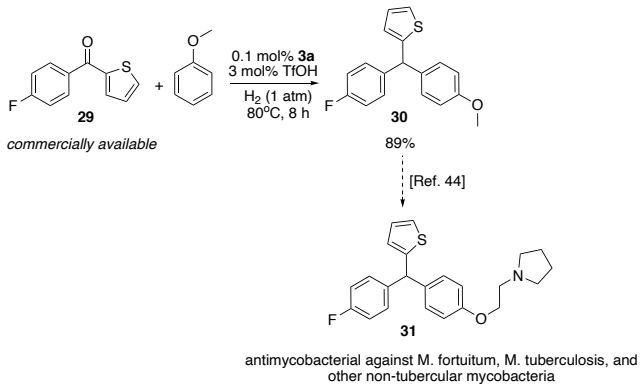
[a)] Reaction conditions: carbonyl compound (1.00 mmol), aryl compound (10 mmol), **3a** (0.001 mmol), TfOH (0.03 mmol), H_2 (1 atm), 80°C, 5-8 h; [b)] 19% of diphenylmethane as side product.

Substrate scope. Expansion of the substrate scope included variation of both the ketone and the aryl components and generally gave excellent conversions and yields (Table 3). Aryl substrates with substituents that uniquely define the direction of the electrophilic attack such as *m*-xylene and mesitylene were alkylated with acetophenone in excellent yields and complete chemoselectivity, providing single products **19** and **20**, respectively (entries 1,2). Anisole was alkylated in the para- and ortho-positions, in analogy to the general selectivity of Friedel-Crafts alkylation of mono-substituted arenes (entry 3).[65] Modification of the ketone substrate from acetophenone to benzophenone **16** gave quantitative conversion to triarylmethanes **22**–**24** (entries 4–6). Monitoring of the reaction of reductive Friedel-Crafts alkylation of mesitylene with benzophenone by ^{1}H NMR spectroscopy indicated a transient resonance at δ_H = 5.80 assigned to carbinol proton Ph_2CH-OH (Fig. S76, S78), in agreement with the higher resistance of this intermediate towards dehydration than 1-phenylethanol formed from acetophenone. Time-dependent analysis of the reaction composition provides an excellent fit with a consecutive reaction and a markedly lower rate constant for hydrogenation, k_{hydrog} = 0.35 h^{-1}, than the subsequent Friedel-Crafts coupling, k_{FC} = 4.3 h^{-1} (Fig. S77) This order of magnitude difference is in agreement with the proposed mechanism and provides a quantitative measure for the slow nature of the hydrogenation *vs* Friedel-Crafts alkylation step.

Furthermore, high selectivity was achieved also with a smaller amount of toluene (10 vs 40 equiv. for acetophenone). Interestingly, also aldehydes serve as substrates. Thus, heating benzaldehyde (**17**) with mesitylene and toluene under the optimized conditions produces (phenyl)(aryl)methane products **25** and **26**, respectively, in excellent yields (entries 7, 8). Previous attempts to use benzaldehydes for reductive Friedel-Crafts alkylation under acidic conditions resulted in triarylmethanes due to double alkylation.[47] Selective formation of (phenyl)(aryl)methane products strongly supports the proposed cascade mechanism with initial hydrogenation of the aldehyde followed by Friedel-Crafts alkylation of the aryl substrate. Moreover, substrates with more acidic α-hydrogen protons such as 2-phenylacetophenone **18** led

preferentially to formal elimination from the carbocation intermediate and (*E*)-stilbene **28** is produced predominantly, although Friedel-Crafts alkylation of mesitylene also occurred, providing **27** as a minor product (24%, entry 9).

Scheme 6. One-step synthesis of precursor **30** of the antimycobacterial agent **31**



This novel approach to triarylmethanes such as **22–24** is attractive as such systems have been widely applied as core structures for dyes,[66] pH indicators,[67] fluorescent probes,[68, 69] and as a valuable synthon in antitumor[70] and antibacterial[71] agents. For instance, triarylmethane **31** composed of three different aryl groups displays attractive antibacterial activity *in vitro* and *in vivo* against *M. fortuitum*, *M. tuberculosis*, and other non-tubercular mycobacteria.[72] Here, we have applied the iridium-catalyzed reductive Friedel-Crafts cascade to generate the heterotriaryl core of this potent pharmaceutial from the commercially available precursor **29** in a single step and with high yield and selectivity (Scheme 6). Further conversion of the triaryl product **30** into the final antibiotic has been previously described and is unproblematic.[44] In comparison, such compounds were previously prepared in a three-step procedure starting from phenyl sulfone, which wascoupled with 1-bromo-3-fluorophenyl and and subsequently with 4-iodoanisole in the presence of 10% $Pd(OAc)_2$, followed by desulfonation in the presence of 10% $Sc(OTf)_3$ in an overall 39% yield.[44] While the procedure presented here affords the triaryl methane **30** as a racemic mixture, our work suggests that enantioselective product formation may emerge upon replacing HOTf by a chiral Brønsted acid rather than from an enantiopure iridium complex.

CONCLUSIONS

Here we provide a synthetic access to iridium complexes **5a-c** containing both a metal-bound hydride and a triazolylidene-bound proton, which can be considered as dihydrogen adducts of complex **6** and consequently serve as hydrogenation catalyst in the presence of ketones. While these complexes spontaneously lose H_2, their hydride precursors **4a-c** are stable and can be activated with HOTf without compromising the Ir–C bond and the catalyst's integrity. Ketone hydrogenation is not particularly fast, which has been exploited in a cascade process involving subsequent acid-mediated Friedel-Crafts alkylation via alcohol dehydroxylation. Tailoring of the relative concentrations of ketone and the corresponding alcohol intermediate as well as the arene substrate provides excellent conversions and exquisite selectivities with low catalyst loadings (down to 0.02 mol% iridium complex) and with various different carbonyl substrates including aldehydes and diaryl ketones. The latter systems offers a new approach to pharmacologically interesting triarylmethane, though the excess of arene currently required poses limitations if the arene is precious. Key for this cascade process is the constantly low concentration of *in situ*-generated alcohol (to avoid homocoupling and ensure high selectivity) as well as the robustness of the Ir–C bond under the highly acidic Friedel-Crafts conditions (to avoid catalyst degradation), revealing unique benefits of such Ir–H/N–H systems. Based on these conclusions, lower reaction temperatures may be accessible by developing ketone more active hydrogenation catalysts that preserve the inertness towards Brønsted acids.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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Notes

The authors declare no competing financial interest.

ELECTRONIC SUPPORTING INFORMATION

Experimental procedures for the synthesis of iridium complexes, spectroscopic data for all complexes and products, general catalytic procedures and optimization details, kinetic analysis, and crystallographic data. CCDC 1997999, 1998000, 1998001, 1998003 and 2004712. For ESI and crystallographic data in CIF or other electronic format see DOI:10.1039/xxx.

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(56) Only complex **5b** was sufficiently stable to be characterized by 1H-13C HSQC NMR spectroscopy, which confirmed that the resonances at 15.77 and –14.46 ppm in the 1H NMR spectrum are not correlated to any carbon nucleus (Fig. S33).
(57) Although sufficiently large solid pieces were formed upon precipitation, X-ray diffraction analysis revealed no diffraction pattern and pointed to an amorphous structure. However, exposure of complexes 6a–c to hydrogen gas did not lead to any reaction even at elevated temperatures. Similarly, the protic carbene hydride complexes 5a–c could not be stabilized if the protonation occurred under hydrogen atmosphere.
(58) Notably, dissolution of **6b** in MeCN induced the formation of the solvento complex **6b'** with a non-coordinating triflate anion, which showed an MS pattern distinctly different from **6b** (Fig. S44) and lacked a m/z signal for an iridium species with bound triflate (Fig. S45).
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