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General and Facile Method for *exo*-Methlyene Synthesis via Regioselective C−C Double-Bond Formation Using a Copper−Amine Catalyst System

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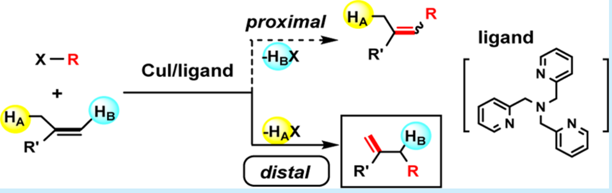
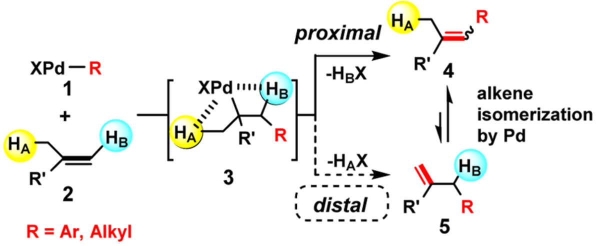
Ⓢ *Supporting Information*

ABSTRACT: In this study, for distal-selective β-hydride elimination to produce exomethylene compounds with a newly formed Csp^3−Csp^3 bond between tertiary alkyl halides and α-alkylated styrenes, a combination of a Cu(I) salt and a pyridine-based amine ligand (TPMA) is found to be a very efficient catalyst system. The yields and regioselectivities were high, and the regioselectivity was found to be dependent on the structure of the alkyl halide, with bulky alkyl halides showing the highest distal selectivities.



The Heck reaction, which is widely known due to the award of the Nobel prize in Chemistry in 2010, is one of the most powerful options to obtain arylated or alkenylated alkenes. Over the past few decades, tremendous progress, including mechanistic insights, has been made in this area, and our knowledge of this reaction is increasing all the time.[1,2] The Heck reaction is mainly used for the synthesis of internal alkenes because the synthesis of external alkenes is very challenging due to a serious limitation of the Heck reaction, namely *the low regioselectivity in the formation of the C−C double bond* after β-hydride elimination.[3−6] In the Heck reaction of olefin **2**, there are two possible pathways for β-hydride elimination; i.e., the proximal hydrogen atom (H_B) or the distal hydrogen atom (H_A) with respect to the newly formed C−C bond can be eliminated to form olefin **4** (proximal double bond) or **5** (distal double bond), respectively (Scheme 1). Although steric and/or electronic factors in an intermediate may govern the regioselectivity of the C−C double-bond formation, this reaction tends to give the proximal product **4** as the major product in most cases because an internal alkene is more stable than a terminal one.[7−14] Even if **5** is generated selectively through intermediate **3**, the double-bond isomerization of **5** into **4** due to the presence of the Pd used in the Heck reaction is problematic.[15] This undesired isomerization makes the distal-selective Heck reaction much more difficult. Although biased olefins, such as cyclic olefins[16] or allylic alcohol derivatives,[17] are good substrates to obtain high distal selectivities, this subtle phenomenon could be one reason for the slow development and limited scope of the transformations in the regisoselective Heck reaction with unbiased olefins, such as α-alkylated olefins. Chirik et al.[18] and Watson et al.[19−21] very recently reported distal-selective C−C double-bond formations with nonbiased olefins achieved by elegant ligand choice in silyl-Heck reactions, whereas regioselectivities in alkylative Heck reactions are still unsolved.

Scheme 1. Proximal versus Distal Selective β-Hydride Elimination in the Heck Reaction



In this context, we envisaged the development of a highly distal-selective alkylative Heck-type reaction with α-alkylated styrene **2**, an unbiased acyclic olefin, to generate distal product **5** with a terminal C−C double bond (Scheme 2 bottom). Recently, we reported that the copper(I)-catalyzed tertiary-alkylative Heck-type reaction between α-halocarbonyl compounds **1** and styrenes **2** gave Heck-type products **4** in high yields.[22] This reaction does not involve an ordinary carbometalation reaction followed by β-hydride elimination step but proceeds through an atom-transfer radical addition (ATRA)[23] to generate an intermediate **I** followed by elimination with a base to produce Heck-type product **4** (Scheme 2 top). On the other hand, reaction with α-alkylated styrene **2** generates intermediate **II**, which produces isomer **4** or **5** as in traditional Heck reactions (Scheme 2 bottom). Considering the intermediate **II**, a steric contribution would give distal product **5** but an electronic contribution would give proximal product **4** (H_B increases the acidity due to an electron withdrawing group). If the regiochemistry follows from site-selective elimination with a base by a steric effect, the copper(I)-catalyzed Heck-type

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Scheme 2. Our Previous Work on the Alkylative Heck-Type Reaction Involving ATRA (Top) and This Work (Bottom)

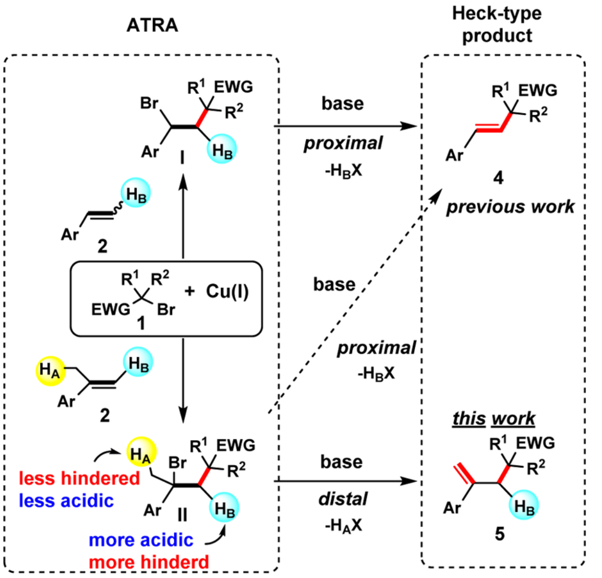
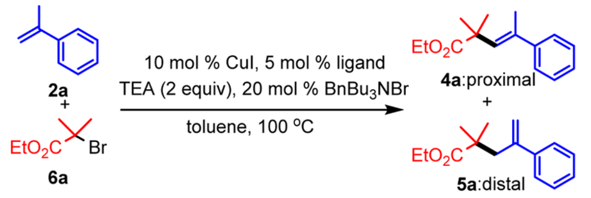
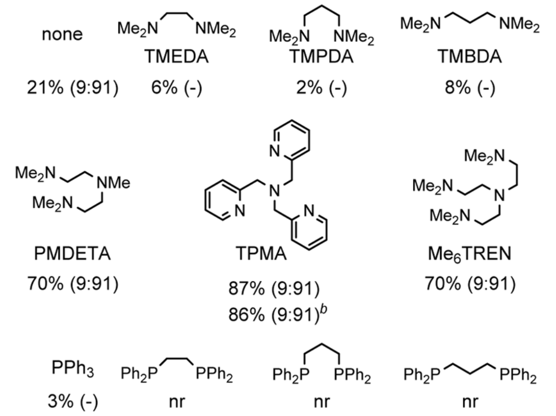


Table 1. Optimization of *tert*-Alkylation in Heck Reaction[a]



ligands / yields (proximal:distal)



none	TMEDA	TMPDA	TMBDA
21% (9:91)	6% (-)	2% (-)	8% (-)
PMDETA	TPMA	Me$_6$TREN	
70% (9:91)	87% (9:91) 86% (9:91)[b]	70% (9:91)	
PPh$_3$	Ph$_2$P PPh$_2$	Ph$_2$P PPh$_2$	Ph$_2$P PPh$_2$
3% (-)	nr	nr	nr

copper catalyst[c]

CuCl	CuBr	CuI
77% (9:91)	78% (9:91)	87% (9:91)
(CuI)$_4$(SMe$_2$)$_3$	Cu(COD)(acac-F$_6$)I	CuI(TBAI)
70 (9:91)	66 (11:89)	82% (9:91)

[a] Conducted at 100 °C for 20 h in toluene with **2a** (1 equiv), **6a** (1.5 equiv), CuI (10 mol %), ligand (5 mol %), TEA (2 equiv), and BnBu$_3$NBr (20 mol %). The selectivities are determined by ^{1}H NMR analysis of the crude mixture. [b] 1.5 equiv of PMDETA was used instead of TEA. [c] Conducted at 100 °C for 20 h in toluene with **2a** (1 equiv), **6a** (1.5 equiv), Cu (10 mol %), TPMA (5 mol %), TEA (2 equiv), and BnBu$_3$NBr (20 mol %).

reaction of **1** with α-alkylated styrene **2** would give the highly distal-selective Heck-type product **5** (Scheme 2 bottom). Herein, we report a highly regioselective C−C double bond formation in tertiary-alkylative Heck-type reactions leading to exomethylene compounds.

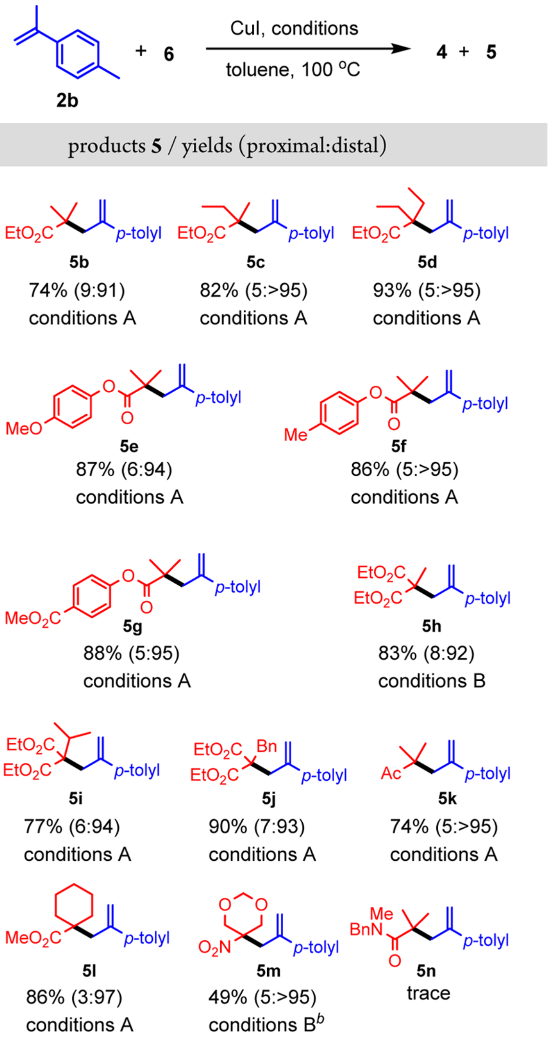
As expected, the reaction of **2a** with **6a** in the presence of CuI, triethylamine (TEA), and benzyltributylammonium bromide gave the desired product in 21% yield with high distal selectivity (proximal/distal = 9:91, Table 1). In ATRA or ATRP (atom-transfer radical polymerization) reactions,[23] the combination of Cu(I) and multidentate amines is an effective way to generate alkyl radicals.[24] The presence of 1 equiv of a multidentate nitrogen-based ligand with respect to the Cu(I) complex resulted in the formation of a very stable Cu(amine)X (X = Br, Cl or I) complex.[25] Indeed, the yield in the reaction with a tridentate amine (PMDETA: *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine) was higher than that obtained with a bidentate amine, e.g., TMEDA (*N*,*N*,*N*′,*N*′-tetramethylethylenediamine), TMPDA (*N*,*N*,*N*′,*N*′-tetramethyl-1,3-diaminopropane), or TMBDA (*N*,*N*,*N*′,*N*′-tetramethylethyl-1,4-diaminobutane). Tetradentate amines, such as Me$_6$TREN (tris[2-(dimethylamino)ethyl]amine) and TPMA (tris(2-pyridylmethyl)amine), resulted in good yields, 70% and 87%, respectively, with high regioselectivities. The reactivity depends on the efficient generation of radical species in a process that is defined by k_{act} values. These values are obtained from the reaction of an alkyl halide with an excess of the Cu(I) complex and irreversible trapping of the resulting radicals by nitroxides or by redox potentials.[23] According to the literature, k_{act} values increase in the following order: TMEDA (0.015) < TPMA (62) < Me$_6$TREN (450). In our reaction, TPMA was more effective than Me$_6$TREN, probably due to the moderate efficiency of the radical generation leading to a relatively mild reaction. In this reaction, using phosphine ligands, which are effective in the nickel-catalyzed alkylative Heck reaction,[26] proved unsuccessful. Various copper(I) salts were effective as catalysts, but CuI gave the highest yield. The effect of an ammonium salt is unclear; however, it may be needed to support the solubility of the copper species. Generally, the combination of radical species and styrene derivatives is very effective in promoting ATRP, but the desired reaction predominated over ATRP because excess amine suppressed the polymer growth.[25]

The results for the distal-selective Heck reactions with several structures of **6** under conditions **A** or **B** are shown in Table 2. Almost all substrates **6** possessing sterically bulky substituents or various functional groups reacted smoothly with **2b** to give moderate-to-good yields with high distal selectivities. These results demonstrate the broad applicability of our protocol. The steric bulkiness of **6** tended to increase distal selectivities.

For example, ethyl 2-bromoisobutyrate led to **5b** with a 9:91 selectivity, whereas the substituted isobutyrate that led to **5c** or **5d** resulted in 5:>95 selectivities. A similar trend was observed in the synthesis of **5h**, **5i**, and **5j**. Substituted phenoxy esters leading to **5e**, **5f**, or **5g** tended to give slightly higher selectivities than **5b**, and electronic effects were not observed. Applicable functional groups for this reaction include not only esters but also ketones and nitro groups, as exemplified by **5k** and **5m**, respectively. However, the reaction was sluggish with an amide group (see **5n**). In this case, methacrylamide was obtained in high yields.

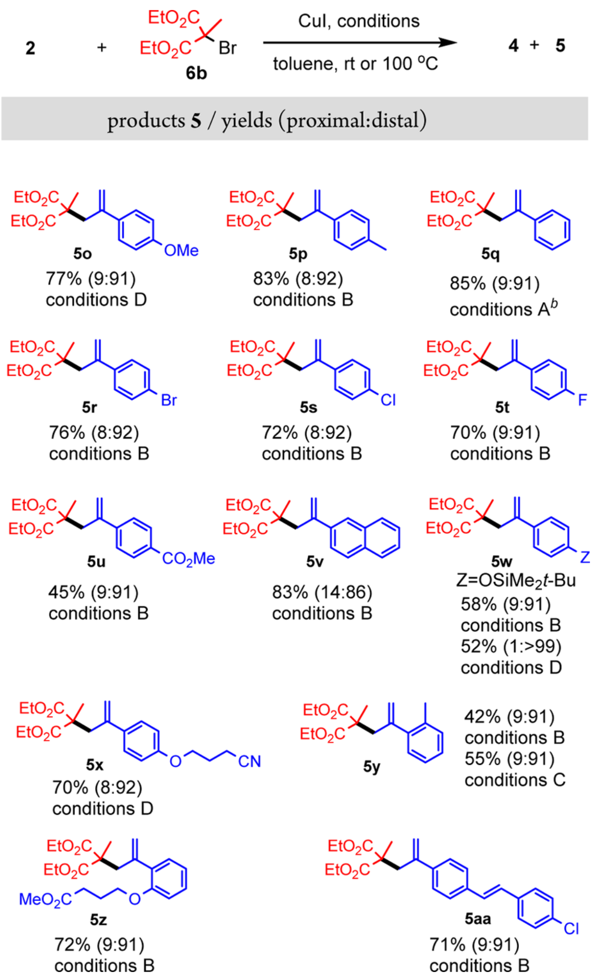
The reactivities of substituted styrenes **2** under conditions **A**−**D** are listed in Table 3. To compare the regioselectivities for various styrenes **2**, compound **6b** was used as a reaction partner as it previously showed a range of selectivities (see Table 2). The product yields did not strongly depend on the stereo and/or electronic properties of the aromatic rings in styrenes **6**. For

Table 2. Reactions of Alkyl Halides with **2b**[a]



[a] All reactions were carried out under the conditions **A** or **B**. The selectivities are determined by NMR analysis of the crude mixture. Conditions A: **2b** (1 equiv), **6** (1.5 equiv), CuI (10 mol %), TPMA (5 mol %), TEA (2 equiv), TBABr (20 mol %), toluene, 100 °C. Conditions B: **2b** (1 equiv), **6** (1.5 equiv), CuI (10 mol %), TPMA (5 mol %), PMDETA (1.5 equiv), $BnBu_3NBr$ (20 mol %), toluene, 100 °C. [b] 1,4-Dioxane was used instead of toluene.

Table 3. Reactions of Substituted α-Methyl Styrenes with **6b**[a]



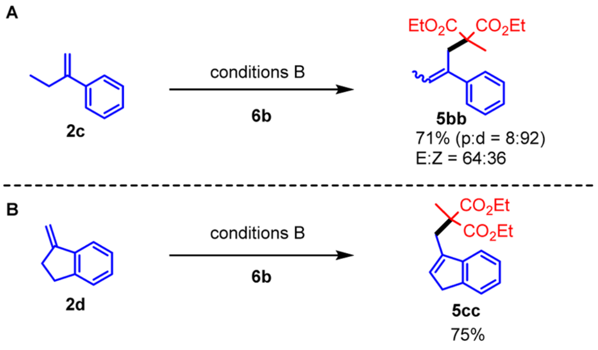
[a] All reactions were carried out under conditions A–D. The selectivities are determined by NMR analysis of the crude mixture. Conditions A: **2** (1 equiv), **6b** (1.5 equiv), CuI (10 mol %), TPMA (5 mol %), TEA (2 equiv), TBABr (20 mol %), toluene, 100 °C. Conditions B: **2** (1 equiv), **6b** (1.5 equiv), CuI (10 mol %), TPMA (5 mol %), PMDETA (1.5 equiv), $BnBu_3NBr$ (20 mol %), toluene, 100 °C. Conditions C: **2** (1 equiv), **6b** (1.5 equiv), CuI (10 mol %), Me_6TREN (10 mol %), PMDETA (1.5 equiv), $BnBu_3NBr$ (20 mol %), toluene, 100 °C. Conditions D: **2** (1 equiv), **6b** (1.5 equiv), CuI (10 mol %), PMDETA (1 equiv), $BnBu_3NBr$ (20 mol %), CH_2Cl_2, rt. [b] 1,4-Dioxane was used instead of toluene.

example, the yield of **5o**, which contains an electron-donating group, was virtually identical to that of the halogen-substituted products **5r**, **5s**, and **5t**. The ester-substituted styrene that led to **5u** gave a lower yield. Although the bulky substrate leading to **5z** gave a good yield, simple 2-methyl-substituted styrene, leading to **5y**, showed only moderate reactivity. In this reaction, silyl-protected phenol derivatives leading to **5w** did not show high reactivity even at an elevated temperature when compared with 4-methoxy-α-methystyrene, which gave **5o**. Styrenes containing a nitrile group or an internal double bond provided good yields of the products **5x** and **5aa**, respectively. In most cases, the use of a high temperature enabled efficient Heck reactions, whereas the reactions of α-methylstyrenes containing electron-donating groups in the para-position of the benzene rings proceeded with **6b** to afford the products **5o**, **5w**, and **5x** at room temperature. The regioselectivities were all very similar in the reaction with substituted styrenes.

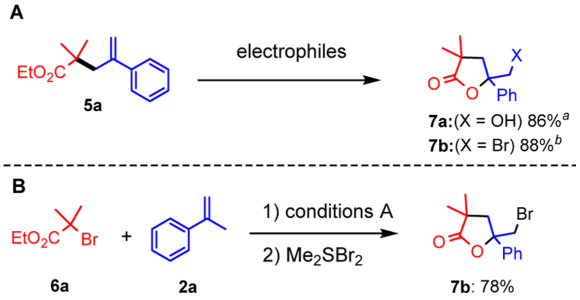
Although the reaction of α-methylstyrene derivatives **2** gave good distal selectivities, comparable results were also obtained with α-alkylated styrene derivatives. α-Ethylstyrene **2c** reacted smoothly with **6b** to produce the desired product **5bb** with high distal selectivity (Scheme 3A). In the case of the reaction with **2d**, **5cc** was produced exclusively (Scheme 3B). These results suggest that the distal selectivities obtained in our reactions are not dependent on the size of the α-substituents in the styrenes.

The products synthesized by the reaction reported here can provide ready access to lactone derivatives, one of which is a key fragment of plakortone (Scheme 4A).[27] Thus, in the presence of mild electrophiles, such as *m*-CPBA or Me_2SBr_2, electrophilic cyclization can afford lactone building blocks that possess alcohol or bromine functional groups in good yields. Our mild conditions can realize the one-pot transformation, Heck-type reaction followed by bromo lactonization, to produce a 78% yield of **7b** (total yield in two steps) (Scheme 4B).

Scheme 3. Reaction with Other α-Alkylated Styrene Derivatives



Scheme 4. Electrophilic Cyclizations



^{a}Conducted at rt in CH_2Cl_2 with *m*-CPBA. ^{b}Conducted at rt in CH_2Cl_2 with Me_2SBr_2.

In summary, the distal-selective α-hydride elimination in the Heck-type olefination to give various exomethylene compounds[28−30] in good yields and with high regioselectivities is described. The regioselectivities are dependent on the structure of **6**. These reactions were carried out using a copper(I)−TPMA catalyst system at room temperature or at 100 °C. Further investigations, including other types of addition and mechanistic studies, are currently underway.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and spectroscopic data for all new compounds. 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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