

α -Alkylation of Ketones by Addition of Zinc Enamides to Unactivated Olefins

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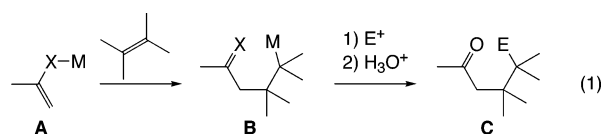
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Abstract: A zinc enamide generated from the corresponding *N*-aryl imine undergoes addition to an unactivated olefin, such as ethylene, 1-octene, and isobutylene, to generate an α -alkylated γ -zincioimine intermediate in good to excellent yield. Terminal and *gem*-disubstituted olefins react with >99% regioselectivity, allowing the C–C bond formation to take place at the more hindered carbon of the double bond. The organozinc intermediate undergoes further C–C bond formation with a carbon electrophile to give, upon hydrolysis of the imine, an α -alkylated ketone bearing a variety of functionalized primary, secondary, and tertiary alkyl groups.

Introduction

Addition of a metal enolate to a carbonyl compound is a fundamental repertoire for carbon–carbon bond formation. However, little attention has been paid to its isoelectronic olefinic variant, addition of a metal enolate to a simple olefin, because of its unfavorable thermodynamics and kinetics. One naturally expects that the addition of a heteroatom-stabilized anion **A** across an unactivated carbon–carbon double bond would first require a high activation energy, and second suffer from unfavorable thermodynamics.^{1,2} Despite this inherent difficulty, such a transformation would provide an alternative approach for the α -alkylation of carbonyl compounds:³ (1) a sequential three-component coupling reaction that affords multifunctionalized compounds unavailable by the conventional alkylation or Michael addition reactions; (2) the use of industrially abundant alkenes that have been scarcely utilized for the synthesis of fine chemicals; and (3) the synthesis of α -secondary and α -tertiary alkylated ketones from substituted alkenes that continues to be difficult in the conventional alkylation reaction relying on the use of a secondary⁴ or tertiary alkyl halide.⁵

We previously reported the addition⁶ of a zincated hydrazone **A** ($X = \text{NN}(\text{CH}_3)_2$, $M^+ = (\text{C}_4\text{H}_9)\text{Zn}^+$)⁷ to a variety of alkenes



X; O, NR, M^+ ; counter metal cation, E^+ ; electrophile

such as ethylene and vinyl metals,⁸ and an asymmetric synthesis of α -substituted ketones by the reaction of a chiral zinc enamide **A** ($X = \text{chiral amino ether}$, $M^+ = \text{CH}_3\text{Zn}^+$).⁹ Whereas the carbocation and the successive electrophilic trapping have been achieved in high overall yield for ethylene, the first reaction with substituted alkenes^{7a} was found to be too slow to be synthetically useful.¹⁰ We decided to systematically reinvestigate the imine and hydrazone compounds to achieve high reactivity and selectivity toward unactivated olefins so that we could establish the carbometalation approach as a generally useful α -alkylation reaction of carbonyl compounds.

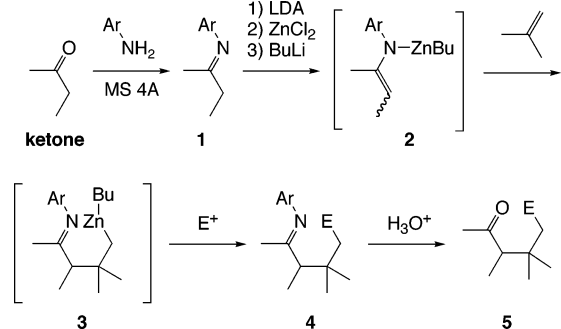
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Scheme 1. α -Alkylation of Ketone by Carbometalation Approach



We found a significant increase of the reactivity of the zinc enamide by proper choice of the nitrogen substituent, and that the enamide thus reacts smoothly with 1-alkenes. The carbometalation reaction generates a γ -zincioimine intermediate in high yield, which can then be trapped with a variety of carbon electrophiles either with or without a transition metal catalyst. The overall result represents an efficient cross-coupling reaction of an imine, an alkene, and a carbon electrophile under mild reaction conditions. One bonus is that the reaction provides a new entry to α -secondary and α -tertiary alkylated ketones that have been difficult to obtain by the conventional method relying on the reaction of a metal enamide or enolate with an alkyl halide.

Results and Discussion

Scheme 1 outlines the procedure for the alkylation of a ketone based on our carbometalation approach. The imine **1** prepared from the corresponding ketone is deprotonated with lithium diisopropylamide (LDA). The resulting lithium enamide was allowed to react with zinc chloride and then with butyllithium to generate the *N*-aryl zinc enamide **2**. The reaction of **2** with a variety of simple olefins was examined under neat conditions or in hexane. The γ -zincioimine product **3** was trapped with an electrophile to obtain primary, secondary, and tertiary alkylated ketones **5** after hydrolysis of the imine group in **4**.

Reaction of 1-Octene and Isobutylene with Zinc Enamide Possessing a Variety of Substituents on Enamide Nitrogen.

In the past several years,^{7,8a,9} we have examined imine, oxime, and hydrazone derivatives of several ketones as a metal enamide precursor, and eventually we focused our attention on the imines bearing a variety of aryl substituents on the nitrogen atom, which are expected to exert electronic and steric influences directly on the transition state of the carbometalation reaction. We first studied the addition of a variety of zinc enamides to 1-octene, which gave poor results under our previous conditions developed for zincated hydrazones.^{7a}

The zinc enamide **7** was prepared from the corresponding 3-pentanone imine **6** by a sequence of deprotonation with *tert*-butyllithium (or LDA, vide infra), transmetalation with zinc chloride, and ligand exchange with butyllithium (Scheme 1). The ligand exchange is necessary to accelerate the addition reaction, as we previously noted.^{7,9} The butyl group was chosen here because of its availability, while methyl and *tert*-butyl ligands are equally useful. Solvent was removed in vacuo from the solution of **7**, and 1-octene was then added. The addition reaction was initiated at 60 °C and continued for 24 h. Note that our previous conditions, optimized for the addition of a zincated hydrazone such as **7** [R = N(CH₃)₂] to 1-octene, call

for a temperature of 30 °C for 11 days in Et₂O to achieve 30% yield.^{7a} The carbometalation reaction took place with 100% regioselectivity, favoring the C–C bond formation at the C-2 position of the 1-octene.^{7a,9} After protonation of the carbon–zinc bond and hydrolysis of the imine moiety with acetic acid, the ketone **8** was obtained as a mixture of diastereomers (syn: anti = 7:3 to 6:4). The poor diastereoselectivity may be attributed to mutual face selection and/or the geometrical flexibility of the zinc enamide intermediate.¹¹

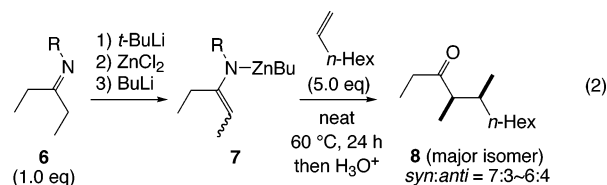


Figure 1 shows the effect of the substituent of the enamide nitrogen atom. The zincated hydrazone **7** [R = N(CH₃)₂] gave the adduct **8** in 28% yield (entry 1). The *N*-cyclohexyl zinc enamide is unstable at room temperature, producing tiny particles of metallic zinc, and hence no adduct was obtained under the reaction conditions (entry 2). The *N*-2-methoxyethyl zinc enamide, on the other hand, is stable under the reaction conditions, but not reactive enough (17% yield, entry 3). The *N*-phenyl zinc enamide showed certain reactivity to give the desired product in 62% yield (entry 4). The *N*-2-methoxy phenyl enamide was less reactive, and the 4-methoxy one was found to be far more reactive (entry 5 vs 6). Finally, 89% yield was achieved by the use of *N*-4-diethylaminophenyl zinc enamide (entry 7). We therefore conclude that an electron-donating substituent enhances the reactivity of zinc enamide.

Having achieved the high-yielding α -secondary alkylation with 1-octene by the use of *N*-aryl zinc enamides, we then examined the reaction of isobutylene so as to perform an α -tertiary alkylation of ketone. We found, at this juncture, that the use of LDA in THF for deprotonation of imine **6** gives a result comparable to that obtained with the use of *t*-BuLi, when resulting diisopropylamine and THF are removed in vacuo before the reaction with ZnCl₂ (eq 3).

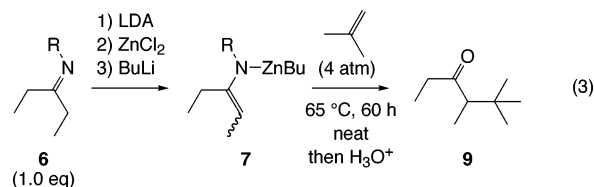


Figure 2 shows the results of the screening of various zinc enamides in the reaction with isobutylene. The zincated hydrazone **7** [R = N(CH₃)₂] gave the α -tertiary butyl ketone **9** as the sole product but only in 6% yield (entry 1). The *N*-cyclohexyl zinc enamide and *N*-2-methoxyethyl zinc enamide did not react with this hindered olefin (entries 2 and 3). The parent *N*-phenyl zinc enamide afforded **9** in 8% yield (entry 4). As found in the reaction of 1-octene, an electron-donating substituent at the 4-position increases the reaction rate and the product yield (entry

(11) The reaction of a cyclohexanone imine with 1-octene showed the same range of the low diastereoselectivity (data not reported). We are thus assuming that the poor diastereoselectivity in the reaction of the 3-pentanone imine is due to low selectivity of mutual face selection, but not to the *E/Z* isomerism of the zinc enamide intermediate.

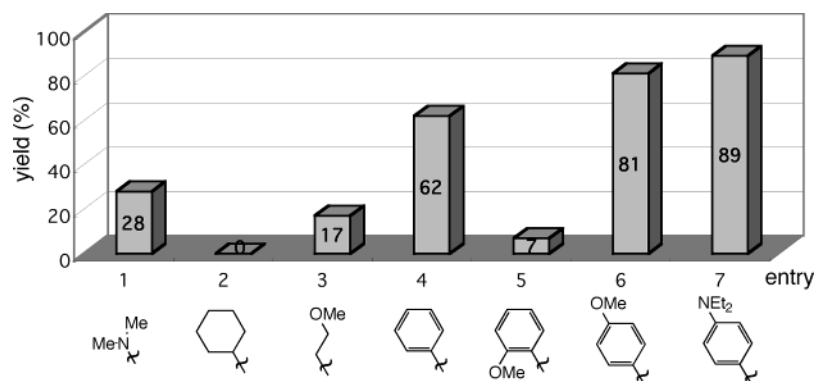


Figure 1. Chemical yields of the reaction of 1-octene with zinc enamides possessing a variety of substituents on the enamide nitrogen. The yield was determined by GC analysis with tridecane as an internal standard.

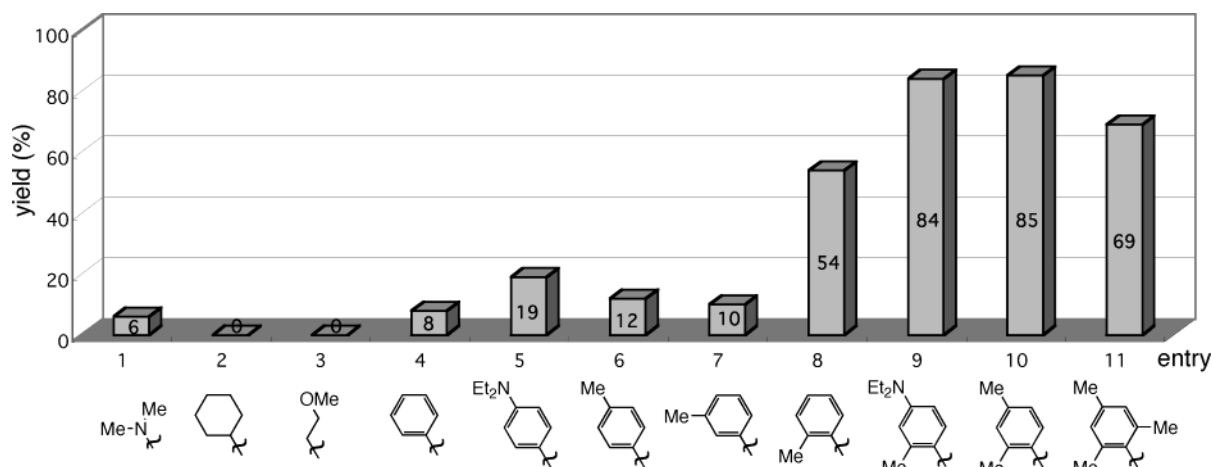


Figure 2. Chemical yields of the reaction of isobutylene with zinc enamides possessing a variety of substituents on the enamide nitrogen. The yield was determined by GC analysis with decane as an internal standard.

5). The 2-methyl substitution enhances considerably the reactivity of the zinc enamide in comparison with the 3- or 4-methyl substitutions (entries 6–8). Whereas a simple electronic effect based on the Hammett rule cannot explain the observed tendency, the 2-methyl substitution can exert a certain steric effect on the transition structure⁹ and may contribute to conformational stabilization of the transition state. 2-Methyl-4-diethylaminophenyl substitution further improved the product yield (entry 9). 2,4-Dimethyl substitution was found to be the optimum in terms of both the reactivity and availability of the starting arylamine (entry 10). 2,4,6-Trimethyl substitution may cause a steric problem to lower the yield (entry 11).

It should be noted that the zinc enamide, which shows excellent reactivity toward the unactivated olefins, does not add to an electron-deficient olefin used commonly as a Michael acceptor under the reaction conditions. For instance, the zinc enamide **10** reacts with *tert*-butyl acrylate to give an acrylate polymer rather than a 1:1 adduct (70% recovery of the parent imine **6**) under the reaction conditions (65 °C, 12 h in hexane), whereas **10** gives the adduct **8** in 92% yield (Table 1, entry 3). As discussed previously for the reaction of an allylic metal compound with an olefin,¹² the present reaction utilizes the favorable interaction between the zinc atom and the olefin as

well as the stability of alkyl zinc intermediate to achieve a useful synthetic outcome.

Addition of the Aryl Zinc Amide to a Variety of Olefins.

Examination of the reactivity of the zinc enamide **10** toward various unactivated olefins revealed the wide scope of the reaction. The high reactivity of **10** is apparent already in the addition to ethylene (entry 1), where the alkylated product was obtained in 94% yield under atmospheric pressure of ethylene; note that zincated hydrazones^{7a} and imines possessing a chiral etheral side chain⁹ require 5–30 atm of ethylene atmosphere to achieve sufficient conversion. The addition to propylene was also accomplished under 1 atm of propylene atmosphere to afford the isopropylated ketone **12** in 86% yield (entry 2).

The high reactivity of the aryl zinc enamide enables us to carry out the addition of **10** to 1-octene by the use of a nearly stoichiometric amount (1.2 equiv) of the olefinic substrate to achieve 92% yield (entry 3), whereas a zincated hydrazone such as **7** [R = N(CH₃)₂] needed 10 equiv of 1-octene to achieve 30% yield, even after 11 days.^{7a} The addition introduces exclusively a secondary alkyl group to the α -position of the ketone. Unfortunately, the relative stereochemistry between the newly formed chiral centers has thus far been uncontrollable, and the ratio stays in a range of 7:3 to 6:4 (syn:anti). Interestingly, the regioselectivity of the addition of **10** to styrene is such that a primary and a secondary alkylated product are produced in a 46:54 ratio (entry 4). The formation of such an isomeric mixture stands in contrast to the general tendency of

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Table 1. α-Alkylation of 3-Pentanone with Various Alkenes

entry	olefin	conditions	product ^a	% yield
1		1 atm, hexane 50 °C, 12 h		94 ^b
2		1 atm, hexane 65 °C, 60 h		86 ^b
3		1.2 eq, hexane 65 °C, 12 h		92 ^{b,d}
4		1.2 eq, hexane 30 °C, 12 h		90 ^{c,e}
5		3.0 eq, neat 65 °C, 72 h		77 ^c
6		4 atm, neat 65 °C, 60 h		85 ^b
7		5 atm, neat 80 °C, 36 h		84 ^b

^a Regioselectivity of the carbocation was >99:1 unless otherwise noted. ^b Determined by GC analysis with decane or tridecane as internal standard. ^c Isolated yield. ^d Syn:anti = 67:33. ^e Linear (**13**):branched (**14**) = 46:54, syn:anti = 66:34.

the carbometalation of styrene,¹³ where a benzylic anion forms preferentially.^{7a,9}

The reaction of methylenecyclohexane illustrates the generality of the tertiary alkylation reaction (77% yield, entry 5). Together with the results shown in Figure 1, entry 6 illustrates the success in the *tert*-butylation with isobutylene (entry 6). Heating at 80 °C accelerates the addition reaction, and a high yield was achieved after a shorter reaction period (36 h), as shown in entry 7.

Alkylation of a Variety of Ketones with Simple Olefins.

Having established an effective procedure for the generation of the zinc enamide and its addition to a simple olefin, we examined the scope of the reaction for the ketone part. The zinc enamide of 5-nonanone **16** reacted with isobutylene more slowly than the lower homologue (Table 2, entry 1). The cyclohexanone zinc enamide **18** was as reactive as **10** to react with ethylene under atmospheric pressure to give 2-ethylcyclohexanone in 90% yield (entry 2). The addition of this cyclic zinc enamide to propylene gave exclusively a branched product, **20** (entry

Table 2. Alkylation of a Variety of Ketones with Alkenes

entry	Zn enamide ^a	olefin	conditions	product ^b	% yield
1			5 atm, neat 80 °C, 72 h		76 ^c
2			1 atm, hexane 65 °C, 24 h		90 ^d
3			8 atm, neat 65 °C, 24 h		88 ^d
4			2 eq, hexane 50 °C, 12 h		87 ^{c,e}
5			5 atm, neat 80 °C, 72 h		24 ^d
6			10 atm, neat 80 °C, 72 h		74 ^c

^a Zinc enamides (Ar = 2,4-dimethylphenyl) were prepared from the corresponding imines. ^b Regioselectivity of the carbocation was >99:1 unless otherwise noted. ^c Isolated yield. ^d Determined by GC analysis with decane as internal standard. ^e Linear:branched = >98:2.

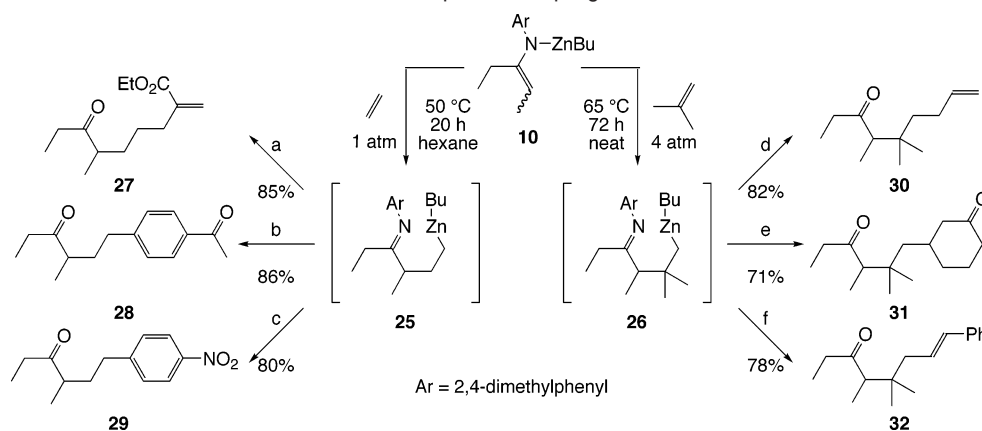
3). The addition to styrene, on the other hand, showed reversed regioselectivity, giving only the linear adduct **21** in 87% yield (entry 4); this selectivity is different also from the one observed for **10** (Table 1, entry 4). The origin of this interesting difference is unclear at this time, but the result suggests that some subtle steric effects overwhelm the electronic effects.³ The cyclic zinc enamide **18** gave 2-*tert*-butylcyclohexanone **22** in 24% yield. An aryl alkyl ketone also took part in the alkylation reaction: the addition of the zinc enamide **23** to propylene proceeded at 80 °C to give the α-isopropylated product **24** in 74% yield (entry 6). An unsymmetrical ketone imine such as 2-methyl-3-pentanone can enolize in two different ways and gave a mixture of α- and α'-alkylated product upon the addition reaction in rather poor yield (data not shown).

Electrophilic Trapping of γ-Zincioimine: One-Pot, Three-Component Couplings. The organozinc intermediates¹⁴ generated by the new carbometalation reaction are stable even at 80 °C and can be used for further C–C bond-forming reaction with or without a transition metal catalyst.¹⁵ Scheme 2 shows the results of the electrophilic trapping of γ-zincioimines **25** and **26**, which are generated by the addition of the zinc enamide **10** to ethylene and isobutylene, respectively.

The zinc intermediate **25** reacts with ethyl 2-bromomethylacrylate to give the ketoester **27** in 85% yield at 25 °C without any additives (Scheme 2a). The Pd-catalyzed cross-coupling

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Scheme 2. Synthesis of Functionalized Ketones via Three-Component Coupling^a

^a Reagents and conditions: (a) ethyl 2-bromomethylacrylate (2.2 equiv), 0 °C, 4 h then H₃O⁺; (b) 4-iodoacetylbenzene (2.2 equiv)/TMEDA (2.0 equiv)/PdCl₂(PPh₃)₂ (5 mol %), 25 °C, 8 h then H₃O⁺; (c) 4-iodonitrobenzene (2.2 equiv)/TMEDA (2.0 equiv)/PdCl₂(PPh₃)₂ (5 mol %), 25 °C, 8 h then H₃O⁺; (d) allyl bromide (2.4 equiv), 25 °C, 3 h then H₃O⁺; (e) iodomethane (0.2 equiv) then in vacuo, 2-cyclohexen-1-one (2.4 equiv)/Me₃SiCl (2.4 equiv)/TMEDA (2.0 equiv)/CuCN (0.3 equiv), 0 °C, 6 h then H₃O⁺; (f) iodomethane (0.2 equiv) then in vacuo, β-bromostyrene (>99.9% E, 2.4 equiv)/TMEDA (2.0 equiv)/CuCN (1.0 equiv), 0 °C, 8 h then H₃O⁺.

reactions with 4-iodoacetylbenzene and 4-iodonitrobenzene proceeded smoothly at 30 °C to yield 86% of the diketone **28** and 80% of the nitro ketone **29**, respectively (Scheme 2b,c), attesting to the high functional group compatibility of such a reaction.⁹ In these latter reactions, the butyl group on the zinc atom that is used as a dummy ligand in the first reaction reacted faster with the electrophile in the second reaction. Therefore, we needed to use at least 2 equiv of the electrophiles.

The addition/trapping sequence can be extended to the more hindered adduct **26** formed by the reaction with isobutylene. For instance, allylation of **30** was achieved in 82% yield without any additives (Scheme 2d). In the presence of 2.4 equiv of Me₃-SiCl¹⁶ and 30 mol % of CuCN, **25** underwent 1,4-addition¹⁷ to 2-cyclohexen-1-one (Scheme 2e) to give the corresponding cyclohexanone derivative **31** in 71% yield after hydrolysis with acetic acid. Coupling with β-bromostyrene (Scheme 2f) proceeded in the presence of 1 equiv of CuCN to afford the cross-coupling product **32** in 78% yield. In this reaction, we added 20 mol % of iodomethane before the 1,4-addition or the coupling with β-bromostyrene for the purpose of trapping of unreacted zinc enamide that interferes with the cross-coupling reaction. *N,N,N',N'*-Tetramethylethylenediamine (TMEDA) was necessary to bring the reaction to completion since the reaction otherwise stopped halfway.¹⁸ The examples of the three-component coupling reactions shown in Scheme 2 demonstrate the new opportunities provided by the present carbometalation reaction in the synthesis of densely functionalized organic molecules.

Conclusion

The addition of a metal enolate or its equivalent to an alkene has thus far been regarded as a difficult reaction to perform

because of its apparently unfavorable thermodynamics.¹⁹ The addition of a zinc enamide to an alkene reported here has opened a new possibility for the chemical transformation in the synthesis of α-alkylated ketones. A particularly useful nature of the present reaction is its potential to introduce a wide variety of secondary and tertiary alkyl groups next to the carbonyl group—a synthetic sequence rather difficult to achieve so far. We have shown that installation of an electron-donating aryl group on the enamide nitrogen dramatically enhances the reactivity of the zinc enamide to effect high-yielding and regioselective carbocation of unactivated olefins. For instance, the zinc enamide **10** undergoes smooth addition to a variety of alkenes to produce the corresponding γ-zincioimines. Furthermore, the organozinc addition product serves as a carbon nucleophile for the succeeding C–C bond formations, which allows further introduction of a wide range of functional groups onto the alkylated carbonyl compounds. We have demonstrated a possibility for the utilization of unactivated olefins, provided directly as a primary product of the chemical industry, for controlled C–C bond formation. The use of industrially abundant carbon resources, such as ethylene and 1-alkenes, is highly attractive and desirable and will become an important subject in organic synthesis.²⁰

Experimental Section

General. Flash column chromatography was performed on Kanto Silica gel 60 (spherical, neutral, 140–325 mesh) as described by Still et al.²¹ High-pressure reactions were conducted in a glass autoclave purchased from Taiatsu Techno Co. (Hyper Glass Cylinder). Proton nuclear magnetic resonance (¹H NMR) and carbon nuclear magnetic resonance (¹³C NMR) spectra were recorded with JEOL AL-400 (400 MHz), JEOL ECX-400 (400 MHz), or JEOL ECA-500 (500 MHz) NMR spectrometers. Gas chromatographic (GC) analyses were performed on Shimadzu GC-14B instruments equipped with an FID detector and a capillary column, HR-1 (Shinwa, 25 m × 0.25 mm i.d.,

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0.25 μm film), or a CP-Chirasil-DEX CB (Chrompack, 25×0.25 mm i.d., 0.25 μm film). IR spectra recorded on a FT/IR-420 (JASCO) or a React IR 1000 reaction analysis system equipped with DuraSample IR (ASI Applied System) are reported in cm^{-1} . High-resolution mass spectra are taken with the EI (electron impact) method on a JEOL GC-mate II. ZnCl_2 (anhydrous, beads) was purchased from Aldrich Inc. 2,4-Dimethylaniline was purchased from Wako Co. Isobutylene was purchased from Tokyo Kasei Kogyo Co. and dried over molecular sieves in an autoclave before use. Ethylene and propylene were purchased from Nippon Sanso Co.

Preparation of Zinc Enamide (Procedure A). To a solution of diisopropylamine (0.16 mL, 1.1 mmol) in THF (1.2 mL) was added dropwise BuLi (1.55 M in hexane, 0.65 mL, 1.02 mmol) at 0 °C. After 30 min, imine **33** (0.209 mL, 1.0 mmol) was slowly added at 0 °C. After 6 h, the solvents were removed in vacuo (30 min, 0 °C, 0.1 mmHg). Residual sludgy lithium enamide was dissolved in Et_2O (0.5 mL), and ZnCl_2 (0.5 M in Et_2O , 2.0 mL, 1.0 mmol) was added at 0 °C. After 30 min, BuLi (1.55 M in hexane, 0.65 mL, 1.0 mmol) was added at -78 °C (or added dropwise at 0 °C), and the reaction mixture was warmed to ambient temperature.

Addition to Ethylene; 4-Methylhexan-3-one (11) (Procedure B). After the reaction performed according to procedure A, Et_2O was removed at 50 °C with N_2 flow. The reaction mixture was heated to 50 °C for 12 h under an ethylene atmosphere (1 atm) and then cooled to 0 °C. Acetic acid (1.0 mL) and water (0.5 mL) were added at 0 °C. Hydrolysis was carried out at room temperature for 1 h, and then water (4.5 mL) was added at that temperature. The aqueous layer was extracted five times with pentane. The combined organic extracts were washed sequentially with saturated aqueous sodium bicarbonate, 0.5 N HCl, and saturated aqueous sodium bicarbonate. Gas chromatography analysis was carried out (94% yield) by using decane (39.0 μL , 0.2 mmol) as an internal standard. The organic layer was chromatographed on silica gel (3 g, pentane and then 3% Et_2O in pentane) to obtain the corresponding ketone (0.068 g, 60% yield).

Addition to 1-Octene; 4,5-Dimethylundecan-3-one (8). After the reaction performed according to procedure A, the solvents were removed in vacuo (10 min, room temperature, 0.1 mmHg). 1-Octene (0.19 mL, 1.2 mmol) and hexane (0.1 mL) were added, and then the reaction mixture was heated to 65 °C for 12 h. Acetic acid (1.0 mL) and water (0.5 mL) were added at 0 °C. Hydrolysis was carried out at 65 °C for 1 h, and then water (4.5 mL) was added at ambient temperature. The aqueous layer was extracted five times with pentane. The combined organic extracts were washed sequentially with saturated aqueous sodium bicarbonate, 0.5 N HCl, and saturated aqueous sodium bicarbonate. Gas chromatography analysis was carried out (92% yield, syn:anti = 7:3) by using tridecane (48.8 μL , 0.2 mmol) as an internal standard. The organic layer was chromatographed on silica gel (5 g, pentane and then 3% Et_2O in pentane) to obtain the corresponding ketone (0.178 g, 90% yield): R_f = 0.66, 10% Et_2O in pentane; IR (neat) 1712 (vs, C=O), 1459, 1378, 1261, 1108, 1023, 975.3, 804.5; EI-HRMS calcd for $\text{C}_{13}\text{H}_{26}\text{O}$ $[\text{M}]^+$ 198.1984, found 198.1988.

Major diastereomer (syn; determined by comparison of the NMR shifts with those of 4,5-dimethyldecane-3-one²²): ^1H NMR (400 MHz, CDCl_3) δ 0.78 (d, J = 7.2 Hz, 3H, COCHCHCH_3), 0.88 (t, J = 7.2 Hz, 3H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 0.96 (d, J = 7.2 Hz, 3H, COCHCH_3), 1.05 (t, J = 7.2 Hz, 3H, COCH_2CH_3), 1.10–1.35 (m, 10H, $\text{CH}(\text{CH}_2)_5\text{CH}_3$), 1.80–1.90 (m, 1H, COCHCH), 2.37–2.51 (m, 3H, COCHCH , COCH_2CH_3); ^{13}C NMR (100 MHz, CDCl_3) δ 7.8, 11.3, 14.0, 15.3, 22.6, 27.3, 29.4, 31.8, 34.5, 35.3, 50.6, 215.3.

Minor diastereomer (anti): ^1H NMR (400 MHz, CDCl_3) δ 0.87 (d, J = 7.2 Hz, 3H, COCHCHCH_3), 0.88 (t, J = 7.2 Hz, 3H, $\text{CH}_2\text{CH}_2\text{CH}_3$),

1.01 (d, J = 7.2 Hz, 3H, COCHCH_3), 1.04 (t, J = 7.2 Hz, 3H, COCH_2CH_3), 1.10–1.35 (m, 10H, $\text{CH}(\text{CH}_2)_5\text{CH}_3$), 1.73–1.83 (m, 1H, COCHCH), 2.37–2.51 (m, 3H, COCHCH , COCH_2CH_3); ^{13}C NMR (100 MHz, CDCl_3) δ 7.7, 13.1, 14.0, 17.8, 22.6, 26.7, 29.5, 32.7, 35.1, 35.1, 51.6, 215.5.

Addition to Isobutylene; 4,5,5-Trimethylhexan-3-one (9). After the reaction performed according to procedure A, the solvents were removed in vacuo (10 min, room temperature, 0.1 mmHg). Isobutylene (ca. 0.5 mL) was added at -78 °C, and the reaction mixture was charged in an autoclave. The autoclave was maintained at 65 °C for 60 h with stirring (4 atm) and cooled to ambient temperature. After the removal of unreacted isobutylene, the reaction mixture was moved to an ice bath, and acetic acid (1.0 mL) and water (0.5 mL) were added. Hydrolysis was carried out at 90 °C for 6 h, and then water (4.5 mL) was added at ambient temperature. The aqueous layer was extracted five times with pentane. The combined organic extracts were washed sequentially with saturated aqueous sodium bicarbonate, 0.5 N HCl, and saturated aqueous sodium bicarbonate. Gas chromatography analysis was carried out (85% yield) using decane (39.0 μL , 0.2 mmol) as an internal standard. The organic layer was chromatographed on silica gel (3 g, pentane and then 3% Et_2O in pentane) to obtain the corresponding ketone (0.108 g, 76% yield).

Palladium-Catalyzed Coupling Reaction of Organozinc Intermediate with 4-Iodoacetylbenzene; 6-(4-Acetylphenyl)-4-methylhexan-3-one (28). The addition reaction was carried out according to procedure B on a 10 mmol scale at 50 °C for 24 h. The solvents were removed in vacuo. To the reaction mixture were added TMEDA (3.0 mL, 20 mmol), 4-iodoacetylbenzene (5.4 g, 22 mmol), $\text{PdCl}_2(\text{PPh}_3)_2$ (0.35 g, 0.5 mmol), and THF (20 mL) in turn at 0 °C. The reaction mixture was stirred at room temperature (ca. 25 °C) for 8 h, and then acetic acid (5 mL) and water (5 mL) were added at 0 °C. Hydrolysis was carried out at room temperature for 1 h, and then water (40 mL) was added at ambient temperature. The aqueous layer was extracted five times with Et_2O . The combined organic extracts were washed sequentially with saturated aqueous sodium bicarbonate, 0.5 N HCl, and saturated aqueous sodium bicarbonate, and then in vacuo. The crude product was chromatographed on silica gel (100 g, pentane and then 10, 20% Et_2O in pentane) to obtain the corresponding diketone (1.928 g, 83% yield): R_f = 0.18, 20% Et_2O in pentane; IR (neat) 1710 and 1679 (C=O), 1606 (aromatic C=C), 1358, 1267, 1182, 956.0, 819.9; ^1H NMR (400 MHz, CDCl_3) δ 0.96 (t, J = 7.2 Hz, 3H, CH_2CH_3), 1.04 (d, J = 7.2 Hz, 3H, CHCH_3), 1.55 (dq, J = 7.2, 13.5 Hz, 1H, CHCHH), 1.93 (dq, J = 7.2, 13.5 Hz, 1H, CHCHH), 2.30–2.50 (m, 3H, $\text{CHC}(\text{=O})\text{CH}_2$), 2.49 (s, 3H, CCH_3), 2.54 (t, J = 7.2 Hz, 2H, CH_2Ar), 7.17 (d, J = 8.5 Hz, 2H, aromatic CH), 7.79 (d, J = 8.5 Hz, 2H, aromatic CH); ^{13}C NMR (100 MHz, CDCl_3) δ 7.6, 16.6, 26.4, 33.3, 33.9, 34.2, 45.2, 128.4 (2C), 128.4 (2C), 135.0, 147.5, 197.6, 214.6; EI-HRMS calcd for $\text{C}_{15}\text{H}_{20}\text{O}_2$ $[\text{M}]^+$ 232.1463, found 232.1424. Anal. Calcd for $\text{C}_{15}\text{H}_{20}\text{O}_2$: C, 77.55; H, 8.68. Found: C, 77.33; H, 8.81.

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Supporting Information Available: Experimental procedure and characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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