

Photoorganocatalysis

 Visible Light-Enabled sp^3 -C–H Functionalization with Chloro- and Bromoalkynes: Chemoselective Route to Vinylchlorides or AlkynesTapas Adak,^[a] Marvin Hoffmann,^[b] Sina Witzel,^[a] Matthias Rudolph,^[a] Andreas Dreuw,^[b] and A. Stephen K. Hashmi^{*[a, c]}

Abstract: An unprecedented direct atom-economic chemo- and regioselective hydroalkylation of chloroalkynes and an sp^3 -C–H alkynylation of bromoalkynes was achieved. The reaction partners are unfunctionalized ethers, alcohols, amides, and even non-activated hydrocarbons. We found that a household fluorescent bulb was able to excite a diaryl ketone, which then selectively abstracts a H-atom from an sp^3 -C–H bond. The product of a formal alkyne insertion into the sp^3 -C–H bond was obtained with chloroalkynes, providing valuable vinyl chlorides. The photo-organocatalytic hydrogen atom transfer strategy gives rise to a broad range of

diversely functionalized olefins. When bromoalkynes are applied in the presence of a base, a chemoselectivity switch to an alkynylation is observed. This reaction can even be performed for the alkynylation of unactivated sp^3 -C–H bonds, in this case with a preference of the more substituted carbon. Accompanying quantum chemical calculations indicate a vinyl radical intermediate with pronounced linear coordination of the carbon radical center, thus enabling the formation of both diastereoisomers after H-atom abstraction, suggesting that the (*Z*)-diastereoisomer is preferred, which supports the experimentally observed (*E/Z*)-distribution.

Introduction

Aryl alkenes are ubiquitous structural motives used for the synthesis of bioactive compounds and drugs.^[1] Aryl alkenes can also serve as subunits for molecular motors.^[2] Hetero atom-functionalized derivatives are also of considerable importance for pharmaceutical chemistry.^[3] A key building block for downstream transformations of aryl alkenes are haloarylethenes, the halogen can be further transformed in diverse coupling reac-


tions (e.g. Suzuki–Miyaura-, Heck-, Stille- or Sonogashira couplings)^[4] as well as Buchwald–Hartwig amination reactions.^[5] Due to the immense importance of this building block, strategies to synthesize vinyl halides are of high value for organic chemists. While vinyl chloride^[6] is the most useful vinyl halide, which is used on a scale of millions of tons per year for polymerization to PVC, also substituted vinyl chlorides and vinyl bromides are most frequently used in cross coupling and as precursors for Grignard and organolithium reagents.^[7]


The most common strategies to access olefins are the use of elimination reactions, Wittig olefinations,^[8b] Peterson olefinations^[8a,c] or the Julia–Lythgoe reaction.^[8d] These often are carried out under harsh reaction conditions, require multistep syntheses, and are often incompatible with sensitive functional groups.^[8] In terms of olefination reactions, transition metal-catalyzed (Au, Cu, Ag, Co, Ni, Rh, Ir, Fe)^[9] additions to alkynes as synthetic access to alkenes are well established (Scheme 1), but halovinylations are still underdeveloped. This can be rationalized by the observation that with transition metal-catalyzed reactions with haloalkynes usually an alkyne product is formed by the insertion of the metal into the carbon-halogen bond^[10] (Scheme 1). Stephenson and other groups recently reported an elegant access to vinyl halides. It is based on halogenation reactions of alkynes (and alkenes) via halide atom transfer pathways.^[11] Duan's group reported a palladium-catalyzed chlorine atom transfer to alkynes for chlorovinylations, but the reactions show low selectivity.^[12] Hoveyda's group reported cross-metathesis reactions of alkenyl halides.^[13] These few examples of halo-olefinations by Cl/Br-atom transfer to alkynes exist, but haloolefinations by a sp^3 -C–H atom transfer to haloalkynes are still unknown. While the majority of metal-free


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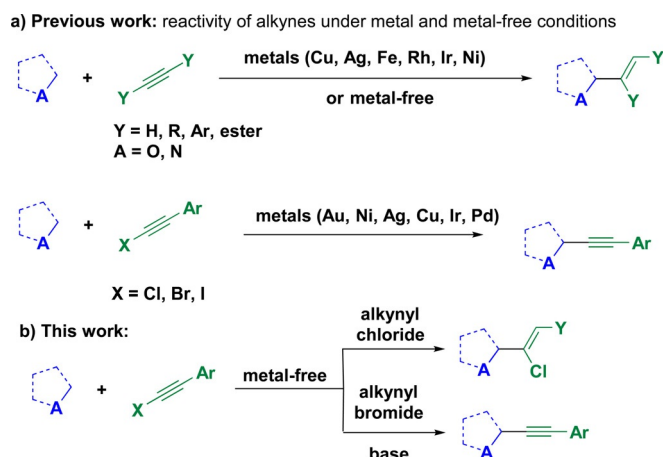
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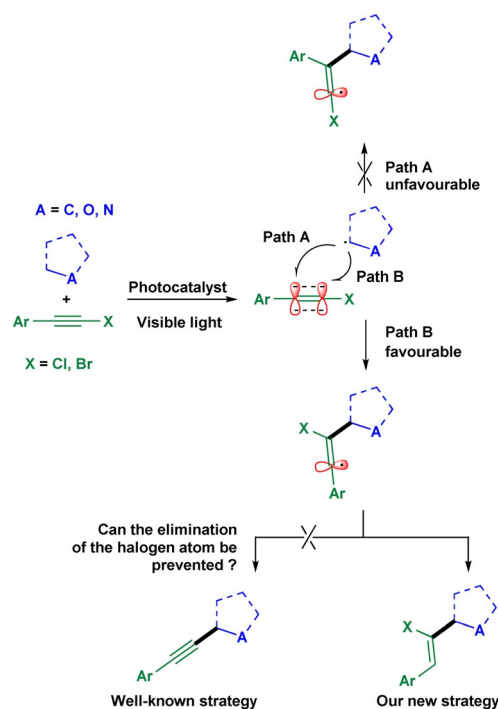


Scheme 1. Previous work and our assumption.

photo-catalyzed reactions are focusing on the connection of radicals to a sp^2 -C centre,^[14] we envisioned that the direct coupling of a photochemically generated radical to the sp -carbon of an alkyne might allow the formal insertion of the chloroalkyne into an alkyl C–H bond. This process would directly deliver synthetically useful chloroolefins in perfect atom-economy. To the best of our knowledge, this process was never evaluated with haloalkynes, despite the attractive target. Recently reported sp^3 -C–H atom abstraction reactions with normal alkynes indicate that such a process might be feasible, but typically these reactions require an over-stoichiometric amount of an oxidant or a radical initiator.^[15] For example, in 2015, Wang's group reported the eosin-Y-catalyzed vinylation of THF with alkynes by using a large excess of *t*BuOOH (4 equivs) as radical initiator as well as oxidant and two equivs of formic acid in the presence of 4 Å molecular sieves. Furthermore, the reaction was limited to THF only, while other C–H coupling partners (dioxane, diethyl ether, methanol, etc.) or even diphenyl acetylene under these harsh conditions led to decomposition. An Ir-based photocatalyst^[16] is well-known for direct C–H atom abstractions via single electron transfer. But this catalyst is quite expensive, in most cases needs a base and additional additive. In 2017, Wu's group developed a direct oxidant- and additive-free sp^3 -C–H functionalization by using a Ni/Ir-catalyzed hydroalkylation of internal alkynes under blue LED irradiation.^[17] Unfortunately, the regioselectivity was poor. Later, MacMillan's group also reported a Ni/Ir-catalyzed 1,1,3,3-tetramethylguanidine-assisted decarboxylative hydroalkylation of terminal alkynes.^[18]

Radical additions to vinyl halides are known.^[19] Thus the question arises, if after the formation of the desired vinyl halides via a radical pathway these vinyl halides would further react to saturated products. We assumed that by avoiding peroxide-type radical initiators with an aldehyde-/ketone-based H-atom abstractor, a selective formation of vinyl chlorides might be possible (Scheme 2).

An sp^3 -C–H atom transfer promoted by visible light irradiation and using a diarylketone catalyst is a challenging strategy for the development of new chemical transformations in syn-



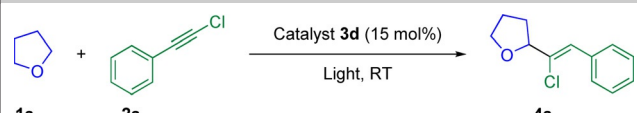
Scheme 2. Our strategy.

thetic chemistry.^[20] We hypothesized that a household fluorescent bulb could activate a C=O photocatalyst via a $n \rightarrow \pi^*$ excitation, which then could form a reactive short-lived radical species by abstracting a sp^3 -C–H atom next to the hetero (O, N) atom (Scheme 2) of ethers/amides or alcohols and even hydrocarbons. This reactive species could then undergo radical addition reactions with the alkyne. The assumed role of the carbonyl group, which acts as radical initiator as well as H-abstracter, is in line with pioneering photoreactions like the Norrish–Yang cyclization^[21] or related studies by Breslow.^[22]

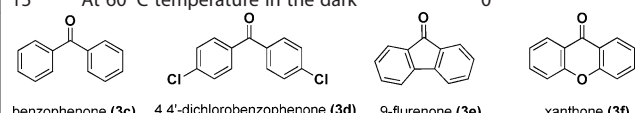
Results and Discussion

We started with the chloroalkyne **2a** as a test substrate in THF (0.05 M) together with benzophenone (15 mol%) as photocatalyst (Table 1, entry 1) under 23 W CFL (CFL = compact fluorescent lamp) light irradiation. Based on the 2D NMR analysis (see supporting information, COSY, NOESY, HMBC) we could confirm that the product originated of an attack of the THF radical at the sp -C center adjacent to the chlorine atom (Scheme 2, Path B), delivering the corresponding vinyl halide (**4a**) in 76% in a 3:1 (*Z/E*) diastereomeric distribution. Interestingly, no dechlorination to the alkyne took place, which might be explained by the mild conditions. As expected, benzaldehyde and acetone showed no catalytic activity under these conditions (entries 2–3). After exploring various photocatalysts (see Supporting Information), the isolated yield improved to 93% in the presence of a dichloro-substituted benzophenone (**3d**) as photosensitizer (Table 1, entry 4). Other photocatalysts, like xanthone and 9-fluorenone, were less efficient (entries 5–6). Other known transition metal photocatalysts such as $Ru(bpy)_3(PF_6)_2$ showed no significant photocatalytic activity for this reaction. Acetoni-

Table 1. Optimization of the reaction conditions.



Entry	Catalyst	Yield (%) ^[a] (Z/E) ^[b]
1	Benzophenone instead of 3 d	76 (3:1)
2	Benzaldehyde instead of 3 d	0
3	Acetone instead of 3 d	0
4	4,4'-Dichlorobenzophenone (3 d)	96 (93 ^[c] , 3:1)
5	9-fluorenone instead of 3 d	52 (2.8:1)
6	Xanthone instead of 3 d	59 (2.9:1)
7	Ru(bpy) ₃ (PF ₆) ₂ instead of 3 d	0
8 ^[d]	CH ₃ CN as solvent	56
9 ^[d]	Acetone as solvent	64
10	Water as solvent	71 (1.3:1)
11	Blue LED/Sunlight instead of white CFL bulb	42/60 (3:1)
12	K ₂ HPO ₄ used as a base	45
13	No light	0
14	No catalyst	0
15	At 60 °C temperature in the dark	0

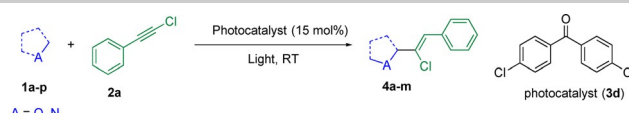


Reaction conditions: unless otherwise noted, all reactions were carried out as follows: **2 a** (0.2 mmol), catalyst (15 mol%) in degassed THF (0.05 M) under irradiation of 23 W CFL bulb at room temperature for 16 h. [a] The yield was determined from the crude ¹H NMR spectra by using 1,3,5-trimethoxybenzene as an internal standard. [b] The (Z/E)-ratio (confirmed by 2D NMR analysis) was determined by the crude ¹H NMR spectra. [c] Isolated yield after 3 hours reaction time with two 23 W CFL bulb. [d] 1:1 ratio of solvent and THF.

trile or acetone as co-solvent did not improve the yield (entries 8–9) and the addition of base slightly decreased the yield of the product (entry 12). The use of a blue LED or sunlight as alternative light sources gave a lower yield (entry 11). No reactivity was observed in the dark at 60 °C (entry 15). The chlorovinylated reaction was sensitive to oxygen but not to moisture. However, a lower yield (71%) and a drop in diastereoselectivity (1.3:1; Z/E) was observed, when water was used as co-solvent (THF/H₂O = 1:1). Therefore, dry solvents were needed to increase the stereoselectivity. It required no further additives and precautions for our protocol.

With optimized condition in hand, we next explored the scope regarding the ether component (Table 2). Cyclic ethers such as THF, dioxane, and oxetane were tolerated well (entries **4 a–4 c**). It also converted acyclic ethers with alkyl chains to the corresponding vinyl derivatives in good yield (58–75%, **4 d–4 f**). With dimethoxyethane, we observed both methyl and methylene reactivity, giving regioisomers **4 d** and **4 d'** in a combined yield of 72% yield. Gratifyingly, alcohols were also found to be reactive substances for the radical coupling reaction in yields ranging from 71–88% (**4 g–4 j**). No C–O addition product was detected. Benzylic alcohol reacted with the benzylic position in 71% yield (entry **4 i**). Amides as substrates delivered the chlorovinylated products adjacent to the nitrogen atom (**4 k–4 m**) in good yield (58–68%) after prolonged reaction time.

Table 2. Substrate scope with respect to the sp³-C–H bond.



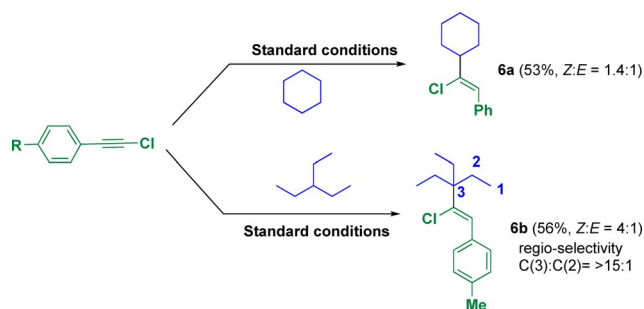
Category	Substrate	Yield (%) (Z/E)
Ether	4 a (93%, 3:1)	
	4 b (68%, 1.4:1) ^b	
	4 c (72%, 2.2:1)	
	4 d (40%, 6.6:1)	
	4 d' (32%, 10:1)	
	4 e (58%, 2:1)	
4 f (75%, 1.4:1)		
Alcohol	4 g (88%, 2.5:1)	
	4 h (87%, 2.5:1)	
	4 i (82%, 3:1)	
	4 j (71%, 3:1) ^c	
Amide	4 k (62%, 3:1) ^b	
	4 l (68%, 1.1:1) ^b	
	4 m (58%, 2:1) ^b	

Reaction conditions: All reactions were carried out with **2 a** (0.2 mmol), **3 d** (15 mol%) in 0.05 M solvent under irradiation of two 23 W CFL bulbs at room temperature for 3–16 hours. Isolated yields and (Z/E)-isomer ratios are reported. [b] Reaction carried out for 72 hours. [c] Reaction carried out for 48 hours. Major isomers are shown.

The higher C–H bond dissociation energies explained the lower reactivity of ethers and amides compare to THF.^[20d,21] Furthermore, it is noteworthy that no C–O and C–N coupled product was observed for free alcohols and amides.

For the scope with respect to the alkyne, a broad range of alkynes was studied. Excellent regioselectivities and yields were obtained for various chloroalkynes (entries **5 a–5 n**). Chloroalkynes with either electron-donating or electron-withdrawing groups were tolerated, providing slightly higher yields in the case of donor-substituted arylchloroalkynes. Excellent yield (76–84%) and regioselectivity were also observed with phenylchloroalkynes bearing halides at the aryl system (**5 e–5 g**). In the case of an electron-deficient ester, keto, or trifluoromethyl group (**5 h–5 j**), yields were also high. *Ortho*- and *meta*-substituted chloroalkynes participated well in our reaction in 70–84% yield (**5 i–5 n**). A naphthalene motif also worked well, but with lower selectivity (**5 d**, **5 k**). To explore the reactivity of our reaction protocol, we further studied the reaction with other alkyne systems. Gratifyingly, diphenylacetylene (**5 o**) was very reactive to provide 90% of the hydroalkylated product in a 1.3:1 (Z/E) ratio. A bromoalkyne provided a lower yield (**5 p**). An alkyne ester (**5 q**) and terminal alkynes (**5 s–5 v**) also successfully provided the desired vinylated products, while the reaction was not efficient for an iodoalkyne (**5 r**) as starting material. Interestingly, as observed for chloroalkynes the THF radical attacked the carbon next to the ester for the alkynyl ester substrate while a related previous study showed a different reactivity (Table 4, **5 q**).^[15a,17]

Next, we tested if even non-activated alkanes would be suitable substrates. It is noteworthy that cyclohexane could be ac-



tivated with a 53% yield (Scheme 3, **6a**) for the formal insertion product. Gratifyingly, in the case of 3-ethyl pentane (Scheme 4, **6b**) the tertiary position (the most stable radical) was addressed (C_3/C_2 ; 15:1). While the diastereoselectivity for **6a** was low, the bulkier alkyl group in **6b** led to high diastereoselectivity.

We assumed that the low yield of the vinyl bromide **5p** (Table 3a) was caused by a subsequent reaction of **5p** with the radicals. Thus, we tried to avoid this by an HBr elimination to the alkyne product. We were delighted to find that even weak bases allow this (see the Supporting Information), the simple KOAc enabled us to obtain the alkyne products. This alkylation of ethers with a metal-free simple and straightforward photocatalytic system in the absence of any external oxidant offers attractive advantages over the already existing strategies.^[15,10] Bromoalkynes with both electron-rich and electron-poor substituents provided the alkyne products (59–71%, Table 4, **7a–e**) in the presence of KOAc. Only recently Lei's group reported a trimetal-catalyzed (Ni/Cu/Ag) oxidative cou-

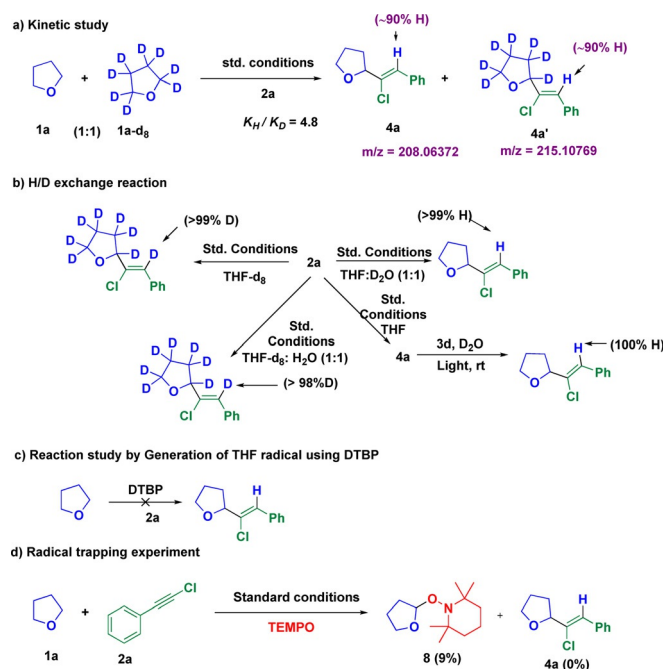


Table 3. Substrate scope with respect to the alkynes.

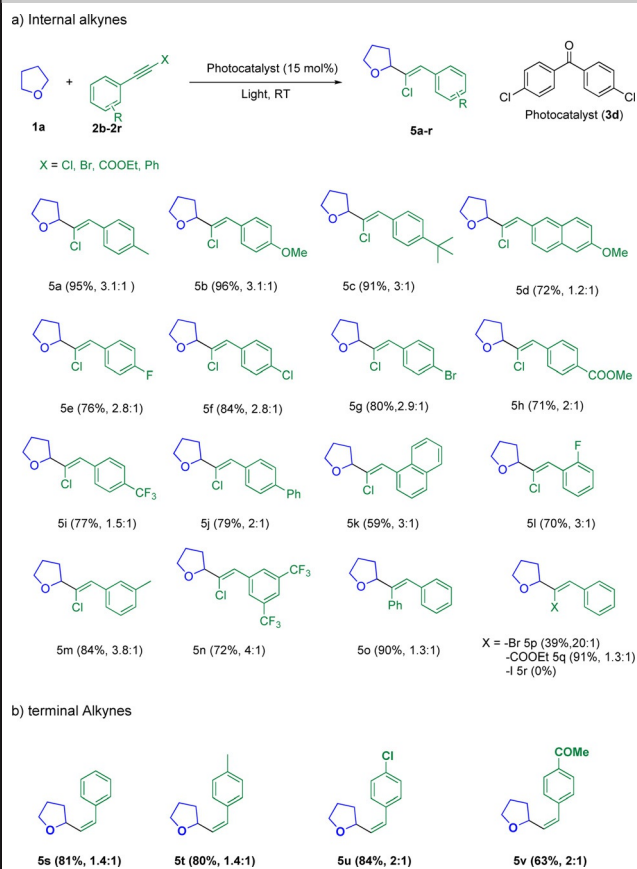
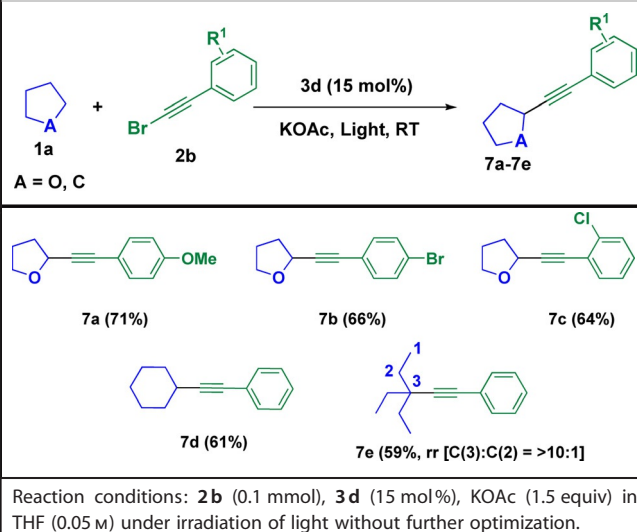


Table 4. Scope with bromo alkynes.

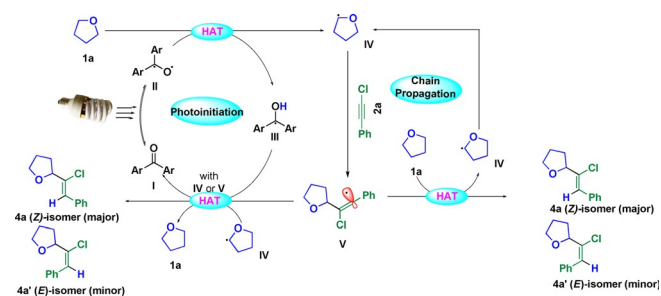


pling of hydrocarbons with alkynes by using DTBP.^[23] Related couplings, for example with a cyclohexyl group (**7d**), under

our photocatalytic conditions, could be conducted completely metal- and oxidant-free. More interestingly, in the previous studies, the major product was the insertion product into the secondary CH bond, ^[23,20e] while we observed activation of the tertiary CH bond ($C_3:C_2=10:1$) which nicely complements the existing strategy (Table 4, **7 e**).

A proposed mechanistic scenario is depicted in Scheme 4. To back-up our proposal, several control experiments were carried out. Different deuterium labeling experiments were conducted in order to understand the proton transfer to the vinylic position. A mixture of THF and $[D_8]$ THF as the coupling partner delivered both the THF and $[D_8]$ THF incorporated products (Scheme 4a). It was noticed that the crossover product of **4 a** and **4 a'** was obtained with THF and $[D_8]$ THF. The kinetic study (competing and parallel) showed a high K_H/K_D value of 4.8, which indicates that the hydrogen abstraction is the rate-determining step. We could confirm that THF acts as the hydrogen source (Scheme 4b). In the case of $[D_8]$ THF as a coupling partner, greater than 99% deuterium incorporated product was isolated. No exchange processes were detected if THF and D_2O (1:1; v/v) were used and only minor traces of deuterium were incorporated in the product. This indicates that the vinyl radical formed by the addition of a THF radical to the chloroalkyne may abstract the H-atom directly from THF only, not from the diaryl alcohol intermediates that are formed by the photocatalyst (**III**, Scheme 5). In this case, an H/D exchange to the alcoholic group would be likely. Moreover, H/D exchange indicated reaction may follow a proton-coupled electron transfer (PCET) pathway (Scheme 5) to complete the catalytic cycle. Next, the addition of TEMPO as radical scavenger confirmed the radical pathway. Indeed, a THF-TEMPO adduct (Scheme 4d) was detected (9% crude NMR yield). Interestingly, tetrahydrofuran radicals generated by the treatment of THF with di-*tert*-butyl peroxide (DTBP) as oxidant, did not provide the desired product **4 a** with chloroalkyne **2 a**. The desired product was neither observed in the absence of light nor with the photocatalyst alone. The light on-off experiment also confirmed the light-dependency of the reaction (see Supporting Information).

Our tentative mechanistic pathway is based on the experimental results depicted in Scheme 4. A weak absorption peak was observed in the range of 320–380 nm in THF at the UV-visible absorption spectrum of 4,4'-dichlorobenzophenone (Figure 1), indicating that the reaction is indeed initiated by photoexcitation of **3 d**.



Scheme 5. Plausible reaction mechanism.

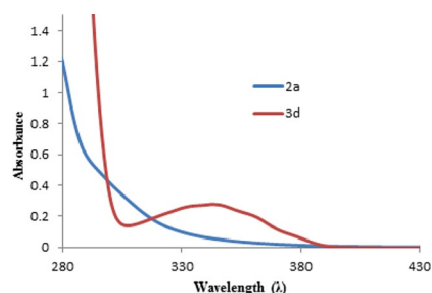


Figure 1. UV-VIS absorption spectra for photocatalyst **3 d** (red) and chloroalkyne **2 a** (blue) in THF.

Based on the absorption spectra and accompanying TDDFT (TDDFT = time-dependent density functional) calculations, the absorption band of **3 d** above 300 nm corresponds to an $n \rightarrow \pi^*$ transition into the first excited singlet state S_1 (see Supporting Information for corresponding electron/hole densities) and subsequently undergoes intersystem crossing to the energetically close triplet excited state (T_3) due to a rather small singlet-triplet gap of 0.14 eV as well as an enhanced spin-orbit coupling element of about 22 cm^{-1} (see Supporting Information for the coupling elements to the other excited triplet states). The diradical intermediate **II** is generated by the relaxation into the corresponding $n \rightarrow \pi^*$ triplet excited state (T_1), which then abstracts the α -H-atom from THF delivering the highly reactive THF radical intermediate (**IV**). After that, the reaction may follow either a direct HAT transfer pathway or a competing radical chain mechanism (quantum yield (ϕ) = 3.87). In this competitive pathway, the short-lived tetrahydrofuran radical undergoes a radical addition reaction to chloroalkyne (**2 a**), resulting in a nearly linear vinyl radical intermediate **V** (supported by DFT study, see below), which next delivers the (*Z/E*)-isomeric distribution by the abstraction of the hydrogen atom from THF which propagates the radical chain. In addition, the THF radical could also reoxidize intermediate **III**, which could regenerate the photocatalyst by HAT.

In order to shed light on the position and diastereoselectivity of the reaction, quantum chemical calculations were performed. Starting from the separated reactants, two attack vectors were scanned in a relaxed potential energy surface scan procedure with steps of 0.1 \AA (Figure 2). The respective transition state, as well as product structures, were confirmed via

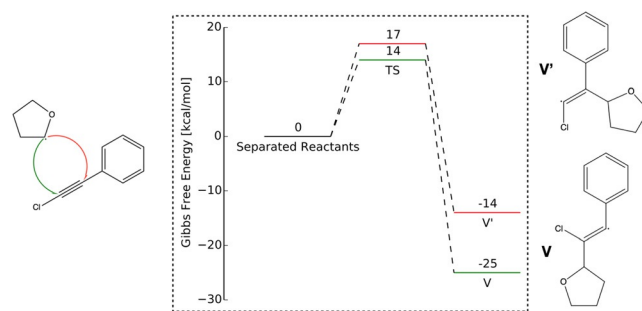


Figure 2. Reaction profile for the two possible attack positions of the THF radical (pbe0-D3/pcseg-2/CPCM(THF)).^[24]

frequency calculation. The resulting transition state for the attack at the halide side of the alkyne (**V**) is favored by about 3 kcal mol^{-1} compared to the transition state for the radical addition next to the phenyl substituent (**V'**). The resulting product geometry of **V** is even more energetically favored by 11 kcal mol^{-1} , which leads to the assumption that during the reaction every molecule will ultimately arrive at **V** driven by thermodynamics. The respective (*E*)-diastereoisomer of **V'** lies merely $0.4 \text{ kcal mol}^{-1}$ below the (*Z*)-isomer and therefore also offers no considerable alternative in the reaction route.

The rationale of the preference for **V** lies in the lower steric hindrance as well as in the resulting resonance interaction of the unpaired electron with the aromatic ring as seen by the delocalization of the spin density (Figure 3). Furthermore, as a result of the delocalization interaction with the aromatic ring, the resulting product (**V**) possesses a pronounced linear character with a bond angle of 162 degrees allowing the overlap of the singly occupied orbital of the carbon with the π -system of the aromatic ring as seen by the delocalization of the spin density.

Conducting a Natural Bond Orbital (NBO) analysis^[25] shows the singly occupied NBO of the carbon atom to be of almost pure *p*-character (94%) compared to the usual sp^2 -type orbital in the case of the constitutional isomer **V'**. The resonance interaction and subsequent stabilization of the singly occupied orbital on the carbon, where the radical is mainly located at, is highlighted by the excessive-high amount of stabilization energy in total of 76 kcal mol^{-1} , compared to a total of 15 kcal mol^{-1} stabilization energy for the singly occupied orbital where the unpaired electron is located at in the case of **V'**.

Also, important to note is the non-existence of a stable (*E*)-isomer of **V**, although the linear character of (**V**) and the *p*-type orbital of the carbon atom allows for the H-abstraction reaction to occur on both sides resulting in (*E*)- and (*Z*)-isomer products from only one stable radical diastereoisomer. Though the resulting (*Z*)-products after H-abstraction is still thermodynamically favored, the (*E*)-isomer only exhibits a marginal higher free energy of around $1.6 \text{ kcal mol}^{-1}$ (Figure 4).

In order to shed light on the influence of a modification to the substituent, the thermodynamics of the two diastereoisomers for two examples, **5j** and **5k**, were calculated (Figure 5). The qualitative trend of the increase in thermodynamic preference of the (*Z*)-isomer in the case of **5k** is in alignment with the experimental findings of enhanced diastereoselectivity as

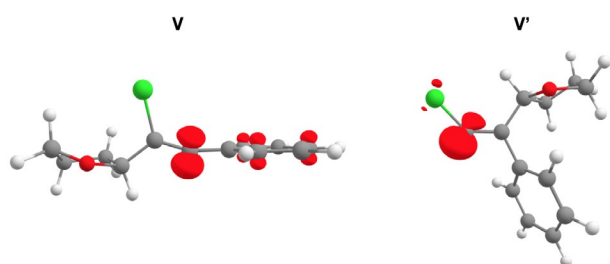


Figure 3. Optimized structures of **V** and **V'** (pbe0-D3/pcseg-2/CPCM(THF)) and their respective spin density (isovalue = 0.02).

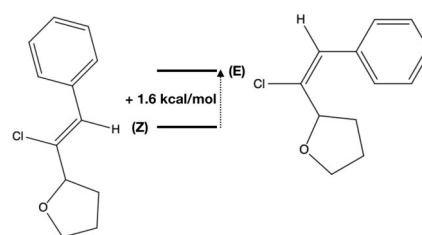


Figure 4. Comparison of the Gibbs free energy for the two resulting diastereoisomers following H-atom abstraction (pbe0-D3/pcseg-2/CPCM(THF)).

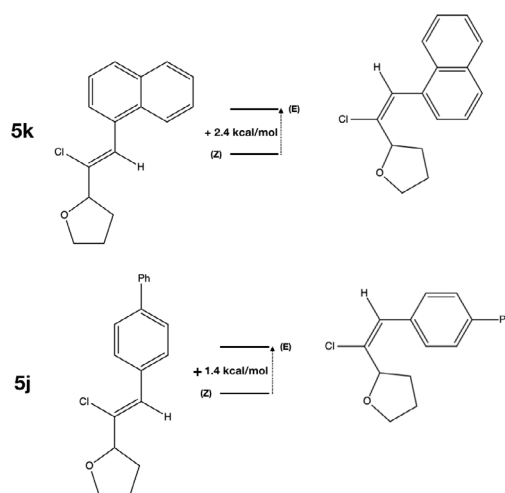


Figure 5. The difference in Gibbs free energy of the diastereoisomers of **5k** (a) and **5j** (b) (pbe0-D3/pcseg-2/CPCM(THF)).

is the experimentally observed lowering in diastereoselectivity goes hand in hand with a lowered thermodynamic preference (*Z*)-isomer for **5j**.

Furthermore, the extended π -system of **5k** results in a pronounced increase in resonance stabilization energy of the radical orbital of about 38 kcal mol^{-1} (in total $114 \text{ kcal mol}^{-1}$) as well as an accompanying increase in linear character as indicated by a bond angle of 179° (Figure 6). Since the π systems of the two phenyl units within **5j** are not fully overlapping due to the relative twisted orientation to each other, there is only a slight increase in resonance stabilization energy of the radical orbital by 12 kcal mol^{-1} (total of 88 kcal mol^{-1}) as well as in bond angle to 166° .

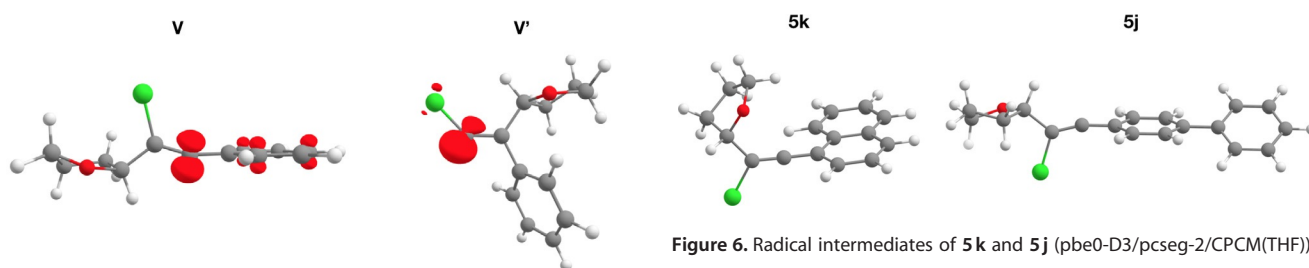
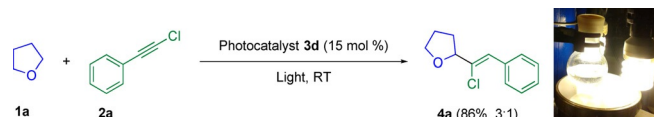


Figure 6. Radical intermediates of **5k** and **5j** (pbe0-D3/pcseg-2/CPCM(THF)).

Gram scale synthesis

To proof the practicability of the protocol we tried to scale up the reaction to the gram scale. This was possible without any significant decrease in yield (Scheme 6). The reaction of chloroalkyne **2a** (1.36 g, 10 mmol) and photocatalyst (15 mol%) in THF (0.05 M) under irradiation of two 23 W CFL bulbs gave 86% (1.78 g) of the desired product. 8 mol% of the catalyst could be recycled.



Scheme 6. Gram scale chlorovinylolation of THF.

Conclusions

In summary, we developed an efficient photocatalytic synthetic strategy for the visible light-promoted hydroalkylation of chloroalkynes/alkynes via direct sp^3 -C–H functionalization of ethers, amides, alcohols, and even unactivated alkanes by using a household fluorescent light bulb. Cheap and readily available diaryl ketones were used as photocatalyst as well as H-atom abstractors. The hydroalkylation of alkynes via sp^3 -C–H bond functionalization was achieved in an atom economic and redox-efficient manner. Especially for the synthesis of vinyl halides from haloalkynes, this process is remarkable as the radical approach opens an orthogonal pathway compared to transition metal-catalyzed strategies that are used for alkynylations. Nevertheless, this process was also feasible if bromoalkynes were used in the presence of a base. This radical alkynylation sp^3 -C–H bond offers an attractive alternative to existing strategies. The mechanistic studies indicate that the solvent/reactant act as a hydrogen source. To the best of our knowledge, this is the first access to chlorovinylated products of ethers and amides. The reaction is highly regioselective and chemoselective under such conditions. Due to the immense importance of vinyl halides as the key building block, this new attractive access from readily available starting materials in an atom-economic manner is of high value to the chemical community.

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Conflict of interest

The authors declare no conflict of interest.

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- [1] a) W.-J. Chung, C. D. Vanderwal, *Angew. Chem. Int. Ed.* **2016**, *55*, 4396–4434; *Angew. Chem.* **2016**, *128*, 4470–4510; b) R. D. Taylor, M. MacCoss, A. D. G. Lawson, *J. Med. Chem.* **2014**, *57*, 5845–5859; c) C. Singh, M. Hassam, V. P. Verma, A. S. Singh, N. K. Naikade, S. K. Puri, P. R. Maulik, R. Kant, *J. Med. Chem.* **2012**, *55*, 10662–10673; d) J. K. Nunnery, N. Engene, T. Byrum, Z. Cao, S. V. Jabba, A. R. Pereira, T. Matainaho, T. F. Murray, W. H. Gerwick, *J. Org. Chem.* **2012**, *77*, 4198–4208; e) V. Rukachaisirikul, A. Rodglin, Y. Sukpondma, S. Phongpaichit, J. Buatong, J. Sakayaroj, *J. Nat. Prod.* **2012**, *75*, 853–858; f) L. V. White, B. D. Schwartz, M. G. Banwell, A. C. A. Willis, *J. Org. Chem.* **2011**, *76*, 6250–6257; g) R. Jana, T. P. Pathak, M. S. Sigman, *Chem. Rev.* **2011**, *111*, 1417–1492; h) K. Nicolaou, P. G. Bulger, D. Sarlah, *Angew. Chem. Int. Ed.* **2005**, *44*, 4442–4489; *Angew. Chem.* **2005**, *117*, 4516–4563; i) G. W. Bemis, M. A. Murcko, *J. Med. Chem.* **1996**, *39*, 2887–2893.
- [2] a) A. Faulkner, T. van Leeuwen, B. L. Feringa, S. J. Wezenberg, *J. Am. Chem. Soc.* **2016**, *138*, 13597–13603; b) R. Göstl, S. Hecht, *Chem. Eur. J.* **2015**, *21*, 4422–4427; c) M. Irie, T. Fukaminato, K. Matsuda, S. Kobatake, *Chem. Rev.* **2014**, *114*, 12174–12277; d) X. Chen, S. Wehle, N. Kuzmanovic, B. Merget, U. Holzgrabe, B. König, C. A. Sotriffer, M. Decker, *ACS Chem. Neurosci.* **2014**, *5*, 377–389; e) W. A. Velema, W. Szymanski, B. L. Feringa, *J. Am. Chem. Soc.* **2014**, *136*, 2178–2191.
- [3] a) A. Grozavu, H. B. Hepburn, P. J. Smith, H. K. Potukuchi, P. J. Lindsay-Scott, T. J. Donohoe, *Nat. Chem.* **2019**, *11*, 242–247; b) D. C. Blakemore, L. Castr, I. Churcher, D. C. Rees, A. W. Thomas, D. M. Wilson, A. Wood, *Nat. Chem.* **2018**, *10*, 383; c) V. K. Tiwari, G. Pawar, H. S. Jena, M. Kapur, *Chem. Commun.* **2014**, *50*, 7322–7325; d) M. Baumann, I. R. Baxendale, *Beilstein J. Org. Chem.* **2013**, *9*, 2265–2319; e) S. Källström, R. Leino, *Bioorg. Med. Chem.* **2008**, *16*, 601–635.
- [4] a) T. Adak, J. Schulmeister, M. C. Dietl, M. Rudolph, F. Rominger, A. S. K. Hashmi, *Eur. J. Org. Chem.* **2019**, 3867–3876; b) Y. Li, B. Zhao, K. Dai, D.-H. Tu, B. Wang, Y.-Y. Wang, Z.-T. Liu, Z.-W. Liu, J. Lu, *Tetrahedron* **2016**, *72*, 5684–5690; c) C. Cordovilla, C. Bartolomé, J. M. Martínez-Illarduya, P. Espinet, *ACS Catal.* **2015**, *5*, 3040–3053; d) D.-H. Lee, Y. Qian, J.-H. Park, J.-S. Lee, S.-E. Shim, M.-J. Jin, *Adv. Synth. Catal.* **2013**, *355*, 1729–1735; e) A. Thakur, K. Zhang, J. Louie, *Chem. Commun.* **2012**, *48*, 203–205; f) G.-P. Lu, K. R. Voigttritter, C. Cai, B. H. Lipshutz, *J. Org. Chem.* **2012**, *77*, 3700–3703; g) P. Espinet, A. M. Echavarren, *Angew. Chem. Int. Ed.* **2004**, *43*, 4704–4734; *Angew. Chem.* **2004**, *116*, 4808–4839; h) A. F. Littke, C. Dai, G. C. Fu, *J. Am. Chem. Soc.* **2000**, *122*, 4020–4028; i) N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457–2483; j) J. K. Stille, *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 508–524; *Angew. Chem.* **1986**, *98*, 504–519.
- [5] a) P. Ruiz-Castillo, S. L. Buchwald, *Chem. Rev.* **2016**, *116*, 12564–12649; b) J. F. Hartwig, *Acc. Chem. Res.* **2008**, *41*, 1534–1544.
- [6] E.-L. D. T. R. T. K. K. Beutel, in *Ullmann's Encyclopedia of Industrial Chemistry*, Weinheim: Wiley-VCH, **2011**.
- [7] a) C. Boga, S. Bordon, L. Casarin, G. Micheletti, M. Monari, *Molecules* **2018**, *23*, 171; b) M. Si-Fodil, H. Ferreira, J. Gralak, L. Duhamel, *Tetrahedron Lett.* **1998**, *39*, 8975–8978; c) H. Neumann, D. Seebach, *Tetrahedron Lett.* **1976**, *17*, 4839–4842.
- [8] a) K. Ando, T. Wada, M. Okumura, H. Sumida, *Org. Lett.* **2015**, *17*, 6026–6029; b) D.-J. Dong, H.-H. Li, S.-K. Tian, *J. Am. Chem. Soc.* **2010**, *132*, 5018–5020; c) A. Barbero, Y. Blanco, F. Garcia Pulido, *synthesis* **2000**, 2000, 1223–1228; d) G. E. Keck, K. A. Savin, M. Weglarz, *J. Org. Chem.* **1995**, *60*, 3194–3204.
- [9] a) X.-Y. Lu, M.-L. Hong, H.-P. Zhou, Y. Wang, J.-Y. Wang, X.-T. Ge, *Chem. Commun.* **2018**, *54*, 4417–4420; b) Y. Xu, M. C. Young, G. Dong, *J. Am. Chem. Soc.* **2017**, *139*, 5716–5719; c) J.-W. Xu, Z.-Z. Zhang, W.-H. Rao, B.-F. Shi, *J. Am. Chem. Soc.* **2016**, *138*, 10750–10753; d) Y. Li, L. Ge, B. Qian, K. R. Babu, H. Bao, *Tetrahedron Lett.* **2016**, *57*, 5677–5680; e) S. Maity, S. Agasti, A. M. Earsad, A. Hazra, D. Maiti, *Chem. Eur. J.* **2015**, *21*, 11320–11324; f) C. W. Cheung, F. E. Zhurkin, X. Hu, *J. Am. Chem. Soc.* **2015**, *137*, 4932–4935; g) B. Liu, T. Zhou, B. Li, S. Xu, H. Song, B. Wang, *Angew. Chem. Int. Ed.* **2014**, *53*, 4191–4195; *Angew. Chem.* **2014**, *126*, 4275–4279; h) N. Kambe, Y. Moriwaki, Y. Fujii, T. Iwasaki, J. Terao, *Org. Lett.* **2011**, *13*, 4656–4659; i) Y. Fujii, J. Terao, N. Kambe, *Chem. Commun.* **2009**, 1115–1117.

- [10] a) Y. Zhao, J. Jin, P. W. H. Chan, *Adv. Synth. Catal.* **2019**, *361*, 1313–1321; b) Z.-Y. Song, C.-L. Zhang, S. Ye, *Org. Biomol. Chem.* **2019**, *17*, 181–185; c) S. Zhang, Q.-J. Yao, G. Liao, X. Li, H. Li, H.-M. Chen, X. Hong, B.-F. Shi, *ACS Catal.* **2019**, *9*, 1956–1961; d) Y. Yang, L. Eberle, F. F. Mulks, J. F. Wunsch, M. Zimmer, F. Rominger, M. Rudolph, A. S. K. Hashmi, *J. Am. Chem. Soc.* **2019**, *141*, 17414–17420; e) Y. Yang, J. Schiebl, S. Zallouz, V. Göker, J. Gross, M. Rudolph, F. Rominger, A. S. K. Hashmi, *Chem. Eur. J.* **2019**, *25*, 9624–9628; f) Y. Yang, P. Antoni, M. Zimmer, K. Sekine, F. F. Mulks, L. Hu, L. Zhang, M. Rudolph, F. Rominger, A. S. K. Hashmi, *Angew. Chem. Int. Ed.* **2019**, *58*, 5129–5133; *Angew. Chem.* **2019**, *131*, 5183–5187; g) K. Ni, L.-G. Meng, K. Wang, L. Wang, *Org. Lett.* **2018**, *20*, 2245–2248; h) Y. Shen, B. Huang, J. Zheng, C. Lin, Y. Liu, S. Cui, *Org. Lett.* **2017**, *19*, 1744–1747; i) K. Jia, F. Zhang, H. Huang, Y. Chen, *J. Am. Chem. Soc.* **2016**, *138*, 1514–1517; j) L. Huang, F. Rominger, M. Rudolph, A. S. K. Hashmi, *Chem. Commun.* **2016**, *52*, 6435–6438; k) J. Xie, S. Shi, T. Zhang, N. Mehrkens, M. Rudolph, A. S. K. Hashmi, *Angew. Chem. Int. Ed.* **2015**, *54*, 6046–6050; *Angew. Chem.* **2015**, *127*, 6144–6148; l) F. Le Vailant, T. Courant, J. Waser, *Angew. Chem. Int. Ed.* **2015**, *54*, 11200–11204; *Angew. Chem.* **2015**, *127*, 11352–11356; m) H. Tan, H. Li, W. Ji, L. Wang, *Angew. Chem. Int. Ed.* **2015**, *54*, 8374–8377; *Angew. Chem.* **2015**, *127*, 8494–8497; n) J. Yang, J. Zhang, L. Qi, C. Hu, Y. Chen, *Chem. Commun.* **2015**, *51*, 5275–5278; o) M. Wan, Z. Meng, H. Lou, L. Liu, *Angew. Chem. Int. Ed.* **2014**, *53*, 13845–13849; *Angew. Chem.* **2014**, *126*, 14065–14069; p) H. Huang, G. Zhang, L. Gong, S. Zhang, Y. Chen, *J. Am. Chem. Soc.* **2014**, *136*, 2280–2283; q) H. Yoshida, Y. Asatsu, Y. Mimura, Y. Ito, J. Ohshita, K. Takaki, *Angew. Chem. Int. Ed.* **2011**, *50*, 9676–9679; *Angew. Chem.* **2011**, *123*, 9850–9853; r) G. Cahiez, O. Gager, J. Buendia, *Angew. Chem.* **2010**, *49*, 1278–1281.
- [11] a) A. Hossain, S. Engl, E. Lutsker, O. Reiser, *ACS Catal.* **2019**, *9*, 1103–1109; b) X.-J. Tang, W. R. Dolbier, *Angew. Chem. Int. Ed.* **2015**, *54*, 4246–4249; *Angew. Chem.* **2015**, *127*, 4320–4323; c) P. Riente, M. A. Pericàs, *ChemSusChem* **2015**, *8*, 1841–1844; d) C.-J. Wallentin, J. D. Nguyen, P. Finkbeiner, C. R. J. Stephenson, *J. Am. Chem. Soc.* **2012**, *134*, 8875–8884; e) J. D. Nguyen, E. M. D'Amato, J. M. R. Narayanan, C. R. J. Stephenson, *Nat. Chem.* **2012**, *4*, 854; f) J. D. Nguyen, J. W. Tucker, M. D. Koniczynska, C. R. J. Stephenson, *J. Am. Chem. Soc.* **2011**, *133*, 4160–4163; g) D. Yang, Y.-L. Yan, B.-F. Zheng, Q. Gao, N.-Y. Zhu, *Org. Lett.* **2006**, *8*, 5757–5760.
- [12] a) Z. Li, W.-L. Duan, *Angew. Chem. Int. Ed.* **2018**, *57*, 16041–16045; *Angew. Chem.* **2018**, *130*, 16273–16277.
- [13] M. J. Koh, T. T. Nguyen, H. Zhang, R. R. Schrock, A. H. Hoveyda, *Nature* **2016**, *531*, 459–465.
- [14] a) W. Lecroq, P. Bazille, F. Morlet-Savary, M. Breugst, J. Lalevée, A.-C. Gaumont, S. Lakhdar, *Org. Lett.* **2018**, *20*, 4164–4167; b) L. Huang, M. Rudolph, F. Rominger, A. S. K. Hashmi, *Angew. Chem. Int. Ed.* **2016**, *55*, 4808–4813; *Angew. Chem.* **2016**, *128*, 4888–4893; c) I. Ghosh, T. Ghosh, J. I. Bardagi, B. König, *Science* **2014**, *346*, 725–728; d) Y. Cheng, X. Gu, P. Li, *Org. Lett.* **2013**, *15*, 2664–2667; e) D. P. Hari, P. Schroll, B. König, *J. Am. Chem. Soc.* **2012**, *134*, 2958–2961; f) J. Yu, L. Zhang, G. Yan, *Adv. Synth. Catal.* **2012**, *354*, 2625–2626; g) Y.-Q. Zou, J.-R. Chen, X.-P. Liu, L.-Q. Lu, R. L. Davis, K. A. Jørgensen, W.-J. Xiao, *Angew. Chem. Int. Ed.* **2012**, *51*, 784–788; *Angew. Chem.* **2012**, *124*, 808–812.
- [15] a) Z.-F. Cheng, Y.-S. Feng, C. Rong, T. Xu, P.-F. Wang, J. Xu, J.-J. Dai, H.-J. Xu, *Green Chem.* **2016**, *18*, 4185–4188; b) J. Li, J. Zhang, H. Tan, D. Z. Wang, *Org. Lett.* **2015**, *17*, 2522–2525; c) C. Li, J. Yang, L. Li, K. Qiang, *Tetrahedron Lett.* **2014**, *55*, 6096–6100; d) J. Zhang, P. Li, L. Wang, *Org. Biomol. Chem.* **2014**, *12*, 2969–2978; e) D. Liu, C. Liu, H. Li, A. Lei, *Angew. Chem. Int. Ed.* **2013**, *52*, 4453–4456; *Angew. Chem.* **2013**, *125*, 4549–4552; f) X. Tusun, C. D. Lu, *Synlett* **2013**, *24*, 1693–1696; g) Y. Yang, H. Huang, X. Zhang, W. Zeng, Y. Liang, *Synthesis* **2013**, *45*, 1325; h) L. Huang, K. Cheng, B. Yao, J. Zhao, Y. Zhang, *Synthesis* **2009**, *2009*, 424.
- [16] a) J. Xie, M. Rudolph, F. Rominger, A. S. K. Hashmi, *Angew. Chem. Int. Ed.* **2017**, *56*, 7266–7270; *Angew. Chem.* **2017**, *129*, 7372–7376; b) S. X. Zhu, S. Das, L. Bui, H. Zhou, D. P. Curran, M. Rueping, *J. Am. Chem. Soc.* **2013**, *135*, 1823–1829; c) A. G. Condie, J. C. González-Gómez, C. R. J. Stephenson, *J. Am. Chem. Soc.* **2010**, *132*, 1464–1465.
- [17] H.-P. Deng, X.-Z. Fan, Z.-H. Chen, Q.-H. Xu, J. Wu, *J. Am. Chem. Soc.* **2017**, *139*, 13579–13584.
- [18] a) N. A. Till, R. T. Smith, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2018**, *140*, 5701–5705; b) L. Guo, F. Song, S. Zhu, H. Li, L. Chusyn, *Nat. Commun.* **2018**, *9*, 4543.
- [19] A. Noble, S. J. McCarver, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2015**, *137*, 624–627.
- [20] a) L. Zhang, X. Si, Y. Yang, M. Zimmer, S. Witzel, K. Sekine, M. Rudolph, A. S. K. Hashmi, *Angew. Chem. Int. Ed.* **2019**, *58*, 1823–1827; *Angew. Chem.* **2019**, *131*, 1837–1841; b) Y. Shen, Y. Gu, R. Martin, *J. Am. Chem. Soc.* **2018**, *140*, 12200–12209; c) D. R. Heitz, J. C. Tellis, G. A. Molander, *J. Am. Chem. Soc.* **2016**, *138*, 12715–12718; d) J.-B. Xia, C. Zhu, C. Chen, *Chem. Commun.* **2014**, *50*, 11701–11704; e) J.-B. Xia, C. Zhu, C. Chen, *J. Am. Chem. Soc.* **2013**, *135*, 17494–17500.
- [21] N. C. Yang, D. D. H. Yang, *J. Am. Chem. Soc.* **1958**, *80*, 2913–2914.
- [22] a) R. Breslow, *Chem. Rec.* **2001**, *1*, 3–11; b) R. Breslow, M. A. Winnik, *J. Am. Chem. Soc.* **1969**, *91*, 3083–3084.
- [23] a) S. Tang, Y. Liu, X. Gao, P. Wang, P. Huang, A. Lei, *J. Am. Chem. Soc.* **2018**, *140*, 6006–6013; b) S. Tang, P. Wang, H. Li, A. Lei, *Nat. Commun.* **2016**, *7*, 11676.
- [24] Advances in molecular quantum chemistry contained in the Q-Chem. 4 program package, Y. Shao, et al., *Mol. Phys.* **2015**, *113*, 184–215.
- [25] F. Weinhold, and E. D. Glendening, "NBO 5.0 program manual: natural bond orbital analysis programs", Theoretical Chemistry Institute and Department of Chemistry, University of Wisconsin, Madison, WI 53706 (2001).

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