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A Detachable Ester Bond enables the Perfect Z-Alkylations of Olefins for the Synthesis of Tri- and Tetrasubstituted Alkenes

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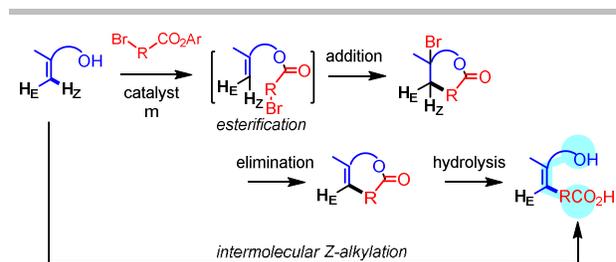
The reaction of 2-vinyl-substituted phenol with an alpha-bromoester undergoes the tandem esterification–alkylation reaction in the presence of a Cu-amine catalyst system to produce benzene-fused lactone. Z-Alkylated styrene is obtained after hydrolysis of the lactone with perfect selectivity. The simple protocol developed in this work opens a new frontier in the multi-substitution chemistry of alkenes.

The stereoselective and regioselective synthesis of multi-substituted olefins possessing different functional groups, which can be observed in numerous bioactive compounds and electronic materials¹, is one of the most challenging issues in synthetic organic chemistry. However, successful strategies for the synthesis of multi-substituted olefins are limited because of the difficulty in achieving perfect Z-selective substitutions of olefins. Although many synthetic approaches toward Z-substituted olefins with various substitution modes have been developed, such as metathesis², Wittig and related olefinations³, reductions of alkynes⁴, C–C double-bond isomerizations⁵, additions to alkynes⁶, and intermolecular Heck reactions⁷, obtaining high Z-selectivities remains difficult because of the geometric distortions of substituents around C–C double bonds.

Recent progress in this area has been achieved through the use of directing groups. For example, Loh and co-workers reported the Z-selective trifluoromethylation of terminal C–C double bonds by using amide as a directing group⁸. However, we hypothesized that the use of a cleavable tether is another possibility for achieving site-selective substitution of olefins (Scheme 1).

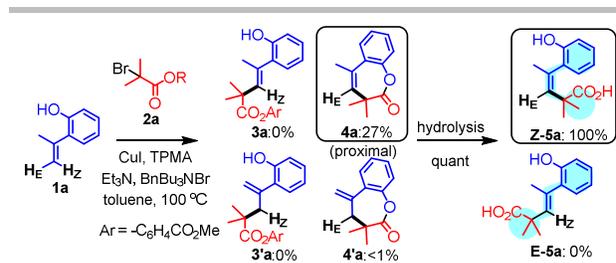
Among chemical bonds, ester bonds, which are easily broken, are one of the most promising functional groups for directing a specific reaction pathway, because esterification followed by intramolecular substitution of an olefin can formally give a perfectly Z-substituted olefin after hydrolysis

of the ester bond. Herein, we report perfect Z-alkylation via a breakable chemical bond.



Scheme 1 Our protocol.

We recently reported the tertiary alkylation of styrenes **1** with bromoester **2** to obtain two different olefins, **3** and **3'**, in the presence of a copper catalyst⁹. During the course of our study, we observed that an aryl bromoester such as **2a** undergoes a tandem esterification–alkylation reaction with phenol-substituted olefin **1a**, catalyzed by CuI/TPMA (tris(2-pyridylmethyl)amine) (Scheme 2). To our surprise, this reaction only provided cyclic compound **4a**, although we expected a complex mixture containing **3a**, **3'a**, **4a**(proximal), and **4'a**(distal) (proximal and distal double bonds with respect



Scheme 2 Z-Olefin **5a** from the reaction of **1a** and **2a**.

to the newly formed C–C bond) from this reaction because of the difficulty in controlling three kinds of reactions. These three reactions are 1) an esterification reaction, 2) hydrogen elimination leading to **4a** and **4'a**, and 3) alkylation reactions

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leading to **3a** and **3'a**. Cyclic compound **4a**, which possesses an internal C–C double bond, was able to be converted into perfect Z-substituted olefin **Z-5a** after simple hydrolysis. We also suspected isomerization of **Z-5a** to **E-5a** during the hydrolysis reaction but no isomerization was observed.

To further develop this reaction, we examined various copper catalysts and amines for the reaction of **1a** and **2a** in the presence of BnBu_3NBr and toluene as a solvent at 100 °C (Table 1). As we demonstrated previously, this reaction could be driven by atom-transfer radical substitution (ATRS which includes atom transfer radical addition followed by base-induced elimination)⁹, in which alkyl radicals are efficiently generated from the reaction of an alkyl halide and a Cu-amine catalyst^{10,11}. Various ligands, including a bidentate amine, e.g., TMEDA (*N,N,N',N'*-tetramethylethylenediamine), TMPDA (*N,N,N',N'*-tetramethyl-1,3-diaminopropane), and TMBDA (*N,N,N',N'*-tetramethylethyl-1,4-diaminobutane), a tridentate amine, e.g., PMDETA (*N,N,N',N'',N''*-pentamethyldiethylenetriamine), and a tetradentate amine, e.g., Me_6TREN (tris[2-(dimethylamino)ethyl]amine), were examined for the alkylation leading to **4a**. As a result, TPMA (tris(2-pyridylmethyl)amine)¹² was observed to provide the best yield, with excellent selectivity (entry 1). The corresponding Z-olefin **5a** was obtained in >90% yield after hydrolysis with aqueous

yields in the reaction with secondary or tertiary amines (entries 1–7).

In particular, trihexylamine was the most effective among the investigated amines, probably because of its mild basicity (entry 6). A base is required to induce smooth esterification, which is the first step of this reaction. But the base also causes the elimination of the hydrogen atom of **2a**, thereby leading to methacrylate via a side reaction. Therefore, bases possessing stronger basicity than trihexylamine tend to induce an elimination reaction, whereas bases possessing weaker basicity than trihexylamine tend to decrease the rate of esterification. Other amines, including aromatic amines, were not effective (entry 8). Copper(I) salts possessing various anions were screened (entries 9–13), but counter anions did not show any substantial differences in chemical yields of **4a** or in selectivities. Increasing the temperature to 120 °C in the presence of CuI , $\text{CuI}\cdot\text{SMe}_2$, and CuOAc resulted in higher yields; moreover, the reaction selectivities were not changed at this temperature (entries 6, 9, and 14). Although we also examined various solvents, such as 1,4-dioxane, 1,2-dimethoxyethane, and *N,N*-dimethylformamide, toluene provided the best results.

Table 1 Optimization^a.

| entry | Cu cat | amine | yield 4a (%) |
|-----------------|--------------------------------------|--|----------------------|
| 1 | CuI | Et_3N | 27 |
| 2 | CuI | Et_2NH | 23 |
| 3 | CuI | $\text{Et}(\text{Propyl})\text{NH}$ | 38 |
| 4 | CuI | $i\text{Pr}_2\text{NEt}$ | 43 |
| 5 | CuI | Bu_3N | 66 |
| 6 | CuI | Hex_3N | 74(78 ^b) |
| 7 | CuI | $(\text{C}_{10}\text{H}_{21})_2\text{NMe}$ | 49 |
| 8 | CuI | 2,6-lutidine | 46 |
| 9 | $\text{CuI}\cdot\text{Me}_2\text{S}$ | Hex_3N | 72(83 ^b) |
| 10 | CuCl | Hex_3N | 63 |
| 11 | CuBr | Hex_3N | 63 |
| 12 | CuCN | Hex_3N | 50 |
| 13 | CuOAc | Hex_3N | 70 |
| 14 ^b | CuOAc | Hex_3N | 86(72 ^c) |

^aConducted at 100 °C for 20 h in toluene with **1a** (1.0 equiv), **2a** (1.5 equiv), Copper salt (10 mol %), TPMA (10 mol %), amine (1.5 equiv), and BnBu_3NBr (20 mol %). The selectivities are determined by ¹H NMR analysis of the crude mixture. ^bThe reaction carried out at 120 °C. ^cIn the absence of BnBu_3NBr .

NaOH at room temperature. The addition of the amine is critical to induce the tandem esterification–alkylation reaction. Amines with long alkyl chains tend to give higher

Table 2 Reactions of **1a** with **2**^a.

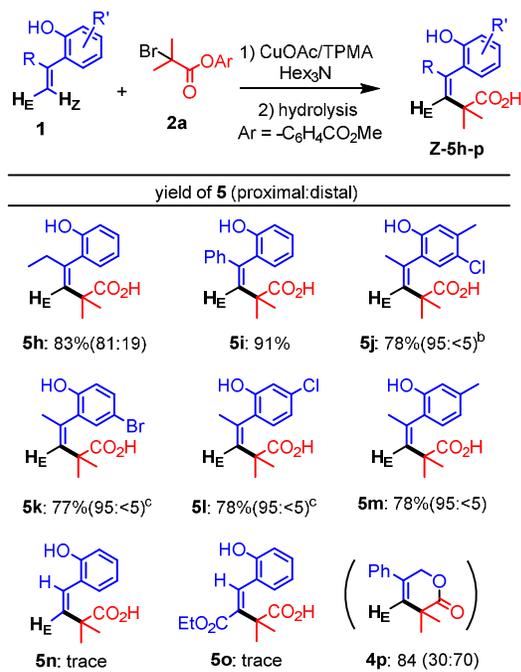
| yield of Z-5 (proximal:distal) | | |
|---------------------------------------|------------------------|------------------------|
| 5b : 85%(95:<5) | 5c : 83%(95:<5) | 5d : 78%(95:<5) |
| 5e : 81%(95:<5) | 5f : 75%(94:6) | 5g : trace |

^aConducted at 120 °C for 20 h in toluene with **1a** (1.0 equiv), **2** (1.5 equiv), CuOAc (10 mol %), TPMA (10 mol %), Hex_3N (1.5 equiv), and BnBu_3NBr (20 mol %). The hydrolysis was carried out in 1,4-dioxane/0.5M NaOH at 80 °C for 4 h. The isolated yields shown in the table are based on **1a**.

The results for the Z-selective alkylations with several structures of **2** under optimized conditions are shown in Table 2. Almost all substrates **2** possessing sterically bulky substituents or secondary- and tertiary-alkyl groups reacted smoothly with **1a** to give good-to-excellent yields without isomerizations. These results demonstrate the broad applicability of our protocol. For example, sterically bulky tertiary-alkyl groups leading to **5b** and **5c** resulted in 80% and 81% yields, respectively. We hypothesized that sterically

bulky substrates easily undergo isomerization from *Z* to *E* because of the steric distortions of substituents around a C–C double bond; however, the bulkiness was not an important factor with respect to the loss of steric geometry of **5** in this reaction. Other tertiary-alkyl groups possessing a cyclohexyl group led to **5d** in good yield. Secondary-alkyl groups possessing an ethyl or butyl group and leading to **5e** or **5f** can also be applied to *Z*-alkylation, unlike our previous reaction⁹. Primary-alkyl groups, however, gave no desired product **5g**. Most reactions were catalyzed by CuOAc, although CuI and CuI·SMe₂ in the case of **5c** and **5e** provided slightly higher yields compared to the yield achieved with CuOAc.

Table 3. Reactions of **1** with **2a**^a.



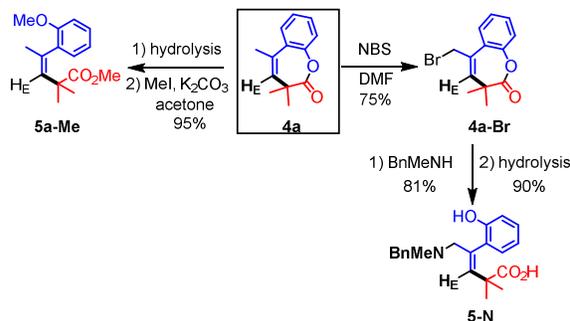
^aConducted at 120 °C for 20 h in toluene with **1** (1.0 equiv), **2a** (1.5 equiv), CuOAc (10 mol %), TPMA (10 mol %), Hex₃N (1.5 equiv), and BnBu₃NBr (20 mol %). The hydrolysis was carried out in 1,4-dioxane/0.5M NaOHaq at 80 °C for 4 h. The isolated yields shown in the table are based on **1**. ^bCuI·SMe₂ was used instead of CuOAc. ^cCuI was used instead of CuOAc.

Subsequently, we examined the reactivities of substituted styrenes **1** listed in Table 3. An increase in the steric demand of alpha-substituents in **1**, including ethyl and phenyl groups, led to products **5h** and **5i** in good yields without *Z* to *E* isomerization. Although steric bulkiness did not affect the tandem esterification–olefination process, in the case of product **5h**, the selectivity (proximal and distal) decreased because of the increased stability of the distal C–C double bond. Chirik¹³ and Watson¹⁴ recently reported selective C–C double-bond formations with olefins, where two possible pathways for β-hydride elimination existed; they achieved selective C–C double-bond formation by elegant ligand choice in Silyl–Heck reactions. However, effective ligands or

amines were not observed in our case. Styrene derivatives possessing substituents, including methyl, chloro, and bromo groups, gave the corresponding products with perfect *Z*-selectivities (**5k–n**). Although CuOAc was generally useful in this reaction, **5k**, **5l**, and **5m** were formed more readily with **2a** in the presence of CuI or CuI·SMe₂. Simple styrene leading to **5n** or styrene substrates **1** possessing beta-substituents leading to **5o** did not give the products but underwent ester-exchange reactions and polymerizations. Although regioselectivity for double bond formation (distal:proximal) was low, aliphatic alcohol group can also be used for intramolecular alkylation. For example, allylic alcohol reacted with **2a** to produce the corresponding **4p** in 84% yield, but the following hydrolysis leading to hydrolyzed **4p** was not obtained.

The alpha-methyl substituted cyclic olefins **4** obtained by the proposed tandem esterification–copper-catalyzed olefination are useful building blocks that can be easily transformed into a wide variety of functionalized *Z*-olefins **5**. For example, simple methyl substituted *Z*-olefin **5a-Me** was obtained with MeI. On the other hand, **4a** can be easily transformed into **4a-Br**, which is a useful building block for classical nucleophilic substitution reactions to obtain more complex trisubstituted olefins (Scheme 3). For example, amine substituted **5-N** was obtained after the reaction of **4a-Br** with BnMeNH followed by hydrolysis from **4a-Br** (81% for amination and 90% for hydrolysis).

Scheme 3 Transformations of **4a**.



The rationale behind the attention accorded selective olefination chemistry has been based, in part, on its potential to streamline routes towards challenging synthetic targets. Thus, we tried to synthesize various carbon functional group-substituted olefin. For example, **4j** obtained from the tandem reaction of **1b** and **2a** can be transformed into bromo-substituted **4j** in 85% yield. Tetrasubstituted olefin **6** was obtained after Suzuki–Miyaura coupling of brominated **4j** followed by hydrolysis in 70% yield for 2 steps (Scheme 4).

Scheme 4 The synthesis of tetrasubstituted alkene **6**. (See ESI).

Conclusions

In conclusion, tandem esterification–olefination followed by hydrolysis to give various multi-substituted *Z*-olefin compounds in good yields and with perfect *Z*-selectivities was described. The selectivities are dependent on the first esterification step to accomplish site-selective alkylations of **1**. These reactions were conducted using a copper(I)–TPMA catalyst system with tri(*n*-hexyl)amine. The developed simple protocol can be used to synthesize tetrasubstituted alkenes in reasonable yield.

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