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Nickel-Catalyzed Reductive Allylation of Tertiary Alkyl Halides with Allylic Carbonates

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Abstract: The construction of all C(sp³)–quaternary centers has been successfully achieved under Ni-catalyzed cross-electrophile coupling of allylic carbonates with unactivated *tertiary* alkyl halides. For allylic carbonates bearing C1– or C3–substituents, the reaction affords excellent regioselectivities by addition of alkyl groups to the unsubstituted allylic carbon terminus. The allylic alkylation method also exhibits excellent functional group compatibility, and delivers the products with high *E*-selectivities.

The creation of congested all C(sp³)-quaternary centers represents a synthetic difficulty in the realm of C-C coupling chemistry.^[1-4] Although Cu- and Co-catalyzed assembly of tertiary alkyl-Mg reagents with unactivated primary and secondary alkyl halides are viable, these methods are limited to unfunctionalized tertiary alkyl groups.^[1] Extension of the same Kumada protocol to the coupling with allylic electrophiles often encounters poor α/γ selectivity issues (Scheme 1).^[2] On the other hand, the assembly of tertiary alkyl halides with benzyland allyl-M (M = Mg, Zn) reagents using Co or Ag as the catalyst provides an alternative approach to all C(sp3)quaternary centers (Scheme 1).^[3] However, such an allylation method also suffers from regionselectivity issues.[3d] Noteworthy is that allylation-induced quaternary carbon scaffolds have proven to be exceedingly useful for accessing complex bioactive molecules.^[5]

In recent years, reductive cross-electrophile coupling between alkyl and other electrophiles continues to attract attentions.^[6] Important progress has been achieved for arylation and acylation of *tertiary* alkyl halides with aryl and acyl electrophiles, respectively.^[7–8] Nonetheless, the formation of quaternary carbons relying on C(sp³)–C(sp³) bond formation remains virtually unexplored.^[9] Only adamantyl bromide has been reported thus far to couple with undecorated allylic acetate using a cobalt-catalyzed reductive protocol.^[10–11] The distinctive reactivity of adamantyl halides from a general pool of unactivated *tertiary* alkyl halides should be noted, qualifying them as a special *tertiary* electrophile in the reductive coupling protocol.^[12]

Herein, we report a mild Ni-catalyzed method enabling facile construction of all (sp³)-carbon quaternary centers from reductive allylation of unactivated *tertiary* alkyl bromides with allylic carbonates. This method provides a convenient entry to allylated alkanes with a broad substrate scope and excellent

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functional group tolerance. The excellent regioselectivity arises from addition of alkyl groups to the unsubstituted allylic carbons.

Scheme 1. Alkyl-allyl coupling methods to all-carbon quaternary centers.



After extensive experiments, we identified an optimal recipe for the coupling of *t*Bu–Br **1** with methyl (2-phenylallyl) carbonate.^[13] As outlined in Table 1, a combination of NiBr₂·glyme/*i*Pr-Pybox **L1**/Zn with pyridine/MgCl₂ as additives in DMA at ambient temperature delivered the coupling product **2a** in a highest 81% yield (entry 1, method A). Without either pyridine or MgCl₂, the reaction yields decreased moderately (entries 2–3). Other nickel sources/ligands proved to be less effective (entries 4-11). Reduction of the precatalyst/ligand loading by half afforded the product in 57% yield (entry 12).

 Table 1. Optimization for the coupling of tBu-Br with methyl 2-phenylallyl carbonate.^[a]

→ _{Br}	+ Ph - OCO ₂ Me - 2 equiv	"method A" NiBr ₂ (glyme) (10%) ligand L1 (15%) pyridine (30%) Zn (300%), MgCl ₂ (100%) DMA, 25 °C	Ph 2a
	N iPr L2a, R L2b, R	$ \begin{array}{c} R \\ N \\ = R \\ = H \\ H \\ \end{array} \begin{array}{c} H \\ N \\ L3 \\ N \\ L3 \\ N \\ \end{array} \begin{array}{c} H \\ R \\ R \\ R \\ R \\ R \\ N \\ \end{array} \right) $	
entry	variation from the s	standard conditions	yield ^[b]
1	none		81% ^[c]

1	none	81% ^[c]
2	no pyridine	72%
3	no MgCl ₂	51%
4	Ni(COD) ₂	77%
5	NiBr ₂	71%
6	Ni(ClO ₄) ₂ •6H ₂ O	71%
7	NiBr ₂ -diglyme	69%
8	L2a instead of L1	26%
9	L2b instead of L1	41%

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10	L3 instead of L1	21%
11	L4 instead of L1	43%
12	Ni (5%), L1 (7.5%)	57%

[a] Standard conditions: **1** (0.15 mmol), allylic carbonate (2 equiv), Ni (10 mol %), ligand (15 mol %), MgCl₂ (1 equiv), pyridine (0.3 equiv), Zn (3 equiv), DMA (1 mL). [b] NMR yield using 2,5-dimethylfuran as the internal reference. [c] Isolated yield.





With method A, installation of electron-donating or -withdrawing groups onto the 2-phenylallyl carbonate did not alter the coupling efficiency, as evident in 3a-b and 4a-b. Both openchain and cyclic tertiary bromides (5-14) were suitable for the coupling reaction conditions. Excellent functional group compatibility was observed for the coupling of a variety of methyl unactivated alkvl bromides with tertiary (2phenylallyl)carbonate. This comprised ester. tosvlate. phthalimidyl, chloride, ketone, amine and hydroxyl groups. The more hindered 3-bromo-3-ethylpentane also furnished 13 in a moderate yield. Formation of the biallyl product 14 was highly effective by double allylation of the *tertiary* alkyl di-bromide precursor. By comparison, 2-methylallyl carbonate was less effective than the 2-aryl counterpart; moderate yield was obtained for **15**.

The coupling strategy was also applied to the allylation of structurally more complex scaffolds, including cyclotryptamine **16** and protected α -allyl cyclohexanone **17**. The results demonstrated the potential utility of this allylation method.



Figure 2. [a] Reaction conditions similar to method A, except that dtBBipy and pyridine 2,6-diamine was used; yields refer to isolated yields. [b] $Ni(COD)_2$ was used. [c] Nil₂ was used. [d] The ratios of the aryl-linear products to the branched isomers were detected to be 8:1 for 28b, 5:1 for 28b, 2:1 for 29a and 15:1 for 29b, respectively. [e] When ligand L1 was used to replace L2a, the ratio of 29a/the branched isomer was boosted to >9:1. [f] NMR yield using 2,5-dimethylfuran as the internal reference. [g] 3-Methylbut-2-en-1-yl phenyl carbonate was used at 40 °C. [h] Mn and TBAC was used. [i] The ratio of *trans*-to *cis*-alkenes was 11:1, and the ratio of *trans*-linear product to *trans*-branched diastereomer was 15:1. [j] (Z)-methyl pent-2-en-1-yl carbonate was used, and the ratio of *trans*-to *cis*-alkenes was 12:1.

Although formation of **18a** was achieved in 66% yield using method A, the same reaction conditions were not suited for allyl

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methyl carbonates decorated with 3-aryl and 3-alkyl groups.[13] To our delight, utilization of bipyridine and pyridine-2,6-diamine as the ligands and/or additives (method B, Figure 2) significantly boosted the coupling efficiency for allyl carbonates of these types (Figure 2). Unlike method A (Table 1, entry 3), MgCl₂ is indispensable.^[13] The incorporation of unsubstituted allyl groups into 18-27 were highly effective under the modified conditions. The reactions were suitable for alkyl halides on a 3 mmol scale, which delivered 18a in 70% yield by using 5 mol % of Ni(COD)₂. Of note is that the quaternary product 23 was obtained in 78% yield wherein the primary bromide remained intact. For 3-aryl decorated allyl carbonates, good results were obtained for phenyl and 4-methoxyphenyl derivatives (28-29), wherein small amounts of branched isomers were detected as minor products (linear/branched ratio >5:1, Figure 2).[13] It should be noted that the ratio of linear/branched isomers of 29a was boosted from 2:1 to 9:1 when L2a was replaced with L1, indicating the impact of catalysts on controlling the regioselectivity. The disubstituted allyl carbonates such as (E)-Methyl (2-methyl-3-phenylallyl) carbonate and methyl (3-methylbut-2-en-1-yl) carbonate generated 30-31 in poor yields, possibly due to steric bulkiness of the substrates. Finally, (E)-3-methyl allyl carbonate delivered the trans-linear product 32a in moderate yield with a trace amount of cis- and branched isomers (15:1 ratio of linear/branched and 11:1 ratio of cis/trans isomers, Figure 2).[13] By contrast, (Z)-methyl pent-2-en-1-yl carbonate furnished 32b in a similar yield with a 12:1 E/Z ratio.

When but-3-en-2-yl methyl carbonate was subjected to the reaction conditions (*method B*), the yield for **32a** was estimated to be ~60% based on ¹H NMR analysis.^[13] However, a 3:1 ratio of *E/Z* isomers was observed. An equivalent *E/Z* ratio was also detected for the coupling of methyl pent-1-en-3-yl carbonate, which delivered a mixture of *E*- and *Z*-**32b** in 51% yield. In lieu of ligand **L2a** with **L5a**, Zn with Mn, and MgCl₂ with MgBr₂ (*method C*), a 64% isolated yield for a mixture of *E*- and *Z*-**32a** was obtained with an *E/Z* ratio of 5.6:1. Using *method C*, a 61% isolated yield for a mixture of *E*- and *Z*-**32b** was determined with an *E/Z* ratio of 9:1 (eq 1).



The coupling of deuterated allylic ether **33** with methyl (2phenylallyl) carbonate furnished a cyclization/coupling product **34** in 58% yield with a 1:1 ratio of diastereoselectivity upon formation of the quaternary carbon stereocenter. Thus, alkyl halides proceeding via a radical process were plausibly proposed in this allylation event.^[14]



The regioselective formation of **32a** from either 1-methyl or 3methyl substituted allyl methyl carbonates may arise from a η^3 allyl–Ni intermediate. Interestingly, subjection of an *E/Z* mixture of allyl-3-d methyl carbonate to the reaction conditions provided the quaternary carbon products **35a** and **35b** in a 1:2 ratio (eq 3) This result suggests that at least for the unsubstituted allyl carbonate, η^1 -allyl-Ni (A) formed by addition of Ni to the terminal alkene carbon may participate in the allylation product formation more favorably than η^3 -allyl–Ni (B) and η^1 -allyl–Ni (C) (eq 4).^[15] By contrast, use of allyl-1-d methyl carbonate resulted in a 2:1 ratio of **35a/35b** (eq 3),^[13] which is consistent with the notion that addition of Ni to the terminal alkene carbon is more favored. However, whether the production of **32a** originates from the η^1 -2-butenyl-1-nickel or η^3 -allyl–Ni intermediate is not clear at this time.^[16]



In summary, we have illustrated an efficient allylation protocol that affords all carbon quaternary centers constituting four $C(sp^3)-C(sp^3)$ bonds. The mild Ni-catalyzed conditions are suited for a wide set of unactivated *tertiary* alkyl bromides and allylic carbonates decorated with different substituents at the allylic carbon positions. The reaction displays excellent regioselectivity by addition of the *tertiary* alkyl groups to the unsubstituted allylic carbon terminus. The preliminary mechanistic studies indicate that *tertiary* alkyl radicals engage in the reaction process.

Acknowledgements

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- Coupling of *tertiary* R-MgX with 1°- and 2°-alkyl halides catalyzed by Cu: a) J. Terao, H. Todo, S. A. Begum, H. Kuniyasu, N. Kambe, *Angew. Chem., Int. Ed.* **2007**, *46*, 2086; b) P. Ren, L. A. Stern, X. L. Hu, *Angew. Chem., Int. Ed.* **2012**, *51*, 9110; c) C.–T. Yang, Z.–Q. Zhang, J. Liang, J.–H. Liu, X.–Y. Lu, H.–H. Chen, L. Liu, *J. Am. Chem. Soc.* **2012**, *134*, 11124; by Co: T. Iwasaki, H. Takagawa, S. P. Singh, H. Kuniyasu, N. Kambe, *J. Am. Chem. Soc.* **2013**, *135*, 9604.
- [2] Coupling of *teriary* R-MgX with allylic electrophiles: a) A. M. Lauer, F. Mahmud, J. Wu, J. Am. Chem. Soc. 2011, 133, 9119–9123; b) X. Han, Y. Zhang, J. Wu, J. Am. Chem. Soc. 2010, 132, 4104–4106; with (*t*Bu)₂Zn: c) B. Breit, P. Demel, D. Grauer, C. Studte, Chem. Asian J. 2006, *1*, 586–597.
- [3] Coupling of *tertiary* alkyl halides with allylic and benzylic metallics: a) S. K. Ghorai, M. Jin, T. Hatakeyama, M. Nakamura, *Org. Lett.* 2012, *14*, 1066; b) H. Someya, H. Ohmiya, H. Yorimitsu, K. Oshima, *Org. Lett.* 2008, *10*, 969; c) Y. Mitamura, Y. Asada, K. Murakami, H. Someya, H. Yorimitsu, K. Oshima, *Chem. –Asian J.* 2010, *5*, 1487; d) T. Tsuji, H. Yorimitsu, K. Oshima, *Angew. Chem., Int. Ed.* 2002, *41*, 4137; e) H. Ohmiya, T. Tsuji, H. Yorimitsu, K. Oshima, *K. Oshima, Chem. Eur. J.* 2004, *10*, 5640.
- [4] α-Carbonyl allylation: a) G. Pupo, R. Properzi, B. List, *Angew. Chem.*, *Int. Ed.* 2016, 55, 6099; b) M. Braun, T. Meier, *Angew. Chem.*, *Int. Ed.* 2006, 45, 6952.
- [5] a) Y. Liu, S.-J. Han, W.-B. Liu, B. M. Stoltz, Acc. Chem. Res. 2015, 48, 740; b) T. Matsuura, L. E. Overman, D. J. Poon, J. Am. Chem. Soc. 1998, 120, 6500; c) D. C. Behenna, Y. Liu, T. Yurino, J. Kim, D. E. White, S. C. Virgil, B. M. Stoltz, Nat. Chem. 2012, 4, 130.
- [6] For reviews on reductive couplings, see: a) D. A. Everson, D. J. Weix, J. Org. Chem. 2014, 79, 4793; b) J. Gu, Wang, X.; Xue, H. Gong, Org. Chem. Front. 2015, 2, 1411; c) C. E. I. Knappke, S. Grupe, D. Gartner, M. Corpet, C. Gosmini, J. A. von Wangelin, Chem.-Eur. J. 2014, 20, 6828; d) D. J. Weix, Acc. Chem. Res. 2015, 48, 1767; e) T. Moragas, A. Correa, R. Martin, Chem.-Eur. J. 2014, 20, 8242; f) J. Y. Nédélec, J. Perichon, M. Troupel, Top. Curr. Chem. 1997, 185, 141.
- a) C. Zhao, X. Jia, X. Wang, H. Gong, J. Am. Chem. Soc. 2014, 136, 17645; b) X. Wang, S. Wang, W. Xue, H. Gong, J. Am. Chem. Soc. 2015, 137, 11562.
- [8] For selected examples of formation of all carbon quaternary centers via neuclophile/electrophle C(sp³)-C(sp²) coupling, see: a) A. Joshi-Pangu, C.-Y. Wang, M. R. Biscoe, J. Am. Chem. Soc. 2011, 133, 8478; Cucatalyzed coupling of *tertiary* R-ZnX with hetero-aryl iodides, see: b) S. Thapa, A. Kafle, S. K. Gurung, A. Montoya, P. Riedel, R. Giri, Angew. Chem. Int. Ed. 2015, 54, 8236; Coupling of *tert-alkyl* halides with Ar-9-BBN: c) S. L. Zultanski, G. C. Fu, J. Am. Chem. Soc. 2013, 135, 624.

Coupling of styrenyl aziridines with organozincs to give all quaternary carbon products, see: d) Huang, C.-Y.; Doyle, A. G. J. Am. Chem. Soc. **2015**. *137*, 5638.

- [9] Catalytic C(sp³)-C(sp³) bond formation via cross-coupling of alkyl electrophiles: a) H. Xu, C. Zhao, Q. Qian, W. Deng, H. Gong, Chem. Sci. 2013, 4, 4022; b) X. Yu, T. Yang, S. Wang, H. Xu, H. Gong, Org. Lett. 2011, 13, 2138. c) J.-H. Liu, C.-T. Yang, X.-Y. Lu, Z.-Q. Zhang, L. Xu, M. Cui, X. Lu, B. Xiao, Y. Fu, L. Liu, Chem.-Eur. J. 2014, 20, 15334; d) E. J. Tollefson, L. W. Erickson, E. R. Jarvo, J. Am. Chem. Soc. 2015, 137, 9760.
- [10] a) X. Qian, A. Auffrant, A. Felouat, C. Gosmini, Angew. Chem., Int. Ed. 2011, 50, 10402; In a recent Pd-catalyzed electrochemical allylic alkylation method, coupling of tBu-I with allyl bromide was disclosed as a sole example for the formation of 4,4-dimethyl-1-pentene, albeit in low yield, see: b) Y.-L.; J.-M. Huang, Org. Lett. 2017, 19, 2022. For more examples of reductive allylation of primary and secondary alkyl halides, see: a) Y. Dai, F. Wu, Z. Zang, H. You, H. Gong, Chem.–Eur. J. 2012, 16, 808; b) L. L. Anka-Lufford, M. R. Prinsell, D. J. Weix J. Org. Chem. 2012, 77, 9989.
- [11] Coupling of Ar-MgX with only adamantyl chloride is known: a) S. K. Ghorai, M. Jin, T. Hatakeyama, M. Nakamura, *Org. Lett.* 2012, *14*, 1066; b) Direct coupling of Ar₂Zn with tertiary bromides including *t*Buand admantanyl-Br, see: J. J. Dunsford, R. Ewan, E. R.;Clark, M. J. Ingleson, *Angew. Chem., Int. Ed.* 2015, *54*, 5688.
- [12] For the coupling of adamantyl halides with CO₂, see: a) M. Börjesson, T Moragas, R. Martin *J. Am. Chem. Soc.* **2016**, *138*, 7504-7507; b) E. Serrano, R. Martin *Angew. Chem. Int. Ed.* **2016**, 11207-11211
 [13] See the Supplementary Information for details.
- [14] a) R. González-Bobes, G. C. Fu, J. Am. Chem. Soc. 2006, 128, 5360;
 b) D. A. Powell, T. Maki, G. C. Fu, J. Am. Chem. Soc. 2005, 127, 510;
 c) X. Yu, T. Yang, S. Wang, H. Xu, H. Gong, Org. Lett. 2011, 13, 2138;
 d) H. Xu, C. Zhao, Q. Qian, W. Deng, H. Gong, Chem. Sci. 2013, 4, 4022; e) S. E. Creutz, K. J. Lotito, G. C. Fu, J. C. Peters, Science 2012, 338, 647.
- [15] For an example of carbonylation of η¹-allyl–Ni, see: A. Bottoni, G. P. Miscione, J. J. Novoa, X. Prat-Resina, J. Am. Chem. Soc. 2003, 125, 10412.
- [16] For mechanistic studies involving allyl-Ni(I) and -Ni(II), see: a) L. S. Hegedus, D. H. P. Thompson, *J. Am. Chem. Soc.* **1985**, *107*, 5663; b)
 E. J. Corey, M. F. Semmelhack, L. S. Hegedus, *J. Am. Chem. Soc.* **1968**, *90*, 2416; c) E. J. Corey, M. F. Semmelhack, *J. Am. Chem. Soc.* **1967**, *89*, 2755.S; d) b) E. J. Corey, L. S. Hegedus, M. F. Semmelhack, *J. Am. Chem. Soc.* **1967**, *89*, 2755.S; d) b) C. J. Corey, L. S. Hegedus, M. F. Semmelhack, *J. Am. Chem. Soc.* **1968**, *90*, 2417.

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