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J. Am. Chem. Soc., **Just Accepted Manuscript** • Publication Date (Web): 12 Apr 2017

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Copper-Catalyzed Dicarbofunctionalization of Unactivated Olefins by Tandem Cyclization/Cross-Coupling

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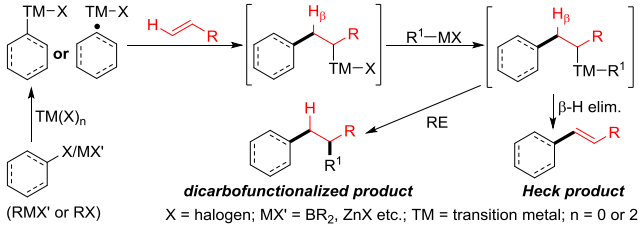
Supporting Information Placeholder

ABSTRACT: We present a strategy that difunctionalizes unactivated olefins in 1,2-positions with two carbon-based entities. This method utilizes alkyl/arylzinc reagents derived from olefin-tethered alkyl/aryl halides that undergo radical cyclization to generate C(sp^3)-Cu complexes *in situ*, which are intercepted with aryl and heteroaryl iodides. A variety of (arylmethyl)carbo- and hetero (N, O)-cycles can be synthesized with this new method.

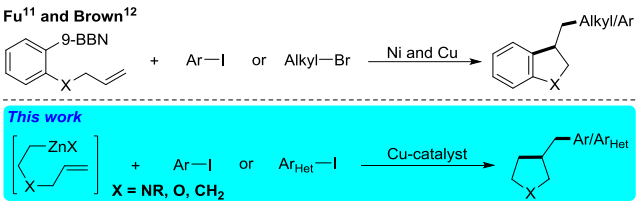
Transition metal (TM)-catalyzed dicarbofunctionalization of unactivated olefins offers a new retrosynthetic protocol in organic synthesis.[1] This transformation generates two carbon-carbon (C–C) bonds in one synthetic step, and finds important applications in rapidly building molecular complexity from simple and readily available feedstock chemicals. Recently, incorporation of cross-coupling as a bond-forming operation into the olefin dicarbofunctionalization manifold[1] has attracted a tremendous interest owing to its unlimited synthetic potential. During a catalytic process in this reaction, an organometallic species (R-MX) or organohalide (R-X) inserts olefins, by migratory insertion[2] or radical addition,[3] in the presence of a transition-metal [TM(X)$_n$] catalyst and generates a new C(sp^3)-TM complex *in situ* (Scheme 1). Further coupling of these C(sp^3)–TM species with C-nucleophiles/electrophiles delivers desired products with two new C–C bonds. However, interception of these transient C(sp^3)–TM species with C-electrophiles/nucleophiles is often met with formidable challenges[4] due to their high propensity to undergo β-hydride (β-H) elimination that leads to the formation of Heck products (Scheme 1).[5]



Scheme 1. Challenges with intercepting C(sp^3)-TM species *in situ* during olefin 1,2-dicarbofunctionalization

Despite potential difficulties with β-H elimination, successful interception of such C(sp^3)-TM species in catalytic olefin 1,2-dicarbofunctionalizations are emerging recently. These reactions generally implement intuitive designs in substrates to prevent complications from β-H elimination, such as by stabilizing C(sp^3)–TM species via π-allylation/benzylation,[6] lacking in β-H,[7] installing coordinating groups[8] or increasing geometric constraints.[9] Despite these significant reports, dicarbofunctionalization of unactivated olefins that bear β-H but lack the intrinsic features to stabilize transient C(sp^3)-TM species are limited.[10]

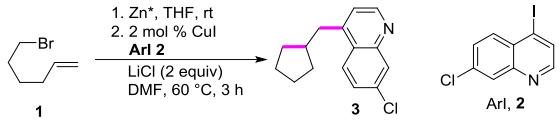
Recently, Fu[11] and Brown[12] reported cyclization/cross-coupling of aryl-9-BBN bearing C/O-tethered olefins with alkyl/aryl halides (Scheme 2). In these reactions, C(sp^3)–Ni and C(sp^3)–Cu species were generated after migratory insertions of the tethered olefins into aryl-Ni/Cu species, which were then intercepted with alkyl-Br and ArI, respectively. Herein, we utilize alkyl-ZnX reagents derived from alkyl halides containing C/O/N-tethered olefins that undergo cyclization by a radical process to generate C(sp^3)–Cu species,[13] which are then intercepted with aryl and heteroaryl iodides (Scheme 2).[14] This method enables us to access a variety of cyclopentyl, furanyl and pyrrodinyl cores. We further show that the current reaction also enables us to couple 3-butenyl-, *O*-allyl- and *N*-allyl-tethered aryl-ZnX reagents with aryl and heteroaryl iodides to construct indanyl, dihydrofuranyl and indolinyl rings. These carbo- and heterocyclic cores are privileged motifs in pharmaceuticals, bioactive molecules and natural products.[15]



Scheme 2. 1,2-Dicarbofunctionalization of olefins

Recently, we disclosed a Cu-catalyzed cross-coupling of alkylzinc reagents with heteroaryl iodides[16] that proceeded in DMF at room temperature (RT) in the presence of LiCl.[17] In order to study the potential of this method for tandem cyclization/coupling sequence, we examined the reaction of 7-chloro-4-iodoquinoline with alkylzinc bromide generated *in situ* from the reaction of 6-bromo-1-hexene with activated zinc.[18,19] Pleasingly, the reaction afforded the cyclization/coupling product **3** in 61% yield (Table 1, entry 1). By raising the temperature to 60 °C, the reaction afforded the desired product **3** in 70% yield (entry 2).[20] The reaction can be easily scaled up to gram quantities (5 mmol), which furnished the product **3** in 64% (0.787 g) isolated yield (entry 2). Reaction can also be performed in DMA, DMSO or NMP (entry 3). Only a trace amount of the product **3** was observed in other solvents (entry 4). The product was formed in low yields with Ni and Pd, suggesting that the current reaction is not catalyzed by these metals (entries 5-6). In addition, the yield of the product **3** also decreased when the standard reaction (entry 2) was conducted in the presence of 1 mol% of either $(Ph_3P)_4Ni$ or $Pd(dba)_2$ (entries 7-8).

Table 1. Optimization of reaction conditions[a]

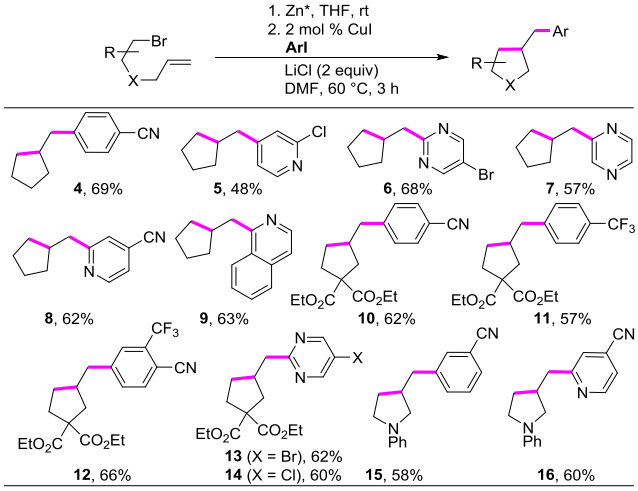


entry	modified conditions	yields (%)[a]
1	RT instead of 60 °C	61
2	none	70 (64)
3	DMA, DMSO, NMP instead of DMF	60-69
4	tolulene, dioxane	traces
5	1 mol% $(Ph_3P)_4Ni$ instead of CuI	15
6	1 mol% $Pd(dba)_2$ instead of CuI	20
7	1 mol% $(Ph_3P)_4Ni$ added	13
8	1 mol% $Pd(dba)_2$ added	41

[a]Yields were determined by GC using pyrene as an internal standard. Value in parenthesis is the isolated yield from a 5.0 mmol scale reaction.

With the optimized conditions in hand, we examined reactions of a variety of *in situ*-generated olefin-tethered alkylzinc reagents with aryl iodides (Table 2).[21] Reactions proceed well with substituted and unsubstituted 6-halohexenes-derived alkylzinc reagents and affords benzylcyclopentane derivatives in good yields (**4**-**14**). Reactions also afford 3-benzylpyrrolidine derivatives **15**-**16** in good yields from the alkylzinc reagent derived from *N*-allyl-*N*-(2-bromoethyl)-aniline. Reactions generally work well with electron-deficient and heteroaryl iodides. Reactions with electron-rich aryl iodides afford <20% products. Heteroaryl bromides furnished no product. A number of functional groups, such as esters, nitriles, bromide, chloride and trifluoromethyl, are tolerated.[22]

Table 2. Cyclization/coupling of alkylzinc reagents[a]

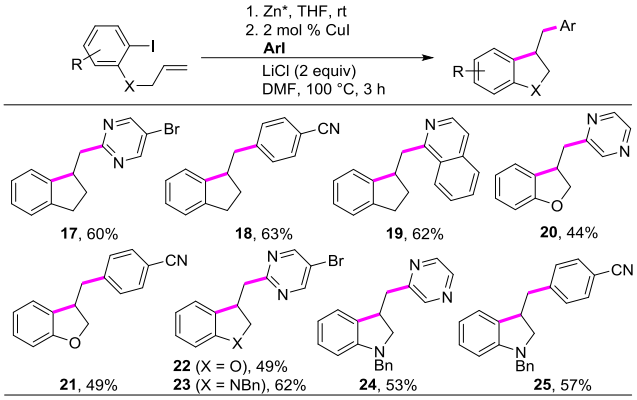


[a]Values are isolated yields from 0.5 mmol scale reactions.

The current method can also be applied for the cyclization-coupling of aryl-ZnX reagents bearing pendant olefins (Table 3).[23] Arylzinc reagents containing 2-(3-butenyl), *o*-allyloxyl and *o*-allylanilinyl groups underwent carbocylization followed by cross-coupling with aryl and heteroaryl iodides affording indanyl, dihydrofuranyl and indolinyl scaffolds in good yields (**17**-**25**). These reactions of C/O/N-tethered olefinic arylzinc reagents afford a complementary method to the previous report by Brown on olefin-tethered aryl-9-BBN reagents where 1-benzylindane derivatives could not be formed, and both synthesizing 3-benzylindoline derivatives and coupling with heteroaryl halides also remained challenging.[24]

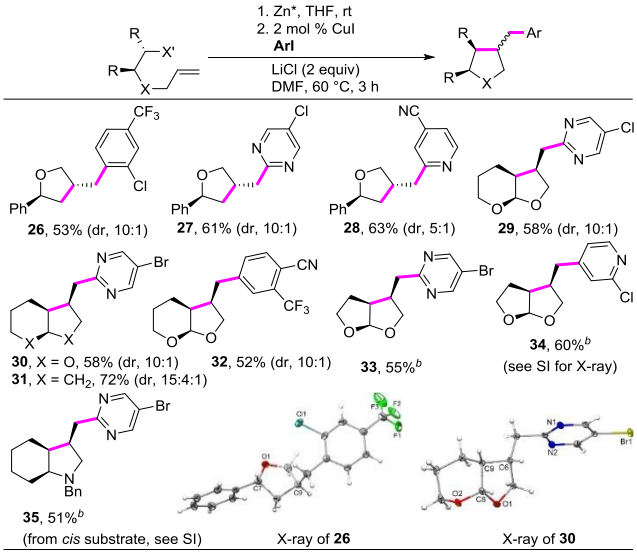
We further examined the scope of the current reaction for diastereoselectivity with alkylzinc reagents derived from chiral racemic olefin-tethered alkyl halides (Table 4). Reactions proceeded with a varying degree of diastereoselectivity depending on substrate types. Reaction of (1-(allyloxy)-2-bromoethyl)benzene-derived alkylzinc reagent with 3-chloro -4-iodobenzotrifluoride, 5-chloro-2-iodopyrimidine and 2-iodoisonicotinonitrile furnished the products in 10:1 (**26**), 10:1 (**27**) and 5:1 (**28**) diastereomeric ratios, respectively. Similarly, cyclization/couplings of alkylzinc reagents derived from *trans*-2-(allyloxy)-3-iodotetrahydropyran with aryl iodides resulted in the formation of products **29**-**30** and **32** predominantly with *cis*,*cis*-stereocenters (dr, 10:1).[25] Surprisingly, the alkylzinc reagent derived from *trans*-2-(allyloxy)-3-iodotetrahydrofuran reacted with aryl iodides to furnish products **33**-**34** with *cis*,*cis*-stereocenters as single diastereomers. Similarly, the alkylzinc reagent prepared from *cis*-*N*-allyl-*N*-benzyl-2-iodocyclohexanamine also furnished the expected product **35** as a single diastereomer. The relative stereochemistry of *trans*- and *cis*,*cis*-products **26**, **30** and **34** were further confirmed by X-ray crystallography.

Table 3. Cyclization/coupling of arylzinc reagents[a]



[a]Values are isolated yields from 0.5 mmol scale reactions.

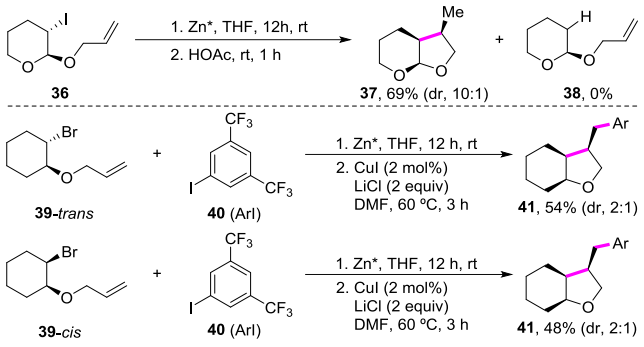
Table 4. Diastereoselective olefin difunctionalization[a]



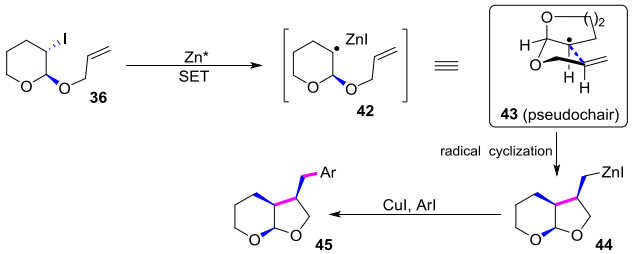
[a]Values are isolated yields from 0.5 mmol scale reactions. [b]Single diastereoisomer. X = Br for **26**-**28**; X = I for **29**-**35**.

We further performed mechanistic studies in order to account for the predominantly *cis*,*cis*-stereochemistry observed for products **29**-**35** and to understand the process of cyclization for both aryl- and alkyl-ZnX reagents derived from olefin-tethered aryl and alkyl halides. First, we prepared an alkylzinc reagent with the alkyl iodide **36** by reacting it with activated zinc in THF at RT

(Scheme 3). Treatment of **36**-derived alkyl-ZnI species with acetic acid at RT resulted in the formation of the cyclized product **37** in 69% isolated yield (dr, 10:1) without the formation of the uncyclized product **38**. The *cis*,*cis*-geometry of the major isomer of the product **37** was confirmed by NOE experiments. Further examination of the cyclization/cross-coupling of both the *cis* and *trans*-isomers of alkyl bromide **39** with iodoarene **40** indicated that these reactions proceeded with the same degree of diastereoselectivity (2:1). Analysis of these results reveals that the alkyl-ZnX reagents derived from olefin-tethered alkyl halides (**36**) undergo cyclization via alkyl radicals (**42)** during their formation by SET (scheme 4).[26] The radical cyclization is consistent with the observed formation of the predominantly *cis*,*cis*-stereocenters in products **29**-**35**, which can be rationalized based on ring closure via pseudochair conformation **43**.[19b]

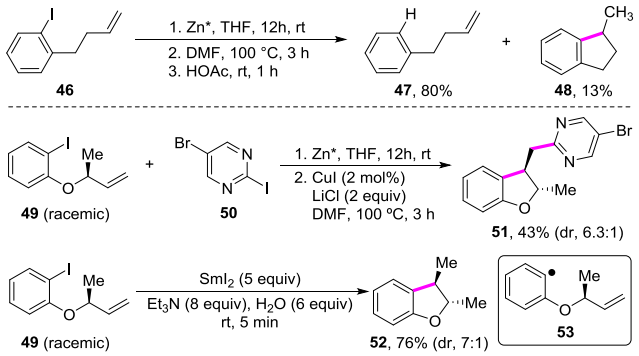


Scheme 3. Mechanistic studies with alkyl halides

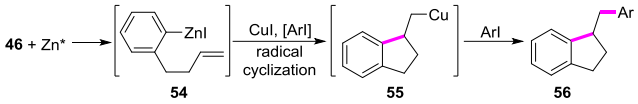


Scheme 4. Proposed pathway for alkyl-ZnI cyclization

We further prepared an arylzinc reagent with iodoarene **46** and conducted protonation reaction with acetic acid under the standard reaction conditions but in the absence of CuI and ArI (Scheme 5). This reaction afforded the uncyclized product **47** in 80% yield along with the cyclized product **48** in 13% yield. In addition, the reaction of olefin-tethered aryl iodide **49** with iodoarene **50** showed that the reaction furnished the expected product **51** in a 6.3:1 diasteromeric ratio. A control cyclization reaction of the same aryl iodide **49** in the presence of SmI_2, which is known to proceed via the formation of the aryl radical **53**,[27] also proceeded with a similar level of diastereoselectivity (7:1) affording the cyclized product **52**. These results are consistent with the initial formation of olefin-tethered arylzinc reagents, which subsequently undergo cyclization/cross-coupling via a radical pathway (Scheme 6).[28,29]



Scheme 5. Mechanistic studies with aryl iodides



Scheme 6. Proposed pathway for aryl-ZnI cyclization

In summary, we have developed a Cu-catalyzed tandem cyclization/coupling of alkyl-ZnX and aryl-ZnX reagents bearing pendant olefins with aryl and heteroaryl iodides. Current method enables the synthesis of various cyclopentyl, furanyl, pyrrodinyl, indanyl, dihydrofuranyl and indolinyl cores that are prevalent in bioactive molecules. We further performed mechanistic studies, which revealed that both the alkylzinc and arylzinc reagents with pendant olefins undergo cyclization onto the tethered olefins by a radical process leading to the formation of new C(sp^3)–Cu species prior to reacting with iodoarenes.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data for all compounds, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interests.

ACKNOWLEDGMENT

We thank the University of New Mexico (UNM) and the National Science Foundation (NSF CHE-1554299) for financial support, and upgrades to the NMR (NSF grants CHE08-40523 and CHE09-46690) and MS Facilities. The Bruker X-ray diffractometer was purchased via an NSF CRIF:MU award to UNM (CHE04-43580). We thank Dr. Diane A. Dickie for X-ray crystallographic analysis of compounds **26**, **30** and **33**.

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(20) Raising the temperature to 60 °C generally increases the cyclization/cross-coupling by 5-10% with the corresponding decrease in direct cross-coupling products.

(21) Reaction of 7-bromo-1-hexene-derived alkyl-ZnBr with 5-bromo-2-iodopyrimidine did not generate any 6-membered cyclization/cross-coupling product.

(22) No dehalogenation of products such as **17** was observed for all entries in Tables 2-4 containing similar compounds.

(23) Reaction of 1-(cinnamyloxy)-2-iodobenzene-derived aryl-ZnBr bearing an internal olefin with 5-bromo-2-iodopyrimidine did not generate any cyclization/cross-coupling product.

(24) For a few examples of coupling with heteroaryl bromides and synthesizing 3-benzyliodoline, see: ref. 12.

(25) The dr observed herein are similar for some compounds and slightly different for others compared to those observed for a Ni-catalyzed radical cyclization (see ref. 19b). The variation could arise from the use of a ligand with the Ni-catalyst.

(26) Like **36**, other olefin-tethered alkyl halides, except 5-hexenyl bromide 1, also afforded cyclized alkylzinc reagents predominantly. 5-Hexenyl bromide 1 furnished a 1:1 ratio of cyclized to uncyclized alkylzinc reagent, which suggested that Cu-catalyst is also invloved in cyclization of 5-hexenylzinc bromide. The result was further confirmed with commercial 5-hexenylzinc bromide, which afforded the cyclization/cross-coupling product **3** in 78% GC yield.

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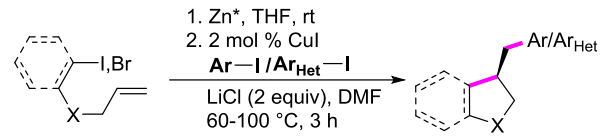
(28) Prior results indicate that the migratory insertion of tethered olefins into a ligand-bound aryl-Cu proceed with >20:1 diastereoselectivity. Under our conditions, the lower dr could also arise due to the lack of an ancillary ligand. See ref. 12.

(29) Reaction of arylzinc reagent **54** in the presence of CuI and LiCl led to partial decomposition of **54**, which suggests that ArI is required during the cyclization process.

Table of Content



alkyl/aryl (X = N, O, CH_2)

34 examples; 44-69% yields

tolerates CO_2Me, CN, Br, Cl, CF_3