

Iron-Catalyzed Nucleophilic Addition Reaction of Organic Carbanion Equivalents via Hydrazones

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Supporting Information

ABSTRACT: Earth-abundant and well-defined iron complexes are found to be cheap and effective catalysts for a series of *"umpolung"* nucleophilic additions of hydrazones. The new catalytic system not only maintains the broad substrate scope of an earlier expensive ruthenium system but also attains chemoselectivity of different kinds of carbonyl groups. Furthermore, the iron catalyst enables this reaction at ambient temperature.



C arbon-skeleton construction is the basis of organic synthesis and the core for forming various organic molecules, in which the nucleophilic reactions of carbanion and its equivalents play a vital role.¹ In classic carbanion addition reactions, stoichiometric amounts of metals are usually needed (Scheme 1, a).¹ Inspired by the classical



Wolff–Kishner reduction,² we have recently found that hydrazones, readily generated *in situ* from aldehydes and hydrazine, can serve as an alkyl carbanion equivalent³ to undergo nucleophilic additions.⁴ In these cases, the hydrazone was established as an organic carbanion equivalent based on just a catalytic amount of metal catalyst rather than a stoichiometric amount of metal reagent. To date, a range of such hydrazone reactions including carbonyl additions,⁵ imine additions,⁶ conjugate additions,⁷ and CO₂⁸ addition have been realized with ruthenium catalysts (Scheme 1, b). Nevertheless, as noted earlier,⁵ the required catalyst is based on a scarce and precious ruthenium. Therefore, major efforts have been made

to develop earth-abundant metal-catalyzed related addition reactions to make the carbanion chemistry safer, cheaper, and more practical.

Iron, an inexpensive and earth-abundant metal, is one of the ideal catalysts for organic reactions. So far, a considerable number of iron-catalyzed organic reactions have been studied by chemists, such as free radical reactions, cross-coupling reactions, C–H functionalizations, Lewis acid–base reactions, etc.⁹ Until now, however, reports about an iron-based Grignard-type reaction have been limited, among which a stoichiometric amount of metal still cannot be avoided.^{9a–h} Early in 1961, a series of iron–bisphosphine complexes were reported,¹⁰ which could coordinate and interact with hydrazine derivatives with the help of a base as was shown by the later literature.¹¹ Thus, we hypothesized that an iron–phosphine complex might also catalyze the nucleophilic addition of hydrazone (as carbanion equivalents) for different kinds of transformations of electrophiles.

Moreover, utilizing such complexes to catalyze organic reactions is of great significance because most earlier studies, as we mentioned above, on related iron—bisphospine complexes were limited to stoichiometric transformations of the complexes themselves instead of being applied to catalyze an organic reaction.

To proceed, several key challenges were envisioned: first, iron is a first-row transition metal which is a comparatively harder Lewis acid and is more likely to coordinate with harder ligands such as water, hydroxide, and nitrogen-containing compounds.¹² Thus, hydrolysis and hydrazinolysis of the catalyst may occur in the reaction system and should be taken into consideration. Second, iron has two commonly stable oxidation states, iron(II) and iron(III), which can easily interchange.¹³ This implies that an iron complex might interact with other components via oxidation/reduction processes in

Received: May 2, 2018

the reaction and affect the main transformation. With all these regards, herein, we report a well-defined iron-phosphine complex as an effective catalyst for a series of "umpolung" nucleophilic additions of hydrazones to carbonyls, imines, and Michael acceptors, which can even proceed at room temperature with a broad substrate scope (Scheme 1, c).

We initiated our research by selecting different iron salts together with 1,2-bis(dimethylphosphino)ethane (dmpe) as ligand, K_3PO_4 as base, and THF as solvent at 100 °C. A trace amount of the desired product was obtained with FeF₂, FeCl₃ (8% yield), and FeCl₂ as catalyst (Table 1, entries 1–5). With

Table	1.	Investigation	of	Reaction	Co	nditions	a,b
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N ^{-NH2} +			cataly base, add	\vec{t}	- С			
1	а	2a				3aa		
entry	catalyst	ligand	base	additive	solvent	t (°C)	3aa (%) ^b	
1	FeSO ₄	dmpe	K ₃ PO ₄	-	THF	100	0	
2	FeF ₂	dmpe	K ₃ PO ₄	-	THE	100	trace	
3	FeCl ₂	dmpe	K_3PO_4	-	THE	100	trace	
4	FeCl ₃	dmpe	K_3PO_4	-	THE	100	8	
5	Fe(acac) ₃	dmpe	K_3PO_4	-	THF	100	0	
6	FeCl ₃	dppe	K_3PO_4	-	THF	100	0	
7	FeCl ₃	dppp	K_3PO_4	-	THE	100	0	
8	FeCl ₃	dppf	K_3PO_4	-	THF	100	0	
9	FeCl ₃	BINAP	K_3PO_4	-	THF	100	0	
10	Fe 1	-	K_3PO_4	-	THE	100	15	
11	Fe 1	-	K_3PO_4	-	THE	60	trace	
12	Fe 1	-	K_3PO_4	-	THF	rt	20	
13	Fe 1	-	K_3PO_4	CsF	THF	rt	72	
14	Fe 1	-	KO ^t Bu	CsF	THF	rt	56	
15	Fe 1	-	K ₂ CO ₃	CsF	THF	rt	8	
16	Fe 1	-	DABCO	CsF	THF	rt	0	
17 ^c	Fe 1	-	K ₃ PO ₄	CsF	THE	rt	90	
18 ^c	Fe 1	-	K_3PO_4	CsF	DMSO	rt	89	
19 ^c	Fe 1	-	K_3PO_4	CsF	dioxane	rt	trace	
20 ^c	Fe 1	-	K_3PO_4	CsF	DCM	rt	0	
21 ^d	Fe 1	-	K_3PO_4	CsF	THF	rt	97	
22 ^d	Fe 2	-	K ₃ PO ₄	CsF	THF	rt	99	
	Fe 1: [Fe(dmp	e) ₂ Cl ₂] [*] [FeCl ₄] ⁻	Fe 2: Fe(dm	pe) ₂ Cl ₂ dr	mpe = P			

^{*a*}General reaction conditions: **1a** (0.25 mmol), **2a** (0.2 mmol), [Fe] catalyst (5 mol %), ligand (5 mol %), base (50 mol %), additive (50 mol %), solvent (0.2 mL) under N₂ atmosphere. See Supporting Information (SI) for details. ^{*b*1}H NMR yield was determined using 1,3,5-trimethoxybenzene as an internal standard. ^{*c*}20 mg of 4 Å molecule sieve was added in the reaction system. ^{*d*}**1a** solution was treated with 4 Å molecule sieves beforehand. See SI for details.

FeCl₃, we then tested different ligands and found that the desired product could only be formed when dmpe was used as the ligand (Table 1, entry 4, entries 6-9), suggesting that this reaction requires an electron-rich and less bulky ligand. However, further explorations showed that the yield with the FeCl₃ catalyst system was extremely low, and dark particles always formed at the end of the reaction. We attributed these observations to the hydrolysis of FeCl₃ at the high reaction temperature (100 °C), which led to catalyst deactivation. To avoid this problem, we premixed FeCl₃ and dmpe (1:1) to form a stable complex $[Fe(dmpe)_2Cl_2]^+[FeCl_4]^-$ to catalyze the reaction. Unfortunately, only a slight improvement of the yield was observed (entry 10). We then speculated that lowering the reaction temperature may alleviate the hydrolysis problem and thus tested the reaction at lower temperatures (Table 1, entries 10-12). To our surprise, a slightly higher yield (20%) was obtained at room temperature than at 100 °C

(15%), which may be due to the inhibition of side reactions such as hydrolysis of the catalyst. It is also worth noting that at 60 °C the yield was even lower than the one at 100 °C. This might be because, at 60 °C, the hydrolysis and other side reactions are still not efficiently inhibited (as at room temperature), whereas the reactivity of the main reaction is lower than at 100 °C. In order to facilitate the ligand exchange step on iron involved in the catalytic process, CsF was added into the reaction system.¹⁴ Delightfully, we found that addition of 50% of CsF to the reaction system increased the yield to 72% (entry 13). The test of a variety of bases showed that K_3PO_4 provided the best yield of 72% (entries 13–16). A close analysis of the reaction mixture found that significant quantities of both starting materials remained unconverted, which suggested the deactivation of the catalyst during the reaction process. According to the procedure of preparing a hydrazone solution (see SI), a trace amount of water may remain in the reaction system and destroy the iron catalyst slowly via hydrolysis. To test this hypothesis, we added some 4 Å molecular sieves directly to the reaction system under the optimized conditions. Indeed, the yield was increased to 90%, and the starting materials were nearly consumed (Table 1, entry 17). We also tested a series of solvents and found that the reaction worked well in some polar solvents such as THF and DMSO (Table 1, entries 17-20). To simplify the reaction system, we further considered whether the 4 Å molecule sieves could be used to pretreat the hydrazone solution before running the reaction (see SI for details). By doing this, the yield of the product was further increased to 97% (entry 21).

On the basis of these conditions (Table 1, entry 21), a variety of ketones were examined in this catalytic system. However, we discovered that compared with aromatic ketones, aliphatic ketones were much less effective under this catalyst system, with a large amount of side products being generated. One of the key side products was azine, which was formed by the condensation of hydrazones and ketones or hydrolyzed hydrazones. As Fe(III) has a high Lewis acidity due to a high positive charge, we asserted that Fe(III) may also assist azine formation while catalyzing the main reaction. Furthermore, Fe(III) could oxidize the dmpe (sensitive to oxidant), decreasing the catalysis efficiency. To avoid these problems, we considered preparing an Fe(II) dmpe complex, which has a lower Lewis acidity, to catalyze this reaction. Indeed, using $Fe(dmpe)_2Cl_2$, a stable complex readily generated by the literature procedure, instead of $[Fe(dmpe)_2Cl_2]^+[FeCl_4]^-$ as catalyst, gave nearly quantitative yield of the desired product under the same conditions (Table 1, entry 22).

With the newly optimized conditions in hand, the substrate scope of both electrophiles and hydrazones was tested again, and much better results were obtained (Scheme 2). First, different types of carbonyl compounds were studied. For acetophenone derivatives, most have high reactivities. Other alkyl aryl ketones also reacted very well, with a slight decrease in yield for longer alkyl chains 3aa-3ca. When changing the alkyl to trifluoromethyl, a very strong electron-withdrawing group, the reaction also gave an extremely high yield (3da). However, benzophenone has a much lower reactivity (3ea). Acetophenones bearing either electron-donating or electronwithdrawing groups gave good yields of the desired products 3fa-3ja. As previously mentioned, iron can also serve as an efficient Lewis acid to catalyze the nucleophilic (both C- and N-) addition to carbonyl compounds, and a main side reaction for aliphatic ketone substrates was the nucleophilic attack by



Scheme 2. Substrate Scope of Carbonyl Compounds and Michael Acceptors^{a,b}

^{*a*}Reaction conditions: For **3ta**–**3wa**, **1** (0.2 mmol), **2** (0.3 mmol), $Fe(dmpe)_2Cl_2$ (5 mol %), base (50 mol %), CsF (50 mol %), and solvent (0.2 mL), rt under N₂. For the rest, **1** (0.25 mmol), **2** (0.2 mmol), $Fe(dmpe)_2Cl_2$ (5 mol %), base (50 mol %), CsF (50 mol %), and solvent (0.2 mL), rt under N₂. See SI for details. Condition A: base: K₃PO₄, solvent: THF. Condition B: base: K₃PO₄, solvent: DMSO. Condition C: base: 'BuOK, solvent: THF. ^bYield of isolated product is reported unless noted. ^cThese products are volatile. ¹H NMR yield was determined using 1,3,5-trimethylbenzene as standard.

the nitrogen on hydrazone to form azine. For linear aliphatic ketones, the shorter the aliphatic chain, the less side products were formed (3ka-3ma). For cyclic ketones, both cyclopentanone and cyclohexanone, as well as some derivatives, could give good yields of the final products 30a-3pa. Ketone substrates containing methoxy or cyclopropyl also gave good yields and sometimes better yields than simple alkyl ketones (3na, 3qa). Aldehydes, being much more reactive than ketones, also worked in this reaction. However, due to their high reactivity, the competing azine formation was difficult to prevent. Under the standard conditions, less than 50% yield of the desired product was obtained. To improve the yield, we considered two possible solutions: to use a stronger base, such as ^tBuOK, or to use DMSO as the solvent (since the azine product was always harder to form in DMSO).¹⁵ After testing these two ideas, we found that using 'BuOK as the base and running the reaction in THF gave the desired product in higher yields for aldehydes (3ra-3sa, 3xa).

In addition to carbonyl 1,2-additions, the iron-phosphine complex also catalyzes the Michael addition of hydrazones to activated alkenes (**3ta-3wa**). To our delight, in contrast to our previously reported ruthenium-catalyzed conjugate addition, Michael acceptors lacking an oxygen coordinating group such

as acrylonitrile also work in this reaction system, which may greatly broaden the scope of conjugate addition of hydrazones. Next, we tested different kinds of hydrazones as nucleophiles in this reaction and found that the scope of hydrazone was relatively limited. Only aromatic aldehyde hydrazones worked well in this reaction. For aliphatic hydrazone, no desired product was observed (3aj). The different behaviors of aromatic and aliphatic hydrazones may be due to the fact that for aromatic hydrazones, the aromatic ring can stabilize the adjacent partial carbanion, while for the aliphatic one, such a stabilization is absent. Thus, for the same reason, hydrazones from aromatic aldehydes with electron-withdrawing groups on the para position generally had high reactivity, and all gave quantitative yields (3ab-3ac). In contrast, when electrondonating groups were in the para position, the hydrazone did not react well in THF. In such cases, the reaction can be improved by using DMSO as solvent (3ad, 3ah). Substituents at the meta position did not influence the reaction significantly (3ae-3ag). Apart from these, other types of aromatic hydrazones also gave high yields of the desired products (3ai).

Aromatic imines, comparatively weaker electrophiles, can also undergo similar nucleophilic addition with hydrazone (Scheme 3). Their reactivity, however, is much lower than



"Reaction conditions: 1 (0.25 mmol), 2' (0.2 mmol), $Fe(dmpe)_2Cl_2$ (5 mol %), K_3PO_4 (50 mol %), CsF (50 mol %), and solvent (0.2 mL), rt under N₂. See SI for details. ^bYield of isolated product is reported unless noted. *These products cannot be isolated efficiently because of similar polarity to byproduct and the low yield. ¹H NMR yield was determined using 1,3,5-trimethylbenzene as an internal standard based on the previous literature.⁸ **The side reaction was observed by the standard ¹H NMR peaks of side products 4* and 5*.

carbonyl compounds, and the substrate scope is more narrow than those. Generally speaking, imines with electron-deficient aromatic substituents favor the reaction (4aa-4ca) with various aromatic aldehyde hydrazones (4aa-4ac, 4ba, 4bb). With electron-rich aromatic rings as substituents, the imine showed low or no reactivity (4da-4ea). On the other hand, a strong electron-withdrawing group other than an aromatic ring on imine nitrogen failed to generate the target product (4fa), and the azine byproduct was formed almost quantitatively.

To study the chemoselectivity of this reaction, we designed competition experiments shown in Scheme 4. Using a 1:1 mixture of acetophenone and acetone, the nucleophilic addition of acetophenone was much more favored than that of acetone, suggesting higher reactivity of acetophenone derivatives than aliphatic ketones for such reactions (eq 1).

Scheme 4. Chemoselectivity Study



Replacing acetone with a long-chain aliphatic ketone increased the product ratio in favor of the acetophenone addition product (eq 2). The reactivity of benzophenone is also much lower than acetophenone probably due to its high steric effect (eq 3). Based on these analysis, we concluded that acetophenone derivatives are more reactive for this transformation than other kinds of ketone substrates.

In conclusion, we have successfully established the use of earth-abundant and well-defined iron complexes to catalyze the nucleophilic additions of hydrazones to a broad scope of carbonyl compounds, imines, and Michael acceptors at room temperature. The study not only marks the first abundantmetal-catalyzed nucleophilic reaction of an organic carbanion equivalent via hydrazones but also opens up a potentially new avenue in homogeneous iron catalysis. In addition, unlike classical Grignard-type reactions, chemoselectivity of various kinds of carbonyl groups can be realized by this reaction. The mechanism,¹⁶ asymmetric studies, and synthetic applications of this reaction and this catalytic system are under further investigation.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.or-glett.8b01391.

General experimental information, experimental procedures, additional control experiments to understand the mechanism, a plausible mechanism for the iron-catalyzed nucleophilic reaction of hydrazones, reaction of **1a** with **2a** at 1 mmol scale, spectroscopic data of products, reference, and NMR spectra of products (PDF)

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The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The authors acknowledge the Canada Research Chair Foundation (to C.-J. Li), the CFI, FRQNT Center for Green Chemistry and Catalysis, NSERC, and McGill University for support of our research. J.G. thanks China Scholarship Council for a visiting scholarship. The authors thank Z. Hearne for proofreading.

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(15) When we pregenerate hydrazone in THF and some other solvents, the azine byproduct, more or less, can be observed. However, in DMSO, we cannot observe any azine product.

(16) A plausible mechanism together with some related control experiments were included in the SI for reference.