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A Simple, Nontoxic Iron System for the Allylation of Zinc Enolates

Gopala K. Jarugumilli and Silas P. Cook*

Department of Chemistry, Indiana University, 800 East Kirkwood Avenue, Bloomington,
Indiana 47405-7102, United States

sicook@indiana.edu

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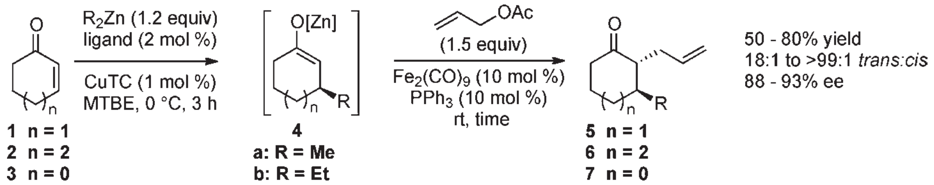
ABSTRACT



Diiron nonacarbonyl in combination with triphenylphosphine has been identified as a low-cost and environmentally benign catalyst system for the allylation of zinc enolates generated in situ from copper-catalyzed asymmetric conjugate addition reactions. The catalyst system provides the allylated product in modest to good yields at room temperature with unprecedented diastereoselectivity in cyclic enone systems. While triphenylphosphine was uniquely effective among the investigated ligands, the exact nature of the active catalytic species remains unknown.

Allylic nucleofuges typify the more reactive alkyl electrophiles available to organic chemists today. However, while allylic alkylation represents one of the more facile carbon–carbon bond-forming processes, additional control of reactivity and selectivity has been realized through the use of transition-metal catalysis.[1] Although allylic alkylation reactions catalyzed by palladium have been the most thoroughly investigated, various procedures involving ruthenium,[2] iridium,[3] molybdenum,[4] tungsten,[5] copper,[6] nickel,[7] and iron[8] have also been reported. Unfortunately, these procedures suffer from the use of costly transition metals,[2−4] exotic and/or expensive ligands,[4,6,7] elevated reaction temperatures,[3,5,8] or multistep catalyst preparation.[8]

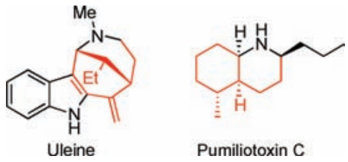


Figure 1. Natural products recently synthesized from intermediates **5a** and **5b** (the substructures of which are highlighted in red).[9]

New routes to enantiomerically pure carbocyclic ketones need continued innovation since these compounds function as important intermediates in the synthesis of biologically relevant molecules. Specifically, building blocks such as **5**−**7** (see abstract) have been used in the synthesis of potential drug candidates and numerous natural products (Figure 1).[9] During a recent foray into the synthesis of another natural product, we sought an inexpensive, simple transition-metal complex to catalyze allylic alkylations. Early work with iron catalysts utilized pyrophoric Na[Fe(CO)$_3$(NO)] that was later

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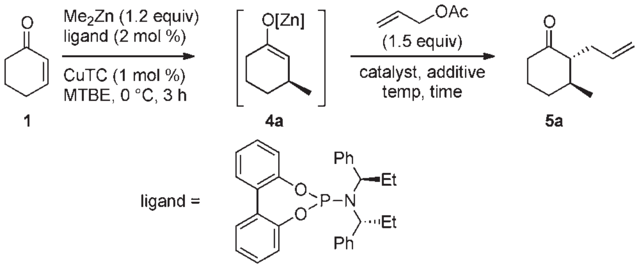
10.1021/ol200059u

refined to the air-stable, soluable, and nonpyrophoric ^{n}Bu$_4$N[Fe(CO)$_3$(NO)] by Zhou and co-workers.[8] Further refinements came when Plietker et al. introduced phosphines and N-heterocyclic carbene (NHC) ligands to improve regioselectivity and catalytic activity while allowing the use of N- and S-nucleophiles.[10] This system was extended to decarboxylative etherification reactions by Tunge and co-workers.[11] While these important studies demonstrate the versatility of the ^{n}Bu$_4$N[Fe(CO)$_3$(NO)] system, the requisite multistep catalyst preparation and elevated reaction temperatures were unsuitable for our needs. To overcome these issues, we began evaluating potential catalysts in the context of zinc enolates, which generally behave as relatively weak nucleophiles.[12] To that end, we were intrigued by reports detailing the use of diiron nonacarbonyl (Fe$_2$(CO)$_9$) in the allylic alkylation of malonate derivatives.[13]

Table 1. Allylation with Palladium and Iron Catalysts[a]

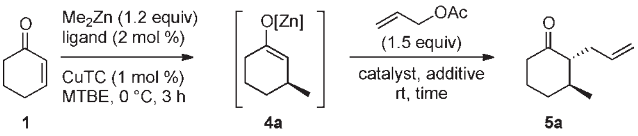


entry	catalyst	additive	time (h)	temp (°C)	yield (%)	dr (*trans*:*cis*)
1	-	-	12	rt	NR	ND
2	Pd(PPh$_3$)$_4$ (1 mol %)	-	12	rt	70	9:1
3	Pd(PPh$_3$)$_4$ (2 mol %)	-	12	rt	90	9:1
4	^{n}Bu$_4$N[Fe(CO)$_3$(NO)] (10 mol %)	-	96	rt	25	ND
5	^{n}Bu$_4$N[Fe(CO)$_3$(NO)] (10 mol %)	-	14	60	50	3:1
6	Fe$_2$(CO)$_9$ (10 mol %)	-	96	rt	15	ND
7	**Fe$_2$(CO)$_9$ (10 mol %)**	**PPh$_3$ (10 mol %)**	**4**	**rt**	**80**	**41:1**
8	-	PPh$_3$ (10 mol %)	24	rt	NR	ND
9	Fe$_2$(CO)$_9$ (2.5 mol %)	PPh$_3$ (5 mol %)	8	rt	60	30:1

[a] NR = no reaction; ND = not determined.

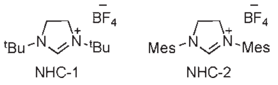
To begin our studies, a small panel of transition-metal complexes were evaluated for their ability to effect the allylation of zinc enolates produced from the asymmetric copper-catalyzed conjugate addition of dimethylzinc (Table 1). In accord with previous observations,[9c,14] tetrakis(triphenylphosphine)-palladium provided the desired product in excellent yield (90%) and decent dr (9:1 *trans*/*cis*) (Table 1, entry 3). Employing the iron complex ^{n}Bu$_4$N[Fe(CO)$_3$(NO)] resulted in a modest 25% yield at room temperature (Table 1, entry 4) and 50% yield at 60 °C with only a 3:1 dr (Table 1, entry 5). Interestingly, the ^{n}Bu$_4$[Fe(CO)$_3$(NO)]-catalyzed reaction was inhibited in the presence of triphenylphosphine. Subjecting zinc enolate **4a** to allyl acetate in the presence of Fe$_2$(CO)$_9$ produced 15% of desired product **5a** after 4 days at room temperature (Table 1, entry 6). Furthermore, the same reaction conducted at elevated temperatures lacked any detectable product **5a**, likely due to product decomposition.[15] When the allylation of zinc enolate **4a** was promoted with Fe$_2$(CO)$_9$ (10 mol %) in the presence of triphenylphosphine (10 mol %), however, a remarkable acceleration in reaction rate was accompanied with an 80% yield and 41:1 dr (Table 1, entry 7). We believe this to be the highest *trans*/*cis* ratio reported for a conjugate addition/allylation sequence reported to date. Lowering the catalyst loading to 2.5 mol % Fe$_2$(CO)$_9$ resulted in slightly diminished yield and dr (Table 1, entry 9).

Table 2. Ligand Influence on Catalyst System[a]



entry	catalyst	additive	time (h)	yield (%)	dr (*trans*:*cis*)
1	Fe$_2$(CO)$_9$ (10 mol %)	Me$_2$NH (10 mol %)[b]	24	20	9:1
2	Fe$_2$(CO)$_9$ (10 mol %)	morpholine (10 mol %)	24	25	10:1
3	Fe$_2$(CO)$_9$ (10 mol %)	PCy$_3$ (10 mol %)	24	15	9:1
4	Fe$_2$(CO)$_9$ (10 mol %)	P(^{n}Bu)$_3$ (10 mol %)	24	31	9:1
5	**Fe$_2$(CO)$_9$ (10 mol %)**	**PPh$_3$ (10 mol %)**	**4**	**80**	**41:1**
6	**Fe$_2$(CO)$_9$ (10 mol %)**	**P(p-tol)$_3$ (10 mol %)**	**14**	**68**	**20:1**
7	Fe$_2$(CO)$_9$ (10 mol %)	P(p-MeOPh)$_3$ (10 mol %)	8	71	26:1
8	Fe$_2$(CO)$_9$ (10 mol %)	P(2-furyl)$_3$ (10 mol %)	24	20	18:1
9	Fe$_2$(CO)$_9$ (10 mol %)	NHC-1/^{t}BuOK (10 mol %)	24	NR	NA
10	Fe$_2$(CO)$_9$ (10 mol %)	NHC-1/NaH (10 mol %)	24	NR	NA
11	Fe$_2$(CO)$_9$ (10 mol %)	NHC-2/^{t}BuOK (10 mol %)	24	10	ND
12	Fe$_2$(CO)$_9$ (10 mol %)	NHC-2/NaH (10 mol %)	24	NR	NA

[a] NR = no reaction; ND = not determined; NA = not applicable; Mes = mesityl group. [b] 2 M solution in THF.



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[14] Naasz, R.; Arnold, L. A.; Minnaard, A. J.; Feringa, B. L. *Chem. Commun.* **2001**, 735.

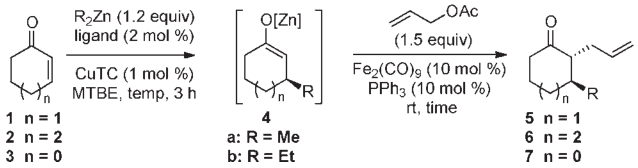
[15] Extended reaction times under these conditions routinely led to lower yields of **5a**.

A cursory ligand survey revealed triphenylphosphine to be unusually effective at enhancing the reactivity (Table 2, entry 5). Even relatively minor changes to tri-*p*-tolylphosphine or tri-*p*-methoxyphenylphosphine resulted in longer reaction times, lower yields, and compromised dr's (Table 2, entries 6 and 7). Substantially more electron-donating phosphines such as tri-*n*-butyl- or tricyclohexylphosphine or electron-deficient phosphines such as tri(2-furyl)phosphine did not support efficient catalysis (Table 2, entries 3, 4, and 8). In contrast to previous work with $Fe_2(CO)_9$ and malonates, amine-based ligands demonstrated a relatively small effect on the reaction (Table 2, entries 1 and 2).[13c]

The unusually high dr was consistent throughout the course of the reaction as verified by samples obtained at low reaction conversion. Additionally, reaction times extended well beyond full conversion led to an erosion in the *trans*/*cis* ratio. The thermodynamic preference for dr appears to be about 2.4:1 *trans*/*cis* as determined by base-catalyzed epimerization studies. Furthermore, a variety of allylic electrophiles such as allylic iodides, bromides, sulfonyl esters, and different carbonates all proved inferior to allyl acetate.[16]

We further probed the scope of this reaction with substrates such as cyclopentenone (**3**) and cycloheptenone (**2**). In the context of cyclohexenone (**1**), dimethylzinc resulted in a higher yield and dr when compared to diethylzinc (Table 3, entries 1 and 2). Interestingly, while dimethylzinc resulted in somewhat diminished yields when compared to diethylzinc with cycloheptenone, the dr was well over 99:1 (Table 3, entries 3 and 4). In line with previous results, the copper-catalyzed conjugate addtion of dimethylzinc into cyclopentenone was problematic (Table 3, entry 6).[17] The use of diethylzinc, however, was successful and produced the desired product **7b** in a modest 50% yield and an 18:1 dr. Although the yields are not uniformly high, the diastereoselectivity of the overall reaction represents a significant improvement over current methods. While for some substrates the low yields could be attributed to incomplete conjugate addition (Table 3, entries 4 and 6), in general longer than necessary reaction times led to product decomposition and lower yields.

Table 3. Allylation of Various Enones with Iron Catalyst[a]

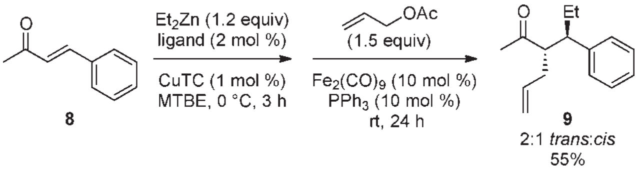


entry	n	product	R_2Zn	temp (°C)	time (h)	yield[b] (%)	dr (trans:cis)	ee (%)
1	1	**5a**	Me	0	4	80	41:1	93
2	1	**5b**	Et	– 30	12	71	30:1	90
3	2	**6a**	Me	0	24	55	>99:1	ND
4[c]	2	**6a**	Me	– 30	24	30	>99:1	90
5	2	**6b**	Et	– 30	24	60	35:1	88
6	0	**7a**	Me	0	-	-	-	NR
7	0	**7b**	Et	– 30	24	50	18:1	ND

[a] NR = no reaction; ND = not determined. [b] Isolated yields. [c] 15 h for conjugate addition.

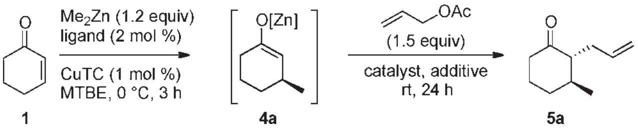
The extension of this methodology to acyclic systems met with limited success. While the reaction of zinc enolates generated from acyclic enones provided products in modest yields, the diastereoselectivity was significantly diminished (Scheme 1). Additionally, the move to more substituted allyl acetates proved synthetically unviable. A reexamination of the iron source and additives led to only limited yields of the desired product.

Scheme 1. Allylation of Zinc Enolates Generated from the Asymmetric Conjugate Addtion to Acyclic Enones



The narrow requirement for triphenylphosphine led to the preparation of several potential active catalyst species (Table 4). Interestingly, no combination of $Fe(CO)_5$ and PPh_3 could reproduce the rate and yield observed for $Fe_2(CO)_9$ and PPh_3 (Table 4, entries 3 to 7). Furthermore, phosphine loadings of less than a 1:2 molar ratio of

Table 4. Examination of Various Iron Sources for Their Ability To Catalyze the Allylation of Zinc Enolates[a]



entry	catalyst	additive	yield (%)	dr (*trans*:*cis*)
1	$Fe(CO)_4PPh_3$ (5 mol %)	-	NR	ND
2	$Fe(CO)_3(PPh_3)_2$ (5 mol %)	-	5	ND
3	$Fe(CO)_5$ (5 mol %)	PPh_3 (10 mol %)	35	16:1
4	$Fe(CO)_5$ (10 mol %)	PPh_3 (20 mol %)	51	28:1
5	$Fe(CO)_5$ (10 mol %)	PPh_3 (30 mol %)	50	25:1
6	$Fe(CO)_5$ (20 mol %)	PPh_3 (40 mol %)	56	48:1
7	$Fe(CO)_5$ (20 mol %)	PPh_3 (10 mol %)	56	40:1

[a] NR = no reaction; ND = not determined.

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(16) See Supporting Information for a table of representative allylic electrophiles.

(17) (a) Degrado, S. J.; Mizutani, H.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2001**, *123*, 755 and references therein.

phosphine/Fe produced low (< 15%) yields while molar ratios up to 2:1 had little effect on the yield or dr.[18] These data suggest a heterogeneity among active iron species produced from $Fe_2(CO)_9$ and PPh_3. To compare the activity of potential active iron catalysts, both $Fe(PPh_3)(CO)_4$ and $Fe(PPh_3)_2(CO)_3$ were prepared according to known literature procedures.[19] Investigation of these complexes in the allylation of zinc enolates revealed them to be nearly inactive (Table 4, entries 1 and 2). Additionally, photolysis of $Fe_2(CO)_9$ to generate $Fe(CO)_5$ and $Fe(CO)_4$ failed to produce a viable catalyst for the reaction. Currently, the specie(s) generated from $Fe_2(CO)_9$ and PPh_3 responsible for the observed activity remain elusive.

In summary, the equimolar combination of diiron nonacarbonyl and triphenylphosphine produces a cheap, nontoxic catalytic system for the allylation of zinc enolates in reasonable yields and high *trans* to *cis* ratios. The efficiency of the system allows the reactions to be run under mild conditions at room temperature. While the exact nature of the active catalytic specie(s) remains unknown, the operational simplicity and affordability of this system should result in the widespread adoption of this technology. Current work is aimed at elucidating the active catalytic specie(s) and expanding the reaction scope of both the nucleophile and electrophile.

Acknowledgment. Financial support for this work was provided by Indiana University.

Supporting Information Available. Experimental procedures describing the synthesis of compounds **5**−**7** and **9**, as well as the characterization data, are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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[18] See Supporting Information for a table of PPh_3 loading with $Fe_2(CO)_9$.

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