H_2-Mediated Copper Catalyzed C–C Coupling Reactions – Selective Formation of Skipped Dienes

Lea T. Brechmann,[a,b] and Johannes F. Teichert[a]*

a) Institut für Chemie, Technische Universität Chemnitz, Straße der Nationen 62, 09111 Chemnitz, Germany; b) Institut für Chemie, Technische Universität Berlin, Straße des 17. Juni 115, 10623 Berlin, Germany.

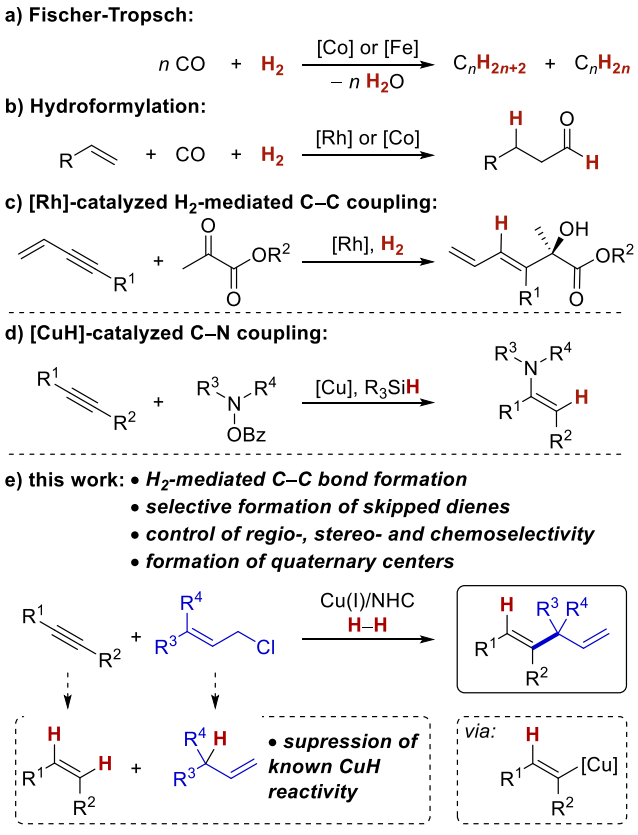
KEYWORDS Copper, hydrogen, coupling reactions, alkynes, dienes, stereoselectivity

ABSTRACT: A simple copper(I)/N-heterocyclic carbene complex facilitates a H_2-mediated C–C coupling reaction of internal alkynes and allylic chlorides. The catalytic protocol delivers the corresponding 1,4-dienes (skipped dienes) with high chemo-, regio- and stereoselectivity without any isomerization to the thermodynamically more stable 1,3-dienes or overreduction to the corresponding alkanes. The H_2-mediated C–C coupling reaction allows for the exploitation "copper hydride catalysis" with H_2 as terminal reducing agent and source of hydrides for forging of new C–C bonds. In this way, this approach gives rise to C–C bond forming reactions with a 3d metal without the need for a stoichiometric organometallic reducing agent.

Efficient C–C bond forming reactions are fundamentally important synthetic methods in organic chemistry for the construction of complex molecules and organic materials. Common and widely applicable reagents for these transformations are organometallic compounds.[1,2] As a consequence, every turnover produces stoichiometric metal-containing waste as unwanted by-product. To circumvent the use of stoichiometric organometallic reagents for C–C bond forming reactions, reductive catalytic methods hinging on dihydrogen (H_2) as terminal reducing agent have been developed.[3] This approach renders the overall reactions more atom efficient.[4,5] Important developments in the field of H_2-mediated C–C coupling reactions are the *Fischer-Tropsch* reaction,[6,7] and catalytic hydroformylation reactions, both based on carbon monoxide as C_1 source (Scheme 1a and b).[8–10] Significant progress extending from C_1 building blocks to more complex carbonyl/carboxyl-acceptors was achieved by rhodium and iridium catalyzed H_2-mediated reductive coupling reactions (for an example, see Scheme 1c).[3,11] However, a generalization of this concept to other types of catalysts (ideally based on readily available 3d metals), reaction types (beyond few examples in cyclizations[12]) and thus more amenable functional groups has not been achieved as of yet.

Copper-catalyzed reductive alkene and alkyne functionalizations relying on hydrosilanes as reducing agent/hydride source are widely applicable methods for the construction of complex molecules.[13,14] Importantly, this so-called "copper hydride catalysis" is characterized by mild reaction conditions and a high tolerance of functional groups.[15] In this approach, a catalytically generated organocopper complex is trapped with a suitable reagent/catalyst resulting in an overall hydrofunctionalization of the unsaturated substrate. This is exemplified by a formal alkyne hydroamination (Scheme 1d).[16] This hydride-driven chemistry has emerged as broadly applicable and could be extended to borylative variants.[17,18] However, copper catalyzed coupling reactions based on H_2 as source of hydride nucleophiles are currently underdeveloped.[19–21] The merging of "copper hydride catalysis" with the use of H_2 would thus represent a significant advancement in terms of atom efficiency for catalytic C–C bond formations.

Scheme 1: Overview of catalytic, H_2-mediated C–C-bond forming processes and reductive hydroaminations.



Herein, we report on such a H_2-mediated copper(I) catalyzed C–C coupling reaction of alkynes with allylic chlorides producing 1,4-dienes (skipped dienes) in a highly selective manner (Scheme 1e).[22] Conceptually, this process gives rise to a vinyl copper(I) complex[23] as key reactive intermediate, which serves as linchpin for a subsequent allylic substitution to effect the envisaged C–C bond forming reaction.

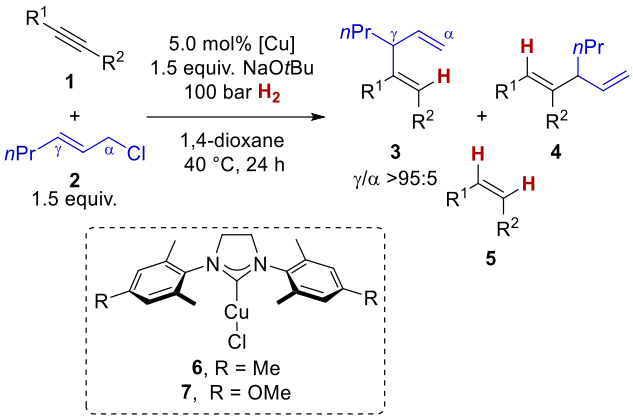
This transformation poses several challenges for catalyst design: i) In order to maintain high applicability of the products in downstream reactions, any overreduction of the 1,4-alkenes under the hydrogenative conditions must be suppressed. ii) Similarly, any isomerization to the thermodynamically more stable 1,3-dienes should be controlled. Ideally, both 1,4- and 1,3-dienes emerge selectively by choice of reaction conditions. iii) Either of the coupling partners (alkyne or allylic chloride) could by themselves react with a copper(I) hydride complex in a detrimental alkyne semihydrogenation[24,25] or an allylic reduction[20] (C–H bond forming reactions). Therefore, the relative rates of the individual reaction pathways must be meticulously controlled to effect the desired C–C bond forming reaction.[19] iv) In the overall process, both regio- and stereoselectivity should be controlled.

We chose simple internal alkynes **1** and (*E*)-1-chlorohex-2-ene (**2**) as model substrates to initially optimize the H_2-mediated reductive coupling reaction (Table 1). In orienting experiments, we had identified copper(I)/N-heterocyclic carbene (NHC) complexes[26] as suitable catalysts (see the Supporting Information for optimization details). As a common trend, we observed that the coupling reaction was most efficient in ethereal solvents, especially 1,4-dioxane. The latter also ensures solubility of NaO*t*Bu as crucial additive for heterolytic H–H bond cleavage.[27]

Several key trends could be elucidated, which are highlighted in Table 1: i) [SIMesCuCl] (**6**) and [SI*p*OMesCuCl] (**7**)[20] were identified as suitable catalysts with the former displaying superior performance at low H_2 pressure (Table 1, entries 1–4). As complex **6** is commercially available, we continued our studies with **6**. ii) Chemoselectivity (alkyne semihydrogenation (giving **5**) vs. reductive coupling towards **3**/**4**) is dependent on the alkyne substitution pattern: whereas for diaryl alkynes semihydrogenation did not pose a significant side reaction, aryl, alkyl alkynes displayed higher chemoselectivity at elevated H_2 pressure (strategy 1, Table 1, entries 5, 6). While dialkyl alkynes did not show any significant conversion, we identified propargylic silyl ethers to react with high chemoselectivity, even at low H_2 pressure of 10 bar (strategy 2, entries 7, 8). iii) Regioselectivity (i.e. placement of the copper atom in the hydrocupration step) can be controlled by electronic effects: whereas aryl, alkyl alkynes are functionalized in the quasi-benzylic position,[28,29] propargylic silyl ethers direct the coupling site to the β-position (entries 5, 6 vs. entries 7, 8).[22a,30] iv) In all cases investigated, the regioselectivity of the allylic substitution (γ/α) was excellent. v) Similarly, overreduction to the corresponding alkane or isomerization to the thermodynamically more stable 1,3-diene did not take place.

In order to ensure chemoselectivity for aryl, alkyl alkynes and to maintain a common protocol for a wide range of substrates, we opted to use 100 bar H_2 for investigation of the reaction scope (Scheme 2).[31] Overall, 1,4-dienes **10** were obtained in excellent stereoselectivity (*Z*/*E* >95:5) and good to excellent regioselectivity regarding the coupling step (γ/α = 91:9–95:5) at 100 bar H_2. A wide variety of electron-poor and electron-rich 1,4-dienes **10a–10f** were obtained in moderate to good yields (37–79%) with good to excellent regioselectivity with respect to hydrocupration (*r.r.* = 89:11–99:1).

Table 1. Optimization



Entry	[Cu]	R^1	R^2	Pressure	Conv.	3/4/5
Diaryl alkynes (for symmetric substrates **3** = **4**): catalyst **6** more reactive at low H_2 pressure						
1	**6**	Ar^1	Ar^1	100 bar	100%	92:8
2	**6**	Ar^1	Ar^1	10 bar	100%	91:9
3	**7**	Ar^1	Ar^1	100 bar	100%	94:6
4	**7**	Ar^1	Ar^1	10 bar	50%	96:4
Control of regioselectivity, strategy 1: aryl-directed regioselectivity; high chemoselectivity at high H_2 pressure						
5	**6**	Ar^2	Alk^1	100 bar	100%	87:4:9
6	**6**	Ar^2	Alk^1	10 bar	100%	62:3:35
Control of regioselectivity, strategy 2: Control of regioselectivity and activation by propargylic silyl ethers						
7	**6**	CH_2OTIPS	Alk^2	100 bar	65%	84:16:0
8	**6**	CH_2OTIPS	Alk^2	10 bar	39%	84:16:0

Ar^1 = Ph, Ar^2 = 3-Cl-C_6H_4, Alk^1 = $(CH_2)_3Ph$, Alk^2 = $(CH_2)_3OBn$. All isomer ratios were determined by GC and/or ^1H NMR analysis.

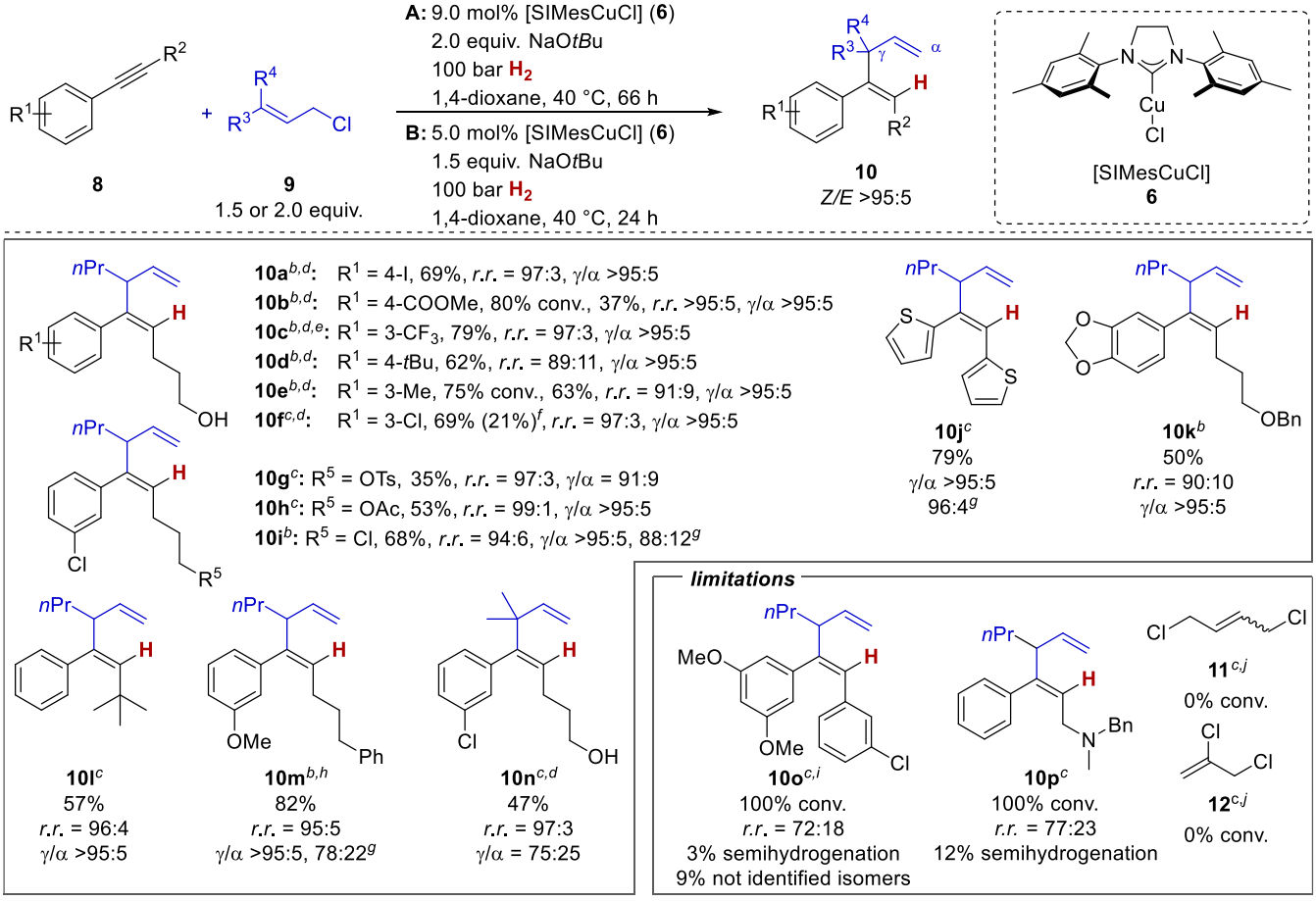
Potential reactive functional groups such as tosylate **10g**, acetate **10h** and chloride **10i** remained intact during the reductive coupling, underscoring the mild reaction conditions. Successful transformation of thiophene derivative **10j** and dioxolane **10k** display that heterocyclic compounds are amenable to the H_2-driven reductive coupling. The catalytic performance is not hindered by steric demand of the substituents as no influence on neither turnover nor regioselectivity was observed for **10l**. A synthetically important inverse prenylation[32,33] was accessible by varying the allyl chloride giving **10n** with moderate yield and very good regioselectivity of the hydrocupration step (47%, *r.r.* = 97:3, γ/α = 75:25). This shows the remarkable potential of the reductive C–C coupling reaction for the construction of quaternary carbon centers. Challenging substrates such as unsymmetric diaryl alkyne **8o** or aryl,propargyl amine **8p**

could be employed in the coupling reaction even though slightly diminished regioselectivities were observed.

We found that propargylic silyl ethers **13** were ideal substrates for the reductive H_2-mediated coupling reaction (Scheme 3). Notably, this substrate class gave good results employing only 10 bar H_2 pressure. After silyl ether deprotection, highly substituted allylic alcohols were accessible with high regio- and stereoselectivity. Therefore, the present method is a highly selective alternative to ylide-based olefination reactions.[34]

To this end, a wide variety of 1,4-dienes bearing an allylic alcohol moiety **14** were accessible in excellent regioselectivities (γ/α >95:5). The minor regioisomer of the *syn*-hydrocupration step could easily be separated by flash column chromatography, giving versatile building blocks with a variety of synthetic handles for downstream modifications in high purity. Sterically demanding substrates such as *tert*-butyl-substituted alkyne **14d** could also be isolated in good yield (70%). While alkyl chloride **14e** could be isolated with 70% yield, the respective alkyl bromide was not tolerated as starting material giving the corresponding 1,3,6-triene **14f**. Notable for the chemoselectivity of the overall process, benzyl ether **14g** was not cleaved under hydrogenative conditions in contrast to many other transition metal catalysts.[35] Employing halogen substituted aryls (**14h**–**14k**), no protodehalogenation[20,25c,36] was observed. Compound **14h** was accessible in gram scale (2.2 mmol, 73% yield) displaying the scalability if the present protocol. Diyne **14m** as chemoselectivity probe underscored the key activating influence of propargylic silyl ether as neither semihydrogenation (typical for these types of copper(I)/NHC catalysts such as **6**)[24,25] nor C–C coupling of the internal alkyne was observed. Furthermore, thioether **14n** and heterocycles like morpholine **14p**, dioxolane **14q** or furan **14r** resulted in acceptable to good yields (41–63%). Also, this protocol could be extended to the selective construction of quaternary carbon centers to give inverse prenylation products (**14s**–**14v**).[32,33] Functionalized allylic chlorides could successfully be converted to 1,4-dienes **14w** and **14x** demonstrating broad usability and potential of building up complex structures. The control of regioselectivity could be fully inverted as observed with silyl ether **15**, which was functionalized in γ-position of the silyl ether. This shows the close interplay of steric and electronic effects on the reaction outcome. Boronic ester **16** only led to 45% conversion even after increasing the H_2 pressure to 100 bar. As a first foray into mechanistic investigations, **14x** was formed from *Z*- as well as *E*-allylic chloride in similar yield and selectivity (64%, γ/α >95:5 for *Z*-allylic chloride and 68%, γ/α >95:5 for *E*-allylic chloride, respectively), indicating a stereoconvergent reaction.

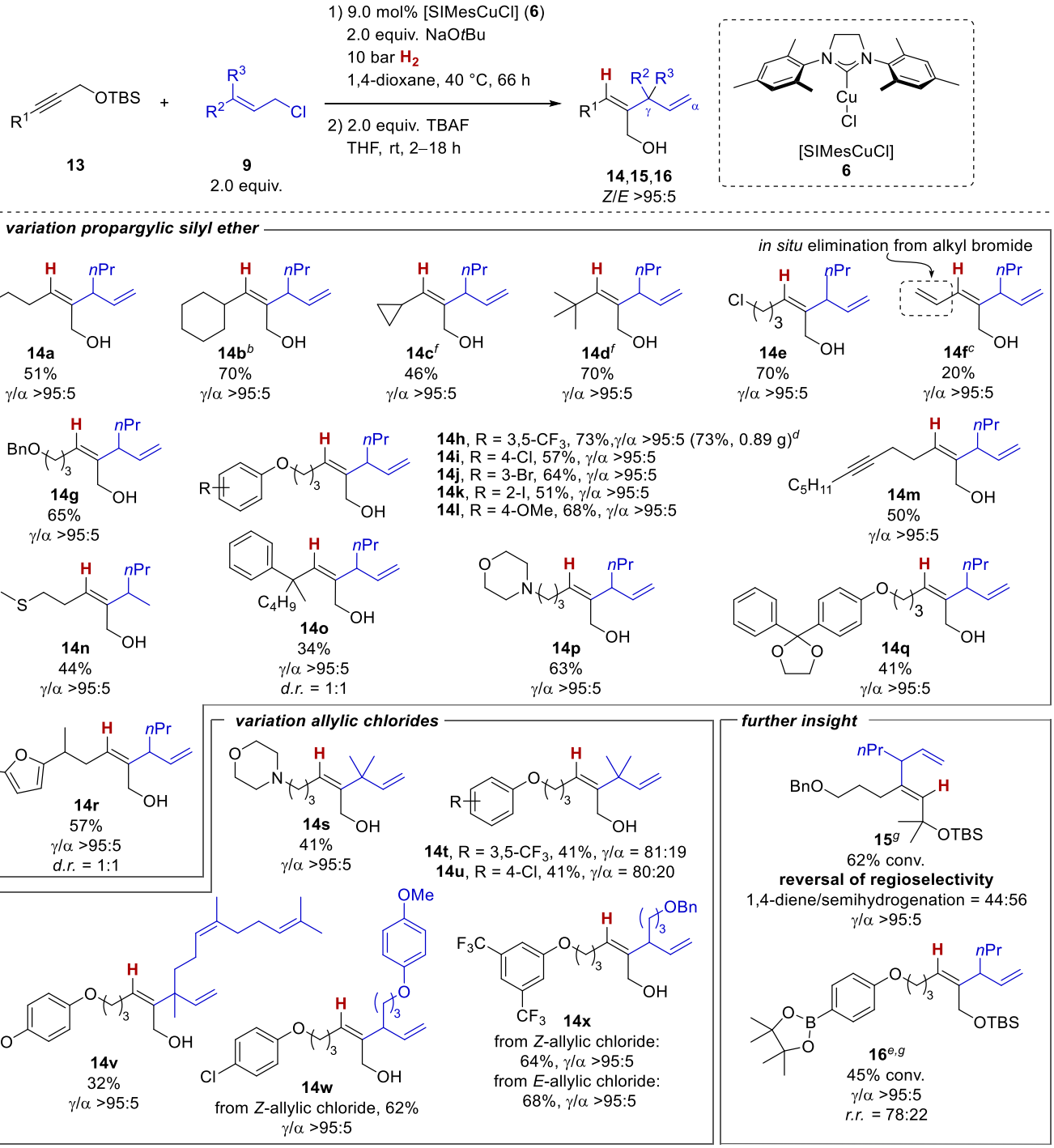
Scheme 2. Copper catalyzed H_2-mediated coupling reaction with aryl, alkyl and diaryl alkynes, substrate scope.[a]



[a] Alkyne (0.3 mmol); allylic chloride (0.45 mmol or 0.6 mmol); isolated yields; *r.r.* = regioselectivity of the *syn*-hydrocupration. All isomer ratios were determined by GC and/or ^{1}H NMR analysis.; γ/α = regioselectivity of the allylic substitution; [b] conditions A were used (allylic chloride (0.6 mmol)); [c]

conditions B were used (allylic chloride (0.45 mmol)); [d] alkyne was used as corresponding silyl ether, crude product was converted to the alcohol by using 2.0 equiv. TBAF; [e] 3.0 equiv. allylic chloride were used; [f] isolated yield from free alcohol as starting material; [g] 1,4-diene/semihydrogenation; [h] 10 bar H_2; [i] [SI*p*OMeMesCuCl] (**7**) was used; [j] shown chloride and diphenylacetylene were used.

Scheme 3. Copper catalyzed H_2-mediated coupling reaction of propargylic silyl ethers at low H_2 pressure, substrate scope.[a]

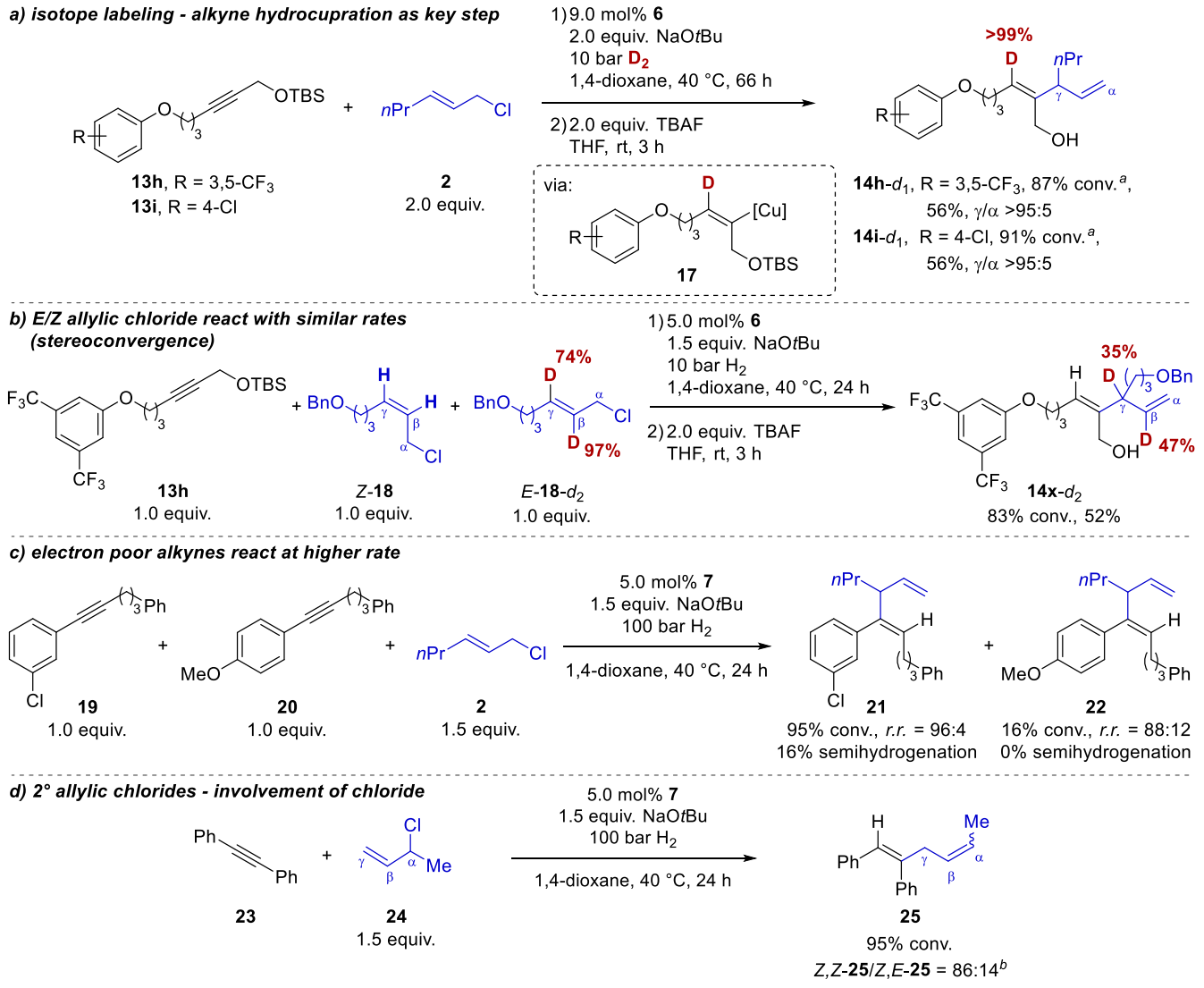


[a] Substrate (0.3 mmol); isolated yields; *r.r.*= regioselectivity of the *syn*-hydrocupration; γ/α =regioselectivity of the allylic substitution. All isomer ratios were determined by GC and/or ^{1}H NMR analysis.; [b] *tert*-butyl((3-cyclohexylprop-2-yn-1-yl)oxy)diphenylsilane was used as starting material, obtained as mixture with TBDPSOH, yield equates to pure product; [c] ((5-bromopent-2-yn-1-yl)oxy)(*tert*-butyl)dimethylsilane was applied as starting material; [d] gram scale reaction, **13h** (1.3 g, 3.0 mmol) as starting material; [e] 100 bar H_2; [f] obtained as mixture with TBSOH, yield equates to pure product; [g] no addition of TBAF solution to the reaction mixture.

MECHANISTIC EXPERIMENTS

To gain further insight into the reaction mechanism, we performed two labelling experiments (Scheme 4a): When the standard reaction protocol was carried out using D_2 (10 bar), the coupling products **14h**-d_1 and **14i**-d_1 were isolated with excellent deuterium incorporation of >99%. Moreover, incomplete conversion with D_2 (87% conv. for **13h**, 91% for **13i**, respectively) in comparison to the H_2-driven reaction gives evidence for a kinetic isotope effect (KIE, see Scheme 3 for comparison). To probe a possible stereoconvergent pathway, we carried out a competition experiment of deuterated *E*-**18**-d_2 (β-position = 97% D, γ-position = 74% D) in the presence of non-deuterated *Z*-**18**. Under standard reaction conditions, we isolated **14x**-d_2 with 52% yield displaying a 47% deuterium incorporation in the β-position and 35% deuterium incorporation in γ-position (Scheme 4b). The lowering of the isotope labelling by a half in both the γ- as well as in β-position of 1,4-diene **14x**-d_2 indicates similar reaction rates of both *E*- and *Z*-allylic chlorides *Z*-**18** and *E*-**18**-d_2. In competition experiments we determined that the electron poor alkyne **19** reacts faster than its electron rich counterpart **20** (Scheme 4c).[29] This, in combination with the abovementioned KIE indicates that the hydrocupration step leading to a vinyl copper(I) complex as reactive intermediate[23] is rate-determining in the overall process. Applying racemic α-substituted secondary allylic chloride **24** to the H_2-mediated coupling reaction gave *Z,Z*-diene *Z,Z*-**25** as major product (Scheme 4d, *Z,Z*-**25**/*Z,E*-**25** 86:14).[37,38] From this result, we conclude

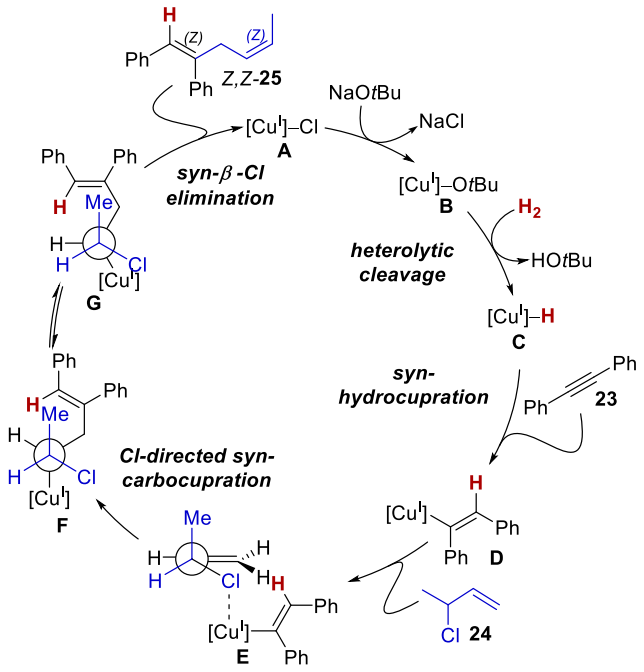
Scheme 4. Mechanistic experiments.



[a] Both **13h** and **13i** give full conversion under similar conditions with H_2. [b] 15% α-product, 7% semihydrogenation, 6% unidentified isomers detected.

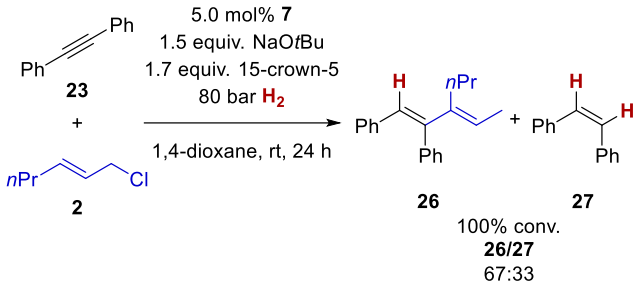
that the step leading to the formation of the double bond in the former allyl moiety of **25** occurs with stereoselectivity. In order to explain this unexpected result and to put forward a potential catalytic cycle giving rise to the thermodynamically less favored *Z,Z*-isomer *Z,Z*-**25**, we hypothesize a mechanism *via* chloride-directed *syn*-carbocupration followed by a *syn*-β-chloride elimination might be operative (Scheme 5). To this end, copper(I) chloride complex **A** is first activated by conversion with *tert*-butoxide into the active copper alkoxide complex **B**. This is preactivated for heterolytic H_2 cleavage *via* σ-bond metathesis[27] with H_2 forming copper(I) hydride complex **C** and *tert*-butanol. Subsequent *syn*-hydrocupration of the alkyne **23** (likely the rate determining step, see above) forms vinyl copper(I) complex **D**.[23] Assuming the methyl group as sterically most demanding substituent[39] in the orthogonal position to the alkene,[40] the unexpected formation of *Z,Z*-1,4-diene **25** (see Scheme 4d) could be explained by a chlorine-directed *syn*-carbocupration forming alkyl copper(I) complex **F**. A preferential *syn*-β-chloride elimination would regenerate the copper chloride complex **A** and liberate the observed *Z,Z*-1,4-diene **25**.[41–44]

Scheme 5. Mechanism of the copper catalyzed H_2-mediated coupling



The present H_2-mediated coupling reaction selectively gives rise to 1,4-dienes without isomerization. However, we were able to expand this methodology to address the thermodynamically more stable 1,3-dienes by slightly amending the reaction conditions (Scheme 6): addition of 15-crown-5 to the standard reaction conditions selectively delivers the 1,3-diene **26**, which enhances the versatility of the present method.[45]

Scheme 6. Selective formation of 1,3-dienes.



CONCLUSION

In summary, we have developed a chemo-, stereo- and regioselective copper(I) catalyzed H_2-mediated C–C coupling reaction. The reaction gives rise to highly substituted skipped 1,4-dienes without any isomerization to the thermodynamically more stable 1,3-dienes observed. Furthermore, the catalyst employed suppresses any overreduction to the corresponding alkanes, retaining the highly versatile functional groups for downstream modification. The present process tolerates a wide variety of functional groups and thus marks a rare example of a catalytic H_2-mediated C–C bond forming reaction with 3d metal catalysts. This approach allows for the replacement of commonly used waste-generating metal hydrides or noble metal catalysts for catalytic C–C bond forming reactions. Specifically the results presented here open up an entry to the widely applicable "copper hydride catalysis" with H_2 as source of hydrides. We believe that the findings presented herein serve as vantage point for method development with easily accessible metal catalysts while at the same time enabling the selective preparation of highly versatile synthetic building blocks.

ASSOCIATED CONTENT

Supporting Information. Detailed starting material synthesis, general procedures, characterization data, and NMR spectra for all compounds (PDF), spectra for synthetic intermediates (PDF).

AUTHOR INFORMATION

Corresponding Author

* E-mail: johannes.teichert@chemie.tu-chemnitz.de

ORCID

Johannes F. Teichert: 0000-0003-1043-8092

Lea T. Brechmann: 0000-0002-9771-6405

Author Contributions

The manuscript was written through contributions of all authors. / All authors have given approval to the final version of the manuscript. / L.T.B. carried out all experiments, J.F.T conceived the concept of the overall project. All authors contributed to the writing of the manuscript.

Funding Sources

This work was supported by the German Research Council (DFG, Emmy Noether Fellowship to J.F.T.).

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

We thank Daniel Neb for initial experiments and Prof. Dr. Martin Oestreich (both TU Berlin) for generous support.

REFERENCES

(1) de Meijere, A.; Bräse, S.; Oestreich, M. *Metal-catalyzed cross-coupling reactions and more*, Wiley-VCH, Weinheim, 2014.

(2) Schlosser, M. Organometallics in synthesis: Third manual, Wiley, Hoboken, 2013.

(3) For reviews, see: a) Santana, C. G.; Krische, M. J. From Hydrogenation to Transfer Hydrogenation to Hydrogen Auto-Transfer in Enantioselective Metal-Catalyzed Carbonyl Reductive Coupling: Past, Present, and Future. *ACS Catal.* **2021**, *11*, 5572–5585; b) Schwartz, L. A.; Krische, M. J. Hydrogen-Mediated C–C Bond Formation: Stereo- and Site-Selective Chemical Synthesis Beyond Stoichiometric Organometallic Reagents. *Isr. J. Chem.* **2018**, *58*, 45–51; c) Nguyen, K. D.; Park, B. Y.; Luong, T.; Sato, H.; Garza, V. J.; Krische, M. J. Metal-catalyzed reductive coupling of olefin-derived nucleophiles: Reinventing carbonyl addition. *Science* **2016**, *354*, aah5133; d) Han, S. B.; Hassan, A.; Krische, M. J. Diastereo- and Enantioselective Reductive Aldol Addition of Vinyl Ketones via Catalytic Hydrogenation. *Synthesis* **2008**, 2669–2679; e) Hassan, A.; Krische, M. J. Unlocking Hydrogenation for C-C Bond Formation: A Brief Overview of Enantioselective Methods. *Org. Process Res. Dev.* **2011**, *15*, 1236–1242; f) Iida, H.; Krische, M. J. Catalytic Reductive Coupling of Alkenes and Alkynes to Carbonyl Compounds and Imines Mediated by Hydrogen. In *Metal catalyzed reductive C-C bond formation*; Krische, M. J., Ed.; *Top. Curr. Chem*., Vol. 279; Springer, Heidelberg, 2007; pp 77–104; g) Ngai, M.-Y.; Kong, J.-R.; Krische, M. J. Hydrogen-mediated C-C bond formation: a broad new concept in catalytic C-C coupling. *J. Org. Chem.* **2007**, *72*, 1063–1072; h) Jang, H.-Y.; Krische, M. J. Catalytic Hydrogen-Mediated Cross-Coupling of Enones and Carbonyl Compounds: Aldol Condensation by Hydrogenation. *Eur. J. Org. Chem.* **2004**, 3953–3958; i) Jang, H.-Y.; Krische, M. J. Catalytic C-C bond formation via capture of hydrogenation intermediates. *Acc. Chem. Res.* **2004**, *37*, 653–661.

(4) Anastas, P. T.; Warner, J. C. *Green chemistry. Theory and Practice*; Oxford University Press, Oxford, 1998.

(5) a) Sheldon, R. A. Fundamentals of green chemistry: efficiency in reaction design. *Chem. Soc. Rev.* **2012**, *41*, 1437–1451; b) Sheldon, R. A. E factors, green chemistry and catalysis: an odyssey. *Chem. Commun.* **2008**, 3352–3365; c) Trost, B. M. Atom Economy—A Challenge for Organic Synthesis: Homogeneous Catalysis Leads the Way. *Angew. Chem. Int. Ed.* **1995**, *34*, 259–281.

(6) Fischer, F.; Tropsch, H. Über die Synthese höherer Glieder der aliphatischen Reihe aus Kohlenoxyd. *Ber. dtsch. Chem. Ges. B* **1923**, *56*, 2428–2443.

(7) a) Rofer-DePoorter, C. K. A comprehensive mechanism for the Fischer-Tropsch synthesis. *Chem. Rev.* **1981**, *81*, 447–474; b) Herrmann, W. A. Organometallic Aspects of the Fischer-Tropsch Synthesis. *Angew. Chem. Int. Ed.* **1982**, *21*, 117–130.

(8) Roelen, O. DE849548C, **1938**.

(9) a) Kumar, R.; Chikkali, S. H. Hydroformylation of olefins by metals other than rhodium. *J. Organomet. Chem.* **2022**, *960*, 122231; b) Chakrabortty, S.; Almasalma, A. A.; Vries, J. G. de. Recent developments in asymmetric hydroformylation. *Catal. Sci. Technol.* **2021**, *11*, 5388–5411; c) Pospech, J.; Fleischer, I.; Franke, R.; Buchholz, S.; Beller, M. Alternative metals for homogeneous catalyzed hydroformylation reactions. *Angew. Chem. Int. Ed.* **2013**, *52*, 2852–2872; d) Breit, B. Synthetic aspects of stereoselective hydroformylation. *Acc. Chem. Res.* **2003**, *36*, 264–275; e) Breit, B.; Seiche, W. Recent Advances on Chemo-, Regio- and Stereoselective Hydroformylation. *Synthesis* **2001**, 1–36; f) Beller, M.; Cornils, B.; Frohning, C. D.; Kohlpaintner, C. W. Progress in hydroformylation and carbonylation. *J. Mol. Catal. A Chem.* **1995**, *104*, 17–85.

(10) a) Cornils, B.; Herrmann, W. A.; Beller, M.; Paciello, R. *Applied homogeneous catalysis with organometallic compounds*; Wiley-VCH, Weinheim, 2017; b) Behr, A.; Neubert, P. *Applied homogeneous catalysis*; Wiley-VCH, Weinheim 2012; c) Arpe, H.-J. *Industrial organic chemistry*; Wiley-VCH, Weinheim, 2010.

(11) Kong, J.-R.; Ngai, M.-Y.; Krische, M. J. Highly enantioselective direct reductive coupling of conjugated alkynes and alpha-ketoesters via rhodium-catalyzed asymmetric hydrogenation. *J. Am. Chem. Soc.* **2006**, *128*, 718–719.

(12) For selected examples employing other transition metals, see: a) Jung, I. G.; Seo, J.; Lee, S. I.; Choi, S. Y.; Chung, Y. K. Reductive Cyclization of Diynes and Enynes Catalyzed by Allyl Platinum N-Heterocyclic Carbene Complexes. *Organometallics* **2006**, *25*, 4240–4242; b) Lee, H.; Jang, M.-S.; Hong, J.-T.; Jang, H.-Y. Platinum-catalyzed reductive coupling of activated alkenes under hydrogenation conditions. *Tetrahedron Lett.* **2008**, *49*, 5785–5788; c) Sylvester, K. T.; Chirik, P. J. Iron-catalyzed, hydrogen-mediated reductive cyclization of 1,6-enynes and diynes: evidence for bis(imino)pyridine ligand participation. *J. Am. Chem. Soc.* **2009**, *131*, 8772–8774; d) Kim, H.-T.; Yoon, H.-S.; Jang, W.-Y.; Kang, Y. K.; Jang, H.-Y. Experimental and Theoretical Investigation of Hydrogenative Cyclization of Allenynes. *Eur. J. Org. Chem.* **2011**, *2011*, 3748–3754; e) Isoda, K.; Sato, Y. Cobalt(I)-Catalyzed Reductive Cyclization of Enynes and Diynes Using Hydrogen Gas as a Reductant. *Org. Lett.* **2023**, DOI: 10.1021/acs.orglett.3c00524.

(13) For reviews, see: a) Larson, G. L.; Liberatore, R. J. Organosilanes in Metal-Catalyzed, Enantioselective Reductions. *Org. Process Res. Dev.* **2021**, *25*, 1719–1787; b) Liu, R. Y.; Buchwald, S. L. CuH-Catalyzed Olefin Functionalization: From Hydroamination to Carbonyl Addition. *Acc. Chem. Res.* **2020**, *53*, 1229–1243; c) Mohr, J.; Oestreich, M. Balancing C=C Functionalization and C=O Reduction in Cu-H Catalysis. *Angew. Chem. Int. Ed.* **2016**, *55*, 12148–12149; d) Sorádová, Z.; Šebesta, R. Enantioselective Cu-Catalyzed Functionalizations of Unactivated Alkenes. *ChemCatChem* **2016**, *8*, 2581–2588.

(14) a) Colonna, P.; Bezzenine, S.; Gil, R.; Hannedouche, J. Alkene Hydroamination via Earth-Abundant Transition Metal (Iron, Cobalt, Copper and Zinc) Catalysis: A Mechanistic Overview. *Adv. Synth. Catal.* **2020**, *362*, 1550–1563; b) Pirnot, M. T.; Wang, Y.-M.; Buchwald, S. L. Copper Hydride Catalyzed Hydroamination of Alkenes and Alkynes. *Angew. Chem. Int. Ed.* **2016**, *55*, 48–57.

(15) For reviews, see: a) Jordan, A. J.; Lalic, G.; Sadighi, J. P. Coinage Metal Hydrides: Synthesis, Characterization, and Reactivity. *Chem. Rev.* **2016**, *116*, 8318–8372; b) Deutsch, C.; Krause, N.; Lipshutz, B. H. CuH-catalyzed reactions. *Chem. Rev.* **2008**, *108*, 2916–2927; c) Rendler, S.; Oestreich, M. Polishing a diamond in the rough: "Cu-H" catalysis with silanes. *Angew. Chem. Int. Ed.* **2007**, *46*, 498–504.

(16) a) Miki, Y.; Hirano, K.; Satoh, T.; Miura, M. Copper-catalyzed intermolecular regioselective hydroamination of styrenes with polymethylhydrosiloxane and hydroxylamines. *Angew. Chem. Int. Ed.* **2013**, *52*, 10830–10834; b) Zhu, S.; Niljianskul, N.; Buchwald, S. L. Enantio- and regioselective CuH-catalyzed hydroamination of alkenes. *J. Am. Chem. Soc.* **2013**, *135*, 15746–15749; c) Shi, S.-L.; Buchwald, S. L. Copper-catalysed selective hydroamination reactions of alkynes. *Nat. Chem.* **2015**, *7*, 38–44.

(17) For reviews about borylative coupling, see: a) Altarejos, J.; Valero, A.; Manzano, R.; Carreras, J. Synthesis of Tri- and Tetrasubstituted Alkenyl Boronates from Alkynes. *Eur. J. Org. Chem.* **2022**, e202200521; b) Alam, S.; Karim, R.; Khan, A.; Pal, A. K.; Maruani, A. Copper-Catalyzed Preparation of Alkenylboronates and Arylboronates. *Eur. J. Org. Chem.* **2021**, 6115–6160; c) Bose, S. K.; Mao, L.; Kuehn, L.; Radius, U.; Nekvinda, J.; Santos, W. L.; Westcott, S. A.; Steel, P. G.; Marder, T. B. First-Row d-Block Element-Catalyzed Carbon-Boron Bond Formation and Related Processes. *Chem. Rev.* **2021**, *121*, 13238–13341; d) Whyte, A.; Torelli, A.; Mirabi, B.;

Zhang, A.; Lautens, M. Copper-Catalyzed Borylative Difunctionalization of π-Systems. *ACS Catal.* **2020**, *10*, 11578–11622.

(18) a) Alfaro, R.; Parra, A.; Alemán, J.; García Ruano, J. L.; Tortosa, M. Copper(I)-catalyzed formal carboboration of alkynes: synthesis of tri- and tetrasubstituted vinylboronates. *J. Am. Chem. Soc.* **2012**, *134*, 15165–15168; b) Yoshida, H.; Kageyuki, I.; Takaki, K. Copper-catalyzed three-component carboboration of alkynes and alkenes. *Org. Lett.* **2013**, *15*, 952–955; c) Bidal, Y. D.; Lazreg, F.; Cazin, C. S. J. Copper-Catalyzed Regioselective Formation of Tri- and Tetrasubstituted Vinylboronates in Air. *ACS Catal.* **2014**, *4*, 1564–1569; d) Rivera-Chao, E.; Fañanás-Mastral, M. Synthesis of Stereodefined Borylated Dendralenes through Copper-Catalyzed Allylboration of Alkynes. *Angew. Chem. Int. Ed.* **2018**, *57*, 9945–9949; e) Rivera-Chao, E.; Mitxelena, M.; Varela, J. A.; Fañanás-Mastral, M. Copper-Catalyzed Enantioselective Allylboration of Alkynes: Synthesis of Highly Versatile Multifunctional Building Blocks. *Angew. Chem. Int. Ed.* **2019**, *58*, 18230–18234.

(19) For a conceptual review, see: Brechmann, L. T.; Teichert, J. F. Catch It If You Can: Copper-Catalyzed (Transfer) Hydrogenation Reactions and Coupling Reactions by Intercepting Reactive Intermediates Thereof. *Synthesis* **2020**, *52*, 2483–2496.

(20) For a single example, see: Pape, F.; Brechmann, L. T.; Teichert, J. F. Catalytic Generation and Chemoselective Transfer of Nucleophilic Hydrides from Dihydrogen. *Chem. Eur. J.* **2019**, *25*, 985–988.

(21) For a related bimetallic approach to H_2-driven cross coupling reactions, see: Semba, K.; Kameyama, R.; Nakao, Y. Hydrogenative Cross-coupling of Internal Alkynes and Aryl Iodides by Palladium/Copper Cooperative Catalysis. *Chem. Lett.* **2018**, *47*, 213–216.

(22) For the related hydrosilane-based methods, please see: a) Mailig, M.; Hazra, A.; Armstrong, M. K.; Lalic, G. Catalytic Anti-Markovnikov Hydroallylation of Terminal and Functionalized Internal Alkynes: Synthesis of Skipped Dienes and Trisubstituted Alkenes. *J. Am. Chem. Soc.* **2017**, *139*, 6969–6977; b) Xu, G.; Zhao, H.; Fu, B.; Cang, A.; Zhang, G.; Zhang, Q.; Xiong, T. Ligand-Controlled Regiodivergent and Enantioselective Copper-Catalyzed Hydroallylation of Alkynes. *Angew. Chem. Int. Ed.* **2017**, *56*, 13130–13134.

(23) Mankad, N. P.; Laitar, D. S.; Sadighi, J. P. Synthesis, Structure, and Alkyne Reactivity of a Dimeric (Carbene)copper(I) Hydride. *Organometallics* **2004**, *23*, 3369–3371.

(24) Thiel, N. O.; Pape, F.; Teichert, J. F. Homogeneous Hydrogenation with Copper Catalysts. In *Homogeneous Hydrogenation with Non-Precious Catalysts*; Teichert, J. F., Ed.; Wiley-VCH, Weinheim, 2020; pp 87–109.

(25) a) Pape, F.; Thiel, N. O.; Teichert, J. F. Z-Selective Copper(I)-Catalyzed Alkyne Semihydrogenation with Tethered Cu-Alkoxide Complexes. *Chem. Eur. J.* **2015**, *21*, 15934–15938; b) Thiel, N. O.; Teichert, J. F. Stereoselective alkyne semihydrogenations with an air-stable copper(I) catalyst. *Org. Biomol. Chem.* **2016**, *14*, 10660–10666; c) Pape, F.; Teichert, J. Tethered NHC Ligands for Stereoselective Alkyne Semihydrogenations. *Synthesis* **2017**, *49*, 2470–2482; d) Wakamatsu, T.; Nagao, K.; Ohmiya, H.; Sawamura, M. Copper-Catalyzed Semihydrogenation of Internal Alkynes with Molecular Hydrogen. *Organometallics* **2016**, *35*, 1354–1357.

(26) For reviews on Cu(I)/NHC complexes and their application in catalysis, see: a) Danopoulos, A. A.; Simler, T.; Braunstein, P. N-Heterocyclic Carbene Complexes of Copper, Nickel, and Cobalt. *Chem. Rev.* **2019**, *119*, 3730–3961; b) Lazreg, F.; Nahra, F.; Cazin, C. S. Copper–NHC complexes in catalysis. *Coord. Chem. Rev.* **2015**, *293-294*, 48–79; c) Egbert, J. D.; Cazin, C. S. J.; Nolan, S. P. Copper N-heterocyclic carbene complexes in catalysis. *Catal. Sci. Technol.* **2013**, *3*, 912–926; d) Lin, J. C. Y.; Huang, R. T. W.; Lee, C. S.; Bhattacharyya, A.; Hwang, W. S.; Lin, I. J. B. Coinage metal-N-heterocyclic carbene complexes. *Chem. Rev.* **2009**, *109*, 3561–3598.

(27) a) Chalk, A. J.; Halpern, J. Medium Effects in the Homogeneous Catalytic Activation of Molecular Hydrogen by Metal Salts. II. Anion and Solvent Effects for Cupric and Cuprous Salts 1. *J. Am. Chem. Soc.* **1959**, *81*, 5852–5854; b) Halpern, J. Homogeneous Catalytic Activation of Molecular Hydrogen by Metal Ions and Complexes. *J. Phys. Chem.* **1959**, *63*, 398–403; c) Goeden, G. V.; Caulton, K. G. Soluble copper hydrides: solution behavior and reactions related to carbon monoxide hydrogenation. *J. Am. Chem. Soc.* **1981**, *103*, 7354–7355.

(28) see ref. 25 for similar regioselectivity.

(29) Wang, Q.; Jia, J.-F.; Guo, C.-H.; Wu, H.-S. Mechanistic investigation of Cu(I)-mediated three-component domino reaction of asymmetrical alkynes with carbon dioxide: Theoretical rationale for the regioselectivity. *J. Organomet. Chem.* **2013**, *748*, 84–88.

(30) Das, M.; Kaicharla, T.; Teichert, J. F. Stereoselective Alkyne Hydrohalogenation by Trapping of Transfer Hydrogenation Intermediates. *Org. Lett.* **2018**, *20*, 4926–4929.

(31) Moreover, during optimization, decomposition of the catalyst was observed. To overcome this limitation and assure full conversion of less reactive substrates portionwise addition of activated catalyst and electrophile was established (A = portionwise 3 x 3 mol% **6**), 66 h; B: one portion 5 mol% **6**, 24 h) (see SI for more details about the optimizations).

(32) Lindel, T.; Marsch, N.; Adla, S. K. Indole prenylation in alkaloid synthesis. In *Alkaloid Synthesis,* Knölker, H.-J., Ed.; *Top. Curr. Chem.,* Vol. 309; Springer, Heidelberg, 2012; pp 67–129.

(33) a) Marsden, S. P.; Depew, K. M.; Danishefsky, S. J. Stereoselective Total Syntheses of Amauromine and 5-N-Acetylardeemin. A Concise Route to the Family of "Reverse-Prenylated" Hexahydropyrroloindole Alkaloids. *J. Am. Chem. Soc.* **1994**, *116*, 11143–11144; b) Schkeryantz, J. M.; Woo, J. C. G.; Danishefsky, S. J. Total Synthesis of Gypsetin. *J. Am. Chem. Soc.* **1995**, *117*, 7025–7026; c) Depew, K. M.; Danishefsky, S. J.; Rosen, N.; Sepp-Lorenzino, L. Total Synthesis of Tryprostatin B: Generation of a Nucleophilic Prenylating Species from a Prenylstannane. *J. Am. Chem. Soc.* **1996**, *118*, 12463–12464.

(34) Wang, J.; *Stereoselective alkene synthesis*; *Top. Curr. Chem*., Vol. 327; Springer, Heidelberg, 2012.

(35) Wuts, P. G. M.; Greene, T. W. *Greene's protective groups in organic synthesis*, 4th ed., Wiley, Hoboken, 2007.

(36) Zimmermann, B. M.; Tran Ngoc, T.; Tzaras, D.-I.; Kaicharla, T.; Teichert, J. F. A Bifunctional Copper Catalyst Enables Ester Reduction with H_2: Expanding the Reactivity Space of Nucleophilic Copper Hydrides. *J. Am. Chem. Soc.* **2021**, *143*, 16865–16873.

(37) Kazmaier, U. Transition metal catalyzed enantioselective allylic substitution in organic synthesis; *Top. Organometal. Chem.*, Vol. 38; Springer, Heidelberg, 2012.

(38) For selected examples giving *Z*-configured alkenes in catalyzed allylic substitution reactions, see: a) Cassani, G.; Massardo, P.; Piccardi, P. New simple synthesis of internal conjugated (Z)-enynes. *Tetrahedron Lett.* **1979**, *20*, 633–634; b) Fañanás-Mastral, M.; Feringa, B. L. Copper-catalyzed regio- and enantioselective synthesis of chiral enol acetates and β-substituted aldehydes. *J. Am. Chem. Soc.* **2010**, *132*, 13152–13153; c) Langlois, J.-B.; Alexakis, A. Identification of a valuable kinetic process in copper-catalyzed asymmetric allylic alkylation. *Angew. Chem. Int. Ed.* **2011**, *50*, 1877–1881; d) Giannerini, M.; Fañanás-Mastral, M.; Feringa, B. L. Z-Selective copper-catalyzed asymmetric allylic alkylation with Grignard reagents. *J. Am. Chem. Soc.* **2012**, *134*, 4108–4111; e) Han, J. T.; Kim, S.-T.; Baik, M.-H.; Yun, J. Direct Stereoconvergent Allylation of Chiral Alkylcopper Nucleophiles with Racemic Allylic Phosphates. *Chem. Eur. J.* **2020**, *26*, 2592–2596; f) Chaves-Pouso, A.; Álvarez-Constantino, A. M.; Fañanás-Mastral, M. Enantio- and Diastereoselective Copper-Catalyzed Allylboration of Alkynes with Allylic gem-Dichlorides. *Angew. Chem. Int. Ed.* **2022**, *61*, e202117696.

(39) Belot, V.; Farran, D.; Jean, M.; Albalat, M.; Vanthuyne, N.; Roussel, C. Steric Scale of Common Substituents from Rotational Barriers of N-(o-Substituted aryl)thiazoline-2-thione Atropisomers. *J. Org. Chem.* **2017**, *82*, 10188–10200.

(40) for clarity, only one of the two possible enantiomers of **24** is depicted, the (R)-enantiomer reacts accordingly.

(41) For a related syn-acetoxy elimination, see: Zhu, S.; Niljianskul, N.; Buchwald, S. L. A direct approach to amines with

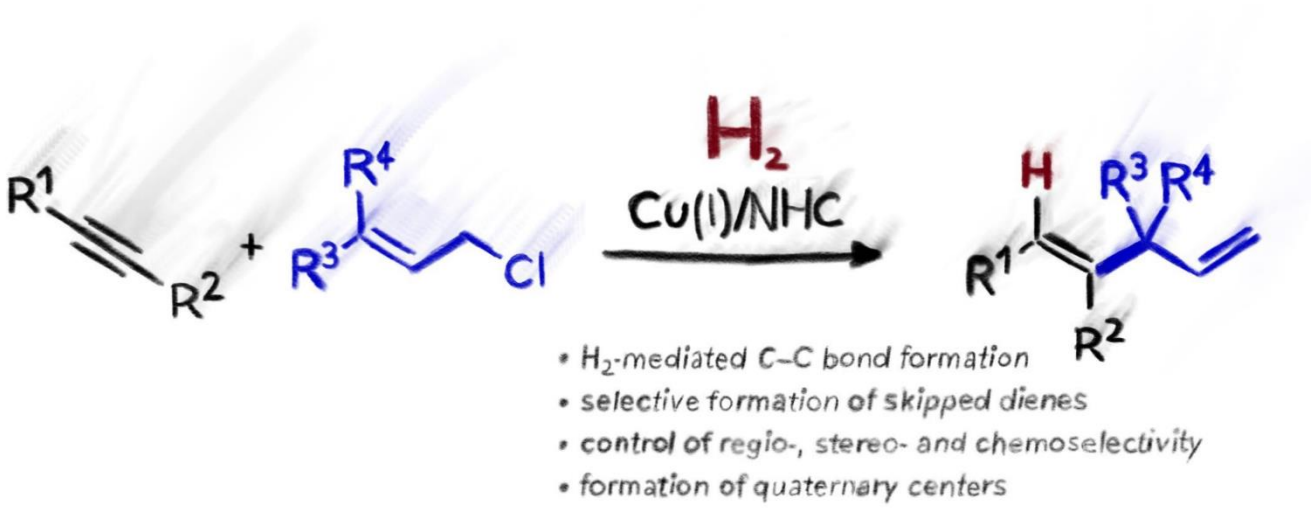
remote stereocentres by enantioselective CuH-catalysed reductive relay hydroamination. *Nat. Chem.* **2016**, *8*, 144–150.

(42) For a related addition Cl-elimination mechanism, see: a) Shido, Y.; Yoshida, M.; Tanabe, M.; Ohmiya, H.; Sawamura, M. Copper-catalyzed enantioselective allylic substitution with alkylboranes. *J. Am. Chem. Soc.* **2012**, *134*, 18573–18576; b) Hojoh, K.; Shido, Y.; Ohmiya, H.; Sawamura, M. Construction of quaternary stereogenic carbon centers through copper-catalyzed enantioselective allylic cross-coupling with alkylboranes. *Angew. Chem. Int. Ed.* **2014**, *53*, 4954–4958; c) Hojoh, K.; Shido, Y.; Nagao, K.; Mori, S.; Ohmiya, H.; Sawamura, M. Copper-catalyzed enantioselective allylic cross-coupling with alkylboranes. *Tetrahedron* **2015**, *71*, 6519–6533; d) Hojoh, K.; Shido, Y.; Ohmiya, H.; Sawamura, M. Copper-catalyzed Enantioselective Intramolecular Alkylboron Allylic Alkylation. *Chem. Lett.* **2018**, *47*, 632–635.

(43) For a related stereoselectivity employing allylic phosphates, see a) Ohmiya, H.; Yokobori, U.; Makida, Y.; Sawamura, M. Copper-catalyzed gamma-selective allyl-alkyl coupling between allylic phosphates and alkylboranes. *J. Am. Chem. Soc.* **2010**, *132*, 2895–2897; b) Ohmiya, H.; Sawamura, M. Copper-Catalyzed Reactions of Alkylboranes. *Bull. Chem. Soc. Jpn.* **2021**, *94*, 197–203; c) Nagao, K.; Yokobori, U.; Makida, Y.; Ohmiya, H.; Sawamura, M. Reversible 1,3-anti/syn-stereochemical courses in copper-catalyzed γ-selective allyl-alkyl coupling between chiral allylic phosphates and alkylboranes. *J. Am. Chem. Soc.* **2012**, *134*, 8982–8987.

(44) Ohmiya, H.; Makida, Y.; Tanaka, T.; Sawamura, M. Palladium-catalyzed gamma-selective and stereospecific allyl-aryl coupling between allylic acetates and arylboronic acids. *J. Am. Chem. Soc.* **2008**, *130*, 17276–17277.

(45) A control experiment indicated that the isomerization process is independent of the copper catalyst.


R1
R2
+
R4
R3
Cl
H2
Cu(I)/NHC
H
R3
R4
R1
R2
• H2-mediated C–C bond formation
• selective formation of skipped dienes
• control of regio-, stereo- and chemoselectivity
• formation of quaternary centers