Homogeneous Catalysis

Dimeric Manganese-Catalyzed Hydroarylation and Hydroalkenylation of Unsaturated Amides

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Dedicated to the 100th anniversary of the School of Chemistry and Chemical Engineering, Nanjing University

Abstract: An unprecedented Mn(I)-catalyzed selective hydroarylation and hydroalkenylation of unsaturated amides with commercially available organic boronic acids is reported. Alkenyl boronic acids have been successfully employed for the first time in Mn(I)-catalyzed carbon–carbon bond formation. A wide array of β-alkenylated amide products can be obtained in moderate to good yields, which offers practical access to five- and six-membered lactams. This protocol has predictable regio- and chemoselectivity, excellent functional group compatibility and ease of operation in air, representing a significant step-forward towards manganese-catalyzed C–C coupling.

Replacement of noble metal catalysts by cheap transition metal catalysts is an admirable choice to address the future natural resources.[1] Manganese is the third most abundant transition metal in the Earth’s crust, and also possesses several promising features, including low price, low toxicity (maximum 1200 ppm tolerance in drugs) and, since it is commonly found in enzymes, good biocompatibility.[1] Consequently, exploration of new and unique catalytic activity of manganese complexes in homogeneous catalysis has gained considerable momentum in recent years.[2–5] For example, with recent efforts, Mn(I)-catalyzed C(sp2)–H bond activation of directed arenes,[6–16] dehydrogenative coupling of alcohols[17,18] and selective hydroisilylation of alkenes[19,20] have opened powerful tools of preparing valuable organic compounds.

In 2018, the first example of selective hydroarylation of 1,3-diynes with aryloboronic acids enabled by a dimeric Mn(I)-catalyzed was reported by our laboratory.[21] However, the major challenges for Mn-catalyzed selective hydroarylation of alkenes stem from largely undeveloped elementary units, such as transmetallation and migratory insertion compared with Pd or Rh catalysts, which have already gained considerable momentum in transition metal-catalyzed conjugate addition of organometallics to electron-deficient alkenes (Scheme 1a).[23–28] The early stoichiometric experiments from Nicholson, Main and Woodgate[29–31] showed that only five-membered stable arylnanganacycles can be used successfully with highly reactive unsaturated esters or nitriles in the presence of trimethylamine N-oxide and Li2PdCl4 (Scheme 1b). Very recently, Wang et al. achieved an elegant manganese(I)-catalyzed transformation through C–H activation of directed arenes without the preparation of five-membered manganacycles.[32] However, it is still very difficult for an unchelated organic manganese compound to undergo the expected carbomanganation of alkenes due to the tendency for ligand migration to occur (Scheme 1b).[33,34] Furthermore, only highly electron-deficient unsaturated esters, ketones, and nitriles are effective substrates in the reaction and Mn(I)-mediated carbomanganation of alkenes has not been achieved with less reactive unsaturated amides. Accordingly, we focused our attention on the development of Mn(I)-catalyzed direct hydrofunctionalization of less electron-deficient unsaturated amides with commercially available aryl- and alkenyl-boronic acids (Scheme 1c). To our knowledge, it represents the first case of successful usage of vinylboronic acids in manganese(I)-catalyzed C–C bond forming reactions.

Scheme 1. The current status of manganese(I)-mediated hydrofunctionalization of alkenes. EWG = electron-withdrawing group.
Initially, in an effort to understand the reactivity of the organomanganese species that are generated, we performed density function theory (DFT) calculations with the Fukui function to compare the reactivity of different kinds of arylmetal intermediates (Scheme 2, upper part). The reaction was carried out in 50 mL autoclave on 1 mmol scale. Our calculations provided new insights into the reaction mechanisms, showing that the use of 10 mol% Mn(CO)5Br instead of 5 mol% Mn2(CO)8Br2 under the standard conditions. Importantly, the resulting vinyl manganese intermediates directly from alkyl boronic acids cannot be generated in a Mn(I)-catalyzed C–H activation manner, and this significantly enhances the synthetic practicality of the hydroarylation reaction. Under the optimized reaction conditions, the desired β-alkenylated amide (5a) can be obtained in an isolated yield of 93% (Scheme 3). The use of Mn1(CO)10 results in a slightly decreased yield (83%), and replacement of 5 mol% Mn2(CO)8Br2 with 10 mol% Mn(CO)5Br gives only a moderate yield (77% vs. 93%). When Pd(PPh3)4, Ni(acac)2 (acac = acetylacetonate anion) or [Rh(COD)Cl]2 (COD = 1,5-cyclooctadiene) were used, only little to traces of the desired hydroalkenylation product (5a) were formed. Instead, the homo-coupling side reaction of alkyl boronic acids (4a) occurred readily with these transition metals in an air atmosphere. Of note, the stoichiometric reaction of primary or secondary amides with allyllic bromides in the presence of strong base, such as nBuLi or NaH is difficult to selectively construct β-alkenylated amides due to the competing reaction sites.

We investigated the scope of the α,β-unsaturated amides, obtaining the results summarized in Scheme 4. Several kinds of β-alkenylated secondary amides are obtained in 92–94% yields (5a–5e) and a wide range of aliphatic and aromatic amides are good reaction partners, affording the desired products (5d–5l) in moderate to good yields. Importantly, manganese-catalyzed hydroalkenylation has excellent functional group compatibility, and tolerates heteroaryl (5d–5f) and acetal (5i) groups. With amides containing two different kinds of olefin moiety, only the electron-deficient alkenes are involved in the selective hydroalkenylation (5j). With primary amides the reaction also proceeds smoothly (5m, 93% yield). Both internal and terminal unsaturated amides are competent partners in this hydroalkenylation, and they can give rise to the desired products in moderate to good yields (5n–5s). Besides the primary and secondary amides, unsaturated protodemetalation side reactions that occur as a result of the high reactivity of metal alkynyl compounds. Based on our successful hydroarylation of unsaturated secondary amides, giving for example 3p (Scheme 2), we found by replacement of CsF with K2CO3, in the hydroarylation reaction, that the challenging arylboronic acids are competent coupling partners with Mn1(CO)2Br as the catalyst. Importantly, the resulting vinyl manganese intermediates directly from alkyl boronic acids cannot be generated in a Mn(I)-catalyzed C–H activation manner, and this significantly enhances the synthetic practicality of the hydroarylation reaction. Under the optimized reaction conditions, the desired β-alkenylated amide (5a) can be obtained in an isolated yield of 93% (Scheme 3). The use of Mn1(CO)10 results in a slightly decreased yield (83%), and replacement of 5 mol% Mn2(CO)8Br2 with 10 mol% Mn(CO)5Br gives only a moderate yield (77% vs. 93%). When Pd(PPh3)4, Ni(acac)2 (acac = acetylacetonate anion) or [Rh(COD)Cl]2 (COD = 1,5-cyclooctadiene) were used, only little to traces of the desired hydroalkenylation product (5a) were formed. Instead, the homo-coupling side reaction of alkyl boronic acids (4a) occurred readily with these transition metals in an air atmosphere. Of note, the stoichiometric reaction of primary or secondary amides with allyllic bromides in the presence of strong base, such as nBuLi or NaH is difficult to selectively construct β-alkenylated amides due to the competing reaction sites.

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rated tertiary amides can also participate smoothly in the hydroalkenylation reaction (5t–5y). The good functional group tolerance makes this protocol useful in the late-stage application in complex unsaturated amides (5z–5cc). It was found that the amide motif in the substrates play an important role in the transition-state since the corresponding unsaturated carboxylic acid (5dd) and nitrile (5ee) can only give moderate yield. We performed the scalable experiments in autoclave, which did not compromise the reaction efficiency and yield (1 mmol scale: 3d, 5t).

Subsequently, a series of structurally diverse alkenyl boronic acids were treated under the optimized reaction conditions (Scheme 5). In general, the manganese-catalyzed hydroalkenylation strategy has a very broad scope and it was found that both the terminal and internal alkenyl boronic acids are good coupling partners, delivering the desired β-alkenylated secondary amides (5ff–5ww) in 55–88% yields. The electronic effect on the phenyl ring has little influence on the reaction efficiency (5ff–5hh) and the electron-rich five-membered heteroaryl rings in 5ii and 5jj tolerate the conditions well. The cyclic and acyclic aliphatic alkenyl boronic acids are also effective coupling partners, readily furnishing the corresponding products (5ll–5uu). Moreover, the electron-deficient alkenyl boronic acid (5vv) and 1,3-conjugated alkenyl boronic acid (5ww) can undergo this transformation smoothly, delivering moderate yields.

With Mn(I)-catalyzed hydroalkenylation of unsaturated amides, we can readily assemble a rich library of structurally diverse β-alkenylated amides. As shown in Scheme 6, several multisubstituted five- and six-membered lactams can be prepared in one step and in moderate to good yields, further stressing the synthetic value of the reaction in organic synthesis and drug discovery.

We found that the addition of 3 equivalents of EtOH can improve the yield of this reaction, and we postulated that it may play a special role as a proton source in the protodemetalation. As shown in Scheme 7a, deuterium-labeling control experiments indicated that the hydrogen atom at the α-
position majorly originates mainly from EtOH or H2O not keto-enol isomerization [Eq. (3)–(5)]. Although it is currently premature to describe a clear mechanistic understanding of Mn(I)-catalyzed hydroarylation and hydroalkenylation of α,β-unsaturated amides, we propose a plausible mechanism in Scheme 7b. Owing to the weak coordination ability of bromide, the dimeric manganese catalyst could become two reactive 16-electron manganese species (8) at 120°C, and these will immediately undergo transmetallation with aryl boronic acids in the presence of external base to generate an intermediate (9). As the use of different inorganic bases can influence the reaction efficiency, we speculated the Mn-mediated transmetallation chemistry with arylboronic acids might be similar to palladium.[44,45] The use of Mn(CO)5Br can work for hydroarylation and hydroalkenylation, but the corresponding yields are lower. We envisioned that the dimeric Mn(CO)5Br[46] is much more prone to generate the 16-electron vacant coordination state (9) than that with Mn(CO)5Br. The vacant coordination state of this Ar–Mn intermediate (9) readily coordinates with alkynes (1). Then, an electron-demand matched migratory insertion can occur exclusively, forming intermediate 11 with the assistance of an amide moiety. Finally, protodemetalation with EtOH or H2O can afford the desired product (3) and regenerate the reactive 16-electron manganese-species (8) for subsequent transmetallation with the aryl boronic acids. Accordingly, the reactive Mn(I)-species during the catalytic cycle may be either 16-electron (CO)4MnBr, (CO)4MnOH, or (CO)4MnOEt. Alternatively, although manganese-catalyzed radical process is less likely, it cannot be absolutely ruled out at present.[40]

In conclusion, an unprecedented dimeric manganese(I)-catalyzed hydroarylation and alkenylation of α,β-unsaturated alkynes with commercially available aryl and alkenyl boronic acids has been developed. The use of ethanol as an additive is an important factor that contributes to a high yield. For the first time, alkenyl boronic acids are successfully employed for Mn(I)-catalyzed carbon–carbon bond formation. The exploration of dimeric manganese-catalyzed asymmetric hydroarylation and hydroalkenylation of alkynes is in progress in our laboratory.

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Conflict of interest

The authors declare no conflict of interest.

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We thank one anonymous reviewer very much to give us this helpful suggestion.

The use of 2 equiv nBuLi results in a very complex reaction mixture, and three kinds of products are produced because of the competing reaction sites. The use of NaH can also lead to similar result, please see Supporting Information for details.

CCDC 1819889 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.