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Research Article

Cascade Reductive Friedel–Crafts Alkylation Catalyzed by Robust Iridium(III) Hydride Complexes Containing a Protic Triazolylidene Ligand

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Cite This: ACS	Catal. 2021, 11, 8999–9007	Read Online	
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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 cascade process to produce triarylmethanes. For this purpose, we have developed a bifunctional iridium system as the efficient catalyst to build heterotriaryl synthons *via* reductive Friedel–Crafts alkylation from ketones, arenes, and hydrogen. The



catalytically active species were generated *in situ* from a robust triazolyl iridium(III) hydride complex and acid and is composed 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. **KEYWORDS:** *cascade reaction, reductive Friedel–Crafts alkylation, protic carbene, iridium, proton hydride transfer*

■ 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 byproducts. Moreover, it optimizes labor costs, as 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 the 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, where ligands participate directly in the bond activation step and undergo a reversible chemical transformation.^{11,12} Such cooperation between the metal as the hydride acceptor and the ligand as the internal Lewis base proceeds synergistically¹³ and substantially lowers the otherwise high H–H bond dissociation energy (435.8 kJ/mol)¹⁴ and the unattractively high pK_a (~35 in tetrahydrofuran (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

Received:February 18, 2021Revised:June 23, 2021Published:July 8, 2021





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 versatile triazolylidene subclasses of NHC ligands³²⁻³⁴ 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 the 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 the 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.49,5

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 a few precedents (Scheme 1).^{42,51,52}

Scheme 1. Strategies for Reductive Friedel–Crafts Alkylation



Tsuchimoto et al. used benzaldehydes and 1,3-propanediol in the presence of 10 mol % Sc(OTf)₃ to form a reactive acetal as the alkylating agent.⁵¹ Using an NHC–Ir complex and 2propanol 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 Et₃SiH for the hydrosilylation of the carbonyl compound and Me₃SiCl for the following nucleophilic substitution to form the corresponding alkyl chloride involved in iron(III)-catalyzed Friedel–Crafts alkylation.

We reasoned that an atom-efficient procedure may be accessible using hydrogen as the reducing agent combined with a bifunctional catalyst composed of a metal center for hydride stabilization and a ligand site for transient proton binding. Herein, we demonstrate that the iridium(III) hydride complexes bearing a 1,2,3-triazolyl ligand with unsubstituted nitrogen that is available for protonation provide 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 efficient and atom-economic access to heterotriarylmethanes 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 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

Scheme 2. Synthesis of Iridium(III) Complexes 3a-c Bearing 1,2,3-Triazolyl Ligands and the ORTEP Plot of Complex 3b (30% Probability)



featured the iridium-bound triazolyl carbon nuclei at $\delta_{\rm C}$ 161.5 \pm 1 in the ¹³C{¹H} NMR spectrum and X-ray diffraction analyses of complexes **3a** and **3b** confirmed the postulated connectivity (Figure S79).

The corresponding iridium(III) hydride complexes 4a-cwere obtained by chloride abstraction using either HSiEt₃ 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 HSiEt₃ was required when the reaction was performed in the presence of a silvl scavenger such as NaOTf or AgOTf, but the formed byproducts 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 concomitant appearance of a series of new signals in the ¹H NMR spectrum. However, these complexes rapidly decompose in moist solutions. 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 (Figure S80).

Scheme 3. Synthesis of Triazolyl Iridium(III) Hydride Complexes 4a-c, 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 2 equiv of AgOTf with 3 equiv of HSiEt₃ yielded a new compound, which was assigned to the protonated iridium hydride 5a based on the downfield-shifted hydride resonance at $\delta_{\rm H} = -14.5$ ppm in

Table 1. Hydrogenation of Acetophenone⁴

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). The formation of the protic carbene complexes 5a-c was supported by a sharp ¹H NMR signal around 15.85 (± 0.08) ppm, while the hydride signal shifted downfield and appeared at $\delta = -14.45 \ (\pm 0.02) \text{ ppm}$ (Table S1). Although these NH-carbene iridium hydride complexes 5a-c dehydrogenated within minutes, they were sufficiently stable to record ¹H NMR spectra, yet more time-consuming NMR spectroscopic experiments were not possible.⁵⁶ Using more concentrated samples or working at lower temperatures resulted in even faster degradation. Attempts to run this reaction in CD₃NO₂ or MeCN did not prevent rapid precipitation while using CD₂Cl₂ instead of THF altered the reactivity and led to ligand protonation as well as hydride abstraction. Weaker acids such as NH₄PF₆, 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 $\mathbf{5a-c}$ were unstable and released H₂, identified by an NMR signal at $\delta_{\rm H} = 4.55$ ppm in the reaction mixtures (THF- d_8). Concomitantly, a red precipitate assigned to $\mathbf{6a-c}$ formed (Figure S31),⁵⁷ which was insoluble in most common polar or nonpolar solvents except CD₃NO₂.⁵⁸ While standard ¹H and ¹³C NMR spectroscopy did not allow us to distinguish complexes $\mathbf{6a-c}$ from a dimeric form with noncoordinating OTf⁻ counterions,^{59–61} the diffusion ordered spectroscopy (DOSY) analysis of the mixture of **6b** and **3b** revealed highly similar diffusion



				yield				
entry	precatalyst	acid loading (mol %)	conversion (%)	8	9	10	11	
1	3a		<2					
2	4a		<2					
3	3a	1	67	29%	18%	<3%	17%	
4	3b	1	68	29%	19%	<3%	17%	
5	3c	1	48	22%	10%	5%	10%	
6	4a	1	70	30%	23%	<3%	15%	
7	4b	1	69	29%	21%	<3%	17%	
8	4c	1	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	10	8%		<3%	<3%	
13 ^b	3a	3	22	6%		<3%	13%	
14 ^c	3a	1	<2					
15		1	27 ^d					
16 ^e	3a	3	52 ^d					

^aReaction conditions: acetophenone (2.1 mmol), iridium complex (21 μmol), toluene (10 mL), H₂ (1 bar), HOTf. ^bAgOTf instead of HOTf. ^cHBF₄·OEt₂ or CF₃COOH instead of HOTf. ^d1,3,5-triphenylbenzene was formed. ^eIn the absence of H₂.

Table 2. Reductive Friedel-Crafts Alkylation of Toluene^a

		x mol% catalyst y mol% HOTf		СН3 +]	
		toluene H ₂ , 80ºC, 22h 7	10 12 (pa	ra/ortho)	13	·	
						yield	
entry	precatalyst	precatalyst loading (mol %)	acid loading (mol %)	conversion (%)	10	12 (para/ortho)	13
1	3a	1	3	100		63% (4.7/1)	37%
2	4a	1	3	100		60% (5.7/1)	39%
3	3a	0.1	3	100		99% (4.5/1)	
4	3a	0.02	1	34	12%	10% (1.0/0)	10%
5	4a	0.02	1	35	12%	11% (1.0/0)	10%
6	3a	0.02	3	100		96% (5.0/1)	<3%
7	3a	0.02	5	100		95% (5.3/1)	<3%
8	3b	0.02	3	100		94% (5.3/1)	<3%
9	3c	0.02	3	63	<3%	42% (4.3/1)	17%
10	4a	0.02	3	100		95% (4.8/1)	<3%
11	4b	0.02	3	100		96% (5.0/1)	<3%
12	4c	0.02	3	64	<3%	45% (4.0/1)	15%
13	6a	0.02	3	100		97% (5.1/1)	<3%
14	6b	0.02	3	100		95% (5.3/1)	<3%
15	6c	0.02	3	63	5%	38% (5.3/1)	18%
16	$[IrCp*Cl_2]_2$	0.1	3	21 ^b			
17	2a	0.1	3	32 ^b			
18			3	52 ^b			
19 ^c	3a	1	1	57	40%	<3%	13%
20 ^d	3a	1	1	100	10%	29% (1.0/0)	57%

^aReaction conditions: acetophenone (2.1 mmol) and iridium complex in toluene (10 mL), H₂ (1 bar), HOTf. ^bFormation of 1,3,5-triphenylbenzene. ^cPlus 2 mol % KOTf. ^dPlus 2 mol % AgOTf.

coefficients for both compounds, indicating similar molecular volumes of both species (Figure 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 HSiEt₃ 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 H₂. Moreover, these reactivities indicate high robustness of the triazolylidene iridium scaffold toward 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 catalyzes the hydrogenation of acetophenone under atmospheric pressure of H₂ (Table 1, entries 1 and 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, and ethylbenzene 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 complexes 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, a much lower conversion of acetophenone was observed under otherwise identical conditions (entry 13). Likewise, HBF₄ or CF₃COOH failed to induce catalytic activity (entry 14).

The aryl substituent on the triazole had only a mediocre influence on the 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 the 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 toward 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 toward 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 and 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 bromidefunctionalized complex 3c was again less active (entries 8 and 9), in agreement with the activity observed for hydrogenation (cf. Table 1). 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 a hydridic Ir-H unit appeared to be essential for imparting reductive Friedel-Crafts alkylation. [IrCp*Cl₂]₂, free ligand 2a, or blank reactions did not show catalytic activity toward 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 and 20).

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 and 20; Figure 1).



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 the internal standard).

This reductive Friedel–Crafts alkylation is presumed to be the product of a cascade reaction starting from the iridiumcatalyzed 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 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

Denyuration Leaus to Ether Rather Than Olenn Formation



and yields 13 as the major product (Scheme 5). Hence, key to the cascade process presented here is the slow formation of

Scheme 5. Conversion of 1-Phenylethanol 8 in the Presence of HOTf



alcohol, which keeps its concentration constantly low. In the presence of a 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 homocoupled product 13 and the trimerization product 14. Higher toluene ratios increase the selectivity toward reductive Friedel-Crafts alkylation, and with 40 equiv 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.

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 and 2). Anisole was alkylated in the para- and ortho-positions, in analogy to the general selectivity of the Friedel–Crafts alkylation of monosubstituted arenes (entry 3).⁶⁵ Modification of the ketone substrate from acetophenone to benzophenone **16**

Entry	Carbonyl compound	Aryl compound	Product	Isolated yield (conversion)
1		¢.		94% (100%)
2	Ph 7			98% (100%)
3	Ph 7	\mathcal{O}_{σ}	(4.8:1)	98% (100%)
4	Ph Ph 16			97% (100%)
5	Ph Ph 16	\bigcirc	Ph Ph 23-para (4.7:1) 23-ortho	97% (100%)
6	Ph H Ph 16	\bigcirc	Ph Ph 24	79% (100%) ^b
7	Ph ^ 0 17		Ph 25	98% (100%)
8	Ph 🔨 O 17	Û	Phartic Phartie Pharti	95% (100%)
9	Ph Ph 18	\mathbf{A}	Ph 27 (1:3) Ph Ph Ph Ph Ph Ph Ph Ph	95% (100%)

Table	e 3.	Substrate	Scope for	Reductive	Friedel-	-Crafts	Alkylation"	
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^{*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 the side product.

resulted in quantitative conversion to triarylmethanes 22–24 (entries 4–6). Monitoring of the reaction of reductive Friedel–Crafts alkylation of mesitylene with benzophenone by ¹H NMR spectroscopy indicated a transient resonance at $\delta_{\rm H}$ = 5.80 assigned to carbinol proton Ph₂CH-OH (Figures S76 and S78), in agreement with the higher resistance of this intermediate toward dehydration than 1-phenylethanol formed from acetophenone. Time-dependent analysis of the reaction composition provides excellent fit with a consecutive reaction and a markedly lower rate constant for hydrogenation, $k_{\rm hydrog}$ = 0.35 h⁻¹, than the subsequent Friedel–Crafts coupling, $k_{\rm FC}$ = 4.3 h⁻¹ (Figure 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 and 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).

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 antitumor⁷⁰ and antibacterial⁷¹ agents. For instance, triarylmethane **31** composed of three different aryl groups displays attractive antibacterial activity *in vitro* and *in vivo* against *Mycobacterium fortuitum*, *Mycobacterium tuberculosis*, and other nontubercular mycobacteria.⁷² Here, we have applied the iridium-catalyzed reductive Friedel– Crafts cascade to generate the heterotriaryl core of this potent pharmaceutical 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

Scheme 6. One-Step Synthesis of Precursor 30 of the Antimycobacterial Agent 31



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 was coupled with 1-bromo-3-fluorophenyl 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 triarylmethane **30** as a racemic mixture, our work suggests that enantioselective product formation may emerge upon replacing HOTf with a chiral Brønsted acid rather than from an enantiopure iridium complex.

CONCLUSIONS

Here, we provide a synthetic access to iridium complexes 5a-ccontaining both a metal-bound hydride and a triazolylidenebound proton, which can be considered as dihydrogen adducts of complex 6 and consequently serve as a 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 offer 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 more active ketone hydrogenation catalysts that preserve the inertness toward Brønsted acids.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.1c00740.

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 (PDF)

- 3b (CIF)
- 3c (CIF)
- 4a (CIF)
- 4b (CIF)
- 6bb' (CIF)

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

Funding

The authors acknowledge generous financial support from the European Research Council (CoG 615653) and from the Swiss National Science Foundation (200021_162868 and 20021_182663, R'equip projects 206021_128724 and 206021_170755).

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The authors thank Aino Visuri and Fabio Notter for technical assistance and the group of Chemical Crystallography of the University of Bern for the X-ray analysis of all reported structures. They acknowledge generous financial support from the Swiss National Science Foundation (20020_182663).

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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 (Figure 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** (Figure S44) and lacked a m/z signal for an iridium species with bound triflate (Figure S45).

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