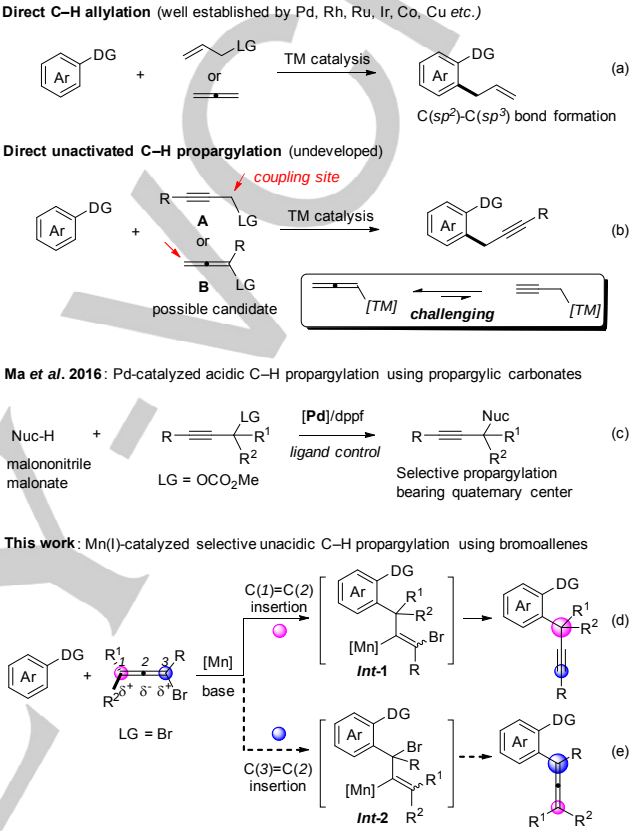
Highly Selective Manganese(I)/Lewis Acid Cocatalyzed Direct C−H Propargylation Using Bromoallenes

Can Zhu, Jonas Luca Schwarz, Sara Cembellín, Steffen Greßies, and Frank Glorius*

Abstract: A manganese(I)/Lewis acid cocatalyzed direct C−H propargylation with high selectivity has been developed. BPh_3 was discovered to not only promote the reactivity, but also enhance the selectivity to afford the propargylation. Secondary, tertiary or even quaternary carbon centers at the propargylic position could be directly constructed. Both internal and terminal alkynes are easily accessible. The chirality was successfully transferred from an axially chiral allene to the central chirality. The reactivity of the manganese catalyst in this reaction was found to be unique comparing other transition metal catalysts.

The efficient construction of carbon-carbon (C−C) bonds is at the core of organic synthesis.[1] One elegant solution is the utilization of transition metal-catalyzed C−H activation reactions, which have emerged as an effective tool for the functionalization and assembly of organic molecules for pharmaceutical and material sciences.[2] Recently, the selective construction of C(sp^2)−C(sp^3) bonds has attracted more and more attention.[3] On the other hand, acetylene is a fundamental and crucial group in organic chemistry, which can be easily transferred to many other functional groups,[4] and also has broad applications in click chemistry.[5] Therefore, the direct C−H propargylation would definitely be an efficient and powerful strategy to realize both the construction of a C(sp^2)−C(sp^3) bond between two molecule fragments, and the introduction of an acetylene moiety in an one-step manner.[6]

So far, many catalysts, such as Pd, Rh, Ru, Ir, Co, Cu complexes could realize the direct C−H allylation, although with an issue of regioselectivity, forming a C(sp^2)−C(sp^3) bond (Scheme 1a).[7] In contrast, the direct C−H propargylation is much less investigated, especially those starting from unactivated C−H bonds (Scheme 1b). The coupling partner in the direct C−H propargylation could be an alkyne with a leaving group (LG) at the propargylic position (**A**), or an allene directly connected to a LG (**B**). However, the control of the selectivity during the reaction is greatly challenging, given the fact that the formation of an allenyl metal complex is more favorable in comparison with a propargylic intermediate. Therefore, in most cases, these reactions of either **A**[8] or **B**[9] give rise to the corresponding allenes rather than the propargylic products. Only in rare cases,[10] such as Friedel−Crafts type reactions,[11] the direct C−H propargylation could be observed as the major



LG = leaving group. TM = transition metal. DG = directing group. Nuc = nucleophile. dppf = 1,1'-bis(diphenylphosphino)ferrocene.

Scheme 1. Previous studies and this work.

pathway, however, limited to electron-rich aromatic systems and/or acidic C−H bonds only.[12] In 2016, Ma *et al*. described a highly efficient Pd-catalyzed acidic C−H propargylation using propargylic carbonates (Scheme 1c).[12a] The ligand controls the selectivity leading to propargylic compounds rather than allenes. To the best of our knowledge, the direct C−H activation/ propargylation is still undeveloped, thus highly desirable.

In the past decade, great progress on C−H activation chemistry has been achieved based on complexes of 4d or 5d noble metals. In contrast, the utility of manganese complexes is unfortunately scarce, although manganese is earth-abundant, inexpensive, and of low toxicity.[13] In this field, recent years have witnessed the significant progress, achieved by the groups of Kuninobu and Takai,[14] Wang,[15] Ackermann,[16] our group[17] and others.[18] Herein, we disclose our recent observations on the highly selective manganese(I)/Lewis acid cocatalyzed direct C−H propargylation using bromoallenes. Bromoallenes are a class of easily accessible, mostly stable compounds.[19] More than 30 natural products have been discovered bearing this

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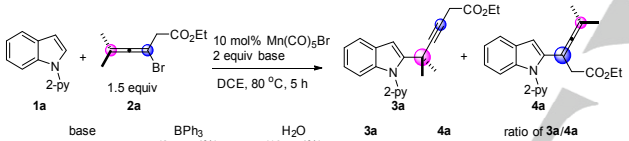
structural motif, while the chemistry of bromoallenes is highly undeveloped.[20] The utility of bromoallenes as the coupling partner in the direct C–H propargylation shows their unique character as potential building blocks in organic synthesis. However, two big challenges still exist: 1) The selective C=C insertion [C(*1*)=C(*2*) vs. C(*3*)=C(*2*)] into the C−Mn bond would lead to a propargylic compound (Scheme 1d) or an allene product (Scheme 1e); 2) This newly formed acetylene would probably be even more reactive towards insertion into the C–Mn bond, compared with bromoallenes.[15a-b,18a]

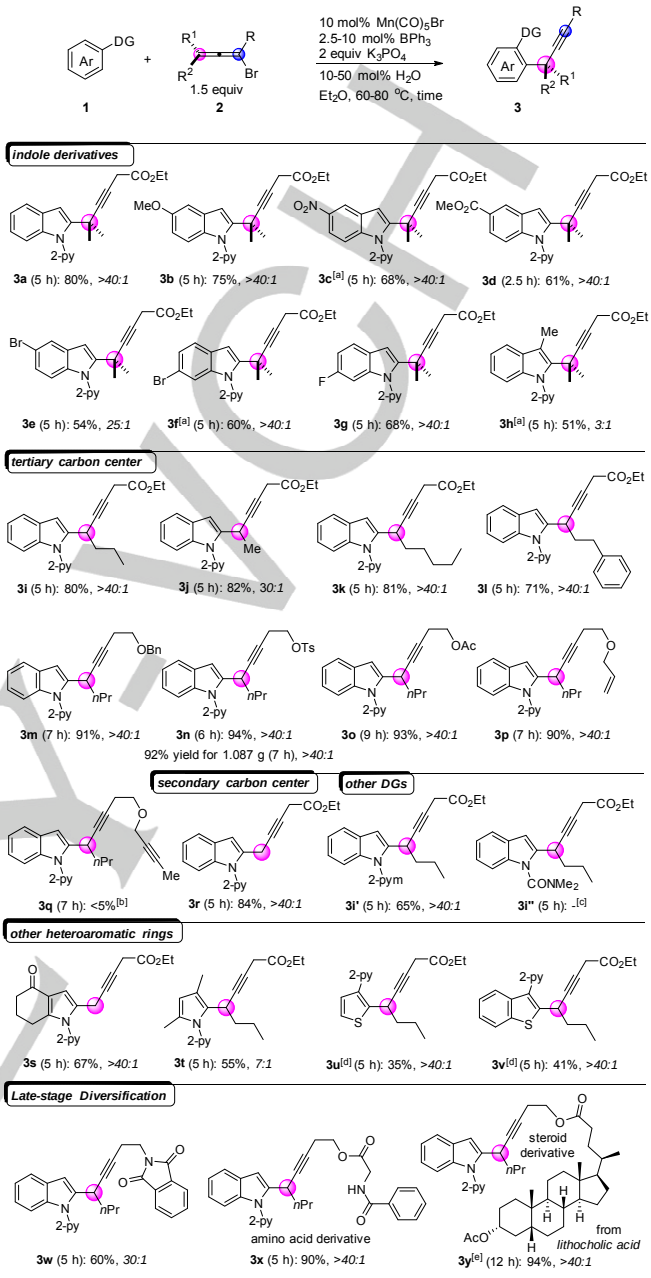
Our initial attempt began with the coupling reaction of *N*-(2-pyridyl)indole **1a** and bromoallene **2a** under the catalysis of Mn(I). Inspiringly, the indole-C(*2*) propargylated product **3a**, bearing an all-carbon quaternary center, was observed in 36% yield as the major product (Scheme 2). However, allene **4a** could also be detected in 12% yield. Base screening suggested that K_3PO_4 was the best (see Table S1 in the Supporting Information). To our delight, the addition of BPh_3 (2.5 mol%) not only promoted the conversion of the starting material, but also enhanced the selectivity of **3a**/**4a** further to 14:1. It is noteworthy that the addition of H_2O (10 mol%) lead to almost full conversion affording **3a** in 76% yield, with much higher selectivity (38:1). Finally, by using BPh_3 (5 mol%) as the cocatalyst, the formation of **3a** was further increased to 83% yield, with excellent selectivity (>40:1).



base	BPh_3 (2.5 mol%)	H_2O (10 mol%)	**3a**	**4a**	ratio of **3a**/**4a**
K_2CO_3	×	×	36%	12%	*3:1*
K_3PO_4	×	×	42%	6%	*7:1*
K_3PO_4[a]	√	×	56%	4%	*14:1*
K_3PO_4[a]	√	√	76%	2%	*38:1*
K_3PO_4[a,b]	**√**	**√**	**83%**	**2%**	***>40:1***

Scheme 2. Optimization of the reaction conditions. [a] Et_2O was used as the solvent. [b] BPh_3 (5 mol%) was used. DCE = 1,2-Dichloroethane.

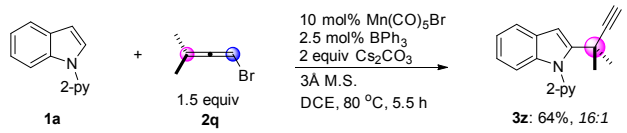
With the optimal reaction conditions in hand, we turned to studying the substrate scope (Scheme 3). Functional groups, such as 5-OMe, 5-NO_2, 5-CO_2Me, 5-Br, 6-Br, and 6-F on the benzene ring were well tolerated to afford the corresponding products **3b-g** in 54-75% yields, with good selectivities (25:1 to >40:1). The introduction of a substituent onto the C(*3*)-position of the indole decreased both the yield and selectivity. Moreover, a tertiary carbon center could also be constructed from tri-substituted allenes, affording **3i-l** in good yields (71-82%) with excellent selectivities (30:1 to >40:1). The scope of bromoallenes was also investigated, and found to be broad in this approach as shown by the formation of **3m-p**. Furthermore, it is noteworthy that the propargylation could also occur to build a secondary carbon center in **3r**, without any further isomerization to the allene under basic conditions.[21] A survey of the directing group showed that reaction worked equally well with 2-pyrimidinyl as the directing group, while carbamoyl group failed to promote such propargylation. Finally, this approach



Scheme 3. Substrate scope. Reaction conditions: **1** (0.2 mmol), **2** (0.3 mmol), $Mn(CO)_5Br$ (10 mol%), BPh_3 (2.5-10 mol%), H_2O (10-50 mol%), and K_3PO_4 (2 equiv) in Et_2O (1 mL) at 60-80 °C. The ratio of **3**/**4** was determined from the crude ^1H NMR. [a] The reaction was run without H_2O. [b] **1a** was recovered in 95% yield. [c] **1i''** was recovered in 95% yield. [d] The reaction was conducted at 90 °C using the corresponding chloroallene instead of bromoallene. [e] Mixed solvent (Et_2O/DCE = 1:1) was used.

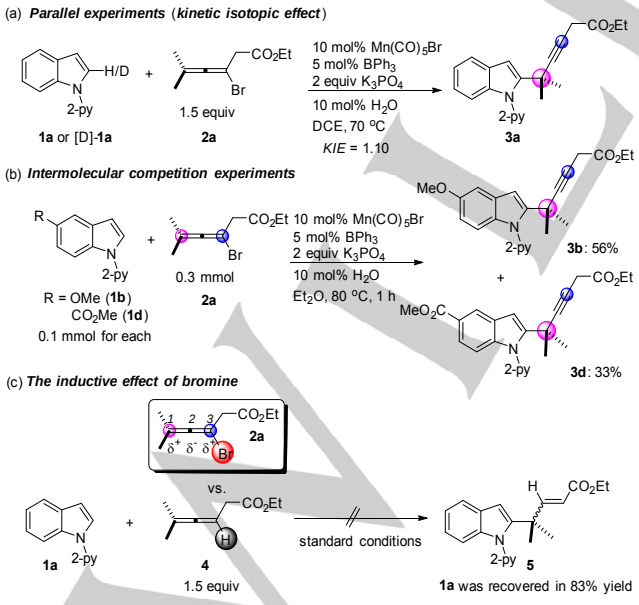
could be extended to other heteroaromatic systems, including pyrrole, thiophene, and benzothiophene, with good selectivity (up to >40:1). The propargylation reaction afforded **3w**, bearing an imide group, in 60% yield. The employment of α-amino acid and lithocholic acid[22] derivatives afforded **3x** and **3y** in 90 and 94% yield, respectively, with >40:1 selectivity, implying the potential application on late-stage diversification in biomolecular and medicinal chemistry.

Terminal-alkyne formation is one of the crucial topics in organic chemistry, but greatly challenging especially in C−H activation reactions, due to the fact that they perform as active coupling partners under many C−H activation catalysts, including the Mn(I) catalyst.[15b,18a] However, to our great surprise, the employment of a tri-substituted allene **2q** in this approach directly afforded the terminal alkyne **3z** in 64% yield, with satisfying selectivity (16:1; Scheme 4). This chemistry will provide a direct and novel strategy to introduce terminal-alkyne groups into molecules, implying broad applications in click chemistry.



Scheme 4. Synthesis of Terminal Alkyne.

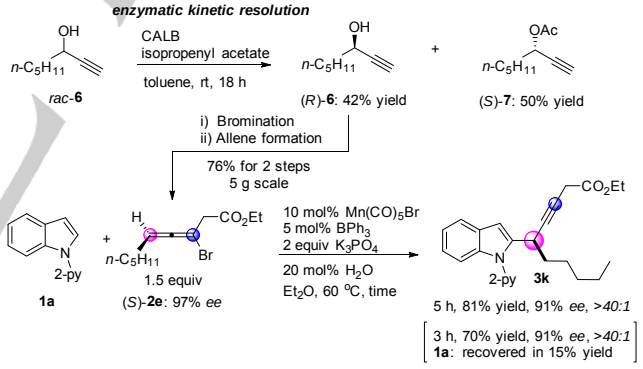
To gain a deeper insight into the reaction mechanism, the deuterium kinetic isotope effect (KIE) was determined from two parallel kinetic experiments with a value of 1.10 (Scheme 5a). These results indicate that the C−H bond cleavage is unlikely involved in the rate-determining step. Moreover, intermolecular competition experiments indicated that electron-rich indoles are more reactive in this reaction (Scheme 5b). The reaction using a simple allene (**4**) in place of bromoallene **2a** could not realize the subsequent insertion of allenyl C−C double bond into C−Mn bond, leading to hydroarylated product **5** (Scheme 5c).[18d] These observations show that the bromine atom on allene performs not only as a leaving group, but also as a crucial element controlling electronic distribution in the allene moiety. The presence of bromine results in the electron deficiency of C(*1*) and C(*3*), while



Scheme 5. Mechanistic Studies.

electron richness at C(*2*). This inductive effect has important mechanistic implications for the reaction of the thiophene or benzothiophene system (see Scheme 3).[23] However, the selective insertion occurring at C(*1*) rather than C(*3*) is due to the nature of the Mn(I) catalyst. In order to show the unique catalytic activity of the manganese catalyst, a series of traditional C−H activation catalysts, including Pd, Rh, Ir, Co, Cu, and Re complexes were tested under the standard reaction conditions (see the Supporting Information). The results indicated that none of these catalysts could promote this transformation. Finally, a robustness screen was applied to exhibit the functional group and heterocycle tolerance of this approach (see the Supporting Information).[24]

Enzymatic kinetic resolution (EKR) is an efficient and scalable approach to produce chiral secondary alcohols.[25] Based on it, chiral propargylic alcohol (*R*)-**6** was easily obtained in 42% yield (Scheme 6). Subsequent transformations afforded 76% yield of chiral bromoallene (*S*)-**2e** with 97% *ee* on 5-gram scale.[19] The employment of chiral bromoallene ((*S*)-**2e**, 97% *ee*) in this approach afforded 81% yield of **3k** with 91% *ee*. The axial chirality in the bromoallene could be successfully transferred to the central chirality at the propargylic position, which is difficult to construct with other methodologies. The slight loss of enantiomeric purity in chirality transfer was probably due to reaction mechanism, rather than racemization process during the reaction, since the same level of enantioselectivity was detected after 3 h.



Scheme 6. Chirality Transfer Experiments.

In conclusion, we have developed a novel manganese(I)/Lewis acid cocatalyzed direct C−H propargylation reaction with high efficiency and selectivity. The propargylation reaction is based on the manganese catalyst, which is earth abundant, and an inexpensive metal. Lewis acid (BPh_3) was introduced as the cocatalyst to enhance the electrophilicity of bromoallene, promoting not only the reactivity, but also the selectivity. Catalytic amount of H_2O was found to accelerate the reaction by increasing the solubility of the base (K_3PO_4) in the solvent. Furthermore, the substrate scope shows good functional-group tolerance and potential applications on late-stage diversification. Secondary, tertiary and even quaternary carbon centers could be constructed at the propargylic position. Moreover, it is noteworthy that the direct C−H propargylation is not only working

for internal alkyne formations, but also for terminal ones, which has not yet been reported in previous studies. Finally, the successful chirality transfer will provide a novel strategy introducing chirality into propargylic positions.

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Keywords: Manganese • Lewis acid • C−H activation • propargylation • bromoallene

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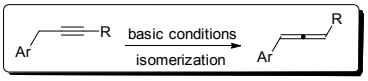

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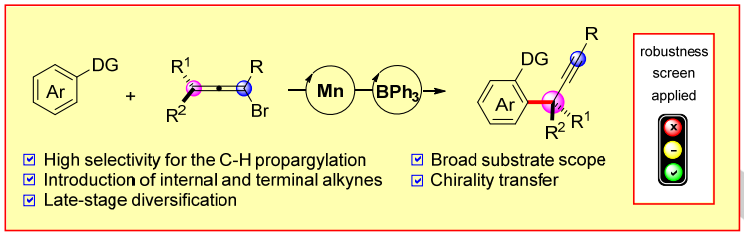

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