Regioselective and Stereospecific Copper-Catalyzed Deoxygenation of Epoxides to Alkenes

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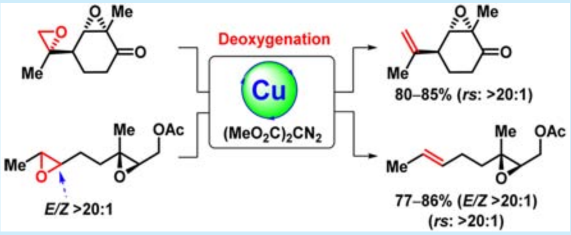
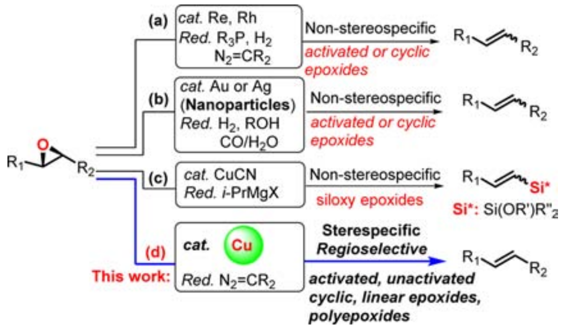
S *Supporting Information*

ABSTRACT: Two copper salts ($Cu(CF_3CO_2)_2$ and IMesCuCl) were identified as earth-abundant, inexpensive, but effective metal catalysts together with diazo malonate for chemo-/regioselective and stereospecific deoxygenation of various epoxides with tolerance of common functional groups (alkene, ketone, ester, *p*-methoxybenzyl, benzyl, *tert*-butyldimethylsilyl, and triisopropylsilyl). In particular, the unprecedented regioselectivity allowed for the first time monodeoxygenation of diepoxides to alkenyl epoxides. Density functional theory mechanistic studies showed that the deoxygenation occurred by collapsing the free ylide, unfavoring the possible intuitive pathway via cycloreversion of possible oxetane.



Deoxygenation of epoxides to alkenes is an important functional group transformation in organic synthesis.[1] Deoxygenation of epoxides has been conventionally performed using a *stoichiometric* reduction procedure[2] until recently, when catalytic deoxygenation was developed with rhodium and rhenium catalysts together with phosphines, molecular hydrogen (H_2), sodium sulfites, or diazo compounds as reductants (Scheme 1a).[3] Although synthetically advantageous over the stoichiometric reduction, most of these catalytic protocols were established with activated or cyclic epoxides (e.g., styrene oxides and cyclohexene oxides), and the substrate scope and stereospecificity were not fully investigated until 2015 when Takai et al.[4] found that the unique combination of Re_2O_7 and $P(OPh)_3$ was effective for the stereospecific deoxygenation of unactivated aliphatic epoxides. Other important progress in this area is the recent green heterogeneous catalysis using Au or Ag nanoparticles as the catalyst (Scheme 1b).[5] However, epoxides such as styrene oxides and cyclohexene oxides were better deoxygenated but without specificity (e.g., Z/E 1:1 alkenes from linear 1,2-*trans*-epoxide). Therefore, it would be of great significance and paramount importance to develop a new catalytic deoxygenation that is (i) stereospecific, (ii) broadly applicable (substrate scope: activated, unactivated, cyclic, linear epoxides), (iii) chemo- and regioselective (unprecedented), and (iv) ideally catalyzed by earth-abundant transition metals. The use of precious transition metals (Rh, Re, and Au) for the catalytic deoxygenation is opposite to the trend of catalysis with earth-abundant transition metals (Fe, Co, Ni, Mn, Cu, Ti, V, Cr, etc.).[6] The only example using copper as the catalyst for deoxygenation with *i*-PrMgX was limited to the siloxy epoxide substrates (Scheme 1c).[7] Herein, we report the identification of two copper catalysts [IMesCuCl and $Cu(TFA)_2$] for efficient stereospecific deoxygenation of various epoxides with diazo malonate (Scheme 1d). In particular, these two copper catalysis protocols are regioselective to different epoxides, which for the first time allow regioselective deoxygenation of diepoxides.

Scheme 1. Representative Catalytic Methods for Deoxygenation of Epoxides to Alkenes



Copper catalysis[8] has been widely used in organic synthesis (conjugate addition of Grignard reagents, Ullmann reaction, Sonogashira coupling, Wacker oxidation, Stryker's catalyst, Click reaction, etc.) in light of its earth abundance, low toxicity, and versatile reactivity. Surprisingly, it is nearly absent in the arena of catalytic deoxygenation of epoxides. To probe the viability of copper catalysis for deoxygenation of epoxides, we thoroughly examined 12 copper salts and various reductants using epoxide **1a** as the model substrate (Table 1).

Three classes of neutral and mild reductants, phosphines, silanes, and diazo compounds, were selected with the knowledge that formation of the very strong P–O, Si–O, and C–O bonds (possible side products: phosphine oxide, silanol, and carbonyl, respectively) might thermodynamically facilitate the deoxygenation (epoxide C–O bond cleavage). Among >200 hypothesis-testing experiments, 84 representative results are summarized in

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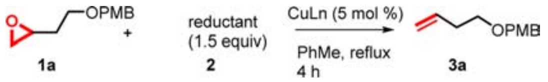
Table 1. Selected Conditions for Copper-Catalyzed Deoxygenation of Epoxide 1a[a]



entry	Cu salt	reductant	conv (%)	yield (%)
1	CuCl, CuBr, CuI, or Cu_2O	R_3P, R_3SiH	0	0
		R_2CN_2	0	0
		$RR'CN_2$	0	0
2	$CuCl_2$	R_3P, R_3SiH	0	0
		R_2CN_2	45	38
		$RR'CN_2$	27	12
3	$CuBr_2$	R_3P, R_3SiH	0	0
		R_2CN_2	55	48
		$RR'CN_2$	40	21
4	$Cu(OAc)_2$	R_3P, R_3SiH	0	0
		R_2CN_2	20	13
		$RR'CN_2$	58	45
5	**$Cu(TFA)_2$**	R_3P, R_3SiH	0	0
		R_2CN_2	**95**	**81**
		$RR'CN_2$	100	62
6	**IMesCuCl**	R_3P, R_3SiH	0	0
		R_2CN_2	**90**	**75**
		$RR'CN_2$	100	53
7	IPrCuCl	R_3P, R_3SiH	0	0
		R_2CN_2	55	52
		$RR'CN_2$	78	46
8	SIPrCuCl	R_3P, R_3SiH	0	0
		R_2CN_2	30	21
		$RR'CN_2$	90	55
9	SIMesCuCl	R_3P, R_3SiH	0	0
		R_2CN_2	29	22
		$RR'CN_2$	65	41

[a] Yield was determined by ^{1}HNMR analysis of the crude reaction mixture using $CHCl_2CHCl_2$ as the internal standard. IMes = 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene; IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene; SIMes = 1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene; SIPr: = 1,3-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazol-2-ylidene. R_3P = Ph_3P, Bu_3P, $P(O^iPr)_3$; R_3SiH = PMHS or Et_3SiH; R_2CN_2 = $(MeCO)_2CN_2$; $RR'CN_2$ = $(MeCO)[P(O)(OMe)_2]CN_2$ (Bestmann–Ohira reagent).

Table 1. All attempts using phosphines/phosphites [Ph_3P, Bu_3P, and $P(O^iPr)_3$] and silanes [$(MeHSiO)_n$ and Et_3SiH] as reductants failed, regardless of the copper salts (entries 1–9). On the other hand, simple Cu(I) salts (CuCl, CuBr, CuI, Cu_2O) could not affect the deoxygenation under various reaction conditions (e.g., different solvents, temperature, higher loadings of the copper salt) (entry 1). Gratifyingly, the combination of Cu(II)/diazo compound (entries 2–5) or (NHC)CuCl/diazo compound (entries 6–9) deoxygenated the epoxide **1a** with conversions ranging from 20% to 100%, providing the alkene **3a** with 12–81% yields. In particular, both $Cu(TFA)_2$/diazo malonate (entry 5) and IMesCuCl/diazo malonate (entry 6) efficiently promoted the deoxygenation with 75–81% yields at 90–95% conversions (83–85% yields based on the conversion). It was also noted that Bestmann–Ohira reagent[9] [seven other diazo compounds had also been evaluated, see the Supporting Information] as the reductant gave generally poorer yields (entries 2–7), except for the use of SIPrCuCl and SIMesCuCl as the copper catalyst (entries 8 and 9). It should be noted that the combination of Cu/diazo compounds has been reported to promote a number of transformations such as cyclopropanation[10] and cyclopropenation,[11] cross coupling with alkynes,[12] ring expansion of vinyl oxiranes and oxetanes,[13] [3 + 2] cycloaddition with terminal alkynes,[14] and a variety of X–H bond insertion reactions.[15] However, such combination was demonstrated for the first time to be efficient for deoxygenation of epoxides without detection of some potential competing reactions such as cyclopropanation,[16] Buchner ring expansion,[17] and carbene C–H insertion.[18] Notably, the bench-stable, structurally well-defined (NHC)CuCl[19] was effective in this catalysis. Nevertheless, this initial discovery must be considered with the broad substrate scope.

The epoxide scope was examined with both $Cu(TFA)_2$ and IMesCuCl as the catalyst and diazo malonate (**2a**) as the reductant in a parallel fashion, and the results are summarized in Table 2. Terminal epoxides (**1b** and **1c**) were excellent substrates for this copper-catalyzed deoxygenation. Most disubstituted epoxides (cyclic or linear, activated or unactivated) could be deoxygenated efficiently to alkenes by this copper catalysis in good to excellent yields. Most importantly, the deoxygenation proceeded in a stereospecific fashion: *trans*-epoxides (**1d**, **1e**, and **1h**) to *trans*-alkenes (**3d**, **3e**, and **3h**) and *cis*-epoxides (**1f** and **1g**) to *cis*-alkenes (**3f** and **3g**). Common alcohol protecting groups including TBS (**1l**), TIPS (**1h**), Bn (**1g** and **1h**), and PMB (**1a**) were well tolerated. Deoxygenation of *α*,*β*-epoxy carbonyl compounds (**1j** and **1k**) occurred smoothly (**3j**,**k**) with slightly lower yields. Notably, ethyl 4,5-epoxy-2-hexenoate (**1m**) embedded with a vinyl epoxide did not undergo the well-established ring expansion[13] or possible competing cyclopropanation. This result suggested that the copper catalysis was highly chemoselective. Not surprisingly, the deoxygenation of 1,1-disubstituted epoxides (**1n**–**p**) with the two catalysts was also efficient. It is noteworthy that the cyclopropane ring survived. The deoxygenation of the trisubstituted epoxides (**1q**–**u** → **3q**–**u**) proceeded smoothly with moderate to good conversions (21–74%). It is interesting to note that the alkene of the epoxide **1s** did not undergo cyclopropanation, a well-known reaction for Cu/diazo combination. The tetrasubstituted epoxides **1v** and **1w** failed to undergo the deoxygenation. These findings together with the lower conversions for trisubstituted epoxides compared to mono- and disubstituted ones allowed us to conclude that this Cu-catalyzed deoxygenation was highly regioselective: the less substituted epoxide is the better substrate for deoxygenation.

The regioselectivity was then examined with three examples (**1x**–**z**, Scheme 2) by exploiting their steric differences. Remarkably, deoxygenation of the diepoxides **1x**–**z** under the standard conditions gave the monoepoxides **1s**, **3y**, and **3z** in excellent yields (77–93%) as the exclusive product, respectively, while deoxygenation of diepoxide **1aa** gave a mixture of **3aa** and **3aa′** in a ratio of 2.4:1 with low conversions. Notably, this is the first example of regioselective catalytic deoxygenation of epoxides.

Mechanistically, we postulated that the copper carbenoid generated from decomposition of diazo malonate reacted with the epoxide oxygen to form the ylide complex A,[20] which either dissociated the copper to generate the free ylide B or underwent ring expansion to the intermediate C (Scheme 3). Both B and C could collapse to afford the alkene and oxomalonate. Alternatively, reductive elimination of the copper from C might produce oxetane D as an intermediate,[21] which would undergo cycloreversion[22] to provide the alkene and oxomalonate. DFT calculation studies[23] indicated that the ring expansion pathway (A → C) experienced a significant energy barrier ($\Delta G^{\ddagger}$

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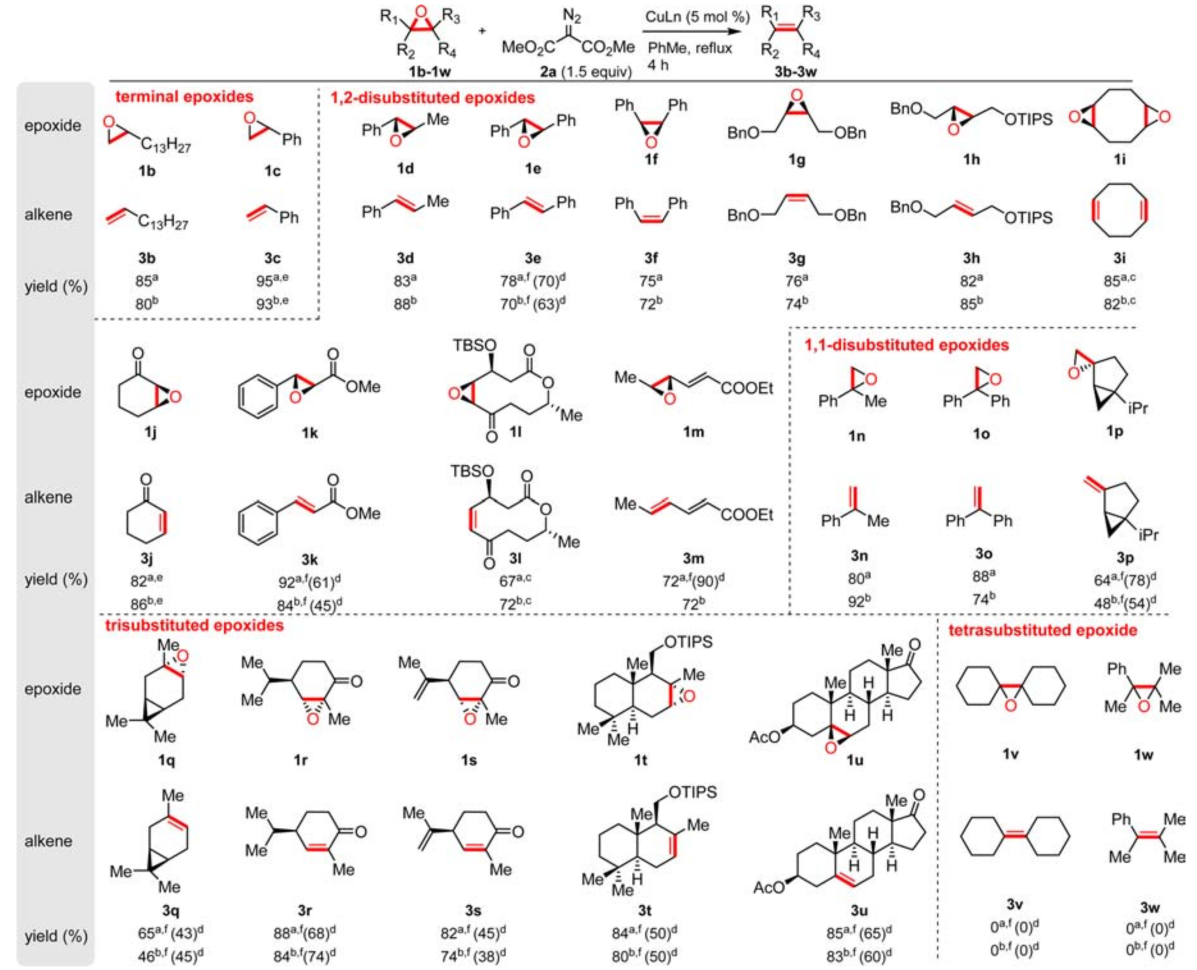
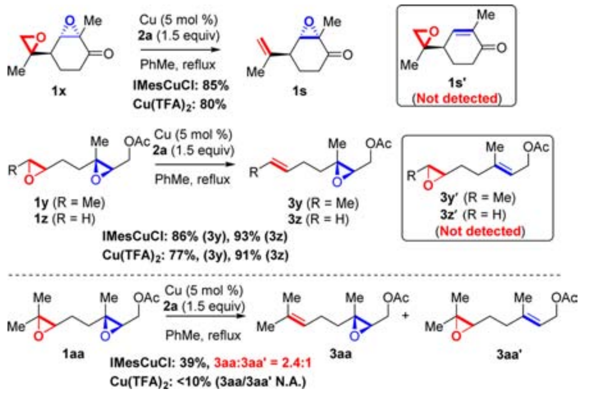
Table 2. Substrate Scope for Cu-Catalyzed Deoxygenation of Epoxides to Alkenes

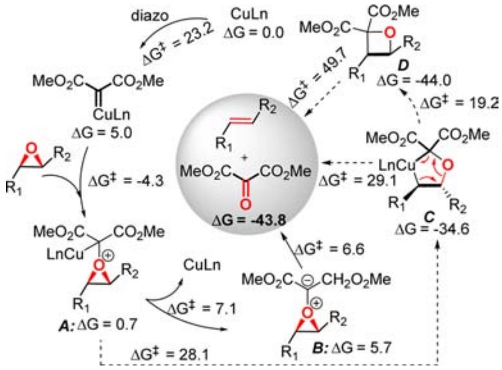


[a] IMesCuCl as the catalyst. [b] $Cu(TFA)_2$ as the catalyst. [c] **2a** (3.0 equiv) was added. [d] Conversion of the epoxide. [e] Yield was determined by ^1H NMR analysis with $CHCl_2CHCl_2$ as the internal standard. [f] Isolation yield based on the conversion of the epoxide.

Scheme 2. Regioselective Deoxygenation of Diepoxides



Scheme 3. Mechanistic Hypothesis and DFT Calculation[a]



[a] The relative free energies are given in kcal/mol. CuLn stands for (NHC)CuCl, where NHC is 1,3-dimethylimidazol-2-ylidene in the DFT calculation.

= 28.1 kcal/mol) as compared to the copper dissociation process ($\Delta G^{\ddagger}$ = 7.1 kcal/mol) (see the SI for details). In addition, DFT also showed that fragmentation of C to the alkene and oxomalonate went through a much higher energy transition state ($\Delta G^{\ddagger}$ = 29.1 kcal/mol), although C is thermodynamically more stable (ΔG = −34.6 kcal/mol). It is believed that the oxetane D is less likely to be an intermediate upon consideration of both the extremely high energetic transition state ($\Delta G^{\ddagger}$ = 49.7 kcal/mol) and the unfavorable thermodynamics (ΔG = 8.5 kcal/mol), although the related cycloreversion of oxetanes has been documented under heat or Lewis acid promoted conditions.[24]

In summary, the combination of Cu/diazo has been identified for the first time to be an efficient catalytic system for regioselective and stereospecific deoxygenation of a variety of epoxides to alkenes. In particular, the regioselectivity by exploiting the inherent steric difference of epoxides was showcased in the monodeoxygenation of three diepoxides, which is unprecedented in the literature and would be very useful in deciding the protection/deprotection technology of alkenes in natural product synthesis. When compared to the prior catalytic deoxygenation, this new catalysis system features (1) stereospecificity; (2) chemo- and regioselectivity; (3) broad substrate scope (30 examples); and (4) the use of inexpensive, earth-abundant transition-metal copper as the catalyst. These features would make the new catalytic protocols a good choice for deoxygenation in organic synthesis.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02405.

Detailed experimental procedures, ^{1}H and ^{13}C NMR spectra, and DFT calculations (PDF)

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Notes

The authors declare no competing financial interest.

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