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

Surendra Thapa, Prakash Basnet, and Ramesh Giri*

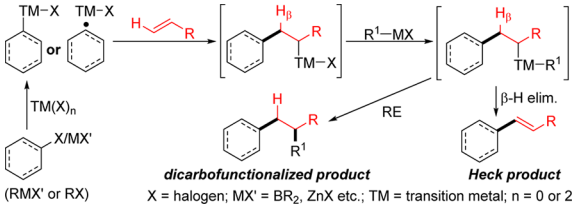
Department of Chemistry & Chemical Biology, The University of New Mexico, Albuquerque, New Mexico 87131, United States

Supporting Information

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 heterocycles (N, O) 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 C−C bonds in one synthetic step and finds important applications in rapidly building molecular complexity from simple and readily available feedstock chemicals. Incorporation of cross-coupling as a bond-forming operation into the olefin dicarbofunctionalization manifold[1] has attracted 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

Scheme 1. Challenges with Intercepting C(sp^3)-TM Species *in Situ* during Olefin 1,2-Dicarbofunctionalization

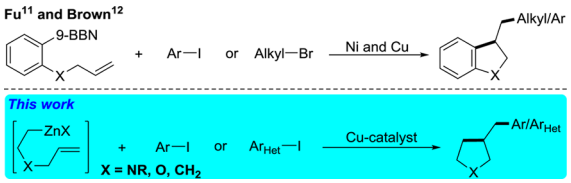


coupling of these C(sp^3)-TM species with C-nucleophiles/electrophiles delivers desired products with two new C−C bonds. However, interception of these transient C(sp^3)-TM species with C-electrophiles/nucleophiles is often met with formidable challenges[4] due to their high propensity to undergo β-hydride (β-H) elimination that leads to the formation of Heck products (Scheme 1).[5]

Despite potential difficulties with β-H elimination, methods for interception of such C(sp^3)-TM species in catalytic olefin 1,2-dicarbofunctionalizations are emerging. These reactions 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 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]

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

Scheme 2. 1,2-Dicarbofunctionalization of Olefins



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 pyrrolidinyl cores. We further show 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]

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] 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] The reaction afforded the cyclization/coupling product **3** in 61% yield (Table 1, entry 1). When the temperature was raised 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

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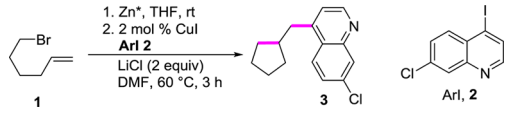
Table 1. Optimization of Reaction Conditions[a]



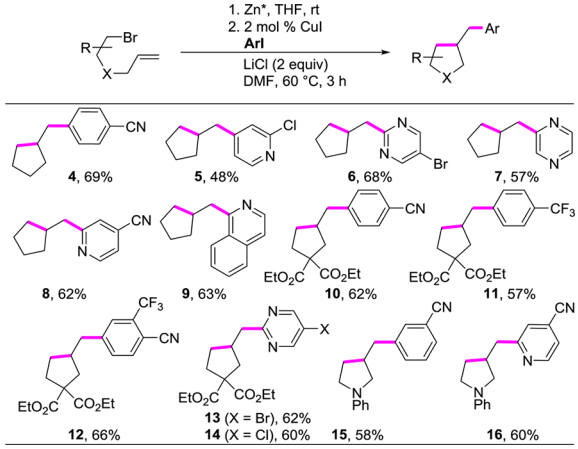
entry	modified conditions	yields (%)[a]
1	RT instead of 60 °C	61
2	none	70(64)
3	DMA, DMSO, NMP instead of DMF	60−69
4	tolulene, dioxane	traces
5	1 mol% $(Ph_3P)_4Ni$ instead of CuI	15
6	1 mol% $Pd(dba)_2$ instead of CuI	20
7	1 mol% $(Ph_3P)_4Ni$ added	13
8	1 mol% $Pd(dba)_2$ added	41

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

low yields with Ni and Pd, suggesting the current reaction is not catalyzed by these metals (entries 5 and 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 and 8).

With optimized conditions, 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

Table 2. Cyclization/Coupling of Alkylzinc Reagents[a]

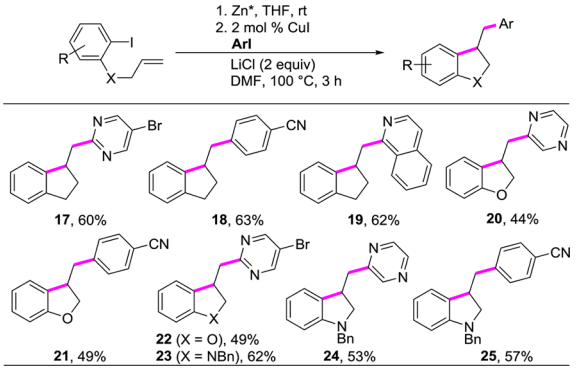


[a]Values are isolated yields from 0.5 mmol scale reactions.

unsubstituted 6-halohexenes-derived alkylzinc reagents and afford benzylcyclopentane derivatives in good yields (**4**−**14**). Reactions also afford 3-benzylpyrrolidine derivatives **15** and **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]

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

Table 3. Cyclization/Coupling of Arylzinc Reagents[a]

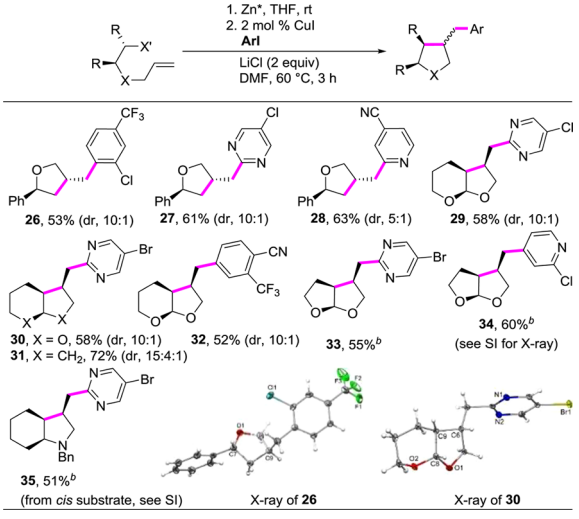


[a]Values are isolated yields from 0.5 mmol scale reactions.

(**17**−**25**). These reactions of C/O/N-tethered olefinic arylzinc reagents afford a method complementary 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 examined the scope of the current reaction for diastereoselectivity with alkylzinc reagents derived from chiral racemic olefin-tethered alkyl halides (Table 4). 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**.

proceeded with varying degrees 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 (dr's), 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** and **34** with *cis*,*cis*-stereocenters as single diastereomers. Similarly, the alkylzinc reagent prepared from *cis*-*N*-allyl-*N*-benzyl-2-iodocyclohexanamine also furnished

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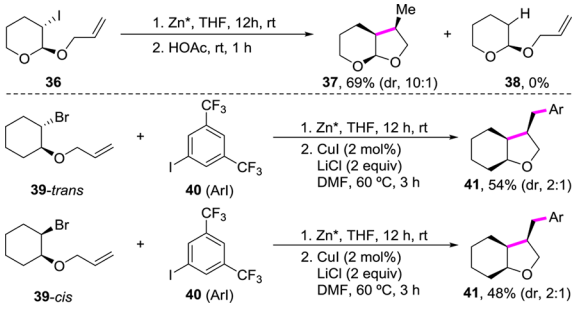
the expected product **35** as a single diastereomer. The relative stereochemistry of *trans*- and *cis,cis*-products 26, 30, and 34 was further confirmed by X-ray crystallography.

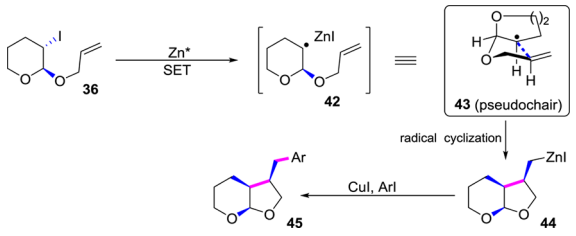
We performed mechanistic studies to account for the predominantly *cis,cis*-stereochemistry observed for products **29**–**35** and to understand the process of cyclization for both aryl- and alkyl-ZnX reagents derived from olefin-tethered aryl and alkyl halides. First, we prepared an alkylzinc reagent 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

Scheme 3. Mechanistic Studies with Alkyl Halides



acetic acid at RT resulted in 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. Examination of the cyclization/cross-coupling of both the *cis*- and *trans*-isomers of alkyl bromide **39** with iodoarene **40** indicated these reactions proceeded with the same degree of diastereoselectivity (2:1). Analysis of these results reveals the alkyl-ZnX reagents derived from olefin-tethered alkyl halides (**36**) undergo cyclization via alkyl radicals (**42**) during their formation by single-electron transfer (SET, Scheme 4).[26] The

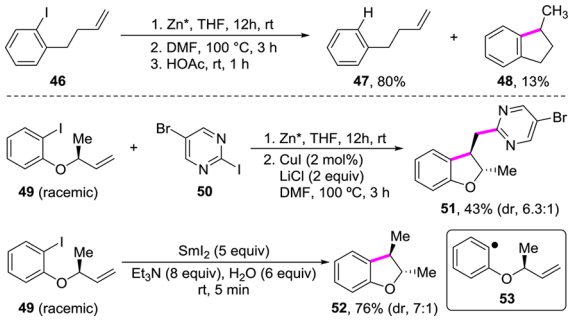
Scheme 4. Proposed Pathway for Alkyl-ZnI Cyclization



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]

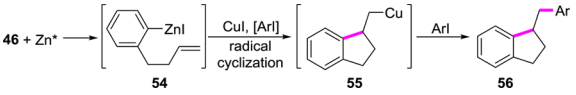
We prepared an arylzinc reagent with iodoarene **46** and conducted protonation reaction with acetic acid under the standard reaction conditions but in the absence of CuI and ArI (Scheme 5). This reaction afforded uncyclized product **47** in 80% yield along with the cyclized product **48** in 13% yield. The reaction of olefin-tethered aryl iodide **49** with iodoarene **50** showed 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, 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

Scheme 5. Mechanistic Studies with Aryl Iodides



olefin-tethered arylzinc reagents, which subsequently undergo cyclization/cross-coupling via a radical pathway (Scheme 6).[28,29]

Scheme 6. Proposed Pathway for Aryl-ZnI Cyclization



In summary, we developed a Cu-catalyzed tandem cyclization/coupling of alkyl-ZnX and aryl-ZnX reagents bearing pendant olefins with aryl and heteroaryl iodides. This method enables synthesis of various cyclopentyl, furanyl, pyrrolidinyl, indanyl, dihydrofuranyl, and indolinyl cores prevalent in bioactive molecules. We 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 formation of new $C(sp^3)$-Cu species prior to reacting with iodoarenes.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b01922.

Experimental procedures; data for 26, 30, 34

■ AUTHOR INFORMATION

Corresponding Author

*rgiri@unm.edu

ORCID

Ramesh Giri: 0000-0002-8993-9131

Notes

The authors declare no competing financial interest.

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(19) For additional references for making alkylzinc reagents, see: (a) Guijarro, A.; Rosenberg, D. M.; Rieke, R. D. *J. Am. Chem. Soc.* **1999**, *121*, 4155. (b) Vaupel, A.; Knochel, P. *J. Org. Chem.* **1996**, *61*, 5743. (c) Cohen, T.; Gibney, H.; Ivanov, R.; Yeh, E. A. H.; Marek, I.; Curran, D. P. *J. Am. Chem. Soc.* **2007**, *129*, 15405. (d) Meyer, C.; Marek, I.; Courtemanche, G.; Normant, J.-F. *Tetrahedron* **1994**, *50*, 11665.

(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's 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 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.

(27) Dahlen, A.; Petersson, A.; Hilmersson, G. *Org. Biomol. Chem.* **2003**, *1*, 2423.

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

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

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