Amine-Promoted *anti*-Markovnikov Addition of 1,3-Dicarbonyl Compounds with Terminal Alkynes under Rhenium Catalysis

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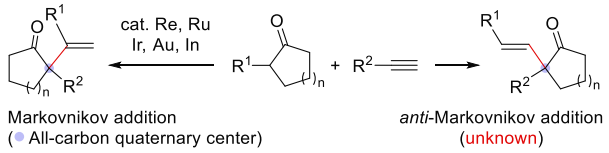
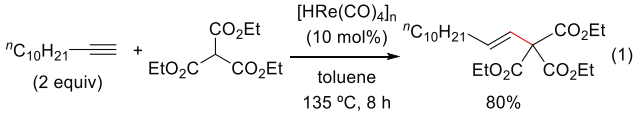
ABSTRACT: Amines have been identified to greatly accelerate the intermolecular *anti*-Markovnikov addition of carbon nucleophiles to unactivated terminal alkynes. Using a combination of $[ReBr(CO)_3(thf)]_2$ and $^{i}Pr_2NEt$, construction of cyclic all-carbon quaternary centers was achieved with various 1,3-ketoesters, diketones, and diesters with lower catalyst loading under milder conditions. The type of addition could be easily controlled by choice of additive, highlighting the unique features of rhenium catalysis

Rhenium complexes are powerful tools for the construction of complicated molecules from simple starting materials. Especially, the unique reactivity of rhenium carbonyl complexes has enabled unique carbon–carbon bond formation based on the activation of both nonpolar alkynes and polar carbonyl compounds.[1] Because group 7 rhenium complexes are located in the middle of early and late transition metal complexes in the periodic table, we rationalized this versatile reactivity was resulted from the hard and soft Lewis acidity that rhenium possesses.[1a,j] Thus, tight control of the unique Lewis acidic nature of rhenium complexes was hypothesized to be possible through the proper choice of base additives. The present study demonstrates the ability to control regiodivergent addition reactions of carbon nucleophiles to unactivated terminal alkynes for the construction of cyclic all-carbon quaternary centers.[2] This type of structure is found in a wide range of natural products, biologically active compounds, and pharmaceuticals. Although several synthetic approaches for creating these fundamental structures have been reported, most required reactive halogenated or metalated reagents, and produced stoichiometric amounts of inorganic salt waste.[2] Catalytic intermolecular addition of enol equivalents with terminal alkynes can circumvent this disadvantage, and produce useful carbonyl and alkenyl functionalities in the resulting adducts.[3] From a mechanistic perspective, the addition pattern of terminal alkynes can be classified into two types; Markovnikov and *anti*-Markovnikov addition (Scheme 1).[4] Although rhenium, ruthenium, iridium, gold, and indium catalysts effectively promote the addition reaction, they provide only Markovnikov adducts.[5] Thus, the intermolecular *anti*-Markovnikov addition of carbon nucleophiles remains a challenge.

Scheme 1. Construction of an All-Carbon Quaternary Center by Addition of Enol Equivalents with Terminal Alkynes



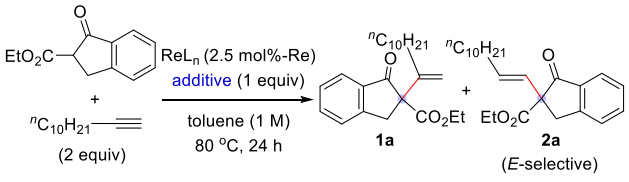
Recently, we reported the rhenium-catalyzed *anti*-Markovnikov addition of carbon nucleophiles with unactivated terminal alkynes.[1g] In contrast to the well-investigated *anti*-Markovnikov addition of heteroatom nucleophiles, this was a rare example of the corresponding *intermolecular* addition of carbon nucleophiles.[6] While this study provided a significant advance for regioselective carbon–carbon bond formation, limited substrate scope (applicable only methanetricarboxylates and symmetrically substituted 1,3-diesters), high catalyst loading (10 mol% of $[HRe(CO)_3]_n$ required), and elevated temperatures (135-150 °C) remained obstacles for the practical use of the reaction (Eq 1). The *anti*-Markovnikov addition of various 1,3-dicarbnyl compounds, including 1,3-ketoesters and diketones, using a combination of $[ReBr(CO)_3(thf)]_2$ and $^{i}Pr_2NEt$ under relatively mild conditions is described in this study.



Our study commenced with an attempt to perform *anti*-Markovnikov addition of indanone ester with 1-dodecyne at 80 °C with a reduced amount of rhenium catalyst (2.5 mol%). The $[HRe(CO)_3]_n$, which was the best catalyst in our previous study,[1g] afforded a mixture of Markovnikov adduct **1a** and *anti*-Markovnikov adduct **2a** in 27% and 31% yield, respectively (Table 1, entry 1). In contrast, Markovnikov adduct **1a** was obtained selectively in 94% yield in the presence of $[ReBr(CO)_3(thf)]_2$ catalyst (entry 2). Previous our study on the *anti*-Markovnikov addition of methanetricarboxylates revealed that a rhenium vinylidene species, generated *via* 1,2-hydrogen shift of a terminal alkyne, was a key intermediate for controlling the regio- and stereoselectivity of the overall addition reaction, and its generation is included as a rate determining step.[1g] Thus, the ability of additives to accelerate the rate of the 1,2-hydrogen shift was next investigated.[7] The results revealed that the use of Et_3N completely switched the regioselectivity to provide **2a** in 68% yield without formation of **1a** (entry 3). The yield of **2a** was highest in *n*-octane, although

reaction in other solvents, such as chlorobenzene, cyclohexane, and 1,4-dioxane, also afforded **2a** selectively (entry 4, and Table S1 in SI for details of reaction conditions optimization). After surveying various additives, the combination of bulky *tert*- and *sec*-alkylamines with $[ReBr(CO)_3(thf)]_2$ were most effective to promote selective *anti*-Markovnikov addition (entries 4-6). Among them, $^{i}Pr_2NEt$ gave the best result to afford **2a** in 80% yield as a single regio- and stereoisomer (entry 6). Decreasing the concentration from 1.0 to 0.25 M to prevent the competitive undesirable oligo- or polymerization of 1-dodecyne slightly increased the yield of **2a** (entry 7). Finally, an isolated yield of 94% was acheived when 0.5 equiv of 1-dodecyne was added at the beginning and additional 1-dodecyne was added three times (0.5 equiv each) at 3 h intervals (entry 8).[8] Markovnikov adduct **1a** was obtained selectively in 94% yield under the same conditions without $^{i}Pr_2NEt$, which demonstrates that addition regioselectivity could be easily and completely controlled by the choice of additive (entry 9).

Table 1. Effect of Amines on Regioselective Addition of Indanone Ester with 1-Dodecyne

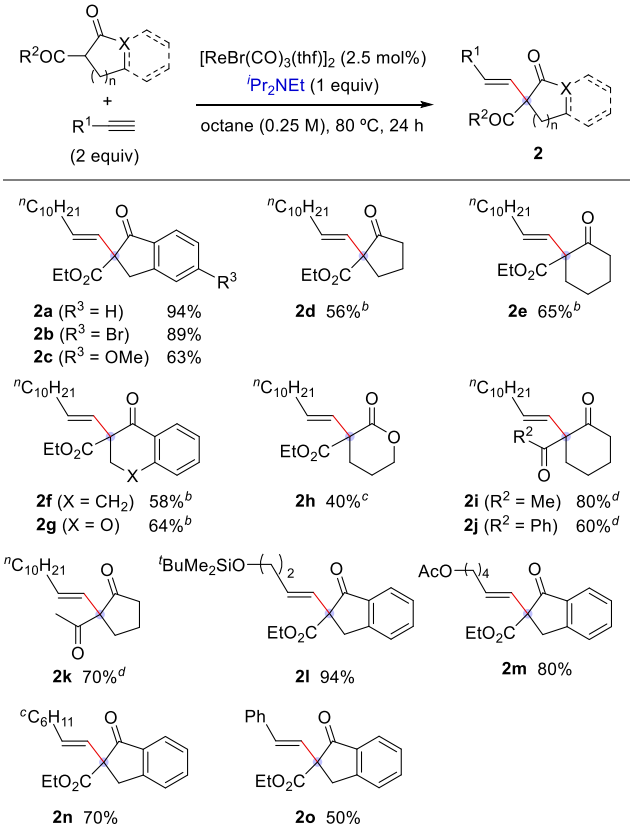


entry	ReL_n	additive	Yield of **1a**[a]	Yield of **2a**[a]
1	$[HRe(CO)_3]_n$	——	27%	31%
2	$[ReBr(CO)_3(thf)]_2$	——	94%	0%
3	$[ReBr(CO)_3(thf)]_2$	Et_3N	0%	68%
4[b]	$[ReBr(CO)_3(thf)]_2$	Et_3N	0%	78%
5[b]	$[ReBr(CO)_3(thf)]_2$	DABCO	0%	1%
6[b]	$[ReBr(CO)_3(thf)]_2$	$^{i}Pr_2NEt$	0%	80%
7[c]	$[ReBr(CO)_3(thf)]_2$	$^{i}Pr_2NEt$	0%	86%
8[c,d]	$[ReBr(CO)_3(thf)]_2$	$^{i}Pr_2NEt$	0%	96% (94%)
9[c,d]	$[ReBr(CO)_3(thf)]_2$	——	96% (94%)	0%

[a]Determined by ^{1}HNMR. The value in parentheses is the isolated yield. [b]In octane (1 M). [c]In octane (0.25 M). [d]0.5 equiv of alkyne was added at the beginning and additional alkyne was added three times (0.5 equiv each) at intervals of 3 h.

Under the reaction conditions listed in Table 1, entry 8, indanone ester having an electron-withdrawing bromo group did not reduce the efficiency of *anti*-Markovnikov addition to afford **2b**, whereas the yield of **2c** decreased with electron-donating methoxy group substituted indanone ester (Table 2). Selective addition at the most acidic C–H bond was observed in the reaction of cyclopentanone ester to provide the corresponding *anti*-Markovnikov adduct **2d** in moderate yield. Addition of six membered-ring 1,3-ketoesters, such as cyclohexanone, α-tetralone, and 4-chromanone esters, also proceeded with complete regio- and stereoselectivity to furnish **2e**, **2f**, and **2g**, respectively. While reaction retarded with cyclic 1,3-diester leading to **2h** even at 120 °C, addition reaction with 1,3-diketones proceeded smoothly to form the corresponding adducts **2i**, **2j**, and **2k** in good yields. In all cases, adducts were obtained as single regio- and stereoisomers. Functional groups, such as siloxy and acetoxy groups, in terminal alkynes were tolerated to provide **2l** and **2m** in high yields. Sterically congested cyclohexylacetylene and phenylacetylene provided the corresponding adducts **2n** and **2o**, respectively. Note that arylacetylenes could not be used as terminal alkynes in the previous $[HRe(CO)_3]_n$-catalyzed system due to their rapid oligomerization.[1g]

Table 2. Rhenium-Catalyzed *anti*-Markovnikov Addition of 1,3-Dicarbonyl Compounds with Terminal Alkynes[a]

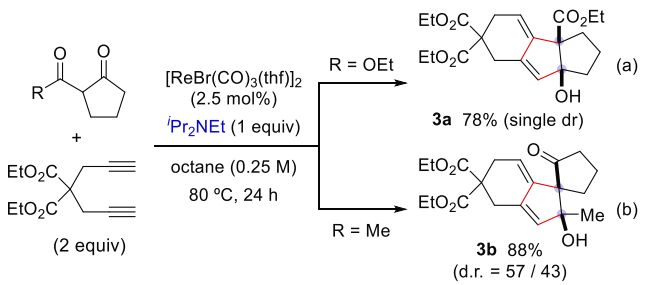


[a]0.5 equiv of alkynes were added at the beginning and additional alkynes were added three times (0.5 equiv each) at intervals of 2 h. [b]$^{i}Pr_2NEt$ (5 equiv). [c]In dioxane at 120 °C. 15% of starting 1,3-diester was recovered. [d]In octane (1 M).

Combination of $[ReBr(CO)_3(thf)]_2$ catalyst and $^{i}Pr_2NEt$ also promoted the sequential cyclization of 1,6-diynes initiated by *anti*-Markovnikov addition.[1j] The reaction enabled construction of vicinal quaternary tetrasubstituted carbon centers.[9] Reaction with cyclopentanone ester gave tricycle **3a** as a single diastereomer in 78% yield *via* the sequential attack of the resulting alkenylrhenium species to the alkynyl and ethoxycarbonyl groups (Scheme 2(a), see Scheme S1 in SI for the mechanism).[10] Use of a 1,3-diketone, such as 2-acetylcyclopentanone ester, as a carbon nucleophile gave spirocycle **3b** in 88% yield as a mixture of two diastereomers (Scheme 2(b)). In this case, the second nucleophilic attack of the alkenylrhenium species occurred selectively at the *exo*-ketocarbonyl group. These unique cyclization modes cannot be achieved without rhenium catalysts. Group 7 rhenium complexes may possess both soft and hard Lewis acidity, because they are situated in the middle of early and late transition metals in the periodic table. This characteristic might be key to the sequential interaction and attack of both nonpolar alkynyl groups and polar carbonyl groups.

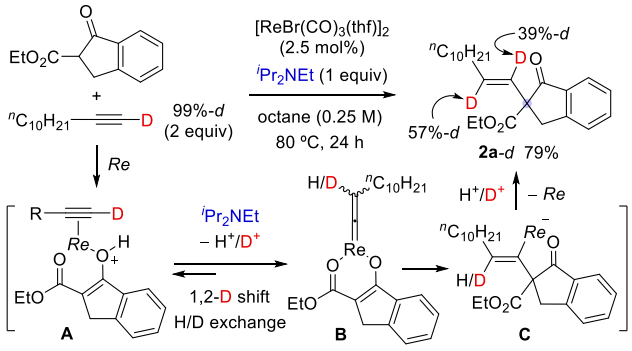
A control experiment using deuterium-labeled 1-dodecyne gave a mixture of deuterated *anti*-Markovnikov adducts **2a**-*d* (Scheme 3). This result indicates that rapid and competitive H/D-scrambling with the active methylene proton of

Scheme 2. Construction of Adjacent All-Carbon Quaternary Centers *via* Sequential Cyclization Initiated by *anti*-Markovnikov Addition to 1,6-Diynes



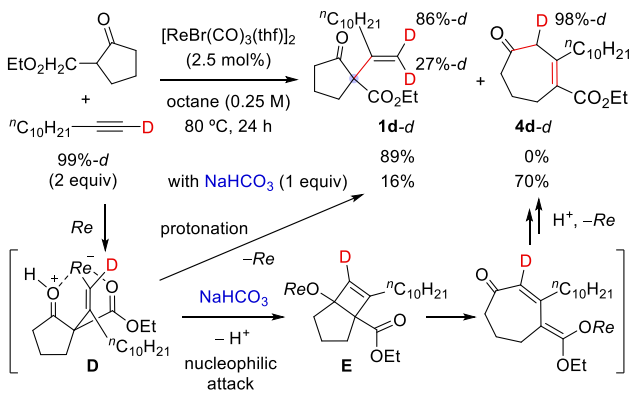
cyclopentanone ester occurred in the course of 1,2-D shifts, leading to the rhenium vinylidene intermediate **B** from π-alkyne complex **A**.[11-13] Equilibrium developed between **A** and **B**, with formation of **B** preferred in the presence of amine (*vide infra*). The partial deuterium atom incorporation at the β-position of a decyl group of **2a**-*d* can be explained by quenching of the alkenylrhenium intermediate **C** by the deuterated cyclopentanone ester.

Scheme 3. Deuterium Labeling Experiments in the Presence of $^{i}Pr_2NEt$



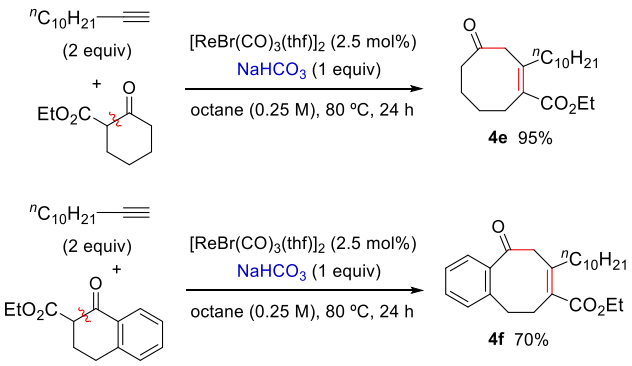
Experimental results in Table 1 demonstrated that the regioselectivity of the addition reaction could be adjusted by the proper choice of additive. A similar reactivity switch was observed for addition reactions of other 1,3-dicarbonyl compounds. In addition, we found selective formation of ring-expanded adduct **4** by using $NaHCO_3$ as an additive.[14] A control experiment using cyclopentanone ester and deuterium-labeled 1-dodecyne in the presence and absence of $NaHCO_3$ provided ring-expanded adduct **4d**-*d* and Markovnikov adduct **1d**-*d*, respectively (Scheme 4).[15] This result demonstrates that

Scheme 4. Deuterium Labeling Experiments in the Presence/Absence of $NaHCO_3$



formation of both **1d** and **4d** did not proceed *via* 1,2-hydrogen shift leading to a vinylidene intermediate. The incorporation of deuterium atom predominantly into the *anti*-position of the decyl group in **1d**-*d* indicates that Markovnikov addition proceeded mainly *via* intermediate **D**.[16] Formation of ring-expanded adduct **4d**-*d* was attributed to intramolecular nucleophilic cyclization of alkenylrhenium intermediate **D**, followed by reductive elimination, ring-opening of intermediate **E** *via retro*-Aldol reaction, and isomerization. Addition of $NaHCO_3$ may prevent the rapid protonation of intermediate **D** leading to **1d**-*d*. This ring expanded addition in the presence of $NaHCO_3$ was confirmed to occur with other 1,3-ketoesters, such as cyclohexanone and tetralone esters, to afford 4-oxo-1-cyclooctene derivatives **4e** and **4f** in high yields (Scheme 5).

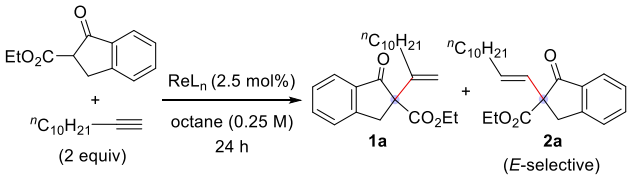
Scheme 5. $NaHCO_3$-Promoted Ring-Expanded Addition of 1,3-Ketoesters with 1-Dodecyne



This unique switching of reactivity was observed only with $[ReBr(CO)_3(thf)]_2$ and $ReBr(CO)_5$ catalysts. Other rhenium complexes, including $[HRe(CO)_3]_n$ and $Re_2(CO)_{10}$, which were effective for our previous *anti*-Markovnikov addition reactions of methanetricarboxylates,[1g,j] gave mixtures of adducts and failed to switch reactivity. This difference in reactivity was thought to be due to the soft Lewis acidic nature of rhenium complexes. Because Markovnikov adduct **1a** *via* direct addition of indanone ester was obtained in high yield with $[ReBr(CO)_3(thf)]_2$ rather than $Re_2(CO)_{10}$, the former may possess stronger Lewis π-acidity toward carbon–carbon triple bonds (Table 3, entry 1 *vs* 3). Thus, greater change in catalytic performance should be observed for $[ReBr(CO)_3(thf)]_2$ upon treatment of Lewis base ($^{i}Pr_2NEt$). This characteristic is key for the current unique regioselectivity switching of addition reactions. Coordination of $^{i}Pr_2NEt$ decreased the Lewis acidity of the rhenium center, and slowed the direct addition of 1,3-dicarbonyl compounds to alkynes leading to Markovnikov adduct **1** (Figure 1). During the slow nucleophile addition, an amine-assisted 1,2-hydrogen shift occurred to form a rhenium vinylidene intermediate, leading to the selective formation of *anti*-Markovnikov adducts **2** with $[ReBr(CO)_3(thf)]_2$ in the presence of amine. Note that coordination of an amine to $[ReBr(CO)_3(thf)]_2$ in the presence of 1,3-dicarbonyl compounds can be monitored by ^{1}H NMR, which clearly showed that $^{i}Pr_2NEt$ acted not only as a base to promote 1,2-hydrogen shift, but also as a ligand to adjust the Lewis acidity of an active rhenium center.[17] Temperature was another factor in determining the regioselectivity, and *anti*-Markovnikov addition occurred preferentially over Markovnikov addition at high temperatures (Table 3). This implies that the equilibrium be-

tween the rhenium vinylidene complex and rhenium π-alkyne complex can be controlled by both the choice of additive and the temperature.

Table 3. Effect of Catalysts and Temperature on the Regioselective Addition Reaction of Indanone Ester[a]



entry	ReL_n	additive	Yield of **1a**[a]	Yield of **2a**[a]
1	$[ReBr(CO)_3(thf)]_2$	80	96%	2%
2		135	84%	10%
3	$Re_2(CO)_{10}$	80	0%	0%
4		100	6%	6%
5		110	6%	24%
6		135	9%	70%

[a]Determined by ^{1}HNMR.

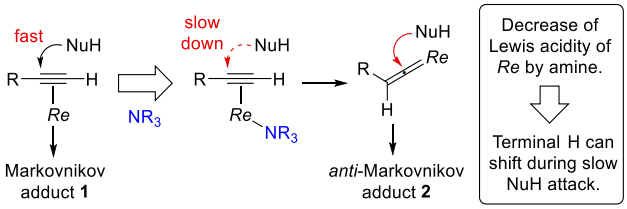


Figure 1. Rational for the Regiodivergent Addition Reaction

In summary, the current study demonstrated the ability to adjust the Lewis acid nature of rhenium complexes by selecting the appropriate base additive. The $[ReBr(CO)_3(thf)]_2$ catalyst was highly effective for the construction of complicated carbon frameworks with a cyclic all-carbon quaternary center *via* addition reaction of carbon nucleophiles to unactivated terminal alkynes. The proper choice of additives enabled control of the regio- and stereoselectivity of the addition reaction, and allowed the selective synthesis of Markovnikov adducts (no additive), *anti*-Markovnikov adducts (with ^{i}Pr$_2$NEt), and ring-expanded adducts (with $NaHCO_3$). The use of amines as additives resulted in application of various 1,3-dicarbonyl compounds, including 1,3-ketoesters, diketones, and diesters as substrates, which greatly expands the limited scope of *anti*-Markovnikov addition of carbon nucleophiles. Amine is thought to act as a base to promote 1,2-hydrogen shift as well as a ligand to adjust the Lewis acidity of $[ReBr(CO)_3(thf)]_2$, which accounts for the current unusual regiodivergent addition reaction. Further studies including the construction of all-carbon quaternary stereocenters are currently investigated in our laboratory.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures, characterization data for all new compounds, and copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge *via* the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) For a review, see: (a) Kuninobu, Y.; Takai, K. Organic Reactions Catalyzed by Rhenium Carbonyl Complexes. *Chem. Rev.* **2011**, *111*, 1938. For representative our contribution on the development of rhenium-catalyzed transformation, see: (b) Kuninobu, Y.; Kawata, A.; Takai, K. Rhenium-Catalyzed Formation of Indene Frameworks *via* C−H Bond Activation: [3+2] Annulation of Aromatic Aldimines and Acetylenes. *J. Am. Chem. Soc.* **2005**, *127*, 13498. (c) Kuninobu, Y.; Tokunaga, Y.; Kawata, A.; Takai, K. Insertion of Polar and Nonpolar Unsaturated Molecules into Carbon−Rhenium Bonds Generated by C−H Bond Activation: Synthesis of Phthalimidine and Indene Derivatives. *J. Am. Chem. Soc.* **2006**, *128*, 202. (d) Kuninobu, Y.; Nishina, Y.; Shouho, M.; Takai, K. Rhenium- and aniline-catalyzed one-pot annulation of aromatic ketones and alpha, beta-unsaturated esters initiated by C-H bond activation. *Angew. Chem. Int. Ed.* **2006**, *45*, 2766. (e) Kuninobu, Y.; Nishina, Y.; Nakagawa, C.; Takai, K. Rhenium-Catalyzed Insertion of Aldehyde into a C−H Bond: Synthesis of Isobenzofuran Derivatives. *J. Am. Chem. Soc.* **2006**, *128*, 12376. For recent examples, see: (f) Murai, M.; Nakamura, M.; Takai, K. Rhenium-Catalyzed Synthesis of 2*H*-1,2-Oxaphosphorin 2-Oxides *via* the Regio- and Stereoselective Addition Reaction of β-Keto Phosphonates with Alkynes. *Org. Lett.* **2014**, *16*, 5784. (g) Hori, S.; Murai, M.; Takai, K. Rhenium-Catalyzed *anti*-Markovnikov Addition Reaction of Methanetricarboxylates to Unactivated Terminal Acetylenes. *J. Am. Chem. Soc.* **2015**, *137*, 1452. (h) Murai, M.; Omura, T.; Kuninobu, Y.; Takai, K. Rhenium-Catalysed Dehydrogenative Borylation of Primary and Secondary C(sp^3)–H Bonds Adjacent to a Nitrogen Atom. *Chem. Commun.* **2015**, *51*, 4583. (i) Nakagiri, T.; Murai, M.; Takai, K. Stereospecific Deoxygenation of Aliphatic Epoxides to Alkenes under Rhenium Catalysis. *Org. Lett.* **2015**, *17*, 3346. (j) Murai, M.; Uemura, E.; Hori, S.; Takai, K. Rhenium-Catalyzed Construction of Polycyclic Hydrocarbon Frameworks by a Unique Cyclization of 1,*n*-Diynes Initiated by 1,1-Difunctionalization with Carbon Nucleophiles. *Angew. Chem. Int. Ed.* **2017**, *56*, 5862.

(2) The definition of all-carbon quaternary centers in this work is "carbon centers substituted with four different carbon-centered functional groups". For reviews on their catalytic construction, see: (a) Christoffers, J.; Baro, A. *Quaternary Stereocenters: Challenges and Solutions for Organic Synthesis*; Wiley-VCH: Weinheim, 2006. (b) Shimizu, M. Construction of Asymmetric Quaternary Carbon Centers with High Enantioselectivity. *Angew. Chem. Int. Ed.* **2011**, *50*, 5998. (c) Hawner, C.; Alexakis, A. Metal-Catalyzed Asymmetric Conjugate Addition Reaction: Formation of Quaternary Stereocenters. *Chem. Commun.* **2010**, *46*, 7295. (d) Trost, B. M.; Jiang, C. Catalytic Enantioselective Construction of All-Carbon Quaternary Stereocenters. *Synthesis* **2006**, 369. (e) Hong, A. Y.; Stoltz, B. M. The Construction of All-Carbon Quaternary Stereocenters by Use of Pd-Catalyzed Asymmetric Allylic Alkylation Reactions in Total Synthesis. *Eur. J. Org. Chem.* **2013**, *2013*, 2745. (f) Minko, Y.; Marek, I. Stereodefined Acyclic Trisubstituted Metal Enolates Towards the Asymmetric Formation of Quaternary Carbon Stereocentres. *Chem. Commun.* **2014**, *50*, 12597. (g) Marek, I.; Minko, Y.; Pasco, M.; Mejuch, T.; Gilboa, N.; Chechik, H.; Das, J. P. All-Carbon Quaternary Stereogenic Centers in Acyclic Systems through the Creation of Several C–C Bonds per Chemical Step. *J. Am. Chem. Soc.* **2014**, *136*, 2682. (h) Zeng, X.-P.; Cao, Z.-Y.; Wang, Y.-H.; Zhou, F.; Zhou, J. Catalytic Enantioselective Desymmetrization Reactions to All-Carbon Quaternary Stereocenters. *Chem. Rev.* **2016**, *116*, 7330. (i) Ling, T.; Rivas, F. All-Carbon Quaternary Centers in Natural Products and Medicinal Chemistry: Recent Advances. *Tetrahedron* **2016**, *72*, 6729.

(3) (a) Dénès, F.; Pérez-Luna, A.; Chemla, F. Addition of Metal Enolate Derivatives to Unactivated Carbon−Carbon Multiple Bonds. *Chem. Rev.* **2010**, *110*, 2366. (b) Patil, N. T.; Kavthe, R. D.; Shinde, V. S. Transition Metal-Catalyzed Addition of C-, N- and O-Nucleophiles to Unactivated C–C Multiple Bonds. *Tetrahedron* **2012**, *68*. 8079.

(4) For representative reviews on the *anti*-Markovnikov additions, see: (a) Beller, M.; Seayad, J.; Tillack, A.; Jiao, H. Catalytic Markovnikov and *anti*-Markovnikov Functionalization of Alkenes and Alkynes: Recent Developments and Trends. *Angew. Chem. Int. Ed.* **2004**, *43*, 3368. (b) Bruneau, C.; Dixneuf, P. H. Metal Vinylidenes and Allenylidenes in Catalysis: Applications in *anti*-Markovnikov Additions to Terminal Alkynes and Alkene Metathesis. *Angew. Chem. Int. Ed.* **2006**, *45*, 2176. (c) Trost, B. M.; McClory, A. Metal Vinylidenes as Catalytic Species in Organic Reactions. *Chem. Asian J.* **2008**, *3*, 164. (d) Bruneau, C.; Dixneuf P. H. *Metal Vinylidenes and Allenylidenes in Catalysis*; Wiley-VCH Verlag: Weinheim, 2008.

(5) (a) Nakamura, M.; Endo, K.; Nakamura, E. Indium-Catalyzed Addition of Active Methylene Compounds to 1-Alkynes. *J. Am. Chem. Soc.* **2003**, *125*, 13002. (b) Kuninobu, Y.; Kawata, A.; Takai, K. Rhenium-Catalyzed Insertion of Terminal Acetylenes into a C−H Bond of Active Methylene Compounds. *Org. Lett.* **2005**, *7*, 4823. (c) Endo, K.; Hatakeyama, T.; Nakamura, M.; Nakamura, E. Indium-Catalyzed 2-Alkenylation of 1,3-Dicarbonyl Compounds with Unactivated Alkynes. *J. Am. Chem. Soc.* **2007**, *129*, 5264. (d) Fujimoto, T.; Endo, K.; Tsuji, H.; Nakamura, M.; Nakamura, E. Construction of a Chiral Quaternary Carbon Center by Indium-Catalyzed Asymmetric α-Alkenylation of β-Ketoesters. *J. Am. Chem. Soc.* **2008**, *130*, 4492. (e) Kaneda, K.; Motokura, K.; Nakagiri, N.; Mizugaki, T.; Jitsukawa, K. Recyclable Indium Catalysts for Additions of 1,3-Dicarbonyl Compounds to Unactivated Alkynes Affected by Structure and Acid Strength of Solid Supports. *Green Chem.* **2008**, *10*, 1231. (f) Onodera, G.; Kato, M.; Kawano, R.; Kometani, Y.; Takeuchi, R. Highly Regio- and Stereoselective Addition of 1,3-Diketones to Internal Alkynes Catalyzed by Cationic Iridium Complex. *Org. Lett.* **2009**, *11*, 5038. (g) Cheung, H. W.; So, C. M.; Pun, K. H.; Zhou, Z.; Lau, C. P. Hydro(trispyrazolyl)borato-Ruthenium(II) Diphosphinoamino Complex-Catalyzed Addition of b-Diketones to 1-Alkynes and *anti*-Markovnikov Addition of Secondary Amines to Aromatic 1-Alkynes. *Adv. Synth. Catal.* **2011**, *353*, 411. (h) Xi, Y.; Wang, D.; Ye, X.; Akhmedov, N. G.; Petersen, J. L.; Shi, X. Synergistic Au/Ga Catalysis in Ambient Nakamura Reaction. *Org. Lett.* **2014**, *16*, 306. For intramolecular addition reactions, known as Conia-ene reaction, see: (i) Conia, J. M.; Le Perchec, P. The Thermal Cyclisation of Unsaturated Carbonyl Compounds. *Synthesis* **1975**, 1. (j) Hack, D.; Blümel, M.; Chauhan, P.; Philipps, A. R.; Enders, D. Catalytic Conia-ene and Related Reactions. *Chem. Soc. Rev.* **2015**, *44*, 6059.

(6) There have been many reports on the catalytic *intramolecular anti*-Markovnikov addition reaction of carbon nucleophiles to alkynes. For selected examples, see: (a) Merlic, C. A.; Pauly, M. E. Sulfenic Acids in the Gas Phase: A Photoelectron Study. *J. Am. Chem. Soc.* **1996**, *118*, 11319. (b) Maeyama, K.; Iwasawa, N. $W(CO)_5$·THF-Catalyzed Endo-Selective Cyclization of ω-Acetylenic Silyl Enol Ethers. *J. Am. Chem. Soc.* **1998**, *120*, 1928. (c) Iwasawa, N.; Miura, T.; Kiyota, K.; Kusama, H.; Lee, K.; Lee, P. H. An Efficient Method for Cyclopentene Annulation onto α,β-Unsaturated Ketones: $W(CO)_5$(L)-Catalyzed 5-Endo-Dig Cyclization of 6-Siloxy-5-en-1-ynes. *Org. Lett.* **2002**, *4*, 4463. (d) Shen, H.-C.; Pal, S.; Lian, J.-J.; Liu, R.-S. Ruthenium-Catalyzed Aromatization of Aromatic Enynes *via* the 1,2-Migration of Halo and Aryl Groups: A New Process Involving Electrocyclization and Skeletal Rearrangement. *J. Am. Chem. Soc.* **2003**, *125*, 15762. (e) Donovan, P. M.; Scott, L. T. Elaboration of Diaryl Ketones into Naphthalenes Fused on Two or Four Sides: A Naphthoannulation Procedure. *J. Am. Chem. Soc.* **2004**, *126*, 3108.

(7) (a) Manabe, T.; Yanagi, S.; Ohe, K.; Uemura, S. New Examples of 1,6- and 1,7-Hydrogen Transfer Promoted by an α-Silyl Group in Rhodium(I)-Catalyzed Radical Reactions of Acyclic Enediynes. *Organometallics* **1998**, *17*, 2942. (b) Ohe, K.; Yokoi, T.; Miki, K.; Nishino, F.; Uemura, S. Chromium- and Tungsten-Triggered Valence Isomerism of cis-1-Acyl-2-ethynylcyclopropanes *via* [3,3]Sigmatropy of (2-Acylcyclopropyl)vinylidene−Metal Intermediates. *J. Am. Chem. Soc.* **2002**, *124*, 526. (c) Onizawa, Y.; Kusama, H.; Iwasawa, N. Efficient Control of π-Alkyne and Vinylidene Complex Pathways for the $W(CO)_5$(L)-Catalyzed Synthesis of Two Types of Nitrogen-Containing Bicyclic Compounds. *J. Am. Chem. Soc.* **2008**, *130*, 802.

(8) The proposed reaction mechanism for *anti*-Markovnikov addition in Scheme 3 indicates that the amount of $^{i}Pr_2NEt$ can be reduced to catalytic amount. Actually, **2a** was selectively obtained in 77% yield even with 10 mol% of $^{i}Pr_2NEt$ in 1,4-dioxane. In contrast, formation of Markovnikov adduct **1a** could not be prohibited when $^{i}Pr_2NEt$ was reduced less than 1 equiv in nonpolar octane.

(9) Molecules containing vicinal all-carbon quaternary centers are found in many natural products. For a review, see: Long, R.; Huang, J.; Gong, J.; Yang, Z. Direct Construction of Vicinal All-Carbon Quaternary Stereocenters in Natural Product Synthesis. *Nat. Prod. Rep.* **2015**, *32*, 1584.

(10) Yield of **3a** obtained in this study was higher than that reported in ref 1j (71% yield with 5 mol% of $Re_2(CO)_{10}$ in dioxane at 135 °C).

(11) H/D-scrambling of terminal acetylenes is often observed during vinylidene formation. See: Odedra, A.; Wu, C.-J.; Pratap, T. B.; Huang, C.-W.; Ran, Y.-F.; Liu, R.-S. Ruthenium-Catalyzed Aromatization of Enediynes *via* Highly Regioselective Nucleophilic Additions on a π-Alkyne Functionality. A Useful Method for the Synthesis of Functionalized Benzene Derivatives. *J. Am. Chem. Soc.* **2005**, *127*, 3406. See also ref 7c.

(12) For rhenium vinylidene complexes, see: (a) Wong, A.; Gladysz, J. A. Syntheses and Reactions of Rhenium Vinylidene and Acetylide Complexes. Unprecedented Chirality Transfer Through a C≡C Triple Bond. *J. Am. Chem. Soc.* **1982**, *104*, 4948. (b) Pombeiro, A. J. L.; Jeffery, J. C.; Pickett, C. J.; Richards, R. L. Reactions of *trans*-$[ReCl(N_2)(Ph_2PCH_2CH_2PPh_2)_2]$ with terminal acetylenes. Preparation and crystal structure of the vinylidene complex *trans*-$[ReCl(C{\equiv}CHPh)(Ph_2PCH_2CH_2PPh_2)_2]$. *J. Organomet. Chem.* **1984**, *277*, C7. (c) Bianchini, C.; Mantovani, N.; Marchi, A.; Marvelli, L.; Masi, D.; Peruzzini, M.; Rossi, R.; Romerosa, A. First Examples of Rhenium-Assisted Activation of Propargyl Alcohols: Allenylidene, Carbene, and Vinylidene Rhenium(I) Complexes. *Organometallics* **1999**, *18*, 4501. Rhenium carbene species have been also proposed as key intermediates in the catalytic reaction. See: (d) Saito, K.; Onizawa, Y.; Kusama, H.; Iwasawa, N. Rhenium(I)-Catalyzed Cyclization of Silyl Enol Ethers Containing a Propargyl Carboxylate Moiety: Versatile Access to Highly Substituted Phenols. *Chem.-Eur. J.* **2010**, *16*, 4716. (e) Kusama, H.; Karibe, Y.; Imai, R.; Onizawa, Y.; Yamabe, H.; Iwasawa, N. Tungsten(0)- and Rhenium(I)-Catalyzed Tandem Cyclization of Acetylenic Dienol Silyl Ethers Based on Geminal Carbo-Functionalization of Alkynes *Chem.-Eur. J.* **2011**, *17*, 4839. (f) Fukumoto, Y.; Daijo, M.; Chatani, N. Rhenium-Catalyzed Regio- and Stereoselective Addition of Imines to Terminal Alkynes Leading to *N*-Alkylideneallylamines. *J. Am. Chem. Soc.* **2012**, *134*, 8762. (g) Xia, D.; Wang, Y.; Du, Z.; Zheng, Q.-Y.; Wang, C. Rhenium-Catalyzed Regiodivergent Addition of Indoles to Terminal Alkynes. *Org. Lett.* **2012**, *14*, 588.

(13) Incorporation of deuterium atom at the alkyne terminal of the recovered 1-dodecyne was also observed. The possibility of vinylidene complex formation *via* 1,3-H shift of the alkynyl(hydrido)rhenium intermediate cannot be ruled out, although this pathway is generally energetically unfavorable. For representative mechanistic study of vinylidene formation, see: (a) Wakatsuki, Y.; Koga, N.; Yamazaki, H.; Morokuma, K. Acetylene π-Coordination, Slippage to σ-Coordination, and 1,2-Hydrogen Migration Taking Place on a Transition Metal. The case of a Ru(II) Complex as Studied by Experiment and ab Initio Molecular Orbital Simulations. *J. Am. Chem. Soc.* **1994**, *116*, 8105. (b) Esteruelas, M. A.; Oro, L. A.; Valero, C. Reaction of $OsHCl(CO)(PiPr_3)_2$ with Cyclohexylacetylene: Formation of a Hydrido-Vinylidene Complex *via* a 1,3-Hydrogen Shift. *Organometallics* **1995**, *14*, 3596. (c) Wakatsuki, Y.; Koga, N.; Werner, H.; Morokuma, K. An ab Initio MO Study on the Transformation of Acetylene to Vinylidene in the Coordination Sphere of Rhodium(I). The Intra- and Intermolecular Proton Transfer Mechanism. *J. Am. Chem. Soc.* **1997**, *119*, 360. (d) Angelis, F.; Sgamellotti, A.; Dynamical Density Functional Study of Acetylene to Vinylidene Isomerization in $(Cp)(CO)_2Mn(HC{\equiv}CH)$. *Organometallics* **2002**, *21*, 2715.

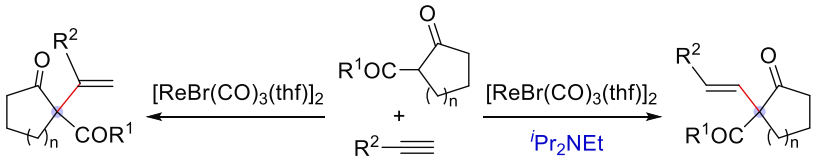
(14) TBAF and MS4A, which were effective additives in our previous ring-expansion reaction, failed to afford **4d**, **4e**, or **4f**. See: (a) Kuninobu, Y.; Kawata, A.; Takai, K. Efficient Catalytic Insertion of Acetylenes into a Carbon−Carbon Single Bond of Nonstrained Cyclic Compounds under Mild Conditions. *J. Am. Chem. Soc.* **2006**, *128*, 11368. For a review of catalytic unstrained carbon-carbon bond cleavage, see: (b) Chen, F.; Wang, T. Jiao, N. Recent Advances in Transition-Metal-Catalyzed Functionalization of Unstrained Carbon–Carbon Bonds. *Chem. Rev.* **2014**, *114*, 8613.

(15) Conversion of Markovnikov adduct **1d** to ring-expanded adduct **4d** did not occur under the $[ReBr(CO)_3(thf)]_2$ / $NaHCO_3$ catalyst system.

(16) A similar intermediate is proposed in the mechanistic study of the manganese-catalyzed addition of 1,3-dicarbonyl compounds with terminal alkynes. See: Yoshikai, N.; Zhang, S.-L.; Yamagata, K.-i.; Tsuji, H.; Nakamura, E. Mechanistic Study of the Manganese-Catalyzed

[2+2+2] Annulation of 1,3-Dicarbonyl Compounds and Terminal Alkynes. *J. Am. Chem. Soc.* **2009**, *131*, 4099.

(17) The complex obtained from reaction of 1,3-dicarbonyl compounds with $[ReBr(CO)_3(thf)]_2$ in the presence of amine was tentatively assigned to be an oxarhenacycle intermediate by NMR (see SI for details). This complex promoted the *anti*-Markovnikov addition of 1,3-dicarbonyl compounds to alkynes. For a review on isolation and structural characterization of rhenacycle intermediates, see: (a) Albrecht, M. Cyclometalation Using d-Block Transition Metals: Fundamental Aspects and Recent Trends. *Chem. Rev.* **2010**, *110*, 576. Isolation of a catalytically active rhenium intermediate is rare. See: (b) Geng, X.; Wang, C. Rhenium-Catalyzed [4+1] Annulation of Azobenzenes and Aldehydes *via* Isolable Cyclic Rhenium(I) Complexes. *Org. Lett.* **2015**, *17*, 2434.



- Fine-tuning of Lewis acid nature of rhenium complexes by base additives.
- Construction of cyclic all-carbon quaternary centers.