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Letter

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Tandem reactions enable trans- and cis-hydro-tertiary-alkylations catalyzed by a copper salt

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KEYWORDS. alkylation, alkyne, addition, silane, diboron, copper

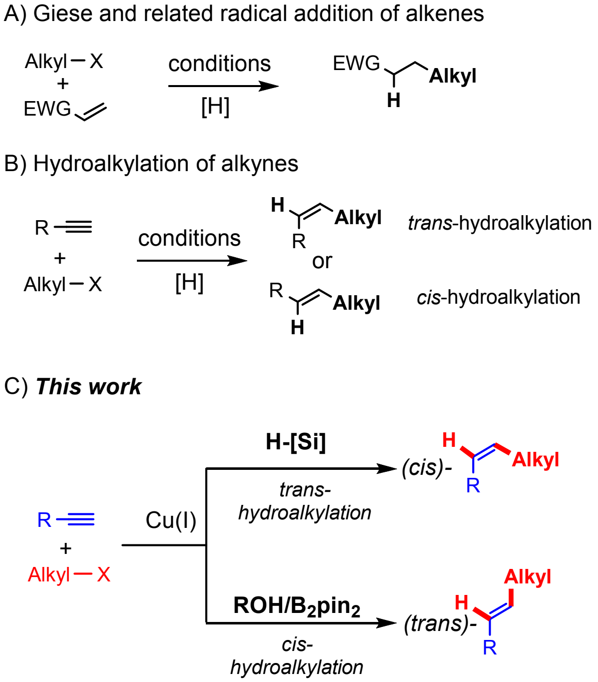
Supporting Information Placeholder

ABSTRACT: A methodology to synthesize trans- and cis-alkenes by well-controlled hydroalkylation of alkyl radicals to alkynes is reported. α-bromocarbonyl compounds are useful alkyl radical precursors in the presence of Cu(I) catalysts. Under copper catalyst conditions and in the presence of silane or alcohol/B_2pin_2, trans- and cis-hydroalkylation occurred with excellent stereoselectivities. The judicious choice of additives allowed for this stereodivergence, giving selective access to the trans-alkylated alkenes with $HSiTMS_3$ and cis-alkylated alkenes with t-BuOH/B_2pin_2 in good yields with selectivities.

Alkyl halides are very attractive compounds for alkylation of molecules which are extensively described as reagents in fundamental organic chemistry text books. Among them, hydroalkylations including Giese and related radical alkylation reactions of alkenes have been well-studied to load complex alkyl groups into alkenes (Figure 1 A).[1,2] Giese reaction involves addition of a nucleophilic alkyl radical to an alkene bearing an electron-withdrawing group (EWG) and is one of the applications of the atom-transfer radical addition (ATRA) established by Kharasch[3] and many chemists[4,5,6], in which an organic halide is added to an alkene to generate a newly formed C–C and C–X bond.[7] On the other hand, the stereocontrolled addition of alkyl groups to alkynes instead of alkenes as substrates is challenging because of difficult control of cis- and trans-isomers (Figure 1 B).[8] These hydroalkylations with alkynes undergo either trans-hydroalkylations leading to cis-alkenes[9] or cis-hydroalkylations leading to trans-alkenes by using nucleophilic alkyl radicals.[10] While several excellent researches on the synthesis of trans- and cis-alkenes[11] have enabled various hydroalkylations with alkynes, stereodivergent hydroalkylation of alkynes using an electrophilic tertiary-alkyl radical has not yet been established.[8] In this context, we envisaged the development of controllable hydroalkylation of alkynes with α-bromocarbonyl compounds in the presence of a copper catalyst. Recently, α-bromocarbonyl compounds are employed as an alkyl radical source in olefinations by our group and other groups.[12] However, the control method of stereoselectivities in the reactions of α-bromocarbonyl compounds and alkynes is unknown. During the course of our study, we found that the reaction of α-bromocarbonyl compound and alkyne in the presence of hydrosilane undergoes trans-hydroalkylation to give cis-alkene, whereas ROH/B_2pin_2, which is reductive borylation conditions, undergoes cis-hydroalkylation to give trans-alkene. Herein, we would like to report our discovery to synthesize trans- and cis-tert-alkylated alkenes using copper-catalyzed hydroalkylations (Figure 1 C).

Our initial screening shown in Table 1 employed the reaction of phenylacetylene (**1a**), α-bromoester (**2a**), CuI, Et_3N, and additives in toluene at 125 ºC (in a sealed tube). This reaction generally gave atom-transfer radical adduct **5a** in the presence of a copper catalyst. As previously demonstrated by our group,[12] this reaction did not occur in the presence of a radical scavenger such as TEMPO or BHT, thereby indicating that this process involves a radical reaction. A copper-TPMA (tris(2-pyridylmethyl)amine) catalyst system underwent the desired hydroalkylation reaction with concomitant formation of **5a**, although poor cis and trans selectivities were obtained (run 1). On the other hand, trans-hydroalkylation leading to **3a** prevailed over cis-hydroalkylation to **4a** in the presence of a proton generated from i-PrOH (run 2). This result encouraged us to investigate additional hydrogen sources. Finally, $HSi(SiMe)_3$ ($HSiTMS_3$) was found to be the best hydrogen source. Although the detailed reaction mechanism is still under investigation, the first radical addition process seems to be very important to carry out trans-hydroalkylation. Lalic's group reported cis-

Figure 1. Hydroalkylations

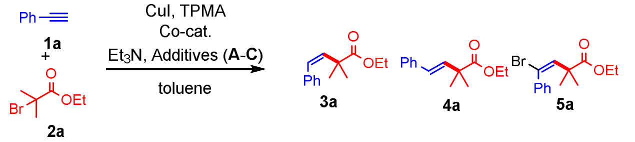

A) Giese and related radical addition of alkenes

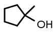
B) Hydroalkylation of alkynes

C) *This work*

hydroalkylation of alkynes in the presence of a silane and a copper catalyst, with hydrocupration being one of the most important steps.[10b,c] We obtained the opposite selectivity as compared to their results. In the absence of a base, no reaction occurred. Therefore, various bases such as t-BuOK, KOAc, Cs_2CO_3, Na_2CO_3, and K_3PO_4 were screened, but the bases did not affect the yield (runs 3–7). Increasing the reaction temperature was very effective in this regard. When the reaction was carried out at 160 ºC, a 94:6 (**3a**:**4a**) mixture was obtained in 75% yield (run 8)[13]. Although **3a** is very bulky, no isomerization to **4a** was observed at the high temperature. Surprisingly, the use of different additives switched the reaction selectivity (runs 9 and 10). Thus, the reaction in the presence of both silane and diboron at 100 ºC resulted in lower chemical yield of **3a**, whereas the reaction in the presence of both alcohol and diboron resulted in 57% yield with 10:90 (**3a**:**4a**) selectivity (runs 9 and 10)[14]. When the reaction was carried out at 160 ºC under the conditions, yield and selectivity were not changed. Although the Marder's group reported that the reaction of alkyl halide with diboron underwent borylation[15], no borylation with **2a** was observed in our case. A proton is necessary to undergo cis-hydroalkylation, but other proton sources were not effective in this reaction. We expect that the reaction involves a Suzuki type coupling. Therefore, various transition metal catalysts were screened as co-catalysts, with $Pt(dba)_2$ showing optimum co-catalyst characteristics. For example, the reaction in the presence of $Pt(dba)_2$ and an alcohol such as EtOH, i-PrOH, and t-BuOH resulted in high yields ranging from 81 to 99% with high trans-selectivities. Without alcohols or alcohols larger than t-BuOH dramatically retarded the reaction, and **5a** was obtained instead of the hydroalkylation product (run 14).

Table 1. Optimization

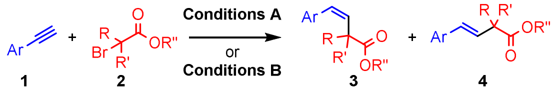


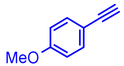
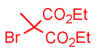
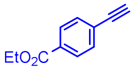
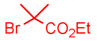
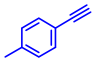
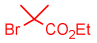
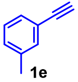
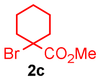
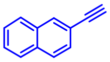
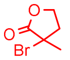
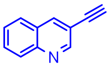
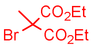
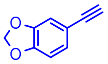
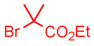
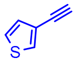
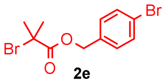
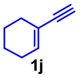
Run	Co-cat. (2 mol%)	A (0.2 equiv)	B (equiv)	C (1.5 equiv)	Temp (°C)	Yield of **3a**+**4a**(%) (**3a** : **4a**)
1	-	K_3PO_4	-	-	125	15 [50:50] (**5a**:38)
2	-	K_3PO_4	iPrOH (1.5)	-	125	12 [99: 1] (**5a**:56)
3	-	K_3PO_4	$HSiTMS_3$ (1.5)	-	125	43 [95: 5]
4	-	tBuOK	$HSiTMS_3$ (1.5)	-	125	53 [68:32]
5	-	KOAc	$HSiTMS_3$ (1.5)	-	125	57 [89:11]
6	-	Cs_2CO_3	$HSiTMS_3$ (1.5)	-	125	49 [94: 6]
7	-	Na_2CO_3	$HSiTMS_3$ (1.5)	-	125	46 [91: 9]
8	-	K_3PO_4	$HSiTMS_3$ (1.5)	-	160	75 [94: 6]
9	-	K_2CO_3	$HSiTMS_3$ (1.5)	B_2pin_2	100	10 [99: 1]
10	-	K_2CO_3	EtOH (2)	B_2pin_2	100	57 [10:90]
11	$Pt(dba)_2$	K_2CO_3	EtOH (2)	B_2pin_2	100	81 [10:90]
12	$Pt(dba)_2$	K_2CO_3	iPrOH (2)	B_2pin_2	100	92 [15:85]
13	$Pt(dba)_2$	K_2CO_3	tBuOH (2)	B_2pin_2	100	99 [12:88]
14	$Pt(dba)_2$	K_2CO_3	 (2)	B_2pin_2	100	0 [-] (**5a**:66)

Conducted at proper temperature for 12-20 h in toluene with CuI (10 mol%), TPMA (10 mol%), Et_3N (1.5 equiv), and additives A, B and C. The yields were determined by ^1H NMR analysis and the ratios were determined by GC analysis. All reactions were carried out in a sealed tube.

Under optimal conditions, we evaluated the reactivities of alkynes **1** and α-bromoesters **2** bearing various structures for trans- and cis-hydroalkylation reactions (Table 2). Although electron-rich alkyne **1b** resulted in good yields and selectivities, electron-poor alkyne **1c** gave moderate yields with good selectivities. These results might imply that generated radical species are electrophilic. Other electronically neutral compounds (**1d**, **1e**, and **1f**) with acyclic and cyclic bromides (**2a**, **2c**, and **2d**) resulted in good yields and high selectivities. Heteroaromatic ring-substituted alkynes **1g** and **1i** can be used for current hydroalkylation reactions. Both nitrogen and sulfur atoms are sometimes not good to maintain the catalytic activities of copper, but trans- and cis-products were smoothly obtained in the reaction with **2b** and **2e**. In the case of the reaction of **1h**, cis-product **3h** was obtained in good yield and selectivity but trans-product **4h** was poor. We optimized again about this substrate **1h** and found that the reaction conditions without Pt catalyst were very effective to give the product in 80% with 97% trans-selective. The reason for the conditions without Pt catalyst is not clear, but in situ generated alkenyl boron from **1h** might be very reactive for Suzuki type reaction. And in the case of **1h**, borylation reaction was inhibited by Pt catalyst but the borylation with other alkynes were no problem in the presence of Pt (See SI). Alkenyl-substituted alkyne **1j** also gave the desired products in good yields with high trans and cis selectivities.

Table 2. Substrate scope



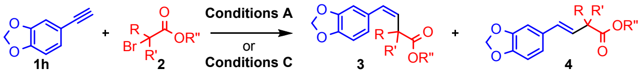
Substrate **1**	Substrate **2**	Conditions A Yield (%) (**3** : **4**)	Conditions B Yield (%) (**3** : **4**)
 **1b**	 **2b**	**3b**: 74[a] (99:1)	**4b**: 70 (15:85)
 **1c**	 **2a**	**3c**: 55 (99:<1)	**4c**:53[a] (13:87)
 **1d**	 **2a**	**3d**: 70 (99:1)	**4d**: 81 (15:85)
 **1e**	 **2c**	**3e**: 72 (84:16)	**4e**: 72 (17:83)
 **1f**	 **2d**	**3f**:65 (77:23)	**4f**: 78 (10:90)
 **1g**	 **2b**	**3g**:67[a] (95:5)	**4g**: 73 (20:80)
 **1h**	 **2a**	**3h**:90 (86:14)	**4h**: 12 (7:93) 80 (3:97)[b]
 **1i**	 **2e**	**3i**: 67[a] (99:1)	**4i**:72 (18:82)
 **1j**	 **2a**	**3j**: 70[a] (99:1)	**4j**: 77 (29:71)

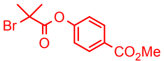
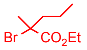
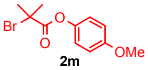
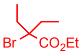
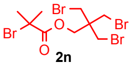
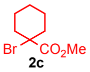
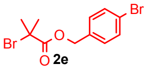
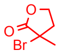
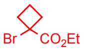
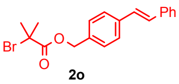
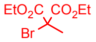
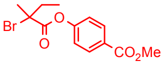
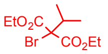
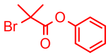
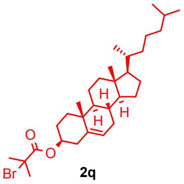
Conditions A: CuI (10 mol%), TPMA (10 mol%), $HSiTMS_3$ (1.5 equiv), K_3PO_4 (20 mol%), Et_3N (1.5 equiv), toluene, 160ºC, 12h. Conditions B: CuI (10 mol%), $Pt(dba)_2$ (2 mol%), TPMA (10 mol%), B_2pin_2 (1.5 equiv), K_2CO_3 (20 mol%), tBuOH (2.0 equiv), Et_3N (1.5 equiv), toluene, 100ºC, 20h. The yields were isolated and the ratios were determined by GC analysis. All reactions were carried out in a sealed tube. [a] Run at 125ºC. [b] Without Pt cat. Pure isomer can be obtained after GPC (if separable).

We also tried alkyl substituted alkynes but the results were poor. Overall, indications of good functional group tolerance can be found from the products **3b**–**3j** and **4b**–**4j**, likely reflecting the mildness of the hydroalkylation event despite high temperatures.

We next examined functionalized α-bromoesters **2** with **1h**, which shows nice reactivity without Pt catalyst in the synthesis of **4**, under conditions A and C (without Pt catalyst) (Table 3). The size of α-alkyl groups affected the yields and selectivities (**2f**, **2g**, and **2h**). Large substrate **2g** gave poor result but selectivity was good. No clear selectivity trends were observed in all cases. The selectivities of trans- or cis-hydroalkylations with slightly small α-bromoesters **2c**, **2d**, and **2i** were also no problem to obtain good results, whereas α-bromoesters **2l**, **2m**, **2n**, **2p**, and **2q** possessing a slightly large ester moiety resulted in excellent selectivities for both alkylations. To our surprise, cis-alkylations generated incredibly congested cis-alkene structures **3**, although the steric bulkiness of α-bromoesters **2** did not affect the selectivities (**2q**). Alternatively, increasing the size of α-bromoesters **2** decreased the yields. In this case, α-bromoesters **2** underwent reduction via debromohydrogenation. To suppress this side-reaction during cis-hydroalylations, the reactions were carried out at 125 ºC instead of 160 ºC or increasing the amounts of Cu and ligand and the yields were slightly increased as a result (**2b**, **2e,** **2f**, **2h**, **2l**, **2m**, **2o**, and **2p**). β-Hydrogen elimination of **2** is another possibility to decrease the product yields, although such by-products were not observed in both alkylations. The electronic effects of α-bromoesters **2** were not observed. For example, electron-rich or -deficient aryl-substituted esters **2k**, **2l**, **2m**, and **2p** and allylic or benzylic esters **2e**, and **2o** did not show significant differences. It is noteworthy that the alkyl–Br bond in **2n** and alkene in **2o**, a well-known reactant for metal-catalyzed reactions, remained fully intact. On the other hand, secondary-alkyl bromides were sluggish (no ATRA and any couplings but consumed the starting materials).

Table 3. Substrate scope

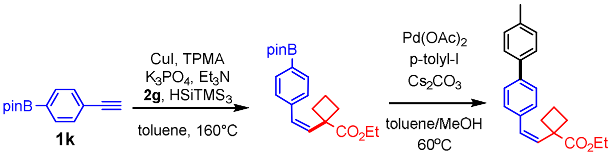


	Conditions A	Conditions C		Conditions A	Conditions C
Substrate **2**	Yield (%) (**3** : **4**)	Yield (%) (**3** : **4**)	Substrate **2**	Yield (%) (**3** : **4**)	Yield (%) (**3** : **4**)
 **2f**	**3k**: 73^{a,b,c} (99:<1)	**4k**: 84^{b} (8:92)	 **2l**	**3t**: 71^{a,b,c} (99:<1)	**4t**: 70 (8:92)
 **2g**	**3l**: 25 (99:1)	**4l**: 37 (17:83)	 **2m**	**3u**: 70^{a,b,c} (99:<1)	**4u**: 72 (6:94)
 **2h**	**3m**: 73^{a,b} (99:<1)	**4m**: 78 (13:87)	 **2n**	**3v**: 46 (99:<1)	**4v**: 55 (<1:99)
 **2c**	**3n**: 85 (83:17)	**4n**: 83 (10:90)	 **2e**	**3w**: 70^{a,b} (99:<1)	**4w**: 77 (13:87)
 **2d**	**3o**: 60 (90:10)	**4o**: 64 (6:94)			
 **2i**	**3p**: 79 (87:13)	**4p**: 68 (25:75)	 **2o**	**3x**: 76^{a,} (99:<1)	**4x**: 85 (11:89)
 **2b**	**3q**: 75^{a,b,c} (84:16)	**4q**: 94 (15:85)	 **2p**	**3y**: 72^{a} (95:5)	**4y**: 86^{b} (<1:99)
 **2j**	**3r**: 60 (99:<1)	**4r**: 65 (<1:99)			
 **2k**	**3s**: 70 (99:<1)	**4s**: 75 (20:80)	 **2q**	**3z**: 44 (99:<1)	**4z**: 53 (5:95)

Conditions A: CuI (10 mol%), TPMA (10 mol%), HSiTMS$_3$ (1.5 equiv), K$_3$PO$_4$ (20 mol%), Et$_3$N (1.5 equiv), toluene, 160ºC, 12h. Conditions C: CuI (10 mol%), TPMA (10 mol%), B$_2$pin$_2$ (1.5 equiv), K$_2$CO$_3$ (20 mol%), tBuOH (2.0 equiv), Et$_3$N (1.5 equiv), toluene, 100ºC, 20h. All reactions were carried out in a sealed tube. The yields were isolated and the ratios were determined by GC analysis. Pure isomer can be obtained after GPC (if separable). [a] Run at 125ºC. [b] 20 mol% of CuI was used. [c] 20 mol% of TPMA was used.

The obtained products via our protocol can be transformed to various functionalized quaternary carbon centers (Scheme 1). For example, borylated alkyne **1k** reacted with **2a** to produce **3aa** in 77% yield without the loss of the carbon–boron bond. The obtained **3aa** can be transformed to two benzene substituted compounds **6** in 80% yield via Suzuki–Miyaura coupling. We also obtained cis- and trans-epoxides from each isomers (see supplementary information). These results show that our controlled addition reaction is a powerful technique for synthesizing useful building blocks.

Scheme 1. Transformations



In summary, we found a new control methodology to synthesize trans- and cis-alkenes. The key to successful synthesis might lie in the atom-transfer radical addition to produce brominated alkene followed by its reduction with hydrosilane. On the other hand, cis-hydroalkylation is carried out via reductive borylation followed by Suzuki-type cross-coupling. Mechanistic studies including the effect of additives, catalyst and temperature are currently underway.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectroscopic data for all new compounds are available free of charge via the Internet at http://pubs.acs.org.”

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Notes

The authors declare no competing financial interests.

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(13) We carried out the reaction of **5a** under the conditions of run 8 without **2a**. As the result, **3a** was obtained. This result indicated that **3a** is generated from ATRA followed by hydrosilane reduction of **5a** (See SI).

(14) We carried out this reaction without **2a**. As the result, reductive borylation product was obtained. Therefore, **4a** could be generated from the borylation followed by Suzuki type reaction (See SI).

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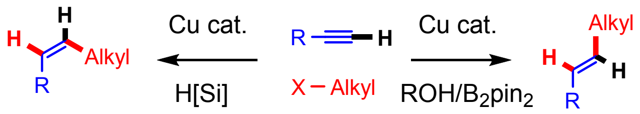

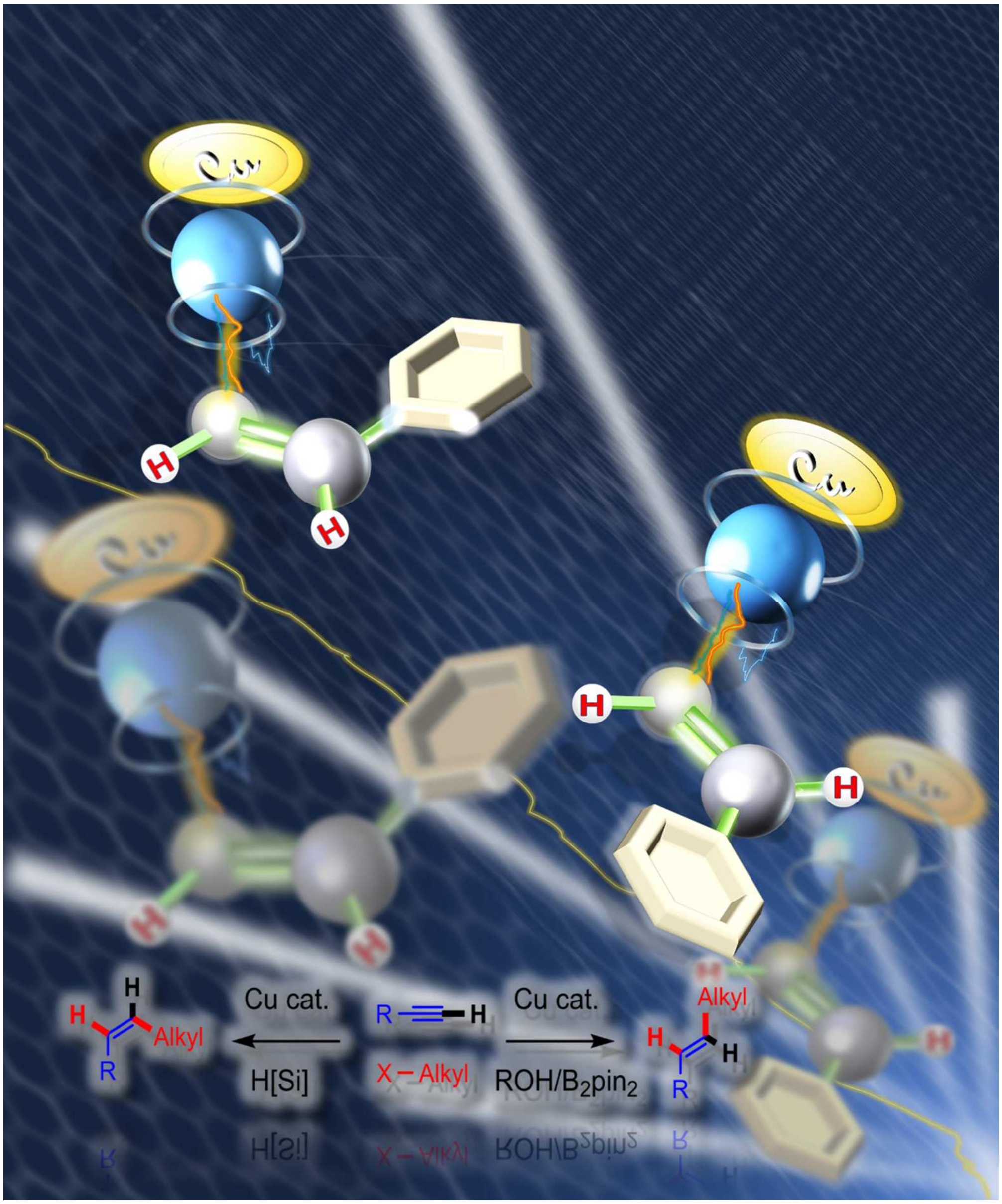

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